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A Comparative Study of Tricarbonylmanganese Photoactivatable CO Releasing Molecules (PhotoCORMs) by Using the Myoglobin Assay and Time-Resolved IR Spectroscopy

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Tricarbonylmanganese(I) complexes of the ligands tris(imidazol-4-yl)phosphane (4-tip^{H}), tris(1,4-diisopropylimidazol-2-yl)phosphane (2-tip^{iPr2}), tris(pyridin-2-yl)phosphane (tpp) and tris(*N*-methylimidazol-2-yl)carbinol (2-tic^{NMe}) were prepared. These act as *N*,*N*,*N* tripodal chelators. The solid-state structure of [Mn(CO)$_3$(tpp)]OTf was determined by X-ray diffraction. The potential of these complexes to act as photoactivatable CO-releasing molecules (PhotoCORMs) was studied with the UV/Vis spectroscopy-based myoglobin assay as well as by time-resolved IR spectroscopy. Within the series of compounds prepared, the steric bulk of the imidazolyl groups seems to significantly influence the CO-release kinetics and stoichiometry when using the myoglobin assay. In contrast, the time-resolved IR data suggest release of all carbonyl ligands upon irradiation. This effect points to a much closer association of myoglobin and PhotoCORMs than previously thought and will require further investigation.

Introduction

Until quite recently, carbon monoxide (CO) was mostly seen as a dangerous air pollutant due to its properties as an odourless and colourless gas with high toxicity to humans caused by its interference with oxygen transport in the blood. It has, however, since then become clear that carbon monoxide is endogenously produced in the human body at a rate of a few millilitres per day by tightly controlled enzymatic heme degradation and serves as an important small-molecule messenger, much like nitric oxide and hydrogen sulfide.[1] In addition, the deliberate application of CO to biological systems was found to give rise to a number of beneficial physiological effects due to its antiinflammatory, antioxidative, and antiapoptotic activities. In animal experiments, it was also shown to affect ocular hypertension as well as coagulation processes associated with transplantations.[2]

Since CO itself is a difficult to dose and highly toxic gas, there is currently significant interest in the application of metal carbonyl complexes as a solid storage form for carbon monoxide. An increasing number of such *CO releasing molecules* (CORMs) has been studied to optimise their CO release characteristics and achieve sufficient water-solubility for therapeutic applications.[3] While Motterlini et al. have pioneered the use of carbonylruthenium complexes, with tricarbonylchloro(glycinato)ruthenium(II) (CORM-3) as the CO releasing molecule most commonly employed in biological studies,[4] more recently iron and carbonyl(pyrone)molybdenum complexes (CORM-F7 and CORM-F10) have also received considerable attention.[5] In these compounds, CO release is usually triggered by ligand exchange reactions in aqueous solution. As an alternative approach, the light-induced liberation of carbon monoxide from dark-stable carbonylmanganese complexes has been explored. Initial studies used [Mn$_2$(CO)$_{10}$] (CORM-1) which, however, does not have good properties for biological applications.[6] In contrast, [Mn(CO)$_3$(tpm)]PF$_6$ [tpm = tris(pyrazol-2-yl)methane] was shown to release CO upon UV excitation and exhibit cytotoxic activity against cancer cells while being inactive even after prolonged exposure in the dark and it could also be conjugated to carrier peptides for targeted delivery.[7] Very recently, iron carbonyl complexes have also been reported which release CO upon irradiation using visible light.[8] Although the number of studies on metal carbonyl CORMs has significantly grown during the

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last few years, only very few systematic studies of the factors which determine the mechanism of CO release have been carried out so far.[9]

In the present contribution, we report on the synthesis and characterisation of a series of $Mn(CO)_3$ complexes of different imidazol-2-yl and imidazol-4(5)-yl phosphane ligands. Since the introduction of the tris(pyrazolyl)boranes (tp) by Trofimenko, scorpionate ligands containing *N* donor atoms have been intensively studied and are well known as ligands for complexes used in biomedical applications.[10] The tris(heteroaryl)phosphanes and carbinols used in this study are neutral analogues of the tp ligand in which the hydrolytically unstable B–N bonds have been replaced by more stable P–C and C–C bonds, respectively.[11] To assess the bioavailability of these new complexes, their distribution coefficients in physiological media have been measured, followed by an investigation of the light-induced CO release from the Mn complexes.

We recently reported on the light-induced CO release from several tripodal tricarbonyl[tris(imidazolyl)phosphane]manganese(I) complexes. The substitution pattern of the imidazolylphosphane ligand was found to determine the number of CO molecules released. While the compounds with the imidazol-2-ylphosphane liberate approximately two equiv. of CO per mole of complex, those with the imidazol-4-ylphosphane release only one molecule of CO per $Mn(CO)_3$ unit.[12] Here, we report on a more detailed investigation of the CO release of *fac*-$Mn(CO)_3$ complexes with tripodal *N*,*N*,*N* ligands and the influence of the ligand substitution pattern on the number of CO molecules released.

