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Hammett Correlations as Test of Mechanism of CO-Induced Disulfide Elimination from Dinitrosyl Iron Complexes

Randara Pulukkody, Samuel J. Kyran, Michael J. Drummond, Chung-Hung Hsieh, Donald J. Daresbourg, and Marcetta Y. Daresbourg*

The displacement of RS\(^+\) from [(NHC)(SPh)Fe(NO)\(_2\)] (NHC = N-heterocyclic carbene) by carbon monoxide follows associative kinetics, rate = \(k_2 [CO] \)^\(^7\) [(NHC)(SPh)Fe(NO)\(_2\)]\(^\text{1}\), resulting in reduction of the oxidized form of the dinitrosyliron unit, {Fe(NO)\(_2\)}\(^9\) (Enemark - Feltham notation) to {Fe(NO)\(_2\)}\(^10\). Thermodynamically driven by the release of PhS-SPh concomitant with formation of [(NHC)(CO)Fe(NO)\(_2\)], computational studies suggested the reactant dinitrosyliron unit serves as a nucleophile in the initial slanted interaction of the \(\pi^*\) orbital of CO, shifting into normal linear Fe-CO with weakening of the Fe-SPh bond. The current study seeks to experimentally test this proposal. A series of analogous {Fe(NO)\(_2\)}\(^9\) [(NHC)(\(p\)-S-\(C_6H_4X\)Fe(NO)\(_2\)] complexes, with systematic variation of the \(para\)-substituents X from electron donor to electron withdrawing groups was used to monitor variation in electron density at the Fe(NO)\(_2\) unit via Hammett analyses. Despite the presence of non-innocent NO ligands, data from \(\nu(\text{NO})\) IR spectroscopy and cyclic voltammetry showed consistent tracking of the variation of the electron density at the {Fe(NO)\(_2\)}\(^1\) unit in response to the aryl substituent. The electronic modifications resulted in systematic changes in reaction rates when each derivative was exposed to CO\(_{10}\). A plot of the rate constants and the Hammett parameter \(\sigma_p\) is linear with a negative slope and a \(\rho\) value of -0.831; such correlation is indicative of rate retardation by electron-withdrawing substituents, and provides experimental support for the unique role of the delocalized frontier molecular orbitals of the Fe(NO)\(_2\) unit.

Introduction

That diatomic molecules in combination with metals play vital roles in a variety of physiological functions is well established. While physiologically beneficial carbon monoxide and nitric oxide concentrations are in picomolar to nanomolar range, increasing concentrations result in cytotoxic effects.\(^1\) Under physiological control CO and NO function as important regulatory and signaling molecules, and are members of a class of endogenously-produced gaseotransmitters.\(^2\) Much current research is directed at the fundamental biochemistry especially significant in the cardiovascular system, as well as development of compounds as pro-drugs, capable of controlled delivery and release of NO and CO to biological targets—the most important in vasodilation activity being iron in porphyrin environments.\(^3\)

As an extensive literature exists for transition metal complexes containing CO and NO, much attention has been directed towards appropriate combinations of ligands and metals designed for specific pharmacological properties.\(^4\) Indeed, explorations of one class of complexes, dinitrosyl iron complexes (DNICs), are inspired by their natural occurrence,\(^5\) and by the intriguing proposal that they might be the “most abundant nitric oxide-derived cellular adduct”, i.e., superseding the S-nitrosothiols (RSNOs).\(^6\) Others have posited that synthetic versions may be developed as NO-release agents.\(^7\)

The chemical properties of CO and NO as ligands to metals are substantially different; the former is viewed as an innocent ligand with weak \(\sigma\)-donor/strong \(\pi\)-acceptor properties in its M-CO bond formation.\(^8\) In contrast, the radical character of NO imparts reactivity that surpasses that of CO, in that its ability to readily switch between the NO\(^-\), \(\cdot\text{NO}\), and NO\(^+\) forms depends on the redox levels accessible by the metal to which it binds, thereby defining non-innocent ligand binding.\(^9\)

