科技部補助專題研究計畫成果報告
期末報告

利用雙亞硝基鐵化合物與氧氣作用探討其在生化上的相關性

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中 華 民 國 105 年 08 月 31 日

中 文 摘 要 ： 一氧化氮在人體內由一氧化氮合成酶所產生，目前已經被發現在人體內扮演許多生理及病理方面的重要角色，包含了對血管舒張收縮的調節、中樞及周遭神經系統的傳導，以及對病原體的免疫。而雙亞硝基鐵化合物（DNICs）及硫醇亞硝基(RSNO)通常被視為扮演生物體內的一氧化氮載體或貯存槽的角色。生物體內的酪胺酸蛋白硝基化(protein tyrosine nitration (PTN))對於許多病理現象(包含發炎現象、神經退化、心血管疾病)來說也是一個相當重要的轉譯後蛋白質修飾(post-translational modification)。日前化學家根據所做的化學反應實驗結果大膽推測雙亞硝基鐵化合物（DNICs）也可能在生物體內扮演促進酪胺酸蛋白硝基化(protein tyrosine nitration (PTN))的反應。此外，生物化學家亦發現雙亞硝基鐵化合物可促進生物體內的半胱氨酸氧化(cysteine oxidation) 。目前已成功合成一系列單核雙亞硝基鐵化合物，將進行對酚類亞硝基化反應、半胱氨酸氧化的反應性探討 。

中 文 關 鍵 詞 ： 雙亞硝基鐵化合物; 酪胺酸蛋白硝基化; 半胱氨酸氧化

英 文 摘 要 ： The discoveries that NO plays a key role for a surprising range of physiological and pathological processes in humans have led many researchers to revisit the chemistry of NO and its derivatives such as dinitrosyl iron complexes (DNICs) in recent years. Dinitrosyl iron complexes (DNICs) and S-nitrosothiols (RSNO) have been suggested as one of the possible forms for storage and transport of NO in biological system. Recently, Prof. Kim has demonstrated that the {Fe(NO)2}10 DNICs served as a nitrating agent to convert 2,4-di-tert-butylphenol to 2,4-di-tert-butyl-6-nitro-phenol in the presence of O2, and claimed that cellular DNICs could provide the possible route to generate protein tyrosine nitration (PTN) which is an important post-translational modification associated with various pathological conditions. In addition, Prof. Kim also showed the possible biological function of cysteine oxidation. In this work,a series of iron nitrosyl complexes with analogous coordination geometry but different electronic configuration have been synthesized. In addition, the study of the O2 reactivity, the ability serving as the nitrating agent in the phenol nitrating reaction and as the oxidant in the thiolate oxidizing reaction is ongoing.

英 文 關 鍵 詞 ： dinitrosyl iron complex; protein tyrosine nitration; cysteine oxidation

Potential Biological Relevance of Dinitrosyl Iron Complexes (DNICs) with Molecular Oxygen

Introduction

As an important key molecule, nitric oxide (NO) has been paid intensive attention because of its physiological functions such as smooth muscle relaxation, neurotransmission, immune response, and blood pressure.[1-4] It has found that nitric oxide can also behave as a cytotoxic effector and/or a pathogenic mediator under NO overproduction.[5, 6] The cytotoxicity of NO is supposed to be related to the formation of some reactive nitrogen species (RNS) such as peroxynitrite or nitric dioxide. It is believed that the presence of reactive oxygen species (ROS), like superoxide radical and hydrogen peroxide, and transition metal centers are necessary for the formation of the reactive nitrogen species (RNS) from NO.[5, 6] In addition, reactive nitrogen species (RNS) and reactive oxygen species (ROS) are involved in the in vivo oxidative reaction in biological system and play an important role in aging and the development of diseases.[7] At low/moderate concentrations, ROS/RNS are important messengers for signal transduction, while at high concentrations, they can induce oxidative damage to DNA, lipids, and proteins, a phenomenon named as oxidative /nitrative stress.[6, 8]

The nitration of biological phenols mediated by RNS, such as seen in protein tyrosine nitration (PTN), is drawing considerable interest because it is an important posttranslational modification associated with various pathological conditions including inflammatory, neurodegenerative, and cardiovascular diseases.[6, 9-15] Additionally, PTN is useful as a diagnostic biomarker for cardiovascular, Alzheimer's, and Parkinson's diseases.[16-18] Recent reports suggests that distinct cellular nitrating agents could be responsible for it specificity at various sites. It is well known that there are two major ways to induce PTN. One is through $\bullet NO_2$ which is generated via

several mechanism, including oxidation of •NO with oxygen,[19] the decomposition of peroxynitrite ($ONOO^-$),[20-22] and the oxidation of nitrite (NO_2^-) by hydrogen peroxide (H_2O_2) catalyzed with peroxidases.[23] The other occurs in the presence of peroxynitrite ($ONOO^-$).[20] However, peroxynitrite doesn't react directly with tyrosine. The mechanism of tyrosine nitration was first found to mediate via peroxynitrite on a free radical based mechanism but it turned out that heme-containing proteins facilitated this reaction by the formation of ferryl intermediates. Prostacyclin synthase was proven sensitive to nitration by peroxynitrite which could be efficiently prevented by an inhibitory substrate analogue. This result indicated that tyrosine nitration was a metal-mediated process in close proximity to the active heme-iron site.[24]

