

Imidazole-Containing (N₃S)-Ni^{II} Complexes Relating to Nickel Containing Biomolecules

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Dimeric (N₂S)Ni complexes and the monomeric N₂S₂ bismercaptodiazacycloheptane nickel complex, (bme-dach)Ni, serve as precursors to two N₂-, N'-/S- complexes where N₂=diazacycloheptane, N'=imidazole and S=thiolate. As rare examples of nickel complexes containing a mixed thiolate/imidazole ligand set, these complexes are characterized by X-ray diffraction, UV/vis, and variable temperature ¹H NMR spectroscopies, and electrochemistry. Density functional theory computations relate the orientation of the imidazole with respect to the N₂N'SNi square plane to the VT NMR observed fluxionality and activation parameters. The superoxide dismutase activity of the imidazole complexes was investigated by the nitroblue tetrazolium assay.

Introduction

The reactivity of tetradentate N₂S₂ ligands containing nucleophilic S-sites in transition metal thiolate complexes has been extensively explored. In our laboratory, metalation, S-oxygenations, and alkylations have been used to establish reactivity of the neutral (bme-daco)Ni(II) complex, bme-daco = bismercaptoethanediazacyclooctane, the neutral (bme-dach)Ni(II) complex, bme-dach = bismercaptoethanediazacycloheptane, as well as the anionic [Ni(II)(ema)]²⁻ complex, ema = N,N'-ethylenebis-2-mercaptoacetamide.^{1–3} Coupled with S-thiolates, such amine, amide, or mixed amine/amide N-donor ligand environments have been

proposed by us and others to serve as biomimetics of metalloenzyme active sites.⁴

The preparation of histidine/cysteine mixed donor binding sites was first demonstrated in small peptidic complexes by Suguri et al., as models of blue copper proteins.⁵ Nickel complexes of -X_{aa}-X_{aa}-His- tripeptide motifs have been studied in detail for their ability to influence DNA damage and cross-linking through oxidative processes.⁶ To explore the potential oxidative chemistry of cysteine thiolates, Burrows and co-workers synthesized the cysteine variants, -X_{aa}-Cys-His- and -Cys-X_{aa}-His-, as possible metal binding sequences.^{7,8} It was found that aerobic oxidation of such complexes with cysteine in the second position, -X_{aa}-Cys-His-, led to the rapid formation of disulfide dimers. In this case, other oxidized products such as metallosulfoxides or metallosulfones were not reported. The dimeric disulfide-bridged complex was found to have no further reactivity with oxygen even though Ni^{II} peptides with carboxylate termini are known to spontaneously decarboxylate in air.⁷ In contrast, the Ni^{II} derivative of N-terminal -Cys-X_{aa}-His- resulted in the formation of a cysteine sulfinic acid under aerobic conditions.⁸ Whether the plethora of possibilities of oxidative products complicate or play fundamental roles in the chemistry underlying biological action is not well understood.

Recently, the molecular structures of NikR and NiSOD revealed nickel(II) sites which contain both N-histidine and

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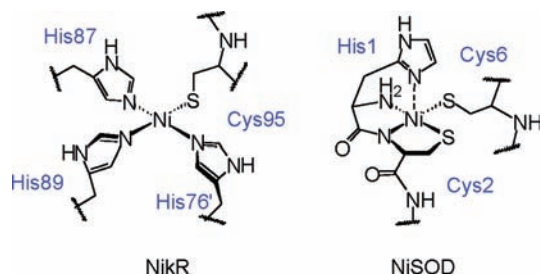


Figure 1. Metal binding site of NikR and the active site of NiSOD.^{9–11}

S-cysteine ligands, Figure 1.^{9–11} The transcription factor NikR serves as a cytoplasmic nickel sensor in *Escherichia coli* and the human gastric pathogen *Helicobacter pylori*. It is responsible for stopping the production of the nickel importer, nikABCDE, when intracellular levels of nickel are sufficient.¹² NikR is a homotetramer protein which incorporates one Ni^{II} ion per subunit in square-planar coordination consisting of the side chains of two histidine and one cysteine residue from one NikR monomer, and a side chain histidine from an adjacent monomer.¹³ Biomimetic studies of this nickel(II) binding site have not been reported.

The Ni^{II/III} redox couple is used in NiSOD catalysis for the disproportionation reaction of superoxide to O₂ and H₂O₂.¹⁴ The reduced form of the active site of NiSOD features a square planar geometry about Ni^{II} consisting of the N-terminus amine nitrogen, a carboxyamido N atom, two cysteine thiolates, and possibly a fifth donor ligand from an axial histidine N atom. The molecular structure of the oxidized form reveals axial imidazole coordination to the Ni metal center, Figure 1.^{9,10}

In recent years, considerable work has been targeted toward understanding how the NiSOD enzyme avoids S-oxygenation and/or S-oxidation in the presence of the products of SOD, O₂, and H₂O₂. Computational investigations have concluded that the presence of one or two amide donors within the N₂S₂ core promotes metal-based chemistry.¹⁵ There has been significant progress in the preparation of synthetic mimics of the NiSOD active site. In particular, a mixed amine/amide donor set in the N₂S₂ core has resulted in a Ni^{II} complex with a ligand environment similar to the reduced state of the native enzyme, and this NiSOD mimic demonstrated enhanced stability toward oxygenation.¹⁶ As cis dithiolate sulfurs in Ni^{II} complexes have been shown to

form stable S-oxygenates in both neutral and dianionic N₂S₂Ni complexes, we have suggested that kinetic control accounts for the lack of S-oxygenates in the enzyme active site of NiSOD.³

Jensen and co-workers have utilized “scorpionate” ligands to mimic the nitrogen donors and dithiocarbamates and organoxanthate to mimic the dithiolate ligands of the NiSOD binding motif to obtain a five-coordinate N₃S₂Ni(II) complex.¹⁷ Although synthetic N₂S₂Ni complexes as NiSOD active site mimics have similar spectroscopic features as the native enzyme and quasi-reversible redox couples in the range of SOD dismutation, Shearer and Zhao’s model complexes did not produce catalytic activity for superoxide dismutation.^{16b} Neither did Jensen et al. report SOD activity.¹⁷ Nevertheless, nickel peptide-based models mimicking the amino acid nickel-hook sequence found in the native NiSOD enzyme have been more successful, demonstrating compatible electrochemistry as well as SOD activity.¹⁸ Studies by Shearer and co-workers also suggest that the His imidazole remains ligated throughout SOD catalysis, and this is supported by computational studies of Siegbahn et al.^{19,20}

Very little is known about how the electronic structure of Ni^{II} complexes containing both imidazole and thiolate ligation responds to oxidation and how this might affect SOD catalysis and response to the H₂O₂/O₂ products. To address this, two synthetic models containing a continuous and discontinuous N₂N’S donor set have been prepared. For this study, a dimeric dithiolate bridged Ni^{II} dication and the readily accessed (bme-dach)Ni(II) were used as the precursors to mixed imidazole/thiolate complexes. The work herein reports the synthesis, characterization, and molecular structures of both continuous tetradentate (N₂N’S) and discontinuous (N₂S–N’) synthetic models incorporating simple imidazoles as His mimics. Variable temperature ¹H NMR studies in correlation with density functional theory (DFT) calculations have been carried out to further investigate the orientation of the imidazole ligand. The physical properties of the derivatives and precursors and preliminary studies of SOD activity are described.

Experimental Section

General Procedures. Air sensitive materials were handled using standard Schlenk techniques or in an Ar-filled glovebox. Solvents were purified and degassed via a Bruker solvent system. All reagents were purchased from Aldrich Chem. Co. and used as received unless noted. Isobutylene sulfide,²¹ (bme-dach)Ni,^{2a} and 4-(chloromethyl)-5-methyl-1H-imidazole hydrochloride²² were prepared according to published procedures.

Physical Measurements. UV–vis spectra were recorded on a Hewlett-Packard 8453 diode array spectrometer and a Cary1E spectrophotometer using quartz cells (1.00 cm path length). Mass spectrometry (ESI-MS) was performed by the Laboratory

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for Biological Mass Spectrometry at Texas A&M University. ^1H NMR spectra were obtained on a Mercury-300 FT-NMR spectrometer and variable temperature ^1H NMR spectra were recorded on an Inova500 spectrometer operating at 500 MHz. CD_3OD was used as solvent, and all resonances were referenced to MeOH (CH_3 : 3.31 ppm) at all temperatures. Conductance measurements of millimolar concentrations of analyte were made using an Orion 160 conductivity meter. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia or by Canadian Microanalytical Services, Ltd., Delta, British Columbia, Canada.