Results and Discussion

Previously, we investigated the CO release characteristics of different tris(imidazol-2-yl)- and tris[imidazol-4(5)-yl]-phosphane ligands and observed that different amounts of CO are released from the corresponding *fac*-$Mn^{I}(CO)_3$ complexes. In order to elucidate the factors which determine the CO release, we have now expanded the series of tripodal ligands and investigated the ligands tris(1,4-diisopropylimidazol-2-yl)phosphane (2-tip$^{i\mathrm{Pr,N}i\mathrm{Pr}}$) and tris[imidazol-4(5)-yl]phosphane 4-tip^{H} as well as tris(pyridin-2-yl)-phosphane (tpp) and tris(1-methylimidazol-2-yl)carbinole (2-tic^{NMe}) which are structurally similar to the previously investigated ligands (Figure 1). The heteroaryl ligands 2-tip$^{i\mathrm{Pr,N}i\mathrm{Pr}}$, tpp and 2-tic^{NMe} as well as complexes **1**–**3** and **8**–**12** were prepared according to published procedures.[12,13]

The synthesis of the new ligand 4-tip^{H}, which is the parent compound of the 4-tip^{R}-class of ligands, was achieved by the reaction of 4-iodo-1-(methoxymethyl)imidazole, ethylmagnesium bromide and phosphorus trichloride in dichloromethane. From the crude reaction mixture, colourless crystals of the magnesium complex [(4-tip^{NMOM})$_2$Mg]-Br_2 were obtained (see Supporting Information). The ligand 4-tip^{H} was isolated as the acetic acid adduct after deprotection in a mixture of ethanol and acetic acid (Scheme 1).

For the syntheses of the manganese complexes, *fac*-[$Mn(CO)_3$(solv)$_3$]OTf was prepared in situ by abstraction of the bromide ligand of pentacarbonylmanganese bromide in acetone using silver triflate. After addition of the respective ligand in acetone, the complexes [L$Mn(CO)_3$]OTf were obtained in good yield (Scheme 2).

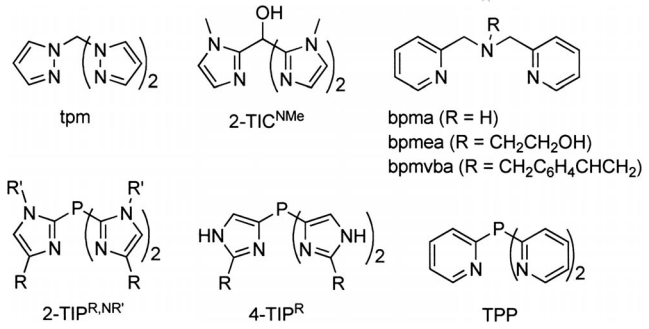
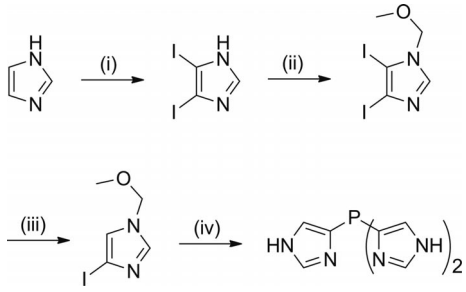
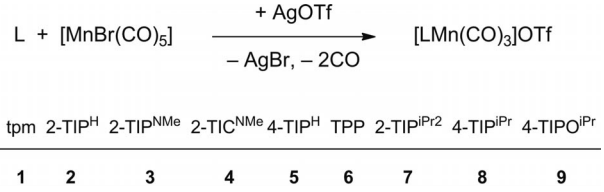


Figure 1. Ligands used for the synthesis of the *fac*-$Mn(CO)_3$ complexes investigated in this study.



Scheme 1. Synthesis of tris(imidazol-4(5)-yl)phosphane, 4-tip^{H} (**1**): (i) KI/I_2, NaOH, H_2O; (ii) MOMCl, KO*t*Bu, THF; (iii) EtMgBr, H_2O, THF; (iv) EtMgBr, PCl_3, $HOAc_{(aq.)}$.



Scheme 2. Syntheses of $Mn(CO)_3$ complexes.

The IR stretching frequencies and, where applicable, the chemical shifts of the ^{31}P NMR resonances of the new compounds **4**–**7** are reported in Table 1. The IR spectra show two bands in the carbonyl region, typical for C_{3v}-symmetrical $M(CO)_3$ compounds. In addition, their ^{1}H NMR spectra show only one set of signals for the protons of the three equivalent imidazolyl rings. Although the phosphorus atom is not coordinated to the metal centre, upon coordination of the ligand to the $M(CO)_3$ moiety, the $^{31}P\{^{1}H\}$ NMR signal of the P(III) atoms in **5** and **7** shifts to higher field by about 25 ppm. This shift is characteristic of complexes in which tip ligands are coordinated in an *N*,*N*,*N* mode.[11,12,14] A similar shift was reported by Johnson for ligands of the type $P(CH_2NHR)_3$.[15]

Table 1. IR and $^{31}P\{^1H\}$ NMR spectroscopic data and water/*n*-octanol distribution coefficients ($\log D_{7.4}$) of complexes $[LMn(CO)_3]$-OTf (**4**–**7**).