Peroxynitrite ($ONOO^-$) is generally generated *in vivo* from the diffusion-controlled reaction between superoxide ($O2^-$) and nitric oxide (•NO).[21, 25, 26] Peroxynitrite is both an oxidant and nucleophile and these chemical properties dictate to the formation of secondary free radical intermediates such as nitrogen dioxide and carbonate radicals.[27] Peroxynitrite has been shown to oxidize various biomolecules including lipids, thiols, amino acid residues, DNA bases, as well as low- molecular weight antioxidants. The most prominent protein modifications mediated by peroxynitrite are the nitration and dimerization of tyrosine residues, the oxidation of cysteine thiol group, as well as the oxidation of methionine sulfur groups.[24] Figure 1 represents the evolution of our understanding of the biochemically relevant reactions in which peroxynitrite participates, including, (a) two-electron oxidation of thiols, (b) homolysis, (c) nucleophilic addition to CO_2 and evolution to radicals, and (d) reaction with transition metal centers.[27]

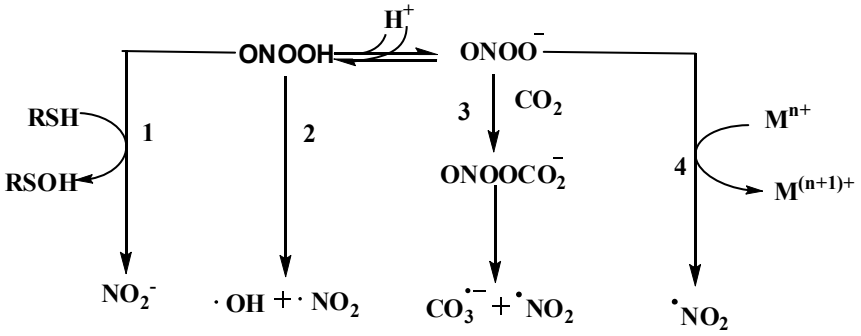
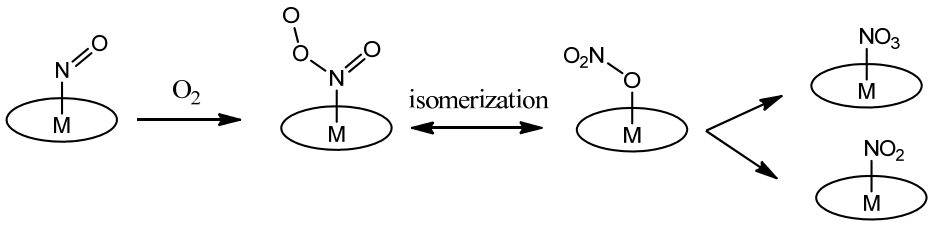


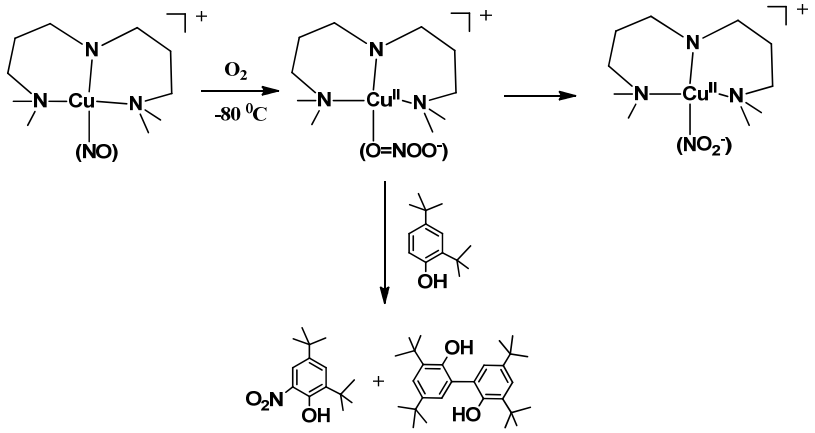
Figure 1.

