ChemPubSoc Europe

DOI: 10.1002/chem.201503176

CHEMISTRY A European Journal Communication

Bioinorganic Chemistry

To Transfer or Not to Transfer? Development of a Dinitrosyl Iron Complex as a Nitroxyl Donor for the Nitroxylation of an Fe^{III}–Porphyrin Center

Yu-Ting Tseng,[a] Chien-Hong Chen,[b] Jing-Yu Lin,[a] Bing-Han Li,[a] Yu-Huan Lu,[a] Chia-Her Lin,[a] Hsin-Tsung Chen,[a] Tsu-Chien Weng,[c] Dimosthenes Sokaras,[c] Huang-Yeh Chen,[d] Yun-Liang Soo,[d, e] and Tsai-Te Lu*[a]

Abstract: A positive myocardial inotropic effect achieved using HNO/NO^-, compared with NO·, triggered attempts to explore novel nitroxyl donors for use in clinical applications in vascular and myocardial pharmacology. To develop M-NO complexes for nitroxyl chemistry and biology, modulation of direct nitroxyl-transfer reactivity of dinitrosyl iron complexes (DNICs) is investigated in this study using a Fe^{III}-porphyrin complex and proteins as a specific probe. Stable dinuclear $\{Fe(NO)_2\}^9$ DNIC $[Fe(\mu\text{-}^{Me}Pyr)(NO)_2]_2$ was discovered as a potent nitroxyl donor for nitroxylation of Fe^{III}-heme centers through an associative mechanism. Beyond the efficient nitroxyl transfer, transformation of DNICs into a chemical biology probe for nitroxyl and for pharmaceutical applications demands further efforts using in vitro/in vivo studies.

HNO/NO^- (nitroxyl), compared to NO·, features a specific biological reactivity in the nitroxylation of Fe^{III}-heme centers and modification of thiol residue in cysteine to sulfonamide/disulfide, in addition to the up-regulation of plasma levels of calcitonin gene-related peptide (CGRP).[1–3] Moreover, a positive myocardial inotropic effect of nitroxyl, during a congestive heart failure condition in particular, stimulated the study of a mechanism for the endogenous generation of nitroxyl and the development of an exogenous nitroxyl donor as a novel approach for the acute treatment of heart failure.[4–7] Angeli's salt ($Na_2N_2O_3$) and Piloty's acid ($PhSO_2NHOH$) were predominantly exploited as nitroxyl-releasing reagents at neutral and basic pH, respectively, to explore the vascular and myocardial pharmacology of HNO/NO^-. Rapid decomposition of Angeli's salt ($k = 6\times10^{-4}\ s^{-1}$ at 25 °C and $k = 4\text{–}5\times10^{-3}\ s^{-1}$ at 37 °C), rapid dimerization of HNO to afford N_2O and H_2O ($k = 8\times10^6\ M^{-1}\ s^{-1}$), and release of NO rather than nitroxyl from Piloty's acid under neutral aerobic conditions, however, limit the clinical potential of these compounds.[7] As a consequence, a long-lasting HNO/NO^- donor derived from steady nitroxyl-releasing compounds with an ON/OFF switch or from stable compounds with dedicated nitroxyl-transfer reactivity toward the Fe^{III} center in heme proteins is a much-needed target for pharmaceutical applications.

