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Experimental and quantum chemical calculations of novel photoactivatable manganese(I) tricarbonyl complexes

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ABSTRACT

[$MnBr(CO)_3(TZ)$] (**1**) and [$Mn(CO)_3(MZ)$] (**2**) (TZ = Tazarotene and MZ = Metamizole) have been synthesized and characterized as new visible light photo-trigged carbon monoxide releasing molecules. The ability to deliver CO to DMSO or myoglobin solution has been studied. TZ behaves as a bidentate ligand *via* the pyridine N-atom and π−C≡C group, while MZ is a mono-negatively tridentate ligand and coordinates to Mn(I) through the pyrazolone C═O, $-SO_3^-$ and tertiary amino groups. These photoCORMs cannot be stored for a long time in DMSO, but they are able to release CO fast upon the exposure to the light (412–468 nm). About one CO equivalent was delivered from CORM **1** to the myoglobin solution upon the exposure to 468 nm LED lamp for 42 min. The electronic configuration of the metal center, hybridization type and nature of bonding have been obtained by natural bond orbital analysis. TD-DFT calculations have been performed to recognize the electronic structure and to explain the related experimental findings. The CORMs have been screened for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* in comparison to their parent drugs.

1. Introduction

Recently, the silent killer carbon monoxide constitutes a group of simple mediators with NO and H_2S called gasotransmitters. Several studied showed that CO in the concentration range of 10–250 ppm [1] stimulates some beneficial functions [2,3] including neurotransmission, vasorelaxation and cytoprotective activity. In addition, CO protects humans against the hyperoxic lung injury and organ transplant rejection as well as promoting the mitochondrial biogenesis. Both NO and H_2S have the ability to interact with a range of intracellular targets, while the chemistry of CO is restricted to react only with the metal ions in the low oxidation state. In 2002, [$Mn_2(CO)_{10}$] and [{$RuCl_2(CO)_3$}$_2$] were introduced by Motterlini and Mann [4] and investigated as *carbon monoxide-releasing molecules* (CORMs). These complexes were able to carrying and liberating controlled quantities of CO within the cellular systems. The trigging of CORMs can be achieved by pH change [5], enzymatically [6], thermally [7] and photochemically [8–17]. The control targeting of organs and tissues without delivering of potentially toxic amounts to the whole body are the main advantages of the photochemical method.

The photolysis profiles and the biological activity of some manganese(I) *fac*-tricarbonyl photoCORMs have been studied. Some of these complexes were able to release CO upon the exposure to high energetic UV source such as [$Mn(CO)_3$(tpa-κ^3N)]Br (tpa: tris(2-pyridylmethyl) amine) [8], [Mn(bpea)$(CO)_3$]PF_6 (bpea: bis(pyrazolyl)methane) [9] and [Mn(tpm)$(CO)_3$]PF_6 (tpm: tris(pyrazolyl) methane) [10]. Several researchers have been focused on shift the triggering source to the visible-near IR region, since the penetration depth of light into tissue is strongly wave length dependent, smallest for UV, medium for visible and reaching its maximum in the near IR region. Complexes such as [MnBr(pmtpm)$(CO)_3$] (pmtpm: 2-pyri-dyl-N-(2'-methyl-thiophenyl)methyleneimine) and [MnBr(qmtpm)$(CO)_3$] (qmtpm: 2-quinoline-N(2′-meth-ylthio-phenyl)methyleneimine [11], [$Mn(CO)_3$(^{i}Pr$_2$Ph-DAB)Br] and [$Mn(CO)_4$(^{i}Pr$_2$Ph-DAB)]PF_6 (^{i}Pr$_2$Ph-DAB = (N,N'-bis(2,6-di-isopropylphenyl)-1,4-diaza1,3-butadiene)] [12] released CO by the illumination with a visible light in the 400–550 nm range. Recently, a series of [MnBr(azpy)$(CO)_3$] (azpy = 2-phenylazopyridine derivatives) capable of releasing CO when illuminated with the red light ($\lambda \geq 625$ nm) has been synthesized by Zobi et al. [13].