In chemistry, the reactivity of dioxygen toward metal nitrosyl complexes has been thoroughly investigated, in particular because of the possible use of these complexes to activate dioxygen.[28] One of the conceivable pathways for this reaction may involve the formation of an N-bound peroxynitrite complex (Scheme 1). Examples of discrete metal−peroxynitrite complex are rare; only a cobalt−peroxynitrite (tris(tetraethylammonium) pentacyanoperoxynitritocobaltate(III)) is known to date to be characterized structurally in 2000 by Prof. Koppenol.[29] In addition to the stable cobalt−peroxynitrite complex, iron (e.g., heme), manganese, and copper complexes have been studied with respect to bio(chemical) $O=NOO^-$ mediated chemistry. For examples, in 2009, Prof. Karlin synthesized $[Cu^{I}(AN)(NO)]^+$ (AN = 3,3'-iminobis(N,N'-dimethylpropylamine)) and then reacted with dioxygen at -80℃ affording $[Cu^{II}(AN)(O=NOO^-)]^+$. After the thermal transformation, $[Cu(AN)(NO_2)]^+$ was afforded.[30] In the meantime, addition of 2, 4-di-tert-butylphenol in to $[Cu^{II}(AN)(O=NOO^-)]^+$ led to 2,4-di-tert-butyl-6-nitro-phenol (Scheme2) via phenol nitration. In addition, Prof. Mondal demonstrated the putative formation of a copper(I)–peroxynitrite intermediate via reaction of the mononuclear copper(II)−nitrosyl complexes with H_2O_2 in 2012 and 2013, respectively.[31, 32] Formation of the peroxynitrite intermediate has been confirmed by its characteristic phenol ring nitration reaction as well as isolation of corresponding Cu(I)–nitrate.

Scheme 1.



Scheme 2.

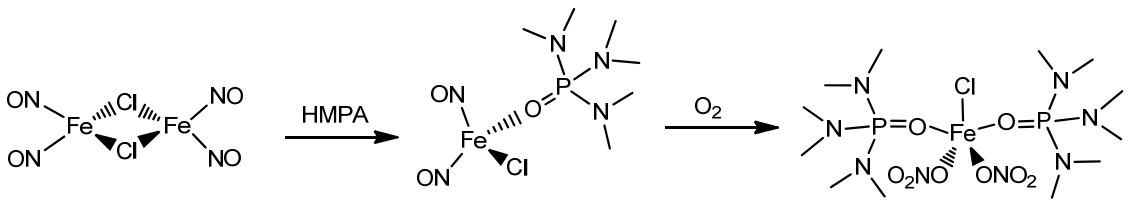


Dinitrosyl iron complexes (DNICs), the endogenous NO-derived species as S-nitrosothiols (RSNO), are thought to serve in a storage capacity and as carriers of NO in biological system.[33-39] DNICs are NO derivatives of biological relevance, found in various tissues and cells during NO overproduction by the inducible nitric oxide synthase. [33-39] *In vivo*, the naturally occurring DNICs are classified into protein-bound DNICs and low-molecular-weight DNICs (LMW-DNICs).[40-43] Protein-bound DNICs derived from NO-mediated degradation of Fe-S cluster containing proteins are considered as the storage of NO or $\{Fe(NO)_2\}$ moiety, and LMW-DNICs yielded via the displacement of protein-bound DNICs with free thiols/thiolates are served probably as the donor of NO or $\{Fe(NO)_2\}$ moiety. Biologically, both sulfur-ligated protein-bound DNICs and LMW-DNICs are possibly identified and characterized by their distinctive electron paramagnetic resonance (EPR) signals at $g = 2.03$.[37, 44-46] In spite of the major thiol components of cellular

DNICs composed of cysteinate residues in proteins and mobile units such as glutathione, the DNICs ligated by cysteinate, histidine, deportonated imidazole, and tyrosinate were found and proposed in enzymology based on EPR spectra.

Although the synthesized DNICs have been widely studied to offer important chemical and biological insights, the study on the O_2 reactivity of DNICs is limited to few examples. In 1989, Prof. Postel reported the first example of DNICs toward O_2. As shown in Scheme 3, oxidation by oxygen of the unstable DNIC $[Fe(NO)_2Cl(HMPA)]$, afforded from reaction of $[Fe_2Cl_2(NO)_4]$ with HMPA, resulted in the formation of the nitrato-complex $[Fe(NO_3)Cl_2(HMPA)]$.[47]

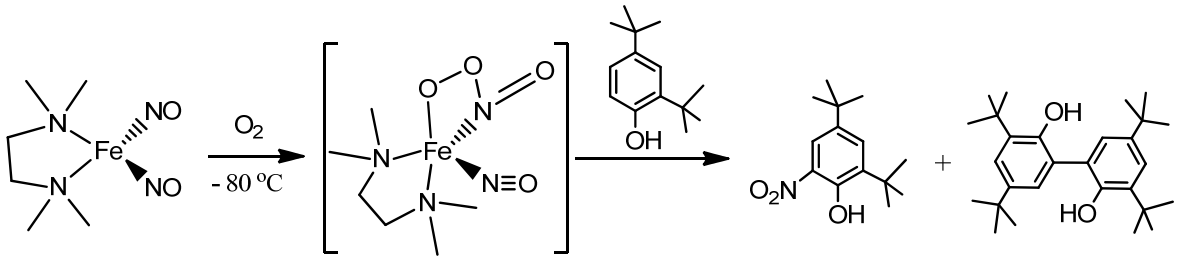
Scheme 3.