Ligand	Compound	δ(CO) / cm^{-1}	δ(^{31}P) / ppm	$\log D_{7.4}$
2-tic^{NMe}	**4**	2037, 1935	–	0.87 ± 0.02
4-tip^{H}	**5**	2033, 1911	–106.0	0.83 ± 0.05
tpp	**6**	2042, 1951	–9.5	-0.52 ± 0.01
2-tip^{iPr2}	**7**	2029, 1923	–116.0	>5

The distribution coefficient $\log D$ was determined at pH = 7.4 in order to assess the bioavailability of the new complexes **4**–**7**. As expected, **7**, having six isopropyl groups, is the most lipophilic compound. The lipophilicity decreases in the series according to **7** >> **4** ≈ **5** > **6**. The lipophilicity of **4**, **5** and **6** is within the range defined by the Lipinski "rule of five" for good drug candidates.[16]

The structure of **6**·0.5CH_2Cl_2 was determined by X-ray diffraction analysis and is shown in Figure 2 with crystallographic data summarised in Table 2. The Mn atom is facially coordinated by the three carbonyl ligands and the tpp ligand giving a slightly distorted octahedral coordination environment. The metric parameters around the Mn atom in **6**·0.5CH_2Cl_2 are comparable with those of **1** and **9**.[7a,12,17] The N–Mn–N angles in **6**·0.5CH_2Cl_2 are slightly larger than in complexes with ligands containing five-membered pyrazolyl or imidazolyl groups according to the "bite" of the ligands.

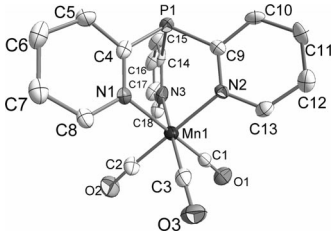


Figure 2. Solid-state structure of **6**·0.5CH_2Cl_2. Cocrystallised solvent molecules, the counter anion and hydrogen atoms are omitted for clarity. Displacement ellipsoids are drawn at the 50% level. Selected bond lengths [Å] and angles [°]: Mn1–C1 1.810(5), Mn1–C2 1.818(5), Mn1–C3 1.828(5), Mn1–N3 2.085(4), Mn1–N2 2.089(4), Mn1–N1 2.090(4), C1–O1 1.149(5), C2–O2 1.142(5), C3–O3 1.138(5), N1–Mn1–C1 179.61(18), N2–Mn1–C2 179.5(2), N3–Mn1–C3 179.07(16), Mn1–C1–O1 177.3(4), Mn1– C2–O2 176.5(4), Mn1–C3–O3 176.7(4).

Table 2. Crystallographic data for **6**·0.5CH_2Cl_2.

Empirical formula	$C_{19.5}H_{13}ClF_3MnN_3O_6PS$
Formula weight	595.75
Crystal system	orthorhombic
Space group	*Pmn*2
a [Å]	23.8743(9)
b [Å]	11.9146(3)
c [Å]	8.1976(3)
Volume [Å^3]	2331.84(14)
Z	4
Density (calculated) [Mg m^3]	1.697
Absorption coefficient [mm^{-1}]	0.906
F(000)	1196
Crystal size [mm]	$0.23 \times 0.05 \times 0.02$
Crystal description	colourless needle
Index ranges	$-15 \le h \le 32$
	$-13 \le k \le 16$
	$-11 \le l \le 7$
Reflections collected	10408
Independent reflections	4597 [R_{int} = 0.0470]
Reflections observed	2657
Completeness to theta	99.9% to 29.13°
Max. and min. transmission	0.9821 and 0.9308
Data/restraints/parameters	4597/3/330
Goodness-of-fit on F^2	0.815
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0443, wR_2 = 0.0680
R indices (all data)	R_1 = 0.0893, wR_2 = 0.0748
Absolute structure parameter	–0.04(2)
Largest diff. peak / hole [e Å^{-3}]	0.807 / –0.367

CO Release Properties

In order to study the suitability of the compounds as new photoactivatable CO releasing molecules (PhotoCORMs), the manganese complexes **4**–**7** of the general formula $[LMn(CO)_3]^+$ (L = 2-tip^{iPr2}, 4-tip^{H}, tpp and 2-tic^{NMe}) were investigated using the UV/Vis-based myoglobin assay.[6,18] All compounds investigated do not release CO in the dark. In Table 3, the number of CO equivalents released per mole of complex n_{CO} and the half-life $t_{1/2}$ are summarised for compounds **4**–**7** and compared with known $Mn(CO)_3$ PhotoCORMs incorporating *N*,*N*,*N* ligands. The steric bulk of the *N*,*N*,*N* ligand seems to determine both n_{CO} as well as $t_{1/2}$. While complexes with sterically less demanding ligands like **1**–**4**, **6** and **10**–**12** liberate approximately two moles of CO per mole of complex, complexes **7**–**9** with the bulkier ligands release only one mole of CO per mole of $Mn(CO)_3$ unit. Interestingly, in complex **5** with the small ligand 4-tip^{H}, an average of only 1.37 mole CO per mole of complex is found. The release of different amounts of CO from the complexes should result in at least transient occurrence of CO-containing intermediates. We thus choose to investigate the photoinduced CO release of selected complexes by time-dependent IR spectroscopy.