Closed to the structures of our photoCORMs described here (Scheme 1), [$Mn(CO)_3$L] (L = histidine [14], bis(pyrazolyl)acetic

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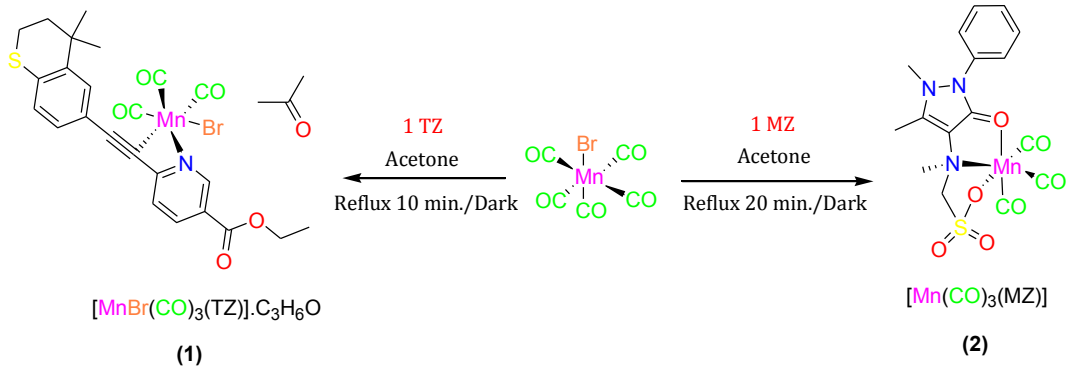

Scheme 1. Synthesis of Mn(I) Tazarotene (TZ) (**1**) and Metamizole (MZ) (**2**) photoCORMs.

acid) [15], 3,3-bis(3,5-dimethylpyrazol-1-yl) propionate derivatives) [16] and $[Mn(CO)_3L'(NC{-}CH_3)]$ (L′ = L-tryptophan) [17] have been reported in the literature. Only one CO equivalent was liberated from the water soluble histidine complex at 365 nm with $t_{1/2}$ of 93.0 ± 9.2 min. The propionate complexes are stable in the dark for 6 h and were able to deliver 2.06–2.38 CO equivalents to the myoglobin at 365 nm. Two Mn(I)-photoCORMs containing N,C-bidentate ligand, similar to CORM 1, were reported in the literature, $[Mn(CO)_4(C^{\wedge}N)]$ ($C^{\wedge}N$ = *ortho*-metallated-2-phenylpyridine derivatives) [18]. The ester-CORM was activated by LED source light at 400 nm, as well as it can be switched on and off.

To avoid the formation of toxic species of M-L fragments after the liberation of CO from the studied metal carbonyls and shift the MLCT band towards the visible region and consequently the triggering by the visible light, two new Mn(I) photoCORMs (Scheme 1) derived Tazarotene and Metamizole have been synthesized and characterized. Tazarotene is the first topical receptor-selective retinoid approved for the treatment of moderate to severe plaque psoriasis, acne vulgaris and photoaging [19]. Metamizole has antipyretic and analgesic activity as well as other beneficial effects such as vascular smooth muscle relaxant, anti-apoptotic, and anticonvulsant [20]. The number of CO equivalent released has been spectrophoto-metrically determined by myoglobin assay. The spectral properties and electronic structure were studied by time dependent density functional theory (TD-DFT) calculations [21,22]. The toxicity of the complexes has been tested against *Staphylococcus aureus* and *Escherichia coli* bacteria and compared to the free drugs.

2. Experimental section

2.1. Instruments

FT IR spectra were recorded as potassium bromide pellets using a Jasco FTIR 460 plus in the range of 4000 to 200 cm^{-1}. Electronic spectra were scanned on OPTIZEN POP automate spectrophotometer. ^1H NMR spectra were recorded on Varian-Oxford Mercury VX-300 NMR at ambient temperature. Chemical shifts δ in ppm indicate downfield shift relative to TMS, and were referenced relative to the signal of the solvent (DMSO). ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (Julius-Maximilians-Universität, Würzburg, Germany) at ambient temperature. Elemental microanalysis was performed using Elementer Vario EL III.