The intrinsic redox propensity of transition metals in metal–nitrosyl complexes modulates the oxidation state of NO and allows the potential use of M–NO complexes in nitroxyl chemistry.[8–13] In particular, the electronic structure of $\{M(NO)_x\}^n$ complexes (M = Fe or Co, $x = 1$ or 2, $n = 7$, 8, 9, or 10) regulates the redox switch for the reductive nitrosylation of the Fe^{III}-porphyrin complex/protein and controls the proton-induced nitroxyl-release reactivity.[14–19] $\{Fe(NO)_2\}^9/\{Fe(NO)_2\}^{10}$ complexes $[Fe(NO)_2(Ar\text{-}nacnac)]^{0/1-}$ exhibit an electrochemically reversible redox couple at −1.34 V, whereas the reduction potential for $[Fe^{III}(TPP)Cl]$ is −0.90 V versus Fc/Fc^+ (Ar-nacnac = anion of $[(2,6\text{-diisopropylphenyl})NC(Me)]_2CH$).[14,20] In contrast to the inertness of the $\{Fe(NO)_2\}^9$ complex $[Fe(NO)_2(Ar\text{-}nacnac)]$ toward $[Fe^{III}(TPP)Cl]$, reductive nitrosylation of $[Fe^{III}(TPP)Cl]$ by $\{Fe(NO)_2\}^{10}$ $[Fe(NO)_2(Ar\text{-}nacnac)]^-$ to afford [Fe(TPP)(NO)] occurs through a redox-coupled nitrosyl transfer pathway according to the formation of intermediates $[Fe^{II}(TPP)Cl]^-$ and $\{Fe(NO)_2\}^9$ $[Fe(NO)_2(Ar\text{-}nacnac)]$. Harrop and co-workers reported a thermally stable $\{Fe(NO)\}^8$ complex $[Fe(LN_4)(NO)]^-$ with a $E_{1/2}$ of −1.38 V for a $\{Fe(NO)\}^7/\{Fe(NO)\}^8$ redox couple.[15] A redox-coupled nitrosyl-transfer mechanism was followed using this $\{Fe(NO)\}^8$ complex $[Fe(LN_4)(NO)]^-$ to achieve the rapid conversion of metmyoglobin (metMb) to MbNO in aqueous buffer solution at pH 7.2. Of interest, replacement of iron by cobalt to afford the $\{Co(NO)\}^8$ complex $[Co(LN_4)(NO)]$ leads to an irreversible E_{ox} peak at 0.75 V and abolishes the reductive nitrosylation reactivity.[16] The release of HNO from this complex was promoted after addition of 1 equiv of HBF_4.[16] This proton-in-

[a] Y.-T. Tseng, J.-Y. Lin, B.-H. Li, Y.-H. Lu, Prof. C.-H. Lin, Prof. H.-T. Chen, Prof. T.-T. Lu
Department of Chemistry, Chung Yuan Christian University No. 200 Chung Pei Rd. Taoyuan, 32023 (Taiwan)
E-mail: TTLu@cycu.edu.tw

[b] Prof. C.-H. Chen
School of Medical Applied Chemistry, Chung Shan Medical University No. 110, Section 1, Jianguo North Rd. Taichung, 40201 (Taiwan)

[c] Dr. T.-C. Weng, Dr. D. Sokaras
SLAC National Accelerator Laboratory 2575 Sand Hill Rd. Menlo Park CA 94025 (USA)

[d] H.-Y. Chen, Prof. Y.-L. Soo
National Synchrotron Radiation Research Center No. 101, Xin'an Rd. Hsinchu, 30076 (Taiwan)

[e] Prof. Y.-L. Soo
Department of Physics, National Tsing Hua University No. 101 Section 2, Guangfu Rd., Hsinchu, 30013 (Taiwan)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201503176.

duced release of nitroxyl was also observed in the proposed $\{Fe(NO)_2\}^9$ intermediate $[Fe(NO)_2P(C_6H_3\text{-}3\text{-}SiMe_3\text{-}2\text{-}S)_2(C_6H_3\text{-}3\text{-}SiMe_3\text{-}2\text{-}SH)]^-$, which was derived from the reaction of the $\{Fe(NO)_2\}^9$ complex $[Fe(NO)_2(Car)_2]^-$ and $P(C_6H_3\text{-}3\text{-}SiMe_3\text{-}2\text{-}SH)_3$.[18]

Regarding the pioneer studies on redox-coupled nitrosyl-transfer and proton-induced nitroxyl-release reactivity of M-NO complexes, we are prompted to elucidate the nature and mechanism for the direct nitroxyl-transfer reactivity of dinitrosyl iron complexes (DNICs) using $[Fe^{III}(TPP)Cl]$, Fe^{III}-myoglobin (metMb) from equine heart, and Fe^{III}-hemoglobin (metHb) from swine as a specific probe under alternative conditions (Figure 1).[14–17,21,22] To gain the insight to the control of direct

