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Asymmetry within the $Fe(NO)_2$ moiety of dithiolate dinitrosyl iron complexes

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ABSTRACT

Dinitrosyl iron complexes have earned attention due to their applications as nitric oxide donors as well as their interesting electronic structures. Typical Fe–NO electromerism issues are complicated in this case by the presence of a second nitrosyl ligand. Each of the formal oxidation states of iron in such complexes – from Fe(III) to Fe(0) – have been shown to be subject to electromerism. Here, broken-symmetry density functional theory data are shown, that reveal asymmetry within iron dithiolate dinitrosyl models in several formal oxidation states. CASSCF calculations on selected models confirm the multiconfigurational character of the $Fe(NO)_2$ moiety, with the largest contributor at only 44% of the total weight of the wave function. This asymmetry is most noticeable in the excited states; it is further enhanced by solvation and reveals itself even in the ground state in dynamics calculations as well as in reaction pathways connecting the dinitrosyl state to a putative hyponitrite adduct.

1. Introduction

Dinitrosyl iron complexes (DNICs) with thiol-containing ligands (cysteine or glutathione) have earned much attention due to their applications as bases for drugs possessing a broad spectrum of therapeutic activities [1–9]. They were also shown to play a role in sulfur-rich protein uptake and degradation [10–12], act as storage sites and transporters of NO, as well as intermediates in the iron-catalyzed degradation and formation of *S*-nitrosothiols [13–17].

The formation of DNICs in vivo occurs through the interaction of NO with ferrous iron [18] or by the attack of NO on protein-based iron–sulfur clusters and other iron-containing proteins [12,19–24]. However, paramagnetic mono- and diamagnetic binuclear forms of DNICs with thiol-containing ligands, i.e. cysteine or glutathione, are easily prepared in vitro by the treatment of aqueous solutions of thiols with gaseous NO in the presence of Fe^{2+} ions at neutral pH [25–27].

Several studies on DNICs with neutral and anionic ligands have recently been reported. Among others, Tsai et al. reported a study in which XAS, SQUID, DFT calculations, and EPR spectroscopy were used to investigate the electronic structure of the $\{Fe(NO)_2\}^9$ unit (which reads as 9 electrons delocalized over the Fe and NO fragments after Enemark–Feltham notation [28]) of a $[S_5Fe(NO)_2]^-$ complex. The EPR signals reported along with the temperature-dependent magnetic moment indicated that the ground state is one unpaired electron with $(S_t, S_L) = (1/2, 1)$ at very low temperature (where S_t is the total spin quantum number of the system; S_L is the sum of the spin quantum numbers of two NO ligands) [29].

The role of DNIC in the biological cycle of degradation and reassembly of the ferredoxin [2Fe–2S] cluster was well illustrated by Ding and co-workers [30]. The authors showed that when *Escherichia coli* cells are exposed to nitric oxide, the ferredoxin [2Fe–2S] clusters are modified to form protein-bound dinitrosyl iron complexes. In the repair of the nitric oxide-modified ferredoxin [2Fe–2S] cluster, the dinitrosyl iron complexes can be directly transformed back to the ferredoxin [2Fe–2S] cluster by cysteine desulfurase and L-cysteine in vitro [30,31]. On the other hand, Tinberg et al. reported the first evidence that DNICs are formed in the reaction of NO with Rieske-type [2Fe–2S] clusters. Results obtained by EPR, Mössbauer, and NRVS spectroscopy demonstrate that NO reacts readily with Rieske centers resulting in a thiolate-bridged diiron tetranitrosyl species as the primary product whereas a mononuclear DNIC account for only a minor fraction of the nitrosylated iron [32].