The lifetime of free NO in the aerobic cellular milieu is reported to be too short to account for its observed physiological functions.\(^1\) Therefore, it is expected that transitory derivatives of NO serve for storage, transport and delivery of NO to required sites. Both organic (RSNOs) and inorganic dinitrosyl iron complexes have been proposed for such NO storage/transport functions in vivo.\(^16,17\) The biological DNICs are derived in vivo from the labile or cellular chelatable iron pool, or by degradation of iron sulfur clusters; the latter generates protein-bound (cysteinyl-S)-Fe(NO)\(_2\) as high molecular weight, HMW, moieties.\(^10,18,22\) Characterized by a prominent EPR signal at 2.03, \(^{19,23}\) the HMW form may be
rendered mobile in low molecular weight, LMW, forms on exchange with free cysteine or other thiolate-rich biomolecules such as glutathione. That glutathione-S transferase may serve as a Fe(NO)₂ transport vehicle has been supported by the isolation and structural characterization of the protein with glutathione-Fe(NO)₂ imbedded within its glutathione-binding site.

Numerous small molecule models assumed to be relevant to biological DNICs have been synthesized and characterized. Synthetic DNIC complexes exist in two redox levels: oxidized, EPR active {Fe(NO)₂} and the reduced, EPR silent {Fe(NO)₂} (Enemark-Feltham notation). The oxidized form can be found in the neutral L(X)Fe(NO)₂ (where for example X = halides, pseudo halides, or thiolate S-donors) or the good sigma donor ligands N-heterocyclic carbenes (NHC) that are apt analogues of imidazoles), and the anionic X₃Fe(NO)₂⁻ complexes. The reduced form can be found in the L₂Fe(NO)₃ state, with the paradigm being the 18-electron species, (OC)₂Fe(NO)₃, a versatile precursor to LFe(CO)(NO)₂ derivatives. The ligand environment is critical in stabilizing the redox state of the DNIC which in turn governs its endogenous role as NO storage or releasing agent. While there exists a variety of four-coordinate {Fe(NO)₂} synthetic DNIC models in the inorganic chemistry literature, several reports have also presented the rare, five-coordinate counterparts. Our work focuses on developing understanding of mixed ligand environments and mechanisms of ligand exchange processes that might regulate switches in redox levels.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** (Top) (a) A sketch of the calculated collision complex, involved in the rate determining step for CO and (NHC)(RS)Fe(NO)₂, proceeding through a 5-coordinate intermediate L. Theory finds that as the Fe-CO bond becomes linear as in (b), the Fe-SR bond lengthens, and releases a thiyl radical, either by direct homolytic Fe-S bond cleavage or via homolytic C-S cleavage from a transient metallothioester group. (Bottom) Corresponding plots of the transition state SOMOs: (a) the unpaired electron on the {Fe(NO)₂} donates into the π* orbital of the side-on entering CO; and (b) the shift of the unpaired electron releases thiyl radical.

As a poor nucleophile, CO exchange reactions with a metal-bound CO or L typically take place by dissociative mechanisms allowing external CO to be trapped by an open site as in eq 1. Recently we reported an example of CO displacement of RS• in a dinitrosyliron complex, the kinetics of which followed a second-order rate expression with activation parameters consistent with an associative mechanism, eq 2. This process entailed a change in the redox state of the reactant DNIC as the oxidized state, {Fe(NO)₂}, converted into the reduced analogue, {Fe(NO)₂}⁻. Proceeding under mild conditions, the thermodynamics of the reaction is driven by the formation of RSSR as a result of the release of RS•. Computational studies were carried out in pursuit of a reasonable mechanistic proposal for the observed reactivity, resulting in the suggestion that the π-density of the {Fe(NO)₂} unit was involved in nucleophilic attack on CO, the latter acting as an electrophile, Figure 1. Theory suggested a side-on approach of CO leading to a 5-coordinate intermediate, species 1 of Figure 1, with the NO ligands accommodating the excess charge. Such nucleophilicity of the iron in {Fe(NO)₂}, especially in the oxidized {Fe(NO)₂}⁻, was unexpected.