Table 3. Photoinduced CO-release of complexes $[LMn(CO)_3]^+$ with tripodal *N*,*N*,*N* ligands, half-life time ($t_{1/2}$) and number of CO molecules released (n_{CO}) as determined by myoglobin assay.

Complex	L	$t_{1/2}$ / min	n_{CO}	Ref.
1	tpm	20	1.96	[7a]
2	2-tip^{H}	25	1.82	[12]
3	2-tip^{NMe}	21	1.83	[12]
4	2-tic^{NMe}	19	1.61 ± 0.29	this work
5	4-tip^{H}	32	1.37 ± 0.08	this work
6	2-tpp	17	2.28 ± 0.01	this work
7	2-tip^{iPr2}	13	1.04 ± 0.28	this work
8	4-tip^{iPr}	30	0.83	[12]
9	4-tipo^{iPr}	27	0.96	[12]
10	bpma	20	1.59	[19]
11	bpmea	20	2.65	[19]
12	Bpmvba	20	1.65	[19]

Time-Resolved Irradiation Experiments

Time-resolved IR spectroscopy was used to follow the course of the CO release upon irradiation of compounds **1**, **3**, **5**–**8**, **10** and **11** in methanol. Relevant sections of the IR spectra taken after 0, 3 and 6 min of irradiation are shown in Figure 3. The two bands of the *fac*-$Mn(CO)_3$ moiety decrease in intensity and a new band appears in the region of 1840 to 1860 cm^{-1} for some of the compounds. In any case, after prolonged irradiation (ca. 90 min) all bands in the carbonyl region of the IR spectra completely disappeared.

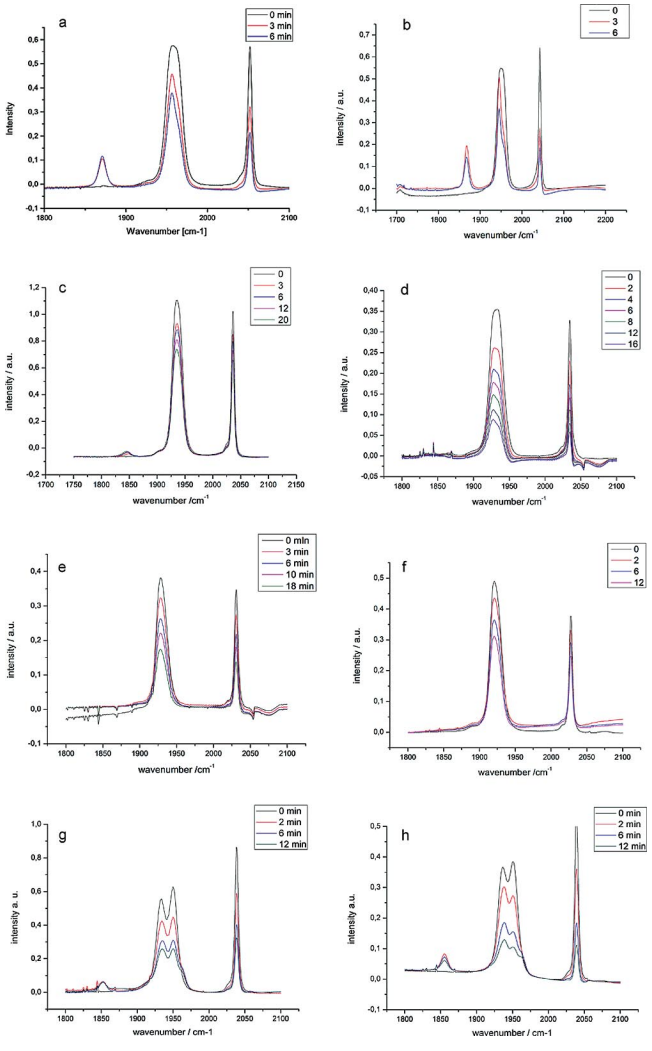


Figure 3. Time-dependent changes in the IR spectra of methanolic solutions of a: $[Mn(CO)_3(tpm)]OTf$ (**1**), b: $[Mn(CO)_3(tpp)]OTf$ (**6**), c: $[Mn(CO)_3(2\text{-}tip^{NMe})]OTf$ (**3**), d: $[Mn(CO)_3(4\text{-}tip^{H})]OTf$ (**5**), e: $[Mn(CO)_3(2\text{-}tip^{iPr2})]OTf$ (**7**), f: $[Mn(CO)_3(4\text{-}tip^{iPr})]OTf$ (**8**), g: $[Mn(CO)_3(bpma)]OTf$ (**10**) and h: $[Mn(CO)_3(bpmea)]OTf$ (**11**); irradiation at 360 nm (150 μW).