Electrochemistry. Cyclic, square wave and differential pulse voltammograms were recorded on a BAS100W potentiostat under an Ar atmosphere using a three electrode cell, which consisted of a glassy carbon disk (0.071 cm^2) working electrode, a coiled platinum wire counter electrode, and $\text{Ag}^0/\text{AgNO}_3$ reference electrode. Samples were measured in DMF with Bu_4NBF_4 (0.1 M) as the supporting electrolyte and at potential scan rates of 200 mV/s. Ferrocene was added as an internal standard, and all potentials are reported relative to $\text{Ag}^0/\text{AgNO}_3$ electrode using $\text{Cp}_2\text{Fe}/\text{Cp}_2\text{Fe}^+$ as reference ($E_{1/2} = 0.00\text{ V}$ vs $\text{Ag}^0/\text{AgNO}_3$ in DMF). The reversibility of the observed redox couples is based on the internal reference ($\text{Cp}_2\text{Fe}/\text{Cp}_2\text{Fe}^+$). The peak-to-peak separations ($E_{\text{pa}} - E_{\text{pc}}$) for the complexes studied herein are larger than the 59 mV expected for a reversible one-electron process, but comparable with $E_{\text{pa}} - E_{\text{pc}}$ for the $\text{Cp}_2\text{Fe}/\text{Cp}_2\text{Fe}^+$ couple under the same conditions. The ratios of the anodic and cathodic peak currents were close to unity for the assigned reversible systems. Bulk electrolysis was carried out using a BAS 100A potentiostat and BAS bulk electrolysis cell containing 30 mL of DMF which was 1.0 mM in **3** and 0.1 M in Bu_4NBF_4 under an argon atmosphere. The working electrode of the BAS bulk electrolysis cell was comprised of reticulated vitreous carbon.

X-ray Crystal Structure Analyses. X-ray data were obtained on a Bruker SMART 1000 CCD based diffractometer (Texas A&M University) operating at 110 K.²³ The X-ray radiation was generated from a Mo sealed X-ray tube ($K\alpha = 0.70173\text{ \AA}$). Structures were solved using SHELXTL,²⁴ absorption correction, SADABS; structure solution, SHELXS-97 (Sheldrick);²⁵ structure refinement, SHELXL-97 (Sheldrick);²⁶ and molecular graphics and preparation of material for publication, SHELXTLPLUS, version 5.1 or later (Bruker). Experimental conditions and crystallographic data are listed in the Supporting Information.

Computational Details. Initial geometries were derived from X-ray structures or deductions based on conformations resulting from fluxional processes in the molecules. In both cases, the conformational space near each of the starting geometries was sampled through simulated annealing calculations in the gas phase using the Cerius² software package.²⁷ The simulated annealing calculations were carried out using the Open Force Field (OFF) module with the Universal Force Field (UFF) for 15 annealing cycles, over a temperature range of 300–5000 K, with $\Delta T = 50\text{ K}$. The compounds were minimized after each annealing cycle resulting in 15 conformations. The initial geometry and low energy conformations were then optimized using DFT, with the Becke three-parameter exchange functional (B3)²⁸ and the Lee–Yang–Parr correlation functional (LYP) (B3LYP).²⁹

All theoretical calculations, including optimization, frequency, and NMR, were performed with the Gaussian 03 suite programs.³⁰ The Stuttgart–Dresden³¹ (SDD) effective core potential and valence basis set were used for nickel. For sulfur, the effective core potential and basis set of Hay and Wadt³² were used with inclusion of a modified polarization function developed by Höllwarth et al.³³ For nitrogen, the correlation-consistent polarized valence double- ζ basis set of Dunning and co-workers³⁴ (cc-pVDZ) was used. All carbon and hydrogen atoms were represented using the split valence double- ζ basis set of Pople and co-workers with polarization functions on heavy and light atoms³⁵ (6-31 g(d',p')).

Synthesis of 1-(2-Mercaptoethyl)-methyl-1,4-diazacycloheptane, me-mdach. Similar to the preparation of the N_2S_2 ligand Hmmp-dach,³⁶ under N_2 , *N*-methylhomopiperazine (5 mL, 0.0402 mmol) was dissolved in 50 mL of dry MeCN. With stirring, the solution was heated to 50 °C under N_2 , and an excess of ethylene sulfide (8 mL, 0.134 mmol) was added slowly forming a white solid and a light yellow solution. Heating was continued for 20 h after which the solution was anaerobically filtered through Celite, giving a light yellow solution. The solvent was removed in vacuo resulting in a yellow oil, 3.33 g, 48% yield. $\text{C}_8\text{H}_{18}\text{N}_2\text{S}$ (MW = 174 g/mol) ⁺ESI-MS: $m/z = 175$ $[\text{M}+\text{H}]^+$. ^1H NMR (CDCl_3): δ (ppm) = 1.83 (q, 2.0 H), 2.38 (s, 2.9 H), 2.64 (m, 4.2 H), 2.77 (m, 5.2 H), 2.86 (m, 2.6 H).

1-(2-Mercapto-2-methylpropyl)-methyl-1,4-diazacycloheptane, mmp-mdach. 1-(2-Mercapto-2-methylpropyl)-methyl-1,4-diazacycloheptane, mmp-mdach, was prepared in a similar manner to the above using isobutylene sulfide. A light yellow oil was isolated in 31% yield. $\text{C}_{10}\text{H}_{22}\text{N}_2\text{S}$ (MW = 202 g/mol) ⁺ESI-MS: $m/z = 203$ $[\text{M}+\text{H}]^+$.

Synthesis of [[1-(2-Mercaptoethyl)-methyl-1,4-diazacycloheptane]nickel(II)] Tetrafluoroborate, [(me-mdach)Ni]₂(BF₄)₂, Complex 1. Under N_2 , me-mdach (0.56 g, 3.22 mmol) was dissolved in 20 mL of dry MeOH. A solution of NaOMe (0.17 g, 3.17 mmol) in 10 mL of dry MeOH was added via cannula, and the mixture was stirred at room temperature (RT) for 1 h. A solution of $\text{Ni}(\text{BF}_4)_2 \cdot 6\text{ H}_2\text{O}$ (0.75 g, 3.23 mmol) in 25 mL of MeOH was added dropwise via cannula producing a red solution. After stirring at RT for 4 h the solvent volume was reduced to about 5 mL. Addition of 25 mL of MeCN resulted in the precipitation of NaBF_4 salts which were separated from the product by filtration in air. The solvent of the filtrate was removed in vacuo resulting in a tacky maroon residue. The residue was dissolved in a minimum of MeOH, and a maroon solid was obtained on addition of diethyl ether. Alumina column chromatography was used to purify the crude product using MeCN as the eluent until a light yellow band was removed, followed by an elution mixture of MeOH/MeCN (1:25), which yielded a maroon band of pure $[(\text{me-mdach})\text{Ni}]_2(\text{BF}_4)_2$ (0.38 g, 37%). X-ray quality crystals were obtained by Et_2O diffusion into a MeCN solution at 5 °C. Elemental anal. Calcd (found) for

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$\text{Ni}_2\text{C}_{16}\text{H}_{34}\text{N}_4\text{S}_2\text{B}_2\text{F}_8$ (MW = 638 g/mol): C, 30.14 (30.40); N, 8.78 (8.65); H, 5.37 (5.25). Absorption spectrum (MeOH): λ_{max} (ϵ , $\text{M}^{-1}\text{cm}^{-1}$) 524 (817), 452 (775), 354 (2503), 305 (13075), 252 (13675), 229 (21330) nm. $^+\text{ESI-MS}$ (MeCN): $m/z = 549$ [(me-mdach) $_2\text{Ni}_2$] BF_4^+ ; 231 [(me-mdach) $_2\text{Ni}_2$] $^{2+}$. Molar conductance at 23 °C: 299 $\text{S cm}^2\text{ mol}^{-1}$ (MeCN); 310 $\text{S cm}^2\text{ mol}^{-1}$ (H_2O).

Chloro-[1-(2-Mercaptoethyl)-methyl-1,4-diazacycloheptane]nickel(II), [(me-mdach)-NiCl] $_2$, Complex 2. Chloro-[1-(2-Mercaptoethyl)-methyl-1,4-diazacycloheptane]nickel(II), [(me-mdach)-NiCl] $_2$, complex 2, was prepared and purified in a similar manner using $\text{NiCl}_2\cdot 6\text{H}_2\text{O}$ as the metal source. The complex was purified by alumina column chromatography yielding pure [(me-mdach)NiCl] $_2$ as a reddish brown solid (31% yield). X-ray quality crystals were obtained by Et_2O diffusion into a MeCN solution at 5 °C. Elemental anal. Calcd (found) for $\text{Ni}_2\text{C}_{16}\text{H}_{34}\text{N}_4\text{S}_2\text{Cl}_2$ (MW = 535 g/mol): C, 36.0 (37.0); N, 10.5 (10.2); H, 6.41 (6.76). Absorption spectrum (MeOH): λ_{max} (ϵ , $\text{M}^{-1}\text{cm}^{-1}$) 527 (967), 490 (sh), 350 (3307), 307 (7816), 247 (17126), 211 (18002) nm. $^+\text{ESI-MS}$: $m/z = 497$ [(me-mdach) $_2\text{Ni}_2\text{Cl}$] $^+$; 231 [(me-mdach) $_2\text{Ni}_2$] $^{2+}$. Molar conductance at 23 °C: 124 $\text{S cm}^2\text{ mol}^{-1}$ (MeCN); 303 $\text{S cm}^2\text{ mol}^{-1}$ (H_2O).