Herein we report experiments designed to test the mechanistic proposal that had suggested such a unique role of the {Fe(NO)₂}⁻ unit in the CO-induced disulfide elimination. We have prepared a series of analogous {Fe(NO)₂}⁻ [{NHC}(p-S-C₆H₅)X]Fe(NO)₂ complexes, where the para-substituents X were systematically varied from electron donor to electron withdrawing groups that might be used in a Hammett analysis of their effects on electron density at the Fe(NO)₂ unit. Data from ν(NO) IR spectroscopy and cyclic voltammetry was used to track the differences of the electron density at the {Fe(NO)₂}⁻ unit in response to the aryI substituent. Systematic changes were observed in the rates of reaction when each derivative was exposed to CO₂, consistent with the electronic changes at the Fe(NO)₂ unit.

### Results and Discussion

#### Synthesis and Isolation

A series of dinitrosyliron complexes containing para-substituted aryl thiolates, (sMes)(S-C₆H₅)Fe(NO)₂ (compounds 1a-1e) was synthesized by homolytic cleavage of the corresponding Roussin’s Red Ester (RRE), µ-(S-C₆H₅)₂[Fe(NO)₂] by two equivalents of the sMes ligand (freshly prepared by combining 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride and NaO'Bu in a 1:1 stoichiometric ratio). Scheme 1 shows the synthetic protocol along with Hammett parameters for the substituents of the p-SC₆H₅X series. The brown RRE solution changed to blue/purple, from which purple solids were isolated upon recrystallization with cold hexane.
The DNICs 1a-1e were stable under inert atmosphere for several months in the solid state. In solution, under inert atmosphere, stability was diminished to 2-3 weeks. Four members of the series (1a, 1b, 1c and 1e) were characterized by X-ray crystallography and their molecular structures are compared in Figure 2. X-ray quality crystals of 1b and 1e were obtained by slow evaporation of concentrated ether solutions, while those of 1a and 1e were obtained from solutions of THF/Hexane. Table 1 lists selected bond distances and angles for 1a, 1b, 1c and 1e. Crystals of the complex 1d have thus far eluded crystallization.

The complexes in Figure 1 are tetrahedral wherein the CN$_2$C$_2$ plane of the siMes bisects the S-Fe-N angles of the trigonal base; that is, the NHC plane does not eclipse the Fe-N or Fe-S bond vectors. The planes of the mesitylenes are roughly perpendicular to the CN$_2$C$_2$ plane and appear to umbrella the Fe(NO)$_2$SR motif. All structures maintain the previously described “attracto” conformation$^{35}$ where the two Fe-N-O with slight deviations from linearity, are oriented towards each other. The Fe-N-O angles and all other metric parameters of structures 1a, 1b, 1c and 1e are comparable to each other and to those of the [siMes(SPh)Fe(NO)$_2$] analogue.$^{40}$ Although barely within significant limits, there appears to be a gradual decrease of Fe-C$_{NHC}$ bond lengths with the electron withdrawing ability of the para substituent on the S-C$_6$H$_4$, concomitant with an increase in the Fe-S bond distance. This correlation is further reflected in the ν(NO) vibrational spectra.

### Table 1. Selected bond distances and angles in [siMes(S-C$_6$H$_4$X)Fe(NO)$_2$] complexes 1a, 1b, 1c and 1e.

<table>
<thead>
<tr>
<th>X</th>
<th>Fe-C</th>
<th>Fe-NO$^a$</th>
<th>Fe-S</th>
<th>N-O</th>
<th>C-Fe-NO$^a$</th>
<th>C-Fe-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCH$_3$</td>
<td>2.052(2)</td>
<td>1.672(2)</td>
<td>2.243(1)</td>
<td>1.172(7)</td>
<td>106.0(1)</td>
<td>112.0(1)</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>2.049(2)</td>
<td>1.674(1)</td>
<td>2.239(1)</td>
<td>1.172(2)</td>
<td>106.0(1)</td>
<td>112.0(1)</td>
</tr>
<tr>
<td>H</td>
<td>2.048(2)</td>
<td>1.675(2)</td>
<td>2.248(1)</td>
<td>1.172(2)</td>
<td>106.0(1)</td>
<td>112.0(1)</td>
</tr>
<tr>
<td>Cl</td>
<td>2.044(2)</td>
<td>1.673(2)</td>
<td>2.259(1)</td>
<td>1.172(3)</td>
<td>106.0(1)</td>
<td>112.0(1)</td>
</tr>
</tbody>
</table>