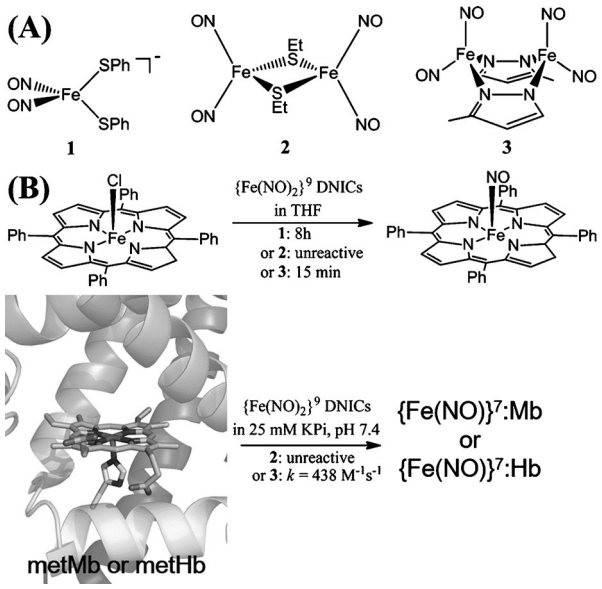

Figure 1. A) $\{Fe(NO)_2\}^9$ DNICs **1**, **2**, and **3** used in this study. B) Utilization of $[Fe^{III}(TPP)Cl]$ and Fe^{III}-porphyrin center in metMb or metHb as a specific probe to characterize the nitroxyl-transfer reactivity of $\{Fe(NO)_2\}^9$ DNICs **1**, **2**, and **3**.

nitroxyl-transfer reactivity, thermally stable mononuclear $\{Fe(NO)_2\}^9$ complex $[Fe(SPh)_2(NO)_2]^-$ (**1**) and dinuclear $\{Fe(NO)_2\}^9$-$\{Fe(NO)_2\}^9$ complex $[Fe(\mu\text{-}SEt)(NO)_2]_2$ (**2**) were selected to avoid the redox-coupled process as well as spontaneous nitroxyl release.[23,24] In addition, dinuclear $\{Fe(NO)_2\}^9$-$\{Fe(NO)_2\}^9$ complex $[Fe(\mu\text{-}^{Me}Pyr)(NO)_2]_2$ (**3**) embedded in a butterfly geometry was synthesized in an attempt to probe the role of electronic structure in the modulation of nitroxyl-transfer reactivity.

Upon addition of one equiv of 3-methylpyrazole into the CH_2Cl_2 solution of freshly prepared $Fe(CO)_2(NO)_2$, a pronounced color change from red to brown occurs after this reaction solution was stirred overnight at ambient temperature. A shift of IR ν_{NO} stretching frequencies from 1808 and 1760 cm^{-1} to 1809, 1795, 1740, and 1726 cm^{-1} indicated the formation of dinuclear DNIC $[Fe(\mu\text{-}^{Me}Pyr)(NO)_2]_2$ (**3**, ^{Me}Pyr = 3-methylpyrazolate) (yield 67%; see Figure S1A in the Supporting Information). This reaction is comparable to the formation of complex $[Fe(\mu\text{-}^{R}Im)(NO)_2]_4$ in the reaction of $Fe(CO)_2(NO)_2$ and imidazole (or isopropylimidazole and benzimidazole) in a 1:1 molar ratio.[25,8] According to the single-crystal X-ray structure of DNIC **3** shown in Figure S1B, a butterfly geometry observed in DNIC **3** may explain the four IR ν_{NO} stretching peaks, as opposed to two strong IR ν_{NO} stretching peaks at 1774 and 1748 cm^{-1} observed in DNIC $[Fe(\mu\text{-}SEt)(NO)_2]_2$ (**2**) containing an approximate center of inversion.[23] DFT calculation of DNIC **3** rationalizes and assigns these four IR ν_{NO} stretching peaks to the two $[Fe(NO)_2]$ cores in DNIC **3** (Figure S1C in the Supporting Information).