If one assumes a step-wise CO release of one or two equiv. of carbon monoxide, as observed in the myoglobin assay, the appearance of one (monocarbonyl complex) or two (dicarbonyl complex) new bands in the carbonyl region of the IR spectra would be expected. However, in the time-resolved IR spectra of all compounds, a decrease in the intensity of the A_1 and E bands was observed and after extended irradiation, they have completely disappeared for complexes **7**–**9** having bulky ligands while no new bands show up, whereas in complexes **3**–**6** and **10** as well as **11** with sterically less demanding ligands, a new band of very low intensity at 1840–1860 cm^{-1} emerged. This can be rationalised if one assumes that one carbonyl ligand is exchanged by a solvent methanol. Substitution of the π acceptor ligand CO by the σ donor ligand CH_3OH results in a strengthening of the remaining Mn–CO bonds. In the related compound $[CpMn(CO)_2(thf)]$, the CO-stretching vibrations are found at 1930 and 1861 cm^{-1}.[20] This might explain why we just see one new band since the second one should then be obscured by the E band of the tricarbonyl complex. As such, dicarbonyl complexes are also photolabile, they are only transient species, which might explain the low intensity of the band at 1840–1860 cm^{-1}.[21] In the cases of $[Mn(CO)_3(tpm)]OTf$ (**1**) and $[Mn(CO)_3(tpp)]OTf$ (**5**), the highest intensities of the newly formed band can be observed. Thus, we performed a band separation on the bands at ca. 2050 cm^{-1} showing a shoulder. Indeed, the separated bands showed an intensity ratio of about 2:1 (E and A_1 band of the corresponding tricarbonyls) as well as two bands of relative intensities of about 1:1 (see Supporting Information). This clearly shows the intermediate formation of dicarbonyl complexes, at least under the conditions of the IR measurements. These findings are in good agreement with the IR experiments performed by the groups of Kurz and Westerhausen on Mn^{I} and Fe^{II} carbonyls in which, depending on the ligands used, transient decarbonylation species were observed.[8,9a] Interestingly, compounds **5**, **7** and **8** which should release only one equivalent on CO per complex do not show the transient formation of a dicarbonyl species.

For compounds $[Mn(CO)_3(2\text{-}tip^{NMe})]OTf$ (**3**) and $[Mn(CO)_3(tpp)]OTf$ (**6**), we also followed the change of the band intensities in the carbonyl region with variation of the excitation wavelength. No CO release was observed above a threshold of 400 nm, which corresponds to an irradiation into the low intensity high wavelength tail of the UV/Vis band of compounds **3** and **6**. Additionally, we investigated the influence of the intensity of the light which was measured at the site of the cuvette using a calibrated optical powermeter. Freshly prepared methanolic solutions of compounds **3** and **6** (1 wt.-%) were irradiated at 360 nm for 3 min. As expected, higher intensities lead to a more pronounced decrease in band intensity of the carbonyl bands (Figure 4). Thus, extreme caution has to be taken when comparing release rates and half-lives reported for PhotoCORMs if experimental details of the irradiation setup have not been reported in sufficient detail. In particular, the absolute intensity of the light source in Einstein/s has to be quoted to facilitate comparison, as can be determined, for example, by actinometry.

We did not detect free CO in any experiment. The signal is expected to appear at 2140 cm^{-1} but usually is very weak in the IR and therefore could not be observed in our measurements.[22]

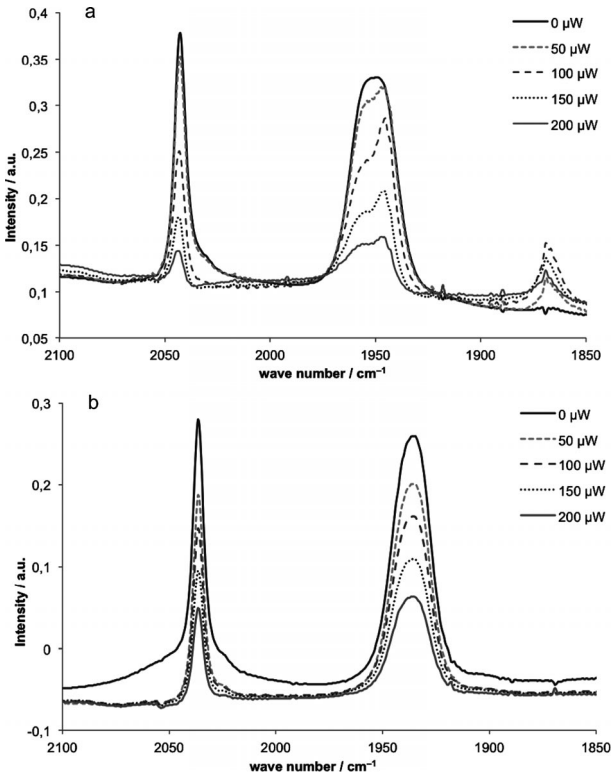


Figure 4. Carbonyl region of solutions of a) $[Mn(CO)_3(2\text{-tip}^{NMe})]$-OTf (**3**) and b) $[Mn(CO)_3(tpp)]$OTf (**6**) in methanol (1 wt.-%) after irradiation for 3 min at 360 nm using intensities of 50, 100, 150 and 200 µW.