$^a$average distance or angles. The maximum deviations from the average distances and angles are shown in the table. Full lists of metric parameters are available in the SI.

### Infrared Spectroscopy

Noticeable shifts in the positions and pattern of the ν(NO) bands in the solution IR spectra allowed monitoring of the complete conversion of the RRE precursor to the corresponding dinitrosoyl iron monomers. The ν(NO) position of both the RRE (a-e) series and the DNIC series (1a-1e), showed small but systematic shifts to lower wavenumber over an overall range of ca. 12 cm$^{-1}$ when the para substituent was varied from electron-withdrawing groups (EWGs) to electron-donating groups (EDGs), in agreement with arguments of π-back bonding (Figure 3). Analysis of the ν(NO) positions and their correspondence to the para substituent on the –SC$_6$H$_4$X using the Hammett parameter$^{41}$ σ$_p$ is given in Figure 3. The unsubstituted analogues (where X = H), the RRE [µ-(µ-(S-C$_6$H$_4$)$_2$)][Fe(NO)$_2$)$_2$], and complex 1 [siMes(SPh)Fe(NO)$_2$], are also included in the above analysis.$^{40}$

Assuming idealized C$_2v$ symmetry, the ν(NO) values were used to calculate the relevant NO force constants using an analogous process to that developed by Cotton-Kraihanzel for CO stretching force constants (eqs 3 and 4),$^{34,35}$ where $k_1$ is the NO stretching force constant and $k_2$ is the interaction constant, Table 2. Figure 4 shows a plot of the calculated force constants ($k_1$) and the Hammett parameter σ$_p$. Thus, although remote from the metal, the X substituent on the ary group has a subtle but systematic effect on the electron density at the metal center, as reported by the ν(NO) values.
EPR Spectroscopy

The EPR spectra of complexes 1a-1e were recorded in THF solution at 295 K. All complexes display broad rhombicity in the EPR signal, with observed \( g \) values: \( g_1 = 2.027 \), \( g_2 = 2.024 \), \( g_3 = 2.020 \) (See SI for a representative EPR spectrum). Varying the substituent at the \textit{para} position does not appear to affect the EPR derived \( g \) value of these complexes.

Electrochemistry

The electronic effect of the X-substituent of the \(-\text{SC}_6\text{H}_2\text{X}\) series as interpreted from the ν(NO) IR values is also reflected in the electrochemistry. The unsubstituted analogue, complex 1 \( [\text{SIMes})(\text{SPh})\text{Fe(NO)}_2 \] , shows a reversible redox event at \(-1.39\) V (in THF solution), which is assigned to the \{Fe(NO)\}_2^+/0 couple, similar to the previously reported IMes analogue.\(^{27}\) Reversibility is indicated by an \( i_{pa}/i_{pc} \) ratio of 0.997 (at a scan rate of 100 mV/s), and is scan-rate-independent in the range 75 to 250 mV/s, see SI. For 1, the \( \Delta E_p \) value is \(~226\) mV. However, under these conditions, the Fe/Fc standard also shows similar separation (see SI), again indicating good reversibility.