Chloro-[1-(2-Mercapto-2-methylpropyl)-methyl-1,4-diazacycloheptane]nickel(II), [(mmp-mdach)NiCl] $_2$, Complex 2-Me $_2$. Chloro-[1-(2-Mercapto-2-methylpropyl)-methyl-1,4-diazacycloheptane]nickel(II), [(mmp-mdach)NiCl] $_2$, complex 2-Me $_2$, was obtained via the above method by using the mmp-mdach ligand. Absorption spectrum (MeOH): λ_{max} (ϵ , $\text{M}^{-1}\text{cm}^{-1}$) 532 (904), 426 (988), 326 (6120), 283 (11940), 244 (21300), 205 (24580) nm. $^+\text{ESI-MS}$ mass spectral analysis for $\text{Ni}_2\text{C}_{20}\text{H}_{42}\text{N}_4\text{S}_2\text{Cl}_2$ (MW = 591 g/mol): $m/z = 553$ [(mmp-mdach) $_2\text{Ni}_2\text{Cl}$] $^+$; 259 [(mmp-mdach)Ni] $^{2+}$. Molar conductance at 23 °C: 104 $\text{S cm}^2\text{ mol}^{-1}$ (MeCN); 299 $\text{S cm}^2\text{ mol}^{-1}$ (H_2O).

Synthesis of [1-(2-Mercapto-2-methylpropyl)-methyl-1,4-diazacycloheptane]nickel(II) Imidazole Chloride [(mmp-mdach)-Ni(Im)]Cl, Complex 3. After degassing and under N_2 , complex 2, [(mmp-mdach)NiCl] $_2$, (0.102 g, 0.173 mmol) and imidazole (0.035 g, 0.514 mmol) were dissolved in 30 mL of dry MeOH, which immediately produced an orange solution. After stirring overnight, the solution volume was reduced to a minimum under vacuum, and Et_2O was added to precipitate the product. The ether was decanted, and the product was washed 2 \times 25 mL of Et_2O to remove excess imidazole. Pure product was isolated as an orange solid (0.092 g, 71% yield). X-ray quality crystals were obtained by Et_2O diffusion into a MeOH solution at -30 °C. $\text{NiC}_{13}\text{H}_{25}\text{N}_4\text{S}_2\text{Cl}$ Elemental anal. Calcd (found) for $\text{NiC}_{13}\text{H}_{25}\text{N}_4\text{S}_2\text{Cl}\cdot\text{H}_2\text{O}$ (MW = 382 g/mol): C, 40.92 (40.88); N, 14.68 (14.45); H, 7.13 (7.07). Absorption spectrum (MeOH): λ_{max} (ϵ , $\text{M}^{-1}\text{cm}^{-1}$) 467 (501), 340 (sh), 288 (10767), 211 (21461) nm. $^+\text{ESI-MS}$ (MeOH): $m/z = 327$ [(mmp-mdach)Ni(Im)] $^+$. Molar conductance at 23 °C: 89 $\text{S cm}^2\text{ mol}^{-1}$ (MeOH); 156 $\text{S cm}^2\text{ mol}^{-1}$ (H_2O).

Synthesis of [1-(5-methyl-1H-imidazol-4-yl)methylthio]ethyl-4-mercaptoethyl-1,4-diazacycloheptane]nickel(II) Chloride [Ni-1'(CH $_2$ -mIm)]Cl, Complex 4. A 100 mL Schlenk flask was charged with (bme-dach)Ni (0.100 g, 0.361 mmol). The solid was degassed and suspended in 25 mL of MeCN. A suspension of 4-(chloromethyl)-5-methyl-1H-imidazole hydrochloride (0.060 g, 0.361 mmol) in 25 mL of MeCN was transferred via cannula. As the reaction proceeded, the solids were drawn into solution followed by formation of a light pink precipitate. The mixture was stirred overnight. Filtration yielded a pink solid which was washed 3 \times 75 mL of MeCN, dissolved in a minimum of MeOH, and recrystallized with Et_2O . The solid was washed 2 \times 25 mL of Et_2O (45 mg, 31%). X-ray quality crystals were obtained by Et_2O diffusion into a MeOH solution. Elemental anal. Calcd (found) for $\text{NiC}_{14}\text{H}_{25}\text{N}_4\text{S}_2\text{Cl}\cdot\text{H}_2\text{O}$ (MW = 426 g/mol): C, 39.50 (40.07); N, 13.16 (13.23); H, 6.39 (6.44). Absorption spectrum (MeOH): λ_{max} (ϵ , $\text{M}^{-1}\text{cm}^{-1}$) 469 (235), 288 (6052), 211 (16983) nm. $^+\text{ESI-MS}$: $m/z = 371$

[Ni-1'(CH $_2$ -mIm)] $^+$. Molar conductance at 23 °C: 103 $\text{S cm}^2\text{ mol}^{-1}$ (MeOH); 164 $\text{S cm}^2\text{ mol}^{-1}$ (H_2O).

Synthesis of [1,4-Bis(3-methylimidazol-4-ylmethyl)-1,4-diazacycloheptane nickel(II)] Tetrafluoroborate, [(bmlme-dach)Ni](BF $_4$) $_2$, Complex 5. Synthesis, purification, and characterization of 1,4-bis(3-methylimidazol-4-ylmethyl)-1,4-diazacycloheptane penta-hydrochloride hydrate ($\text{L}\cdot 5\text{HCl}\cdot\text{H}_2\text{O}$) was executed following the procedure published by Bu et al. with 4-(chloromethyl)-5-methyl-1H-imidazole hydrochloride used in the place of 4-(chloromethyl)-1H-imidazole hydrochloride.³⁷ A solution of $\text{Ni}(\text{BF}_4)_2\cdot 6\text{H}_2\text{O}$ (1.328 g, 3.903 mmol) in 10 mL of MeOH was added dropwise to a stirring solution of $\text{L}\cdot 5\text{HCl}\cdot\text{H}_2\text{O}$ (1.100 g, 3.814 mmol) in 15 mL of MeOH, resulting in immediate precipitation of yellow solid. The reaction mixture was stirred overnight at 22 °C under an N_2 blanket. The ensuing green solution and yellow solid were separated via filtration, and the solid was washed with Et_2O and dried in vacuo to yield 0.757 g (1.45 mmol, 38%). X-ray quality crystals were obtained by slow evaporation from a methanol solution. Elem. Anal. Calcd. (found) for $\text{NiC}_{15}\text{H}_{24}\text{N}_6\text{B}_2\text{F}_8$ (MW = 521 g/mol): C, 34.60 (34.07); H, 4.65 (4.70); N, 16.14 (15.62). Absorption spectrum (MeOH): λ_{max} (ϵ , $\text{M}^{-1}\text{cm}^{-1}$): 449(29), 280 (sh), 233 (2232) nm. $^+\text{ESI-MS}$ in MeOH: $[\text{M}]^{2+}$ $m/z = 173$ [(bmlme-dach)Ni] $^{2+}$. Molar conductance at 23 °C: 198 $\text{S cm}^2\text{ mol}^{-1}$ (MeOH); 223 $\text{S cm}^2\text{ mol}^{-1}$ (H_2O).