For dinuclear $\{Fe(NO)_2\}^9$-$\{Fe(NO)_2\}^9$ DNICs, the Fe···Fe distance regulates the antiferromagnetic coupling between the two $S = {}^1/_2\{Fe(NO)_2\}^9$ cores and dictates the appearance of the distinctive EPR signal at $g = 2.03$ for $\{Fe(NO)_2\}^9$ DNICs.[23,8,27] As shown in Figure S2A in the Supporting Information, dinuclear $\{Fe(NO)_2\}^9$-$\{Fe(NO)_2\}^9$ DNIC **3** displays an isotropic signal with $g = 2.03$ at 77 K. Compared to the EPR silent DNIC **2**, replacement of the μ-SEt ligands by $\mu\text{-}^{Me}Pyr$ ligands in DNIC **3** extends the Fe···Fe distance from 2.708(1) Å to 3.353(1) Å and weakens the magnetic coupling between the two $\{Fe(NO)_2\}^9$ centers.[23] Decrease of temperature-dependent effective magnetic moment of DNIC **3** from 2.56 μ_B at 300 K to 2.44 μ_B at 100 K supports the $\{Fe(NO)_2\}^9$-$\{Fe(NO)_2\}^9$ electronic structure of DNIC **3** with weak magnetic coupling between the two $S = {}^1/_2\{Fe(NO)_2\}^9$ centers (Figure S2B in the Supporting Information).

Reaction of complex $[Fe^{III}(TPP)Cl]$ and DNICs **1**, **2**, and **3**, respectively, was investigated as the initial evaluation for the nitroxyl-transfer reactivity of DNICs (Figure 1).[14,16] As shown in Figure S3A and S3B in the Supporting Information, two strong IR ν_{NO} stretching peaks at 1773 and 1748 cm^{-1} derived from DNIC **2** and the UV/Vis absorption bands at 415, 505, and 569 nm derived from complex $[Fe^{III}(TPP)Cl]$ remain unchanged after the THF solution containing complexes $[Fe^{III}(TPP)Cl]$ and **2** was stirred for 8 h. In comparison, nitroxyl transfer from DNIC $[Fe(SPh)_2(NO)_2]^-$ (**1**) to complex $[Fe^{III}(TPP)Cl]$ affording [Fe(TPP)(NO)] was completed in 8 h according to the shift of IR ν_{NO} stretching peaks from 1737 and 1693 cm^{-1} to 1680 cm^{-1} and the shift of UV/Vis absorption bands from 415, 505, and 569 nm to 408, 534 and 601 nm (Figure 2A and Figure S4 in the Supporting Information). The reported $E_{1/2}$ of −1.33 V for $\{Fe(NO)_2\}^9/\{Fe(NO)_2\}^{10}$ redox couple in DNIC **1** and the absence of E_{ox} between −1.7 V and −0.7 V exclude the redox-coupled process between complexes [Fe(TPP)Cl] and **1**.[24]

Upon addition of 0.25 equiv of DNIC **3** to complex $[Fe^{III}(TPP)Cl]$, formation of $\{Fe(NO)\}^7$ complex [Fe(TPP)(NO)] accomplished within 15 min demonstrates a rapid nitroxyl-transfer reactivity featured by DNIC **3** (Figure 2B and Figure S5 in the Supporting Information). Electrochemical interconversion among $\{Fe(NO)_2\}^9$-$\{Fe(NO)_2\}^9$, $\{Fe(NO)_2\}^9$-$\{Fe(NO)_2\}^{10}$, and $\{Fe(NO)_2\}^{10}$-$\{Fe(NO)_2\}^{10}$ redox couples in DNIC **3** at $E_{1/2} = -0.87$ V and −1.18 V versus Fc/Fc^+, respectively, supports the direct transfer of nitroxyl from $\{Fe(NO)_2\}^9$-$\{Fe(NO)_2\}^9$ DNIC **3** to $[Fe^{III}(TPP)Cl]$ (Figure S6 in the Supporting Information). Formation of complexes [Fe(TPP)(NO)] and $[FeCl_2(Ar\text{-}nacnac)]^-$, derived from the reaction of $[Fe^{III}(TPP)Cl]$ and $\{Fe(NO)_2\}^{10}$ $[Fe(NO)_2(Ar\text{-}nacnac)]^-$, suggests a net NO–Cl exchange mecha-