In 2011, Prof. Kim studied the dioxygen reactivity of an N-bound $\{Fe(NO)_2\}^{10}$ DNIC, $[Fe(TMEDA)(NO)_2]$ (TMEDA = N,N,N',N'-tetramethylethylenediamine).[48] As presented in Scheme 4, the report demonstrated the formation of a stable five-coordinate iron-peroxynitrite [Fe(TMEDA)(NO)(ONOO)], characterized by FTIR and Fe K-edge X-ray absorption spectroscopy when $[Fe(TMEDA)(NO)_2]$ reacted with dioxygen at -80 ℃. In addition, when dioxygen is added to a mixture of $[Fe(TMEDA)(NO)_2]$ and DBP (2,4-di-tert-butylphenol) at -80 ℃ and then is subsequently warmed to room temperature, NO_2-DBP (2,4-di-tert-butyl-6-nitro-phenol) is observed along with 3,3',5,5'-tetra-tert-butyl-1,1'-biphenyl. This result reasonably suggested that DNICs act as mobile nitrating reagent in cells, in addition to the role of NO storage and

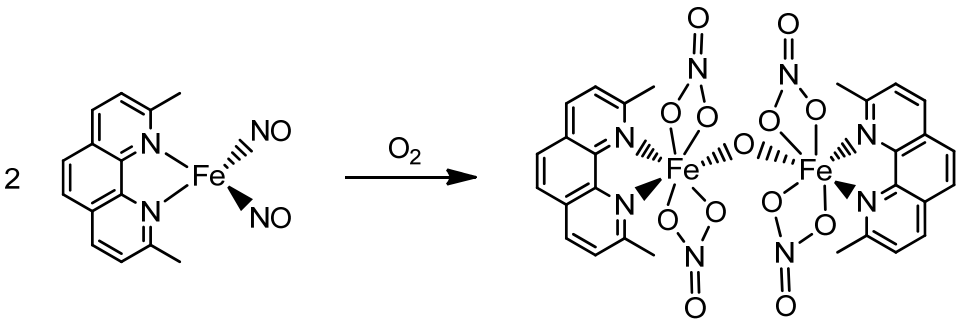
transfer.

Scheme 4.



In 2012, Prof. Kim demonstrated the reaction of another $\{Fe(NO)_2\}^{10}$ DNIC $[Fe(dmp)(NO)_2]$ with dioxygen. As shown in Scheme 5, the reaction resulted in the formation of the room-temperature-stable nitrato-containing complex $[Fe_2O(NO_3)_4(dmp)_2]$. It is noted that $[Fe_2O(NO_3)_4(dmp)_2]$ is incapable of nitrating DBP to NO_2-DBP, but $[Fe(dmp)(NO)_2]$ in the presence of dioxygen does effectively nitrate DBP to NO_2-DBP. This result reveals that the iron-peroxynitrite species plays a critical role in phenol nitration and it forms prior to the formation of $[Fe_2O(NO_3)_4(dmp)_2]$.[49]

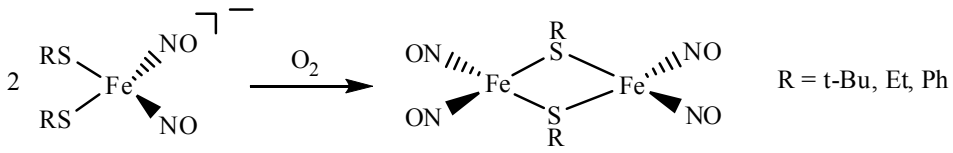
Scheme 5.



In 2013, Prof. Kim proceeded the dioxygen reactivity of thiolate-contaning $\{Fe(NO)_2\}^9$ DNICs. As shown in scheme 6, reaction of dioxygen with $[Fe(NO)_2(SR)_2]^-$ (R = t-Bu, Et, Ph) afforded $[Fe(NO)_2(SR)]_2$. Based on the study of dioxygen reactivity of N-bound $\{Fe(NO)_2\}^{10}$ and S-bound $\{Fe(NO)_2\}^9$ DNICs, the research group concluded that N-bound DNICs oxidation by dioxygen occurs at the

NO group of {Fe(NO)$_2$} unit and S-bound DNICs oxidation by dioxygen occurs at the S-bound ligands.[50]

Scheme 6.



Results and discussion

Synthesis of the [N,N]-bound {Fe(NO)$_2$}^{10} DNIC with pendant amine and the five-coordinate [N,N,N]-bound {Fe(NO)$_2$}^{9} DNIC.