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All other derivatives in the series show similar reversible redox events (scan-rate-independent; see SI), also assigned to the \{$\text{Fe(NO)}_2\}_2^{9/10}$ redox couple. These events range from -1.19 V to -1.44 V for the –NO$_2$, -CF$_3$, -Cl, -CH$_3$ and –OCH$_3$ derivatives respectively. The trend in the $E_{1/2}$ is as expected, shifting to higher negative potentials when moving from electron withdrawing groups to electron donating groups (Figure 5). There is good correlation between $E_{1/2}$ and the Hammett parameter $\sigma_p$ as shown in Figure 6. Also correlating with the $\nu(\text{NO})$ values and force constants, these $E_{1/2}$ values are therefore indicative of the changes in electron density occurring at the Fe(NO)$_2$ unit upon changes in the substituent at a remote position. Table 2 summarizes the characterization data used to obtain Hammett correlations of complexes 1a-1e.

### Table 2. Summary of characterization data used to obtain Hammett correlations of complexes 1a-1e.

<table>
<thead>
<tr>
<th>Complex</th>
<th>$p-X$ substituent</th>
<th>$\nu(\text{NO})$ cm$^{-1}$ (THF)</th>
<th>Force constant (mdyne/Å)</th>
<th>$E_{1/2}$ (mV)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>OCH$_3$</td>
<td>1759</td>
<td>1713</td>
<td>13.26</td>
</tr>
<tr>
<td>1b</td>
<td>CH$_3$</td>
<td>1763$^b$</td>
<td>1717</td>
<td>13.28</td>
</tr>
<tr>
<td>1c</td>
<td>Cl</td>
<td>1770$^b$</td>
<td>1718</td>
<td>13.37</td>
</tr>
<tr>
<td>1d</td>
<td>CF$_3$</td>
<td>1769</td>
<td>1718</td>
<td>13.37</td>
</tr>
<tr>
<td>1e</td>
<td>NO$_2$</td>
<td>1755</td>
<td>1712</td>
<td>13.41</td>
</tr>
</tbody>
</table>

$^a$E$_{1/2}$ values are referenced to Cp$_2$Fe/Cp$_2$Fe$^+$. $^b$Previous work \cite{2000J. Name.}}

**Kinetic Measurements**

The rates of conversion of complexes 1a-1e to 2, were examined using in situ IR spectroscopy (Scheme 2). All iron complexes were subject to pseudo-first-order reaction conditions under an excess of CO and the rate constants, $k$, of each reaction were derived from the respective linear natural log plots (eq 5). A reaction monitor and its respective natural log plot for the reaction between 1b and CO are shown in Figure 8. The kinetic profiles of 1a-1e are similar to that of the closely related unsubstituted analogue, complex 1, reported earlier.\cite{2001J. Name.} Therefore it is reasonable to assume that the reaction follows a similar second order rate expression, first order in each reagent, eq 5.

\[
\text{rate} = k_{obs} [\text{Fe}], \text{ where } k_{obs} = k [\text{CO}] 
\] (5)

Rate constants ($k$) and $t_{1/2}$ values are listed in Table 3, and indicate that the stronger the electron-withdrawing group on the phenyl thiolate, the slower the formation of the product carbonyl complex, 2. In the case of the nitro species, 1e the reaction time is longer than the solution life-time of the reagent,
as such, significant decomposition is observed with the progress of the reaction. It is likely that the decomposed species may induce further decomposition in the product, and in fact this is observed by the decrease in product intensity over time. Thus, only the first 10% of the reaction data, which is linear upon logarithmic treatment, was used to calculate the rate constant for $1e$. Though the error in rate measurement could be higher, it can be concluded to have a slower rate than seen for the other complexes. Decomposition was also observed with the trifluoromethane species, $1d$ the next strongest electron-withdrawing group in the series, but to a smaller extent. A slight deviation in the trend is seen with the methyl derivative, $1b$ where its rate is comparable with the unsubstituted species in this series, $1$ or (sIMes)(SPh)Fe(NO)$_2$.