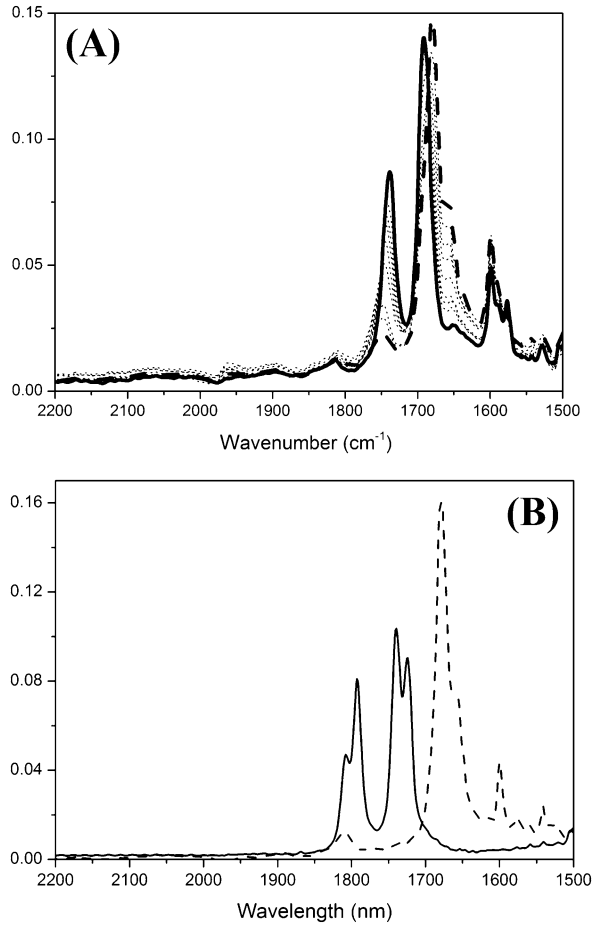

Figure 2. A) Reaction of complex [Fe^{III}(TPP)Cl] and DNIC **1** in a 2:1 molar ratio traced by IR. The spectra are measured after the reaction solution was stirred for 0 (black), 60, 90, 120, 180, 240, 300, 360 (dotted lines), and 480 min (dashed line). B) IR spectra of DNIC **3** (black) and after its reaction with 4 equiv of complex [Fe^{III}(TPP)Cl] for 15 min (dashed line).

nism for the reductive nitrosylation of [Fe^{III}(TPP)Cl] by $\{Fe(NO)_2\}^{10}$ $[Fe(NO)_2(Ar\text{-}nacnac)]^-$.[14] Presumably, direct nitroxyl transfer from DNIC **3** to [Fe^{III}(TPP)Cl] affords [Fe(TPP)(NO)] with the proposed formation of $[Fe(\mu\text{-}^{Me}Pyr)Cl_2]_2$ (see the Supporting Information for details).