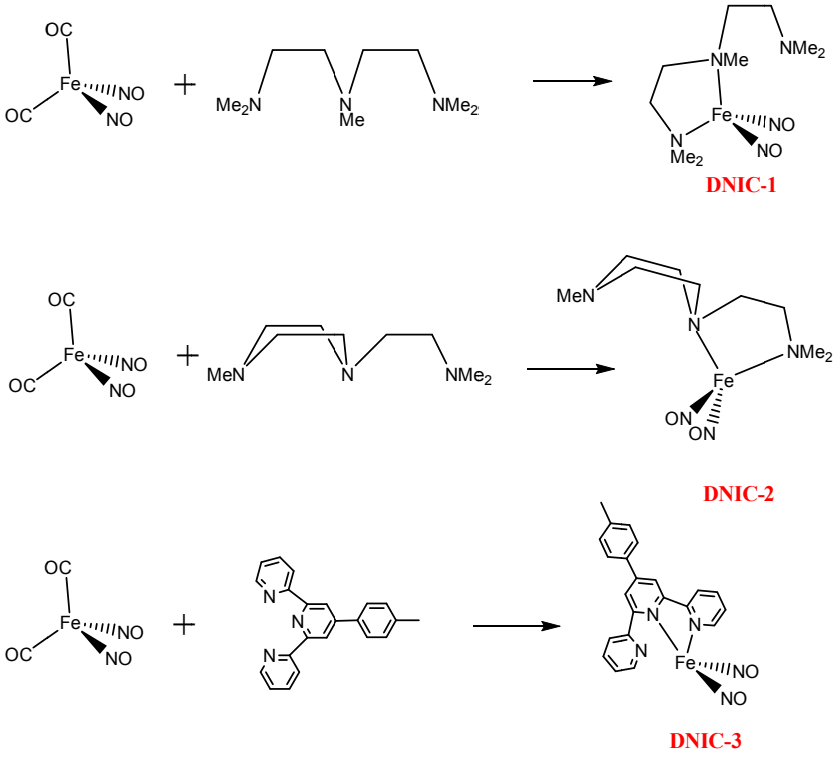
It has been known that the reported {Fe(NO)$_2$}^{10} DNICs were synthesized via replacing the carbonyls of Fe(CO)$_2$(NO)$_2$ by nitrogen-containing ligands. As shown in scheme 7, a series of the [N,N]-bound {Fe(NO)$_2$}^{10} DNIC with the amine in the secondary coordination sphere were synthesized by reaction of Fe(CO)$_2$(NO)$_2$ with N,N,N containing ligands. DNICs **1-3** are designed to mimic the rich N-containing ligand environment and study the possible reactivity of [N,N]-bound {Fe(NO)$_2$}^{10} DNICs with dioxygen in biological environment.

DNICs **2** and **3** have been structurally characterized by single-crystal X-ray diffraction and the structures are depicted in Figures 1 and 2.

In addition to the classical four-coordinate DNICs, there are several five-coordinate {Fe(NO)$_2$}^{9} DNICs are reported. Although the physical characterization of these five-coordinate DNICs is finished, the reactivity of the five-coordinate DNICs with dioxygen is not present. As presented in scheme 8, the five-coordinate DNICs have be synthesized via oxidation of [N,N]-bound {Fe(NO)$_2$}^{10} DNICs with Cp_2FePF_6 or Cp_2FeBF_4 .

Also, DNICs **4-6** have been structurally characterized by single-crystal X-ray diffraction and the structures are depicted in Figures 3 - 5.

Scheme 7.



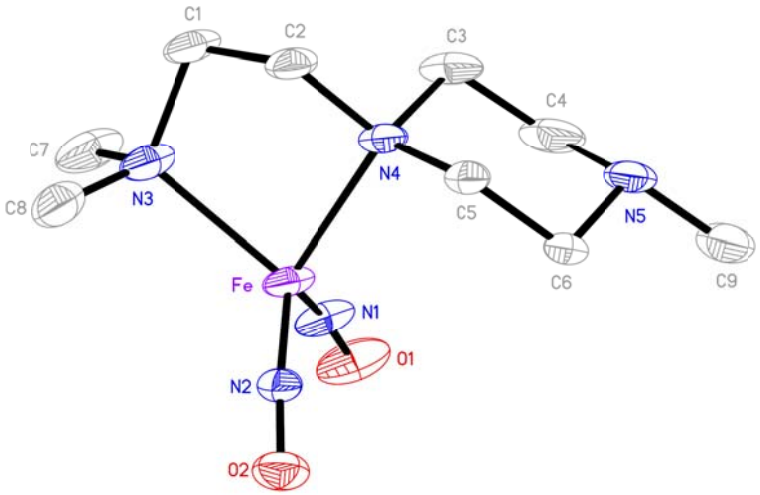


Figure 1. ORTEP drawing and labeling scheme of DNIC **2** with thermal ellipsoids drawn at 50 % probability level.