**Table 3.** Kinetic parameters for reactions of $1a$-$1e$ with CO obtained from linear fits of natural log plots.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Substituent</th>
<th>$k_{ob}$ x 10$^{-3}$ (s$^{-1}$)</th>
<th>$k$ x 10$^{-5}$ (M$^{-1}$s$^{-1}$)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1a$</td>
<td>OCH$_3$</td>
<td>0.103 ± 0.012</td>
<td>12.9 ± 1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>$1b$</td>
<td>CH$_3$</td>
<td>0.0555 ± 0.0030</td>
<td>6.95 ± 0.38</td>
<td>3.5</td>
</tr>
<tr>
<td>$1^{40}$</td>
<td>H</td>
<td>0.0603</td>
<td>7.56</td>
<td>3.2</td>
</tr>
<tr>
<td>$1c$</td>
<td>Cl</td>
<td>0.0424</td>
<td>5.31</td>
<td>4.5</td>
</tr>
<tr>
<td>$1d$</td>
<td>CF$_3$</td>
<td>0.0172</td>
<td>2.16</td>
<td>11.2</td>
</tr>
<tr>
<td>$1e^{ii}$</td>
<td>NO$_2$</td>
<td>0.00270</td>
<td>0.338</td>
<td>71.4</td>
</tr>
</tbody>
</table>

i) Average of 3 trials. ii) Rates based on first 10% of data due to decomposition of reaction mixture over time.

**Conclusions**

For visualizing relationships between structure and reactivity, Hammett correlations are a hallmark of physical organic and physical organometallic chemistry. Such correlations in a series of para substituted [(sIMes)(S-C$_6$H$_4$X)Fe(NO)$_2$] DNICs (compounds $1a$-$1e$) with variations in the donor characteristics of the aryl thiolate were used to provide a firmer experimental foundation for the unusual theoretical proposal that an oxidized {Fe(NO)$_2$} moiety, i.e. {Fe(NO)$_2$}$^{9}$, served as a nucleophile towards CO in a process that releases RSSR.$^{40}$ Significant electronic rearrangement leads to a reduced {Fe(NO)$_2$} product in the form of [Fe(CO)(NO)$_2$(NHC)].

Although variation of the substituent at the para position of the phenyl thiolate takes place remote from the metal center of the {Fe(NO)$_2$}$^{9}$ core, plots of infrared $\nu$(NO) values, calculated NO force constants and voltammetric $E_{1/2}$ values with the Hammett parameter $\sigma_p$ show good correlations, verifying the presence of systematic changes in electron density as experienced by the {Fe(NO)$_2$}$^{9}$ core through changes in the S-donor. Having thus established the presence of electronic changes at the metal...
center between the members of the series of DNICs 1a-1e, rates of their reaction with CO(g), resulting in the formation of the reduced \{Fe(NO)\}_2^{10}\,^9 DNIC, [sMes(CO)Fe(NO)] were examined as monitored by in situ IR spectroscopy. A plot of the second-order rate constants and the Hammett parameter \(\sigma_p\) is linear and has a negative slope, indicative of rate retardation with increasing electron-withdrawing nature of the substituents. Together, these results find that subtle, systematic alterations of the electronic character of the \{Fe(NO)\}_2\,^9 DNIC, \[(sIMes)(CO)Fe(NO)\] were sensitive to the nucleophilicity at the metal center, thereby indicating the importance of the CO interaction in the transition state. This study therefore supports the previous computational studies in the delocalized frontier molecular orbitals of the Fe(NO) unit, whereby the reaction is initiated by the overlap of such filled orbitals with the vacant \(\pi^*\) orbitals of the entering CO ligand.\(^{40}\)

As “cross-talk” between small endogenous gaseotransmitters: CO, NO and H\(\text{S}\) gains rapid interest in the scientific community,\(^2\) the interplay between these molecules and bioorganometallic entities such as DNICs is intriguing. Efforts to understand these processes in the complex biological environment continues to be a challenge, highlighting the importance of the mechanistic understanding obtained in biomimetic studies.

Acknowledgements
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Electronic Supplementary Information (ESI) available: Experimental methods, additional spectroscopic, cyclic voltammetric and kinetic details, X-ray crystallographic data (CIF) from the structure determination and full list of metric parameters for complexes 1a-1e. Crystallographic data for the new structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1004078-1004081. See DOI: 10.1039/b000000x/