Tonzetich et al. reported the synthesis of a pair of homologous DNIC redox isomers, $\{Fe(NO)_2\}^9$ and $\{Fe(NO)_2\}^{10}$, containing

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a sterically hindered β-diketiminate ligand [33]. An interesting observation from this study is that the isomer shifts (δ) in the Mössbauer spectra of the two DNICs were found to be nearly identical, δ 0.19(2) and 0.23(2) mm/s for $\{Fe(NO)_2\}^9$ and $\{Fe(NO)_2\}^{10}$ respectively, which is unexpected for a metal-centered reduction. A theoretical investigation of these structures was reported in the work of Ye and Neese where isomer shifts, electronic characteristics, and molecular orbital diagrams of the DNIC [(Ar-nacnac)Fe-$(NO)_2$] in both its neutral $\{Fe(NO)_2\}^9$ and the one-electron reduced $\{Fe(NO)_2\}^{10}$ forms were calculated and compared to experimental results [34]. Moreover, in a subsequent report, NO-transfer chemistry of these redox isomer pairs has been investigated by the same authors. In this study, iron porphyrins were used as NO acceptors and $\{Fe(NO)_2\}^9$ DNIC was found to undergo a reductive nitrosylation mechanism for which the dissociation of $NO^{\cdot}$ or NO^-.was the rate-limiting step. The one electron reduced species $\{Fe(NO)_2\}^{10}$ was also found to proceed through the same mechanism but a rapid electron transfer preceded the NO transfer; The resulting $\{Fe(NO)_2\}^9$ DNIC was found to nitrosylate the Fe(II) porphyrin generating a $\{Fe–NO\}^8$ species that immediately disproportionated to $\{Fe(NO)_2\}^{10}$ and an NO-free Fe(II) complex [35].

Through calibration with experimental data, Brothers et al. reported results of NO vibrational frequencies (ν(NO)) in context of an attempt to accurately describe the computational framework for a set of mono and di nucleated DNICs. The functional BP86 paired with a basis set of SDD/ECP on the metal and 6-311++G(d,p) on the ligand atoms exhibited the most accurate results, with deviations from experimental vibrational frequencies of no more than ($40\ cm^{-1}$) [36].

Additionally, a theoretical study of Mössbauer isomer shifts and quadrupole splittings by DFT for a wide range of iron nitrosyls was reported by Hopmann et al. A level of theory comprising the hybrid DFT functional OLYP combined with the STO-TZP basis set was found to perform comparably well for iron nitrosyls in terms of isomer shifts. However, quadrupole splittings were less accurately reproduced [37].

Conversely, Lu et al. suggested that the higher Fe–S bond covalency modulated by the stronger electron-donating thiolates promotes the Fe → NO π-electron back-donation to strengthen the Fe–NO bond and weaken the NO-release ability of the mononuclear DNICs; these results are supported by the Raman ν-(Fe–NO) stretching frequency and data derived from the intensity of the S K-edge pre-edge absorption method [38].

A comprehensive DFT and CASSCF theoretical study was reported by Pierloot and co-workers [39] that revealed the multiconfigurational character of iron-nitrosyl $\{FeNO\}^7$ complexes. The authors described the bonding between Fe and NO as antiferromagnetic with a strong non-dynamic (left–right) correlation character. In addition, the Fe(II)–NO^0 and Fe(III)–NO^- resonance structures were found to be the main contributors to the CAS wave function in terms of localized orbitals of the Fe and NO fragments [39].

An extensive review on DNICs with thiol-containing ligands was carried out by Vanin and Burbaev illustrating the works done in the authors' own laboratory and studies reported by others [40]. The first evidence in favor of the ability of DNIC with cysteine or glutathione to initiate S-nitrosation of thiols was reported by Vanin et al. [41]. This study led the authors to conclude that one nitrosyl ligand in DNICs with thiol-containing ligands exists in the form of nitrosonium ion and is responsible for S-nitrosation of cysteine after the decomposition of DNIC whereas the second nitrosyl ligand is released in the form of a neutral NO molecule [41]. Previous studies showed that the synthesis of DNIC with non-thiol ligands is accompanied by the formation of nitrous oxide (N_2O) [42]. On this basis, Vanin et al. suggested a hypothetical mechanism of DNIC formation [43,44], in which they proceeded from the assumption that the binding of two NO molecules to Fe^{2+} ions results in their disproportionation and conversion into NO^+ and NO^- ions. Protonation of the latter yields nitroxyl (HNO), which leaves the coordination sphere of Fe^{2+}. Recombination of two nitroxyl molecules gives nitrous oxide; subsequent incorporation of an NO molecule into the DNIC is accompanied by a transfer of the unpaired electron from the latter to iron and formation of the $\{Fe^+(NO^+)_2\}$ fragment, i.e. $\{(RS^-)_2Fe^+(NO^+)_2\}^+$ for DNIC with thiol-containing ligands, with a d^7configuration of the iron atom ($\{Fe(NO)_2\}^7$ according to Enemark–Feltham notation [28]). This hypothesis is supported by studies confirming the formation of nitrous oxide (N_2O) in the course of DNIC synthesis [45] and the involvement of three NO molecules in the formation of one DNIC [46]; furthermore, the results of EPR signals analyses of DNIC with thiol-containing ligands [1,47,48,25,49] are in good agreement with such mechanism concerning the formation, composition, and distribution of unpaired electron density in these complexes.