To apply DNIC **3** as a novel nitroxyl donor in aqueous conditions, assessment of the nitroxyl-transfer reactivity of DNIC **3** using Fe^{III}-myoglobin (metMb) and Fe^{III}-hemoglobin (metHb) as a specific probe is a critical intermediate step for prospective applications in nitroxyl chemistry and biology (Figure 1).[15,22] UV/Vis absorption bands at 348, 623, and 780 nm exhibited by DNIC **3** remain unchanged for 24 h in 25 mM phosphate buffer (pH 7.4) at 25 °C. This demonstrates the null nitroxyl-release reactivity of DNIC **3**. In the reaction of 10 μM metMb and 10 μM DNIC **3**, shift of the UV/Vis absorption bands from 407, 503 and 629 nm to 419, 543, and 577 nm indicates the rapid formation of $\{Fe(NO)\}^7$ species in myoglobin (MbNO) and demonstrates the efficient nitroxyl-transfer reactivity of DNIC **3** toward the Fe^{III}-porphyrin center (Figure 3A). From the linear dependence of the rate of formation of MbNO on the concentration of DNIC **3** and metMb, a second-order rate constant of 438 ± 15 $M^{-1}s^{-1}$ is derived (Figure 3B and 3C). This also supports the associative mechanism for direct nitroxyl transfer from DNIC **3** to metMb. As shown in Figure 3D, reaction of 5 μM methemoglobin (metHb) and 5 μM DNIC **3** affords HbNO and provides an alternative support to the efficient nitroxyl-transfer reactivity of DNIC **3** toward the Fe^{III}-heme center in aqueous buffer solution at pH 7.4. In contrast, DNIC **2** is unreactive toward the Fe^{III}-porphyrin center in either metMb or metHb (Figure S7 in the Supporting Information).

Efficient nitroxyl-transfer reactivity of DNIC **3** encouraged us to conduct $Fe_{K\beta}$ valence-to-core X-ray emission spectroscopy (V2C XES) and Fe K-edge X-ray absorption spectroscopy (XAS) study (Table S1 and Figure S8 in the Supporting Information).[27–31] V2C XES was used to probe $\Delta E_{\sigma 2s^*-\sigma 2p}$ of NO and provide a quantitative measurement of the NO oxidation state in Fe-NO complexes, based on the linear relationship between $\Delta E_{\sigma 2s^*-\sigma 2p}$ of NO and its oxidation state.[28] For dinuclear DNICs **2** and **3**, replacement of the bridging thiolate ligands in DNIC **2** with bridging pyrazolate ligands in DNIC **3** elongates the Fe–NO bond and enhances the nitroxyl character in DNIC **3** (Table S1 in the Supporting Information). Fe K-edge pre-edge energy of 7114.0 eV observed in DNIC **3**, compared to 7113.5 eV exhibited by DNIC **1** and 7113.8 eV exhibited by DNIC **2**, demonstrates the buildup of an electron-deficient Fe^{III} center containing two NO^- ligands polarized by the pyrazolate bridging ligands. Presumably, decreased Fe–NO bonding interaction between the electron-deficient Fe^{III} center in DNIC **3** and its NO^- ligands, as evidenced by the elongated Fe–NO bond distance (Table S1 in the Supporting Information), boosts the nitroxyl transfer to the Fe^{III}-porphyrin complex and proteins. With the use of V2C XES in spectroscopic measurements for quantitative determination of NO oxidation state, continuing efforts on the study of DNICs, however, are required to unravel the correlation among its electronic structure, dominant Fe-to-NO bonding interaction versus dominant NO-to-Fe bonding interaction, Fe–NO and N–O bond lengths, and dedicated control of nitroxyl-transfer reactivity.

In summary, we explored a stable dinuclear $\{Fe(NO)_2\}^9$ DNIC **3** as a potent nitroxyl donor for direct nitroxyl transfer toward the Fe^{III}-porphyrin complex and proteins through an associative mechanism. Beyond the efficient nitroxyl-transfer reactivity toward Fe^{III}-heme centers, discovery of DNIC **3** as a lead compound will trigger the development of DNICs as a chemical biology probe for nitroxyl and for clinical translation in vascular and myocardial pharmacology.

Acknowledgements

We gratefully acknowledge the financial support from grant MOST 102-2113M-033-009-MY2 and MOST 103-2632M033-001-MY3 from the Ministry of Science and Technology (Taiwan). T.-T.L. also thanks Prof. Jhy-Der Chen for the support with electrochemical studies, Mr. Ling-Yun Jang and Dr. Feng-Chun Lo for the help on the S/Cl K-edge XAS, and Prof. Wen-Feng Liaw for valuable discussions.