Conclusions

Four new $Mn(CO)_3$ complexes with tripodal *N*,*N*,*N* ligands bearing imidazolyl and pyridinyl substituents have been prepared and characterised. CO-release investigations using the myoglobin assay show that these compounds act as photoinducible CO-releasing molecules (PhotoCORMs) upon UV irradiation at 365 nm while they are stable towards decomposition and do not liberate CO spontaneously in the absence of light. We have shown that even when irradiated in the low intensity long wavelength tail at 400 nm of the absorption band of $Mn(CO)_3$ complexes, they do release CO. The CO release characteristics in terms of half-lives and number of CO equiv. released per mole of complex have been compared with related CORMs. The results of the myoglobin assay show that $Mn(CO)_3$ complexes with sterically demanding ligands release approximately one equiv. of CO per complex while complexes having sterically less demanding ligands release 2 equiv. of CO per complex. This might also be relevant when such carbonyl compounds are employed as precursors for oxo-bridged Mn-cluster compounds as the steric hindrance might prevent close association.[9a] In contrast to the results of the myoglobin assay, IR investigations in solution did not provide any evidence of intermediate decarbonylation products. Instead, they clearly support loss of all three CO ligands upon irradiation. This indicates that there is probably a much more intimate interaction of the CORM with the myoglobin as has also been recently observed for $[Mn(CO)_4\{S_2CNMe(CH_2CO_2H)\}]$.[9b] This discrepancy between the results of the myoglobin assay and the IR investigations has recently been studied in detail by Kurz and Berends on closely related $Mn(CO)_3$ complexes.[9a] Although, for a detailed understanding of the CO release mechanism in complex biological medium, a combination of different spectroscopic techniques like UV/Vis, IR and Raman spectroscopy as well as mass spectrometry and EPR will be required, since they can easily and quickly be carried out, the myoglobin assay will remain indispensable for an initial screening of CO activity to selected compounds worth a more detailed investigation as outlined above.

Experimental Section

General: All reactions were carried out in Schlenk tubes under an atmosphere of dry nitrogen using anhydrous solvents purified according to standard procedures. The ligands 2-tip^{iPr,NiPr},[13b] tpp[13a] and 2-tic^{NMe}[13c] as well as 4-iodo-1-methoxymethylimidazole[23] were prepared according published procedures. The metal complexes were prepared using N_2-flushed solvents. All chemicals were purchased from commercial sources and used as received. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker DRX 200 and 500 spectrometers. The ^1H and ^{13}C spectra were calibrated against the residual proton signal of the solvent serving as an internal reference ([D$_4$]methanol): δ_H = 3.31 ppm, δ_C = 49.2 ppm; [D$_6$]acetone: δ_H = 2.05 ppm, δ_C = 29.9 ppm; [D$_6$]DMSO: δ_H = 2.50 ppm, δ_C = 39.5 ppm; D_2O: δ_H = 4.80 ppm while the $^{31}P\{^1H\}$ NMR spectra were referenced to external 85% H_3PO_4. The ^{13}C resonances of carbonyl carbon atoms are in general very hard to detect in this class of compound and could not be identified in **4**–**7**. The ESI mass spectra were recorded on a Finnigan LCQ Deca ion trap API mass spectrometer. Infrared spectra were recorded with a Bruker IFS 66 FTIR spectrometer. The elemental compositions of the compounds were determined with a Perkin–Elmer Analysator 2400 at the Institut für Pharmazeutische und Medizinische Chemie, Heinrich-Heine Universität Düsseldorf.

Tris[imidazol-4(5)-yl]phosphane, 4-tip^H: To a solution of 4-iodo-1-(methoxymethyl)imidazole (6.66 g, 28 mmol) in tetrahydrofuran (100 mL), was added ethylmagnesium bromide (3.0 M in ethyl ether, 9.3 mL, 28 mmol) dropwise at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then phosphorus trichloride (1.23 g, 9 mmol) in tetrahydrofuran (5 mL) was added dropwise. The suspension was stirred at ambient temperature for 16 h. All volatiles were removed in vacuo and the residue was treated with dichloromethane and extracted with aqueous ammonium chloride solution. The organic phase was collected and all volatiles were removed in vacuo. The residue was dissolved in a mixture of ethanol (50 mL) and acetic acid (10 mL) and stirred at 60 °C for 16 h. The volume was reduced to 10 mL and the colourless precipitate collected by filtration, washed with diethyl ether and dried in vacuo. The product thus obtained was pure enough to be used for further reactions without additional work-up; yield 1.28 g (33%). ^1H NMR (D_2O): δ = 7.63 (d, J = 1.3 Hz, 3 H, H_{im}), 8.85 (m, 3 H, H_{im}) ppm. $^{31}P\{^1H\}$NMR (D_2O): δ = –81 ppm.