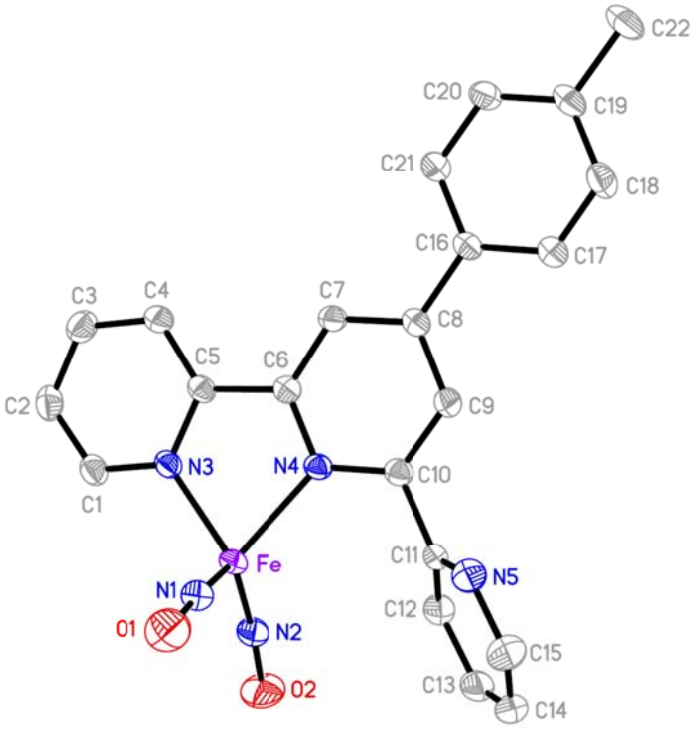
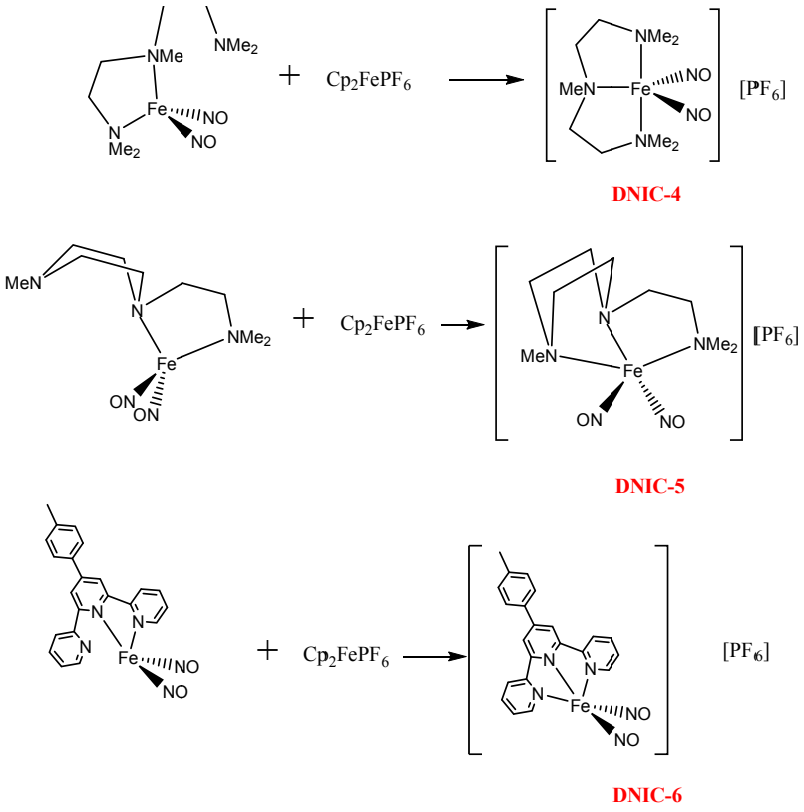


Figure 2. ORTEP drawing and labeling scheme of DNIC **3** with thermal ellipsoids drawn at 50 % probability level.

Scheme 8.