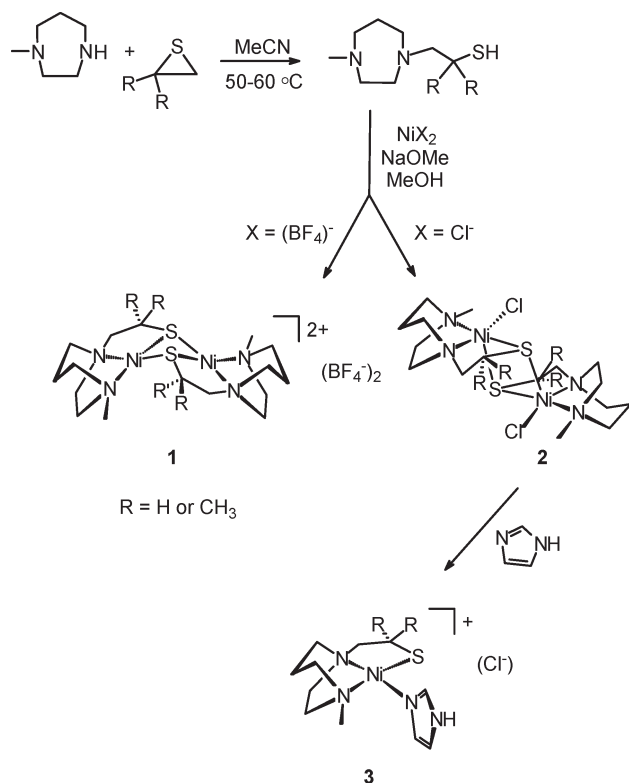
Results and Discussion

Synthesis and Structure of N_2S Bridged Thiolate Dimers: [(me-mdach)Ni] $_2(\text{BF}_4)_2$, **1, and [(me-mdach)NiCl] $_2$, **2**.** There are many examples of $\text{N}_2\text{S}_2\text{Ni}$ complexes in $\mu_2\text{S}_2$ -bridged dimers which demonstrate the diverse structural arrangements encountered by μ -S-thiolate bridging.³⁸ Scheme 1 outlines the synthetic protocol for the N_2S thiolate bridged dimeric complexes **1** and **2** explored herein. Both are isolated as hygroscopic, air stable solids. Complex **1** is a deep maroon solid that is very soluble in MeCN and H_2O and moderately soluble in MeOH. Complex **2** is isolated as a reddish-brown powder and is very soluble in MeOH and H_2O and moderately soluble in MeCN. The molecular structures of **1** and **2** are shown in Figure 2 and a selection of metric data is given in Table 1. The dimeric form of complex **1** involves edged-bridged square planes with symmetry imposed disorder relating to the S to N linkers. The NiN_2S_2 unit is almost perfectly square planar with average standard deviation from the NiN_2S_2 plane of 0.0038 Å. The "hinge" angle in this butterfly type complex, that is, the dihedral angle between the two N_2S_2 best planes, is 116.7°; the $\text{Ni}\cdots\text{Ni}$ distance is 2.837 Å. A similar dimer with gem dimethyl groups on the carbon α to the bridging sulfurs has a greater hinge angle of 135.7° and a $\text{Ni}\cdots\text{Ni}$ distance of 3.034 Å.³⁶ These distances are compatible with other complexes containing (μ_2 -SR) $_2$ bridged Ni_2S_2 rhombs.³⁸ The closest BF_4^- counterion in **1** has an $\text{F}\cdots\text{Ni}$ distance of 5.031 Å.

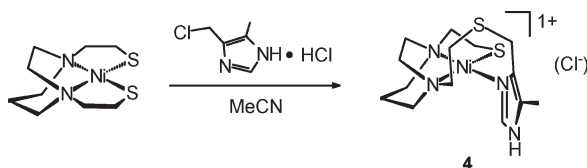
(37) (a) Du, M.; Guo, Y. M.; Bu, X. H.; Ribas, J.; Monfort, M. *New J. Chem.* **2002**, 26, 939–945. (b) Guo, Y. M.; Du, M.; Bu, X. H. *Inorg. Chim. Acta* **2005**, 358, 1887–1896.

(38) (a) Colpas, G. J.; Kumar, M.; Day, R. O.; Maroney, M. J. *Inorg. Chem.* **1990**, 29, 4779–4788. (b) Linck, R. C.; Spahn, C. W.; Rauchfuss, T. B.; Wilson, S. R. *J. Am. Chem. Soc.* **2003**, 125, 8700–8701. (c) Wang, Q.; Blake, A. J.; Davies, E. S.; McInnes, E. J. L.; Wilson, C.; Schroder, M. *Chem. Commun.* **2003**, 3012–3013. (d) Krishnan, R.; Riordan, C. G. *J. Am. Chem. Soc.* **2004**, 126, 4484–4485. (e) Rao, P. V.; Bhaduri, S.; Jiang, J.; Holm, R. H. *Inorg. Chem.* **2004**, 43, 5833–5849. (f) Harrop, T. C.; Olmstead, M. M.; Mascharak, P. K. *Inorg. Chem.* **2006**, 45, 3424–3436. (g) Redin, K.; Wilson, A. D.; Newell, R.; DuBois, M. R.; DuBois, D. L. *Inorg. Chem.* **2007**, 46, 1268–1276.

Scheme 1



Scheme 2



In contrast to the μ -SR bridged square planar Ni₂S₂(μ -S) of **1**, the solid state structure of **2** finds a penta-coordinate Ni^{II} in pseudotrigonal bipyramidal, N₂S(μ -S) Cl coordination (Figure 2). The equatorial plane in each tbp is comprised of one N-donor atom of the tridentate N₂S ligand, a chloro ligand, and a sulfur atom from the adjacent (N₂S)Ni moiety resulting in an Ni₂S₂ diamond core. The S-donor atom and the trans N-donor atom of the tridentate N₂S ligand make up the axial sites. The Ni–S_{axial} bond distance of **2** is slightly longer than Ni–S_{equatorial}. As expected, the average Ni–N and Ni–S distances are longer in the penta-coordinate chloride derivative **2** than in **1**, and an increase in the Ni···Ni distance, from 2.837 Å in complex **1** to 3.268 Å in complex **2** is also observed, Table 1. The N–Ni–N and S–Ni–S angles in complex **1** are acute at 83.6° and 79.6°, while the N–Ni–S angle, within the five-membered ring, is 96.4°. In complex **2**, the \angle N–Ni–N contracts to 77.3°, the \angle S–Ni–S opens to 92.3°, and the \angle N–Ni–S within the five-membered ring contracts to 86.7°.

The dimeric species, [(mmp-mdach)NiCl]₂, **2-Me₂**, is isolated as a hygroscopic, air stable, bright purple powder, which is very soluble in MeOH, H₂O, and MeCN. Thus far crystals have not been obtained; however, conductivity and cyclic voltammetry measurements are similar in **2-Me₂**

Table 1. Metric Data for Complexes **1** and **2**

	1	2
Ni(1)–S(1)	2.069(19) Å	2.369(17) Å
Ni(1)–S(1A)	2.245(16) ₂ Å	2.346(18) Å
Ni(1)–N(1)	1.923(8) Å	2.084(5) Å
Ni(1)–N(2)	1.914(8) Å	2.144(5) Å
Ni(1)···Ni(2)	2.837 Å	3.268 Å
Ni(1)–Cl(1)		2.331(17) Å
N(1)–Ni(1)–N(2)	83.6(3)°	77.3(2)°
N(1)–Ni(1)–S(1)	96.4(5)°	86.7(14)°
N(2)–Ni(1)–Cl(1)		92.9(14)°
S(1)–Ni(1)–Cl(1)		96.6(6)°
S(1)–Ni(1)–S(1A)	79.6(6)°	92.3(5)°
Cl(1)–Ni(1)–S(1A)		114.6(6)°
N(1)–Ni(1)–S(1A)	175.4(5)°	100.6(15)°
N(2)–Ni(1)–S(1A)	100.5(4)°	96.8(15)°
Ni(1)–S(1)–Ni(1A)	82.1(6)°	87.8(5)°

and **2**, suggesting similar structures. The **2-Me₂** complex was cleaved by imidazole in the preparation of complex **3**.

Synthesis and Structure of [(mmp-mdach)Ni(Im)]Cl, **3.** The cleavage of dimeric μ -dithiolate Ni^{II} by monodentate ligands is a fairly common, but not a universally successful, approach to mononuclear square planar nickel complexes.^{36,39} As shown in Scheme 1, addition of excess imidazole to [(mmp-mdach)NiCl]₂ in MeOH results in an orange solid analyzed as complex **3** in high yield. Complex **3** is hygroscopic, soluble in MeOH, H₂O, and DMF and crystallizes on layering a MeOH solution with Et₂O. The molecular structure of the imidazole-cleaved complex is shown in Figure 3, and significant metric parameters are listed in the figure caption. To our knowledge, **3** provides the first molecular structure of a Ni complex containing both thiolate and imidazole donor ligands. The nickel coordination environment is largely square planar with very slight tetrahedral twist distortion, 7.9°, defined by the intersection of the N(1)Ni(1)N(2) and N(3)–Ni(1)S(1) planes. The N–Ni–N angle within the dach donor is 81.5° while the \angle S–Ni–N_{imid} is 91.4°; the \angle N(2)–Ni(1)–N(3) is 97.1°. Notably, the plane of the imidazole ligand is perpendicular to the N₂N'SNi plane, with the amine N(4) in the imidazole ring on the same side of the N₂N'S coordination plane as is the C₃ portion of the dach ring. As in complexes **1** and **2**, the NiN₂C₃ metallodiazacyclohexane ring is in the chair conformation. There is no significant difference in the bond distances of the Ni–N_{amine} and the Ni–N_{imid}. The Ni–S distance of 2.149(3) Å is shorter than any Ni–S distance of complexes **1** or **2**. The extended structure finds a Cl[–] and MeOH molecule within the unit cell which appear to create a H-bonding network as seen by the Cl···O distance of 3.568 Å and Cl···N_{imid} distance of 3.119 Å (Figure 4). The latter is well within the summation of van der Waals' radii of chlorine and nitrogen.