$[Mn(CO)_3(2\text{-tic}^{NMe})]$OTf (4): Pentacarbonylanganese bromide (101 mg, 0.37 mmol) and silver triflate (95 mg, 0.37 mmol) were heated at reflux for 1 h in acetone (20 mL). The precipitate thus formed was filtered off and the yellow solution added to a solution of 2-tic^{NMe} (100 mg, 0.37 mmol) in acetone (10 mL). The reaction

mixture was stirred for 4 h at ambient temperature and filtered. The filtrate was then treated with *n*-pentane, the yellow precipitate collected by filtration, washed with *n*-pentane and dried in vacuo; yield 176 mg (81%). ^{1}H NMR (200 MHz, [D$_4$]methanol): δ = 4.12 (s, 9 H, NCH$_3$), 7.17 (d, $^3J_{H,H}$ = 1.4 Hz, 3 H, H$_{im}$), 7.42 (d, $^3J_{H,H}$ = 1.4 Hz, 3 H, H$_{im}$) ppm. ^{13}C{^{1}H} NMR (125 MHz, [D$_4$]methanol): δ = 37.0, 78.4, 126.1, 132.0, 145.1 ppm. ESI-MS (MeOH): *m*/*z* (%) = 411.1 (36) [M]$^+$, 354.9 (12) [M – 2CO]$^+$, 327.3 (100) [M – 3CO]$^+$. $C_{17}H_{16}F_3MnN_6O_7S$ (560.3): calcd. C 36.44, H 2.88, N 15.00; found C 36.75, H 2.55, N 14.86. IR (KBr): $\tilde{\nu}$ = 2044, 1936, 1907 cm^{-1}. IR (CH_2Cl_2): $\tilde{\nu}$ = 2037, 1935 cm^{-1}.

[Mn(CO)$_3$(4-tip^{H})]OTf (5): Pentacarbonylanganese bromide (66.7 mg, 0.12 mmol) and silver triflate (62 mg, 0.12 mmol) were heated at reflux for 1 h in acetone (20 mL). The precipitate was filtered off and the yellow solution added to a solution of 4-tip^{NH}·3AcOH (100 mg, 0.12 mmol) in acetone (10 mL). The reaction mixture was stirred for 16 h at ambient temperature and then filtered. The filtrate was concentrated to 5 mL and treated with diethyl ether, the yellow precipitate collected by filtration, washed with diethyl ether and dried in vacuo; yield 46 mg (42%). ^{1}H NMR (200 MHz, [D$_4$]methanol): δ = 7.63 (s, 3 H, H$_{im}$), 8.53 (s, 3 H, H$_{im}$) ppm. ^{13}C{^{1}H} NMR (125 MHz, [D$_4$]methanol): δ = 125.4 (d, $J_{P,C}$ = 53 Hz), 133.2, 142.9 ppm. ^{31}P{^{1}H} NMR (81 MHz, [D$_4$]-methanol): δ = –106.0 (s) ppm. ESI-MS (MeOH): *m*/*z* (%) = 371.2 (24) [M]$^+$, 287.3 (100) [M – 3CO]$^+$. $C_{13}H_9F_3MnN_6O_6PS$ (520.2): calcd. C 30.01, H 1.74, N 16.15; found C 29.66, H 1.89, N 16.70. IR (KBr): $\tilde{\nu}$ = 2033, 1911 cm^{-1}.

[Mn(CO)$_3$(tpp)]OTf (6): Pentacarbonylanganese bromide (103 mg, 0.38 mmol) and silver triflate (97 mg, 0.38 mmol) were heated at reflux for 1 h in acetone (20 mL). The precipitate was filtered off and the yellow solution added to a solution of TPP (100 mg, 0.38 mmol) in acetone (10 mL). The reaction mixture was stirred for 4 h at ambient temperature and filtered. The filtrate was treated with *n*-pentane, the yellow precipitate collected by filtration, washed with *n*-pentane and dried in vacuo; yield 141 mg (67%). ^{1}H NMR (200 MHz, [D$_4$]methanol): δ = 7.70 (m, 3 H), 8.19 (m, 3 H), 8.47 (m, 3 H), 9.59 (m, 3 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, [D$_4$]-methanol): δ = 127.9, 137.8 (d, $J_{P,C}$ = 54 Hz), 141.4 (d, $J_{P,C}$ = 16 Hz), 155.9 (d, $J_{P,C}$ = 15 Hz), 159.1 ppm. ^{31}P{^{1}H} NMR (81 MHz, [D$_4$]methanol): δ = –9.5 (s) ppm. ESI-MS (MeOH): *m*/*z* (%) = 419.4 (6) [M + O]$^+$, 320.3 (100) [M – 3CO]$^+$. $C_{19}H_{12}F_3MnN_3O_6PS$ (553.3): calcd. C 41.25, H 2.19, N 7.59; found C 41.55, H 2.50, N 7.12. IR (KBr): $\tilde{\nu}$ = 2033, 1944, 1928 cm^{-1}. IR (CH_2Cl_2): $\tilde{\nu}$ = 2042, 1951 cm^{-1}.