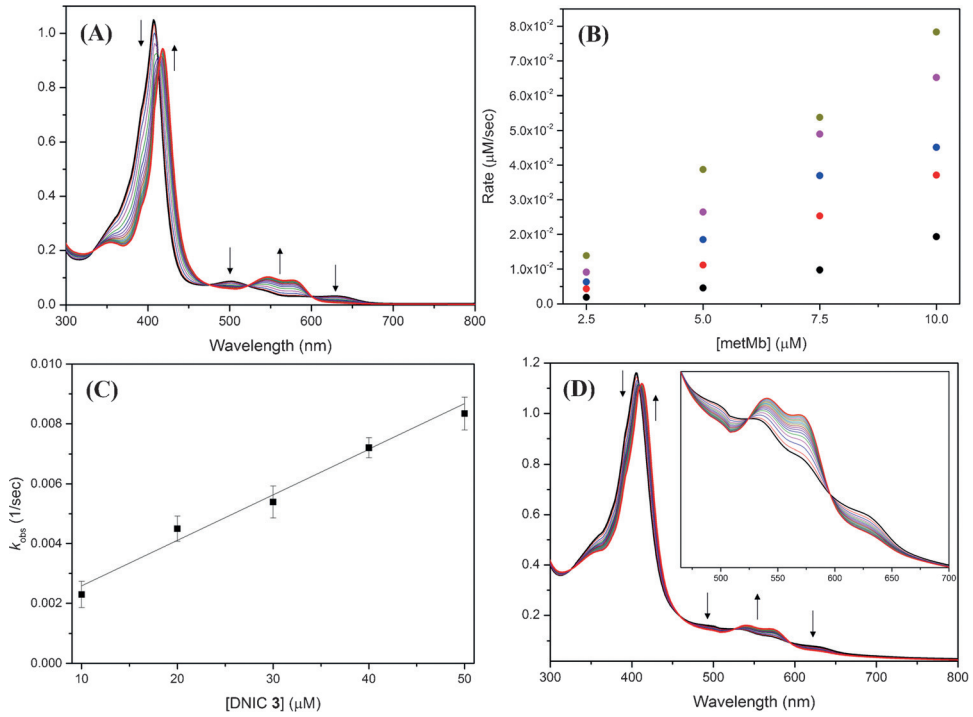

Figure 3. A) Reaction of 10 μM DNIC **3** with 10 μM metmyoglobin (metMb) in 25 mM phosphate buffer at pH 7.4 (black line) results in the formation of MbNO (red line). The UV/vis spectra are measured every 50 s, whereas the arrows indicate the change of the UV/vis spectra. B) Dependence of the rate for the conversion of metMb into MbNO on the concentration of [metMb]. 10, 7.5, 5, and 2.5 μM of metMb and 10 (black), 20 (red), 30 (blue), 40 (magenta), and 50 μM (green) of DNIC **3** were used. Considering the rate law: rate $= k_{obs}$[metMb], five k_{obs} were derived from the linear regression fit to the rate versus [metMb]. C) Dependence of k_{obs} on the concentration of [DNIC **3**]. The slope of the linear regression fit indicates a second-order rate constant k of $438 \pm 15\ M^{-1}s^{-1}$ considering the rate law: rate $= k$[DNIC **3**][metMb]. D) Reaction of 5 μM DNIC **3** with 5 μM methemoglobin (metHb) in 25 mM phosphate buffer at pH 7.4 (black line) results in the formation of HbNO (red line). The UV/Vis spectra are measured every 100 s, whereas the arrows indicate the change of the UV/Vis spectra.

Keywords: bioinorganic chemistry · nitrosyl complexes · nitroxyl · X-ray emission spectroscopy

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Received: August 11, 2015
Published online on October 22, 2015