2.2. Synthesis

0.36 mmol of Tazarotene (126 mg) or Sodium-metamizole (112 mg) (Sigma) were dissolved in oven-dried round flask containing 20 mL acetone and 0.36 mmol $[MnBr(CO)_5]$ (100 mg) (supplied by Sigma-company) under an atmosphere of pure argon and exclusion of light. The reaction mixtures were heated to reflux and then left in the dark for the slow evaporation down to 5 mL. Dark red needles (**1**) were formed in case of Tazarotene, while yellow-orange complex (**2**) was collected with Metamizole. The complexes were separated by filtration, washed with *n*-hexane and dried under Vacuum.

1, Yield: 84% (190 mg, 0.30 mmol). Elemental analysis (%): calcd. $C_{27}H_{27}BrMnNO_6S$: C 51.60, H 4.33, N 2.23, found 51.43, H 4.19, N, 1.99; IR (FT IR, cm^{-1}): 2960 (m, C–H), 2187 (s, C≡C), 2001 (vs, C≡O), 1912 (vs, C≡O), 1720 (s, C=O), 1621 (w, C=N), 1589 (m, C=C), 1546, 1463, 1286 (s, C–O), 1115, 769, 627. ^1H NMR (DMSO-d_6, 300 MHz): δ 9.06 (m, 1H, CH^{Ar}–N), 8.46 (m, 1H, CH^{Ar}–COO), 7.77 (m, 1H, CH^{Ar}–C≡C), 7.30–7.11 (m, 3H, CH^{Ar}), 4.37 (q, 2H, CH_2–COO), 3.06 (m, 2H, S–CH_2/thiochroman ring), 2.07 (m, acetone), 1.88 (m, 2H, C–CH_2/thiochroman ring), 1.34–1.11 (m, 9H, CH_3). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.6, 22.9, 28.9, 28.9, 30.0, 33.2, 30.75, 49.4, 61.8, 84.5, 91.9, 116.7, 124.9, 125.1, 127.3, 129.6, 130.8, 134.2, 137.7, 143.3, 145.7, 150.9, 165.0, 216.9.

–**2**, Yield: 82% (125 mg, 0.28 mmol). Elemental analysis (%): calcd. $C_{16}H_{16}MnN_3O_7S$: C 42.77, H 3.59, N 9.35, found 42.59, H 3.48, N, 9.27; IR (FT IR, cm^{-1}): 2974 (m, CH), 2025 (vs, C≡O), 1917 (vs, C≡O), 1617 (s, C=O), 1586 (m, C=C), 1491, 1455, 1316, 1164, 1046, 762, 515. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.43 (m, 5H, CH^{Ar}), 4.83 (s, 2H, CH_2), 2.79 (m, 6H, N–CH_3), 1.18 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 125 MHz): 17.5, 28.1, 33.8, 71.3, 111.1, 111.1, 118.7, 119.0, 127.1, 128.0, 130.9, 146.8, 157.6, 213.9.

2.3. DFT calculations

The electronic transitions were calculated at TD-DFT/B3LYP/LANL2DZ and TD-DFT/CAM-B3LYP/LANL2DZ level of theories in DMSO using the default polarizable continuum model [23]. Ground state geometry optimization and natural bond orbital analysis were carried out by Gaussian 03 program [24] at the same level of theory.

2.4. Myoglobin assay

A buffered solution (0.1 M phosphate-buffered saline, pH = 7.4, 890 μL) of the standardized horse skeletal muscle myoglobin (Sigma-Aldrich) was reduced in a quartz cuvette by addition of 100 μL sodium dithionite solution. Then, the volume (1 mL) of the quartz cuvette was completed by adding 10 μL of CORM in pure DMSO (10 μM). The concentrations of the stock solutions were chosen to give 10 mM dithionite, 60 μM myoglobin, and 10 μM CORM in the final mixture. The number of CO equivalent released from the studied CORMs was spectrophotometrically determined