[Mn(CO)$_3$(2-tip^{iPr2})]OTf (7): Pentacarbonylanganese bromide (56.8 mg, 0.21 mmol) and silver triflate (53 mg, 0.21 mmol) were heated at reflux for 1 h in acetone (20 mL). The precipitate was filtered off and the yellow solution added to a solution of 2-tip^{iPr2} (100 mg, 0.21 mmol) in acetone (10 mL). The reaction mixture was stirred for 16 h at ambient temperature and filtered. The filtrate was treated with *n*-hexane, the yellow precipitate collected by filtration, washed with *n*-hexane and dried in vacuo; yield 98 mg (60%). ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 1.38 (d, $^3J_{H,H}$ = 6.9 Hz, 6 H), 1.58 (d, $^3J_{H,H}$ = 6.3 Hz, 6 H), 3.65 (sept, $^3J_{H,H}$ = 6.9 Hz, 3 H), 5.36 (sept, $^3J_{H,H}$ = 6.3 Hz, 3 H), 7.74 (d, $^1J_{P,H}$ = 4.1 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, [D$_4$]methanol): δ = 23.7, 25.0, 52.6, 52.7, 117.8, 137.5 (d, $J_{P,C}$ = 15 Hz), 157.0 ppm. ^{31}P{^{1}H} NMR (81 MHz, [D$_6$]acetone): δ = –116.0 (s) ppm. ESI-MS (MeOH): *m*/*z* (%) = 539.5 (100) [M – 3CO]$^+$, 387.5 (29) [M – 3CO – Im]$^+$. $C_{31}H_{45}F_3MnN_6O_6PS$·2$(CH_3)_2CO$ (888.87): calcd. C 48.61, H 6.64, N 9.72; found C 49.02, H 6.58, N 9.69. IR (KBr): $\tilde{\nu}$ = 2029, 1923 cm^{-1}.

Partition Coefficients (log *D*): The *n*-octanol/water partition coefficient of compounds **4**–**7** was determined using the shake-flask method. PBS-buffered doubly distilled water [100 mL, phosphate buffer, [PO_4^{3-}] = 10 mM, [NaCl] = 15 M, pH adjusted to 7.4 with hydrochloric acid] and *n*-octanol (100 mL) were shaken together using a laboratory shaker (Perkin–Elmer) for 72 h to allow saturation of both phases. Then, 1 mg of each compound was mixed in 1 mL of aqueous and organic phase, for 10 min using a laboratory vortexer. The resultant emulsion was centrifuged (3000 g, 5 min) to separate the phases. The concentrations of each complex in the aqueous and organic phases was determined using UV/Vis spectroscopy at 260 nm. Log D_{pH} was defined as the logarithm of the ratio of the concentrations of the complex in the organic and aqueous phase (log*D* = log {[complex$_{(org)}$]/[complex]$_{(aq.)}$}). The value reported is the mean of three separate determinations.

CO Release Studies: All UV/Vis measurements were performed with a Jasco V-670 spectrophotometer at room temperature in a quartz cuvette (*d* = 1 cm). Horse skeletal muscle myoglobin (Fluka) was dissolved in 0.1 M phosphate buffer pH = 7.3 and degassed by bubbling with nitrogen. It was then reduced by the addition of an excess of sodium dithionite in the same solvent and finally buffer added to the cuvette to a total volume of 749 μL. To this solution, 1 μL of complex dissolved in dimethylsulfoxide was added to give a final concentration of 20 μmol L^{-1} of metal complex and 75 μmol L^{-1} of myoglobin with A(557 nm) < 1. Solutions were then either kept in the dark or irradiated for given time intervals under nitrogen at 365 nm with a UV hand lamp positioned perpendicular to the cuvette at a distance of 6 cm. Irradiations were interrupted at regular intervals so that UV/Vis spectra could be recorded. All the measurements were carried out in triplicate to assess the reproducibility of the CO release.

IR Spectroscopy: For the IR experiments, the samples were irradiated using a xenon arc-lamp (75 W) as the light source. The monochromated light (resolution 1 nm) was directed to an optical bench by means of an optical wave guide (quartz). The position of the liquid measurement cell (CaF_2 windows, 0.1 mm Teflon™ spacer) or the powermeter head (wavelength calibrated) was fixed on the optical bench. A greywedge (quartz) was used to adjust the intensity. The intensity at the cell position was measured using a Newport corp. 835 optical powermeter. IR spectra were recorded on a Bruker IFS 113 v IR spectrometer.

Crystallography: Crystallographic data were collected at 183(2) K on an Oxford Diffraction Xcalibur system with a ruby detector using graphite-monochromated Mo-K_α radiation (λ = 0.7107 Å). Suitable crystals were covered with oil (Infineum V8512, formerly known as Paratone N), mounted on top of a glass fibre and immediately transferred to the diffractometer. The program suite CrysAlis^{Pro} was used for data collection, multi-scan absorption correction and data reduction.[24] Structures were solved with direct methods using SIR97[25] and were refined by full-matrix least-squares methods on F^2 with SHELXL-97.[26] In the structure of **6**·0.5CH_2Cl_2, bond lengths of a disordered dichloromethane molecule had to be restrained. The structures were checked for higher symmetry with help of the Platon program.[27]

CCDC-865300 (for **6**·0.5CH_2Cl_2) and -865301 {for [(4-tip^{NMOM})$_2$-Mg]Br_2} 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.

Supporting Information (see footnote on the first page of this article): Preparation of 4,5-diiodoimidazole, 1-methoxymethyl-4,5-diiodoimidazole and 1-methoxymethyl-4-iodoimidazole, band sepa-

ration in the carbonyl region of compounds **1** and **5** during radiation and molecular structure of $[Mg(4\text{-}tip^{NMOM})_2]Br_2$.

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