Synthesis and Structure of [Ni-1'-(CH₂-mIm)]Cl, **4.** Stoichiometric addition of 4-(chloromethyl)-5-methyl-imidazole·HCl to neutral (bme-dach)Ni in MeOH results in solubilization of the insoluble precursors as S-alkylation occurs, Scheme 2. The acidic conditions of the reaction

(39) (a) Kruger, H.-J.; Holm, R. H. *Inorg. Chem.* **1989**, *28*, 1148–1155. (b) Mirza, S. A.; Pressler, M. A.; Kumar, M.; Day, R. O.; Maroney, M. J. *Inorg. Chem.* **1993**, *32*, 977–987. (c) Sellman, D.; Prectel, W.; Knoch, F.; Moll, M. *Inorg. Chem.* **1993**, *32*, 538–546. (d) Sellman, D.; Huabinger, D.; Heinemann, F. *W. Eur. J. Inorg. Chem.* **1999**, 1715–1725. (e) Huang, D.; Deng, L.; Sun, J.; Holm, R. H. *Inorg. Chem.* **2009**, ASAP.

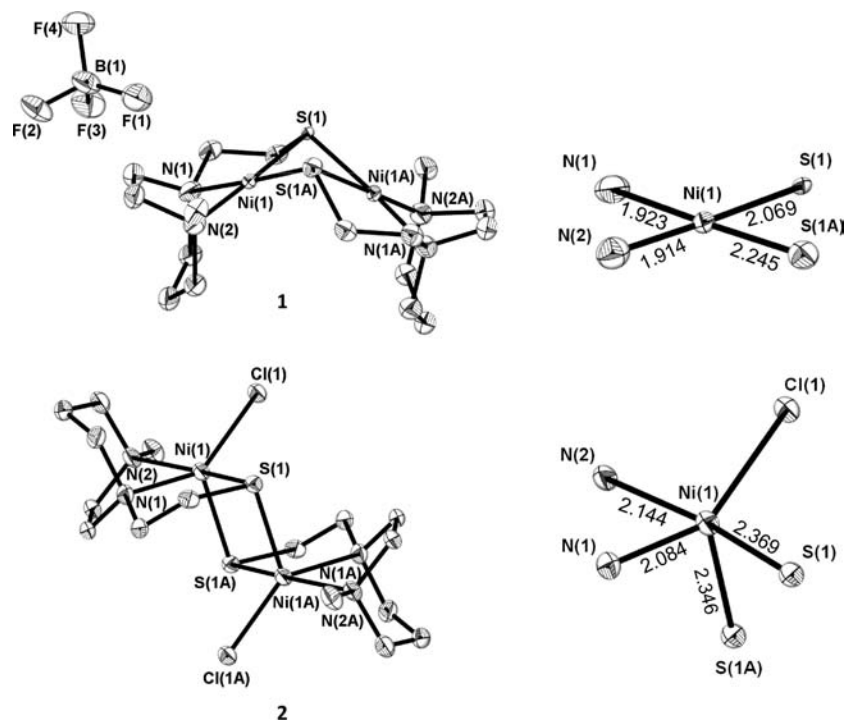


Figure 2. Molecular structure of complexes **1** and **2** shown as thermal ellipsoids at 50% probability. First coordination spheres shown at right.

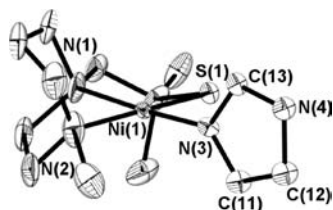


Figure 3. Molecular structure of the cation of **3** shown as thermal ellipsoids at 50% probability. The Cl^- counterion and MeOH molecule are not shown. Selected bond lengths (Å): Ni(1)–S(1), 2.149(3); Ni(1)–N(1), 1.897(10); Ni(1)–N(2), 1.949(10); Ni(1)–N(3), 1.888(9); N(3)–C(13), 1.342(12); N(3)–C(11), 1.372(13); N(4)–C(13), 1.326(13); N(4)–C(12), 1.413(13); C(11)–C(12), 1.316(14). Selected bond angles (deg): N(1)–Ni(1)–N(2), 81.5(5); N(1)–Ni(1)–S(1), 90.4(3); N(2)–Ni(1)–N(3), 97.1; S(1)–Ni(1)–N(3), 91.4(3); N(1)–Ni(1)–N(3), 175.5(4); N(2)–Ni(1)–S(1), 170.6(4).

sacrifice a portion of the (bme-dach)Ni starting material; however, use of the acid-free imidazole results in poorer yields. Purified complex **4** was isolated as a rose-colored solid in 30% yield. It is hygroscopic and soluble in H_2O , MeOH, and DMF; crystals were grown in a solution of MeOH layered with Et_2O . The solid state structure of **4** (Figure 5) reveals a $(\text{N}_2\text{N}'\text{S})\text{Ni}$ square planar binding motif of two amine nitrogens from the dach ring, the imidazole nitrogen and the thiolate sulfur, with a slightly larger distortion from planarity, a 13.2° T_d twist, than was found in complex **3**.

As given in Figure 6, angles and bond distances in complex **4** are similar to those of complex **3**. The thioether-S is oriented over the $\text{N}_2\text{N}'\text{S}$ plane, however the Ni– $\text{S}_{\text{thioether}}$ distance of 3.022 Å is beyond bonding. Although thioethers are weak donors, there are sev-

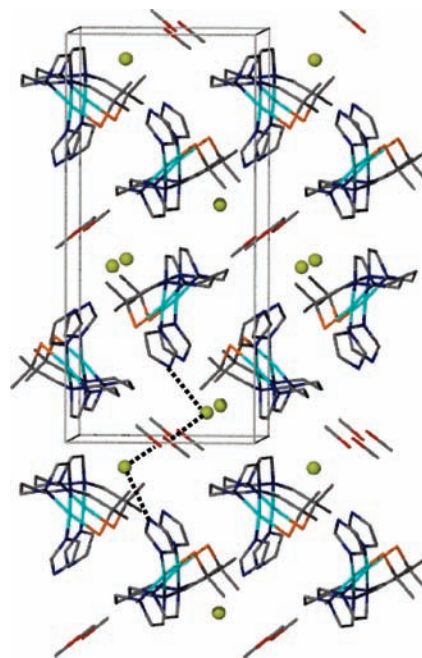


Figure 4. Packing diagram of complex **3**.

ral square planar $\text{N}_2\text{S}_2\text{Ni}$ compounds known in which the sulfur is a thioether within a polydentate ligand or macrocycle.⁴⁰ In addition, S-alkylation by reagents that provide an additional binding site is known to maintain the tetradentate N_2S_2 bonding and expand the coordination number of $\text{N}_2\text{S}_2\text{Ni}$ complexes.⁴¹ The switch of the

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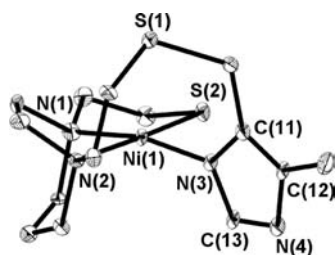


Figure 5. Molecular structure of the cation of **4** shown as thermal ellipsoids at 50% probability. The Cl^- counterion is not shown. Selected bond lengths (Å): Ni(1)–S(2), 2.168(2); Ni(1)–N(1), 1.906(7); Ni(1)–N(2), 1.995(5); Ni(1)–N(3), 1.908(9); N(3)–C(13), 1.322(8); N(3)–C(11), 1.378(10); N(4)–C(13), 1.336(10); N(4)–C(12), 1.381(9); C(11)–C(12), 1.324(11). Selected bond angles (deg): N(1)–Ni(1)–N(2), 82.3(3); N(1)–Ni(1)–S(2), 90.3(2); N(2)–Ni(1)–N(3), 95.5(3); S(2)–Ni(1)–N(3), 91.6(2).