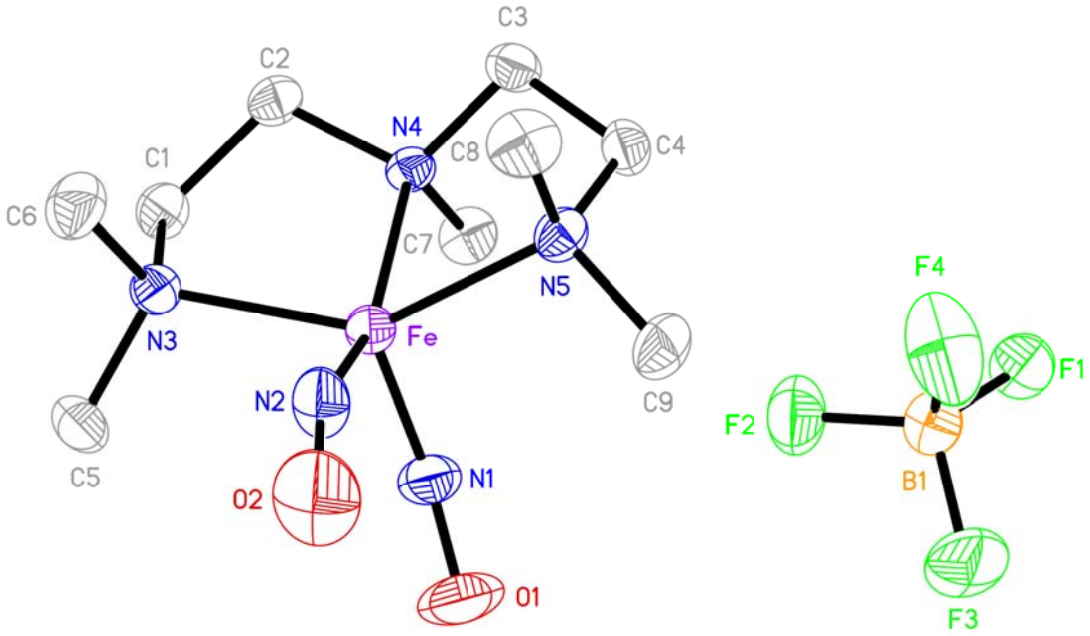


Figure 3. ORTEP drawing and labeling scheme of DNIC **4** with thermal ellipsoids drawn at 50 % probability level.

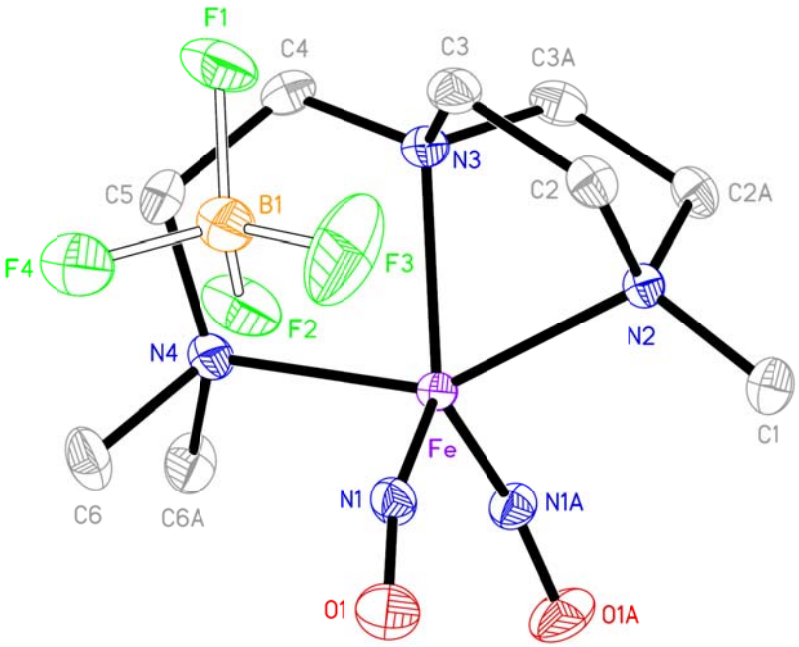


Figure 4. ORTEP drawing and labeling scheme of DNIC **5** with thermal ellipsoids drawn at 50 % probability level.