Thus, though most electronic structure elements deduced from theoretical and spectroscopic studies agree to the symmetrical nature of the $Fe(NO)_2$ moiety, NO-releasing activity of DNICs intrinsically involves some degree of asymmetry. In this study we investigate the electronic structures of a set of DNICs with thiol-containing ligands and show that each of the experimentally studied formal oxidation states of iron in such complexes – from Fe(III) to Fe(0) is subject to electromerism.

2. Models and theoretical methods

The chemical structure investigated in this study is a mononuclear dithiolate dinitrosyl iron complex. Oxidation states of iron starting from Fe(0) to Fe(III) were taken into consideration thus 4 models ($[Fe(SCH_3)_2(NO)_2]^{2-}$, $[Fe(SCH_3)_2(NO)_2]^-$, $[Fe(SCH_3)_2(NO)_2]^0$, and $[Fe(SCH_3)_2(NO)_2]^+$) were investigated. However, due to the challenging issues in the description of the electronic structures of DNICs arising from the near degeneracy of the NO π^* and metal d orbitals, the Fe(II)–NO^0 vs. Fe(III)–NO^- case reported by Pierloot and co-workers [39] being a typical example, Enemark's and Feltham's notation [28] $\{Fe(NO)_2\}^n$ (which avoids the oxidation state ambiguity by counting d and π^* electrons together as n) was utilized throughout this work. Thus, ($[Fe(SCH_3)_2(NO)_2]^+$, $[Fe(SCH_3)_2(NO)_2]^0$, $[Fe(SCH_3)_2(NO)_2]^-$, and $[Fe(SCH_3)_2(NO)_2]^{2-}$ are addressed as $\{Fe(NO)_2\}^7$ $\{Fe(NO)_2\}^8$, $\{Fe(NO)_2\}^9$ and $\{Fe(NO)_2\}^{10}$ respectively.

Structure optimizations at the DFT level were performed using GAUSSIAN09 software package [50] with GAUSSVIEW [51] as front-end. The meta GGA M06-L functional [52] was employed in all calculations coupled with the triple ζ 6-311+G(d,p) basis set. We point out that the M06-L functional has been designed to include medium-range electron correlation effects and has been specifically recommended for transition-metal containing systems; M06-L offered the best agreement of several tested functionals compared to large multireference calculations and completely renormalized coupled cluster calculations [53] and several benchmark studies have confirmed its excellent accuracy in this respect [53–61]. Additionally, calculations were also performed using the pure BP86 [62] and the hybrid B3LYP [63] functionals, these results can be viewed in the Supporting information. All calculations were performed within the broken-symmetry (BS) unrestricted methodology in order to determine whether these complexes are to be described as spin-coupled (antiferromagnetic) or pure spin Kohn–Sham determinant (ferromagnetic). The general notation BS(m,n) was adopted where m denotes the alpha (spin-up) electrons and n denotes the beta (spin-down) electrons at the two interacting fragments and the final relative energies are reported here. The detailed steps of this procedure along with the broken symmetry calculation analyses for all complexes can be found in the Supporting information. In