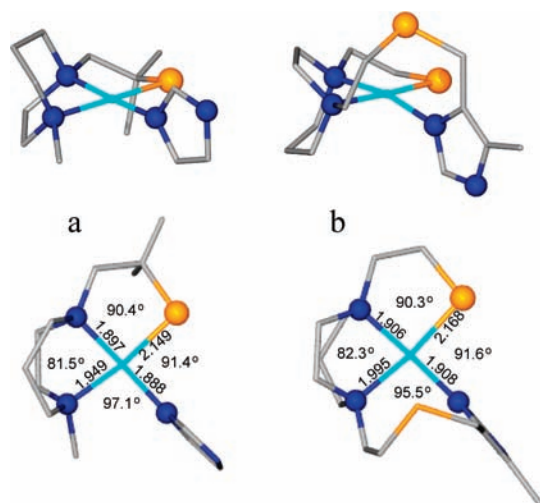


Figure 6. Ball and stick drawings of (a) [(mmp-mdach)Ni(Im)]Cl, **3**, and (b) [Ni-1'(CH₂-mIm)]Cl, **4**. Counter anions are not shown. Top: side view; Bottom: View \perp to N₂S plane with selected metric parameters.

donor atom from the thioether to the N-imidazole in **4** indicates that the greater binding ability of the imidazole nitrogen over the thioether sulfur overwhelms the favorable chelate effect for the thioether, going from a five-membered ring to a less favored eight-membered ring. Scheme 3 outlines likely intermediates (in brackets) in the reaction pathway; neither of these has thus far been verified.

As was also seen in complex **3**, the orientation of the imidazole plane in **4** is perpendicular to the N₂N'S plane. The N(2)⋯S(1)⋯C(11) linker or imidazole tether is sufficiently long so as not to interfere with the optimal binding of the imidazole donor (*vide infra*). The closest chloride ions in the crystal lattice are located 3.046 Å away from the N of the imidazole ligand (Supporting Information, Figure S1).

Synthesis and Structure of [(bmIme-dach)Ni](BF₄)₂, **5.** Complex **5**, prepared as described in Scheme 4, is isolated as a gold solid that is soluble in MeCN, MeOH, H₂O, and DMF. Figure 7 displays the thermal ellipsoid plot for complex **5** along with alternate views that highlight the slight staggering of the imidazole rings while the NiN₄ plane (Td twist of 7.9°) is largely coplanar with the imidazole ligand planes. The dihedral angle between the planes of the pendant imidazole rings is 11.4°. An analogue of complex **5**, lacking the methyl group on the

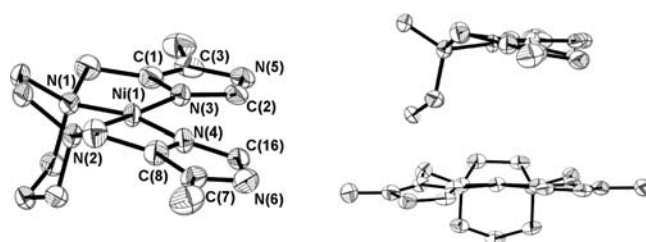
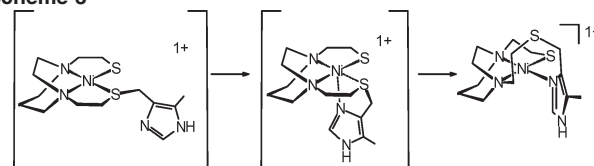
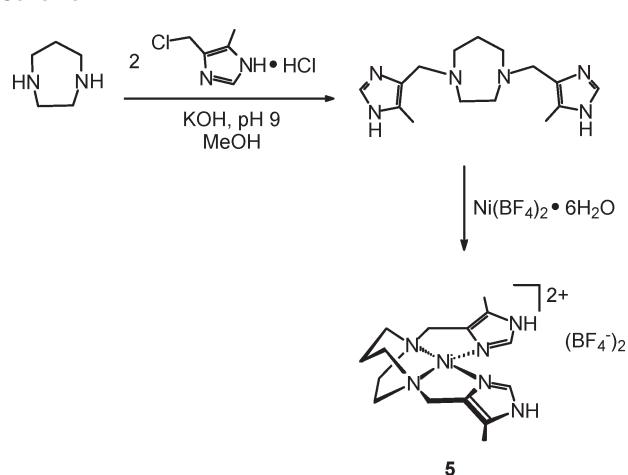


Figure 7. Molecular structure of the dication of **5** shown as thermal ellipsoids at 50% probability. The BF_4^- counterions are not shown. Selected bond lengths (Å): Ni(1)–N(1), 1.913(3); Ni(1)–N(2), 1.904(3); Ni(1)–N(3), 1.873(3); Ni(1)–N(4), 1.894(3); N(3)–C(1), 1.373(5); N(3)–C(2), 1.332(5); N(5)–C(2), 1.334(5); N(5)–C(3), 1.377(6); C(1)–C(3), 1.376(6); N(4)–C(8), 1.386(5); N(4)–C(16), 1.339(5); N(6)–C(7), 1.383(6); N(6)–C(16), 1.342(6); C(7)–C(8), 1.359(6). Selected bond angles (deg): N(1)–Ni(1)–N(2), 83.3(2); N(3)–Ni(1)–N(4), 104.1(2); N(1)–Ni(1)–N(3), 86.5(2); N(2)–Ni(1)–N(4), 85.8(2); N(1)–Ni(1)–N(4), 167.0(2); N(2)–Ni(1)–N(3), 169.6(2).

Scheme 3



Scheme 4



imidazole and isolated as a perchlorate salt, reported by Bu et al. has similar metric parameters; however, a smaller dihedral angle exists between the imidazole ring planes (6.1°).³⁷ The extended packing structure of complex **5** shows π – π stacking between imidazole rings as suggested by interplanar distances of 3.432 Å (Figure 8). In contrast, the crystal structure of Bu's complex shows the formation of intermolecular hydrogen bonds between the imidazole N–H and the O atom of the ClO_4^- counterion resulting in a dimeric structure.³⁷

Despite the differences in the imidazole orientation of the tetradentate ($\text{N}_{\text{amine}})_2(\text{N}_{\text{imid}})_2\text{Ni}$, complex **5**, and the complexes **3** and **4**, the Ni–N_{imid} bond distances are significantly the same. A final note on the monomeric nickel N₂N'S and N₂N'2 complexes is in regards to angles within the square plane. Figure 6 shows minor differences in the free imidazole complex **3** and the long tethered imidazole complex **4**. In complex **5**, the $\angle\text{N}(1)\text{–Ni–N}(2)$ is largely the same as in complexes **3** and **4**, while the angle

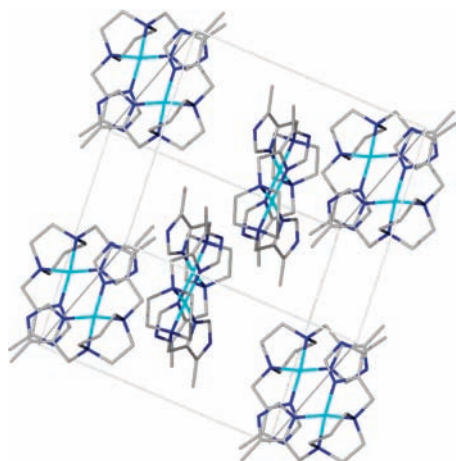


Figure 8. Packing diagram of complex **5** showing π - π stacking between imidazole rings.

Table 2. Molar Conductivities at 25°C

compound	Λ_M at 10^{-3} M ($\text{cm}^{-1} \text{mol}^{-1} \Omega^{-1}$)		
	H ₂ O	MeCN	MeOH
[(me-mdach) ₂ Ni ₂](BF ₄) ₂ , 1	310	299	
[(me-mdach)NiCl] ₂ , 2	303	124	
[(mmp-mdach)NiCl] ₂ , 2-Me₂	299	104	
[(mmp-mdach)Ni(Im)](Cl), 3	156		89
[Ni-1'(CH ₂ -mIm)](Cl), 4	164		103
[(bmIme-dach)Ni](BF ₄) ₂ , 5	223		198

between donor atoms trans to the diazacycle donors, N(3) and S or N(3) and N(4), opens substantially from 91.4° and 91.6° in **3** and **4**, respectively, to 104° in complex **5**.

Conductivity Measurements. The results of molar conductivity measurements are listed in Table 2. As expected, because of the non-coordinating BF₄⁻ counterion, complex **2** behaves as a 2:1 electrolyte in both MeCN and H₂O solutions, while the Cl⁻ derivative, complex **1**, is a 1:1 electrolyte in MeCN and acts as a 2:1 electrolyte in H₂O.⁴² Note that the conductivity of **2-Me₂** follows that of complex **1** with a single Cl⁻ dissociating in the polar organic solvent; both Cl⁻ ions dissociate in H₂O. The molar conductance values for the mononuclear square planar complexes, **3** and **4**, are consistent with a 1:1 electrolyte in both MeOH and H₂O solutions and complex **5** is a 2:1 electrolyte in MeOH and H₂O.

Electronic Absorption Spectra. Typical square planar nickel complexes exhibit d-d transitions in the range of 400–600 nm. Higher energy and more intense features can be assigned as ligand-to-metal charge transfer (LMCT) transitions. Nickel complexes with RS⁻ ligands show such intense absorbances within the 250–350 nm range, which are attributed to RS⁻ → Ni^{II} charge transfer transitions.⁴³ Table 3 lists the electronic absorption data for complexes **1–5** and **2-Me₂**. The UV-vis absorption spectrum of [(me-mdach)Ni]₂(BF₄)₂, **1**, in which the Ni²⁺ ions are held in a square planar geometry exhibit two d → d bands with λ_{max} at 452 and 524 nm, in addition to high energy LMCT absorptions at 229, 252, 305, and 354 nm (ϵ values >10,000 M⁻¹ cm⁻¹). In complex [(me-mdach)NiCl]₂, **2**,

four intense LMCT absorptions are observed and a broad d → d band is seen at 527 nm with a shoulder at 490 nm.

The absorptions for **2-Me₂** are similar to complex **2**. The absorption spectrum of the imidazole cleaved dimer, (mmp-mdach)Ni(Im)](Cl), **3**, displays one d-d band with λ_{max} at 467 nm and two intense ligand to metal charge transfer bands at 211 and 288 nm. Similar absorptions are observed for the square planar complex **4**. In complex **5**, all absorptions are of low intensity.

Electronic absorption spectroscopy was used to investigate whether donor switching of the N-imidazole to the S-thioether of Ni-1'(CH₂-mIm)](Cl) might occur during incremental addition of acetic acid to a methanolic solution of **4**, with the expectation that protonated imidazole might promote thioether binding. No changes in the absorption spectrum were observed over a pH range of 8.5 to 3.4, indicating that the coordination environment was constant. These results are consistent with DFT computations which found that the crystallographically observed imidazole bound structure was the isomer of lower energy with an energy difference between the two of 3.34 kcal/mol, Figure 9.

Electrochemical Properties. A summary of electrochemical properties of complexes **1–5**, **2-Me₂**, and (bme-dach)Ni are given in Table 4. All seven complexes show an irreversible oxidation event, which is ascribed to thiolate oxidation in the case of complexes **3**, **4**, and (bme-dach)Ni.

The cyclic voltammograms for the N₂S μ -thiolate bridged Ni dimers, **1**, **2**, and **2-Me₂**, are shown in Supporting Information, Figure S2. Two well-defined reduction events are observed in each; the first reduction is reversible when the scan direction is reversed before the second reduction, and is assigned to a Ni^{II}Ni^{II}/Ni^{II}Ni^I couple. The second reduction, presumably accessing an unstable Ni^INi^I redox level in the intact dimers, engenders degradation as seen by its irreversibility and also in the differential pulse voltammetry of the first reduction process (Supporting Information, Figure S3). All three dimers display similar electrochemistry in both the anodic and cathodic regimes with differences in potentials relating to the extent of counterion interaction or the presence of gem-dimethyl groups in **2-Me₂**.

Figure 10 displays the cyclic voltammograms of mononuclear complexes **3–5** and (bme-dach)Ni. Figure 10, panels a and b, show fully reversible Ni^{II}/Ni^I reduction events at -1.59 and -2.50 V for complex **5** and (bme-dach)Ni, respectively. The greater accessibility of the former is a result of the dicationic charge, as well as the differences in donor ability of the imidazole versus the thiolate ligands. For complex **4** a reproducible broad feature (deconvoluting into at least 3 maxima by square wave voltammetry, Supporting Information, Figure S4) is centered at -1.82 V, and a fully reversible reduction is seen at -2.50 V, identical to the Ni^{II}/Ni^I couple of the (bme-dach)Ni dithiolate complex, Figure 10 b. Multiple scans did not affect the form of the CV; however, bulk electrolysis of **4** was informative. A potential of -2.26 V was applied to a solution of pure, crystalline complex **4** dissolved in DMF and stopped when the total charge (Q) approached a calculated value of 3 electrons per molecule. The cyclic voltammogram obtained on this solution showed almost total loss of the broad feature at -1.82 V

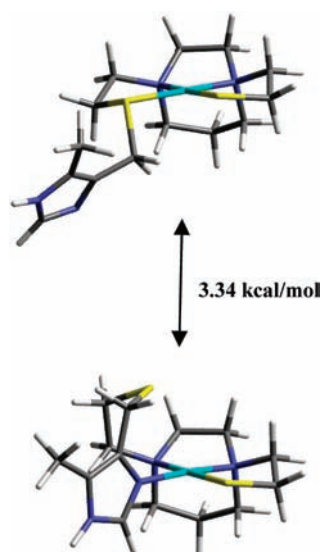
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Table 3. Summary of Electronic Absorption Spectra for Complexes 1–5 and 2-Me₂^a

	UV-vis: λ_{\max} (nm) (ϵ , M ⁻¹ cm ⁻¹)					
	CT transitions			d → d transitions		
[(me-mdach) ₂ Ni ₂](BF ₄) ₂ , 1 ^b	229 (21330)	252 (13765)	305 (13075)	354 (2503)	452 (775)	524 (817)
[(me-mdach)NiCl] ₂ , 2	211 (18000)	247 (17126)	307 (7816)	350 (3310)	490 (sh)	527 (967)
[(mmp-mdach)NiCl] ₂ , 2-Me₂	205 (24575)	244 (21298)	283 (11940)	326 (6115)	426 (988)	532 (904)
(mmp-mdach)Ni(Im)(Cl), 3	211 (21460)			288 (10767)	340 (sh)	467 (501)
[Ni-1'-(CH ₂ -mIm)](Cl), 4	211 (16980)			288 (6052)		469 (235)
[(bmIme-dach)Ni](BF ₄) ₂ , 5		233 (2232)		280 (sh)		449 (29)

^a Unless specified otherwise, all results were obtained from MeOH solutions. ^b The electronic spectrum of [(me-mdach)₂Ni₂](BF₄)₂ was measured in MeCN.

**Figure 9.** DFT optimized isomeric forms of complex **4**. (top) S-thioether bond (bottom) N-imidazole bound.**Table 4.** Electrochemical Data for Complexes 1–5^a

complex	E_{ox} (V)		E_{red} (V)	
	E_{pa}		$E_{1/2}$	E_{pc}
[(me-mdach)Ni ₂](BF ₄) ₂ , 1	+0.14		-1.30	-2.02
[(me-mdach)NiCl] ₂ , 2	+0.06		-1.45	-2.03
[(mmp-mdach)NiCl] ₂ , 2-Me₂	+0.04		-1.58	-1.91
(mmp-mdach)Ni(Im)(Cl), 3	-0.07			-1.96
				-2.13
				-2.31
[Ni-1'-(CH ₂ -mIm)](Cl), 4	-0.18		-2.50	-1.82
[(bmIme-dach)Ni](BF ₄) ₂ , 5	+0.77		-1.59	-1.21
(bme-dach)Ni	-0.14		-2.50	

^a Ar deaerated DMF solution (0.1 M ⁿBu₄NBF₄). All experiments were recorded using a glassy carbon working electrode ($A = 0.071$ cm²) referenced to Fc/Fc⁺ and a Pt counter electrode at a scan rate of 200 mV/s.

while the reversible wave at -2.50 V and the oxidation wave at -0.18 V remained unchanged, see Supporting Information, Figure S5. The lack of current increase following bulk electrolysis in the -2.50 V event was of concern. As the addition of excess (bme-dach)Ni did not change the intensity or potential of the CV waves, it may be assumed that the solubility limit of (bme-dach)Ni in DMF was reached. This was confirmed by control experiments with pure (bme-dach)Ni.

The low intensity, broad feature centered at -1.82 V in complex **4** and the first two reduction waves in complex **3**

(DPV shown in Supporting Information, Figure S6) are tentatively assigned to complexes of different imidazole coordination in number or isomeric form. Consistent with this assignment, on addition of free imidazole to a solution containing complex **3** the multiple events become one broad intense feature centered at about -2.05 V (Supporting Information, Figure S7).

Computational Studies. DFT computational studies were carried out with a goal of determining the activation barrier to imidazole rotation about the Ni–N bond. Using the X-ray crystal structures as a starting point, DFT optimized structures accurately reproduced the experimental coordination geometries, see Supporting Information, Figure S8 and Table S2. Supporting Information, Table S3 lists the energies and compositions of the frontier molecular orbitals of complexes **3** and **4**; the corresponding MO contour plots are shown in Figure 11.

The highest-occupied molecular orbitals (HOMOs) of complexes **3** and **4** both display Ni $d_{\pi} - S_{p\pi}$ antibonding orbital character, with electron density from the Ni d_{yz} (12.3%) and $S_{\text{thiolate } p_z}$ (58.8%) orbitals of complex **3**; in complex **4**, the distribution is Ni d_{yz} (17.1%) and $S_{\text{thiolate } p_z}$ (57.1%). The S-thiolate contribution to the HOMO is slightly more in the untethered imidazole derivative, **3**, as compared to the tethered imidazole complex, **4**, while the Ni orbital contribution is slightly greater in the tethered imidazole compound. Similarly there are small differences between the orbital makeup of the lowest unoccupied molecular orbitals (LUMOs) in complexes **3** and **4**, which are in the σ -framework of the molecules. The HOMO–LUMO gaps in complexes **3** and **4** are nearly identical at 3.63 and 3.59 eV, respectively.

The most significant differences in molecular orbitals are observed in the HOMO-1. The HOMO-1 of complex **3** is composed largely of the overlap of the Ni d_{z^2} (54.0%), Ni s (15.5%) and $S_{\text{thiolate } p_y}$ (12.4%) orbitals whereas the HOMO-1 of complex **4** shows a large contribution from the $S_{\text{thioether}}$ of 23.4% in addition to the Ni $d_{\pi} - p_{\pi}$ overlap.

As discussed above, the $S_{\text{thiolate}} - \text{Ni}$ interaction dominates the frontier molecular orbitals in complexes **3** and **4**. The $N_{\text{imidazole}} - \text{Ni}$ bonding interaction is seen in lower lying orbitals which show large contributions of Ni and the N-imidazole character for both the ground and the DFT derived transition state for rotation of the imidazole about the Ni–N bond in complex **3**, vide infra. This interaction will be described in detail in a future publication.

Variable Temperature ¹H NMR Studies. As shown in Figure 6, solid state structures find the orientation of the

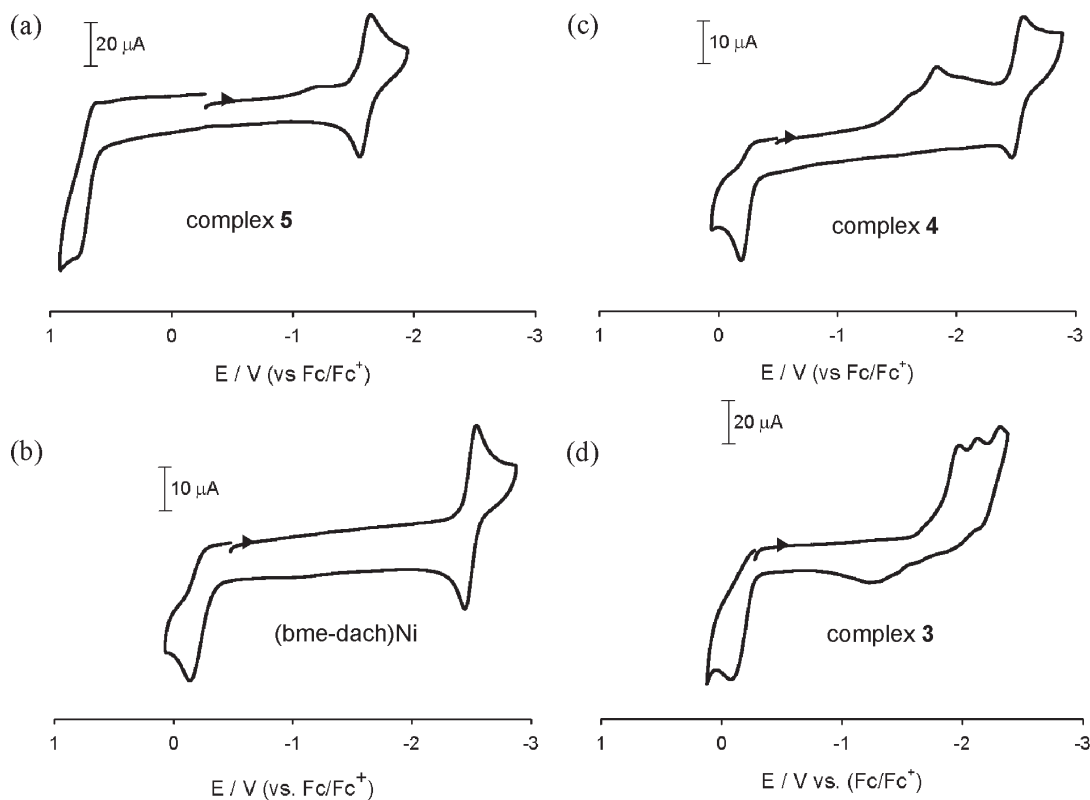


Figure 10. Cyclic voltammograms of mononuclear square planar Ni^{II} complexes in DMF and referenced to Fc/Fc⁺. (a) [(bmIme-dach)Ni](BF₄)₂, **5**; (b) (bme-dach)Ni; (c) [Ni-1'-(CH₂-mIm)](Cl), **4**; (d) (mmp-mdach)Ni(Im)](Cl), **3**.

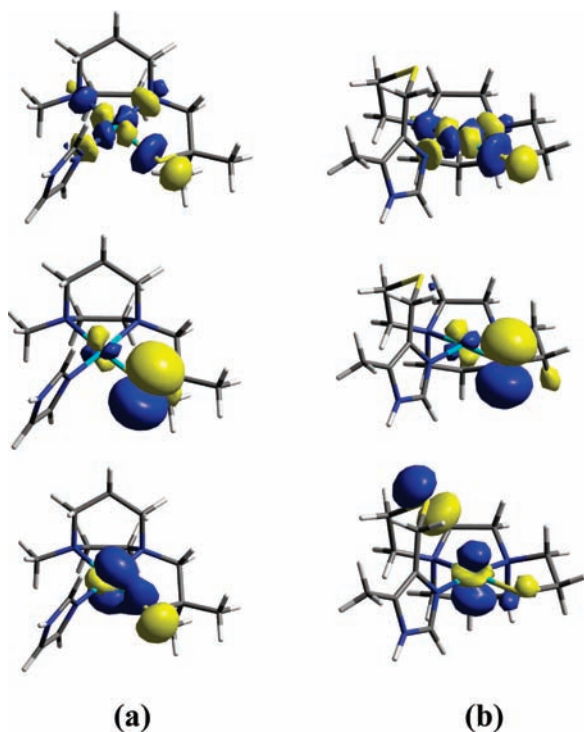


Figure 11. Frontier molecular orbitals of (a) [(mmp-mdach)Ni(Im)]Cl, **3**, and (b) [Ni-1'-(CH₂-mIm)]Cl, **4**. In each column, the orbitals descend in the order LUMO, HOMO, and HOMO-1.

imidazole ligand plane in both [(mmp-mdach)Ni(Im)]Cl, **3**, and [Ni-1'-(CH₂-mIm)]Cl, **4**, to be perpendicular to the NiN₂N'S plane and largely eclipsing the N-Ni-N'

vector. To further explore the imidazole ligand orientational preference, the solution phase conformation of the imidazole ligand in complex **3** was investigated via variable temperature ¹H NMR spectroscopy. At 23 °C, the spectrum of **3** in CD₃OD shows three sharp singlets attributed to the C-H hydrogens on the coordinated imidazole ligand positioned at 8.11, 7.33, and 7.12 ppm, Figure 12. The assignments given in Figure 12 are in agreement with DFT computations, *vide infra* (Supporting Information, Figure S9). Upon lowering the temperature, resonances *a* and *b* broaden and by -80 °C each have split into two signals, indicating the presence of two isomers. Integration shows *a'* and *a''* to be in a ratio of ~1. The resonance due to the proton labeled *c* remains sharp throughout the temperature range, and the resonances derived from *b* overlap with *c* and an impurity. Note that impurities are readily seen at room temperature. The lower field impurity is unaffected by temperature changes. However, the higher field impurity, which has not been identified, undergoes broadening as do the signals of interest.

Thermodynamic (isomer ratios) and kinetic barriers associated with the fluxional process were obtained by using conventional equations, eqs 1 and 2.

$$\Delta G^\circ = -RT \ln(K_{\text{eq}}), \quad K_{\text{eq}} = [a']/[a''] \quad (1)$$

$$\Delta G = -RT \ln(k_T h/k_b T_{\text{coal}}), \quad k_T = (\pi \Delta \nu / 2) \quad (2)$$

The ratio of the two isomers (57:43) at -80 °C (193 K) resulted in a ΔG° of 0.2 kcal mol⁻¹. From the chemical shift difference of *a'* and *a''* (164.7 Hz) and the