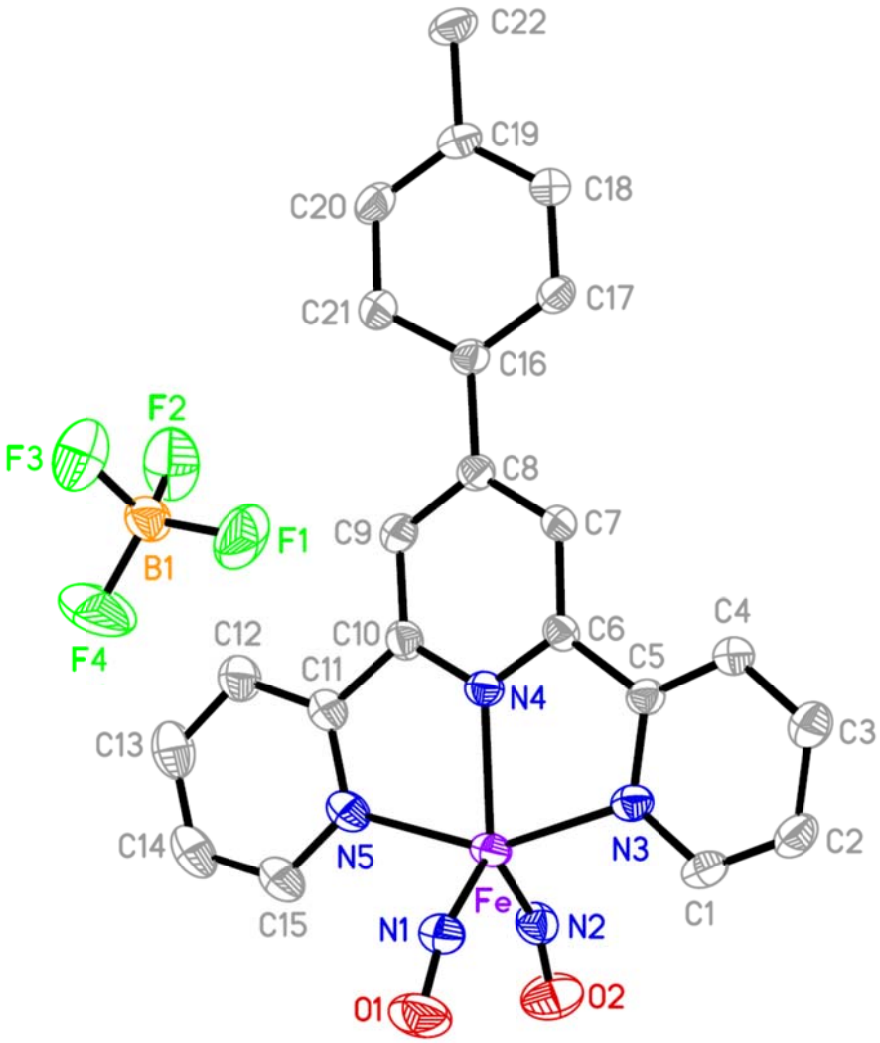


Figure 5. ORTEP drawing and labeling scheme of DNIC **6** with thermal ellipsoids drawn at 50 % probability level.

Conclusions

A series of mononuclear four coordinate $\{Fe(NO)_2\}^{10}$ and five coordinate $\{Fe(NO)_2\}^{10}$ have been synthesized successfully and characterized by IR, UV/vis, ^1H NMR, EPR and SQUID. Studies on the electronic structure (NO/Fe oxidation states) of the series of $\{Fe(NO)_2\}^9/\{Fe(NO)_2\}^{10}$ DNICs by X-ray absorption spectroscopy and DFT calculations are ongoing. Also, the reactivity of dioxygen toward $\{Fe(NO)_2\}^9/\{Fe(NO)_2\}^{10}$ motifs are currently being investigated in our laboratory.

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科技部補助計畫衍生研發成果推廣資料表

日期:2016/06/28

科技部補助計畫	計畫名稱: 利用雙亞硝基鐵化合物與氧氣作用探討其在生化上的相關性
	計畫主持人: 陳建宏
	計畫編號: 103-2113-M-040-001- 學門領域: 無機化學

無研發成果推廣資料

103年度專題研究計畫成果彙整表

計畫主持人：陳建宏	**計畫編號：**103-2113-M-040-001-
計畫名稱：利用雙亞硝基鐵化合物與氧氣作用探討其在生化上的相關性	

成果項目					量化	單位	質化 （說明：各成果項目請附佐證資料或細項說明，如期刊名稱、年份、卷期、起訖頁數、證號...等）
國內	學術性論文	期刊論文			0	篇	
		研討會論文			0		
		專書			0	本	
		專書論文			0	章	
		技術報告			0	篇	
		其他			0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	0	件	
				已獲得	0		
			新型/設計專利		0		
		商標權			0		
		營業秘密			0		
		積體電路電路布局權			0		
		著作權			0		
		品種權			0		
		其他			0		
	技術移轉	件數			0	件	
		收入			0	千元	
國外	學術性論文	期刊論文			0	篇	
		研討會論文			0		
		專書			0	本	
		專書論文			0	章	
		技術報告			0	篇	
		其他			0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	0	件	
				已獲得	0		
			新型/設計專利		0		
		商標權			0		
		營業秘密			0		
		積體電路電路布局權			0		
		著作權			0		
		品種權			0		
		其他			0		

	技術移轉	件數	0	件	
		收入	0	千元	
參與計畫人力	本國籍	大專生	1	人次	
		碩士生	2		
		博士生	0		
		博士後研究員	0		
		專任助理	0		
	非本國籍	大專生	0		
		碩士生	0		
		博士生	0		
		博士後研究員	0		
		專任助理	0		
其他成果 （無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。）					

科技部補助專題研究計畫成果自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現（簡要敘述成果是否具有政策應用參考價值及具影響公共利益之重大發現）或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估
   ■達成目標
   □未達成目標（請說明，以100字為限）
   　□實驗失敗
   　□因故實驗中斷
   　□其他原因
   說明：

2. 研究成果在學術期刊發表或申請專利等情形（請於其他欄註明專利及技轉之證號、合約、申請及洽談等詳細資訊）
   論文：□已發表　□未發表之文稿　■撰寫中　□無
   專利：□已獲得　□申請中　■無
   技轉：□已技轉　□洽談中　■無
   其他：（以200字為限）

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性，以500字為限）
   可利用各種物理方法去分析不同電子結構的單核雙亞硝基鐵化合物上各原子的電子密度分布，分析的結果可以用以解釋不同DNICs與氧氣反應的反應機構及進行酚類亞硝基化反應、半胱氨酸氧化的差異性。

4. 主要發現
   本研究具有政策應用參考價值：■否　□是，建議提供機關
   （勾選「是」者，請列舉建議可提供施政參考之業務主管機關）
   本研究具影響公共利益之重大發現：■否　□是
   說明：（以150字為限）
   可歸納出不同DNICs與氧氣反應的反應機構及進行酚類亞硝基化反應、半胱氨酸氧化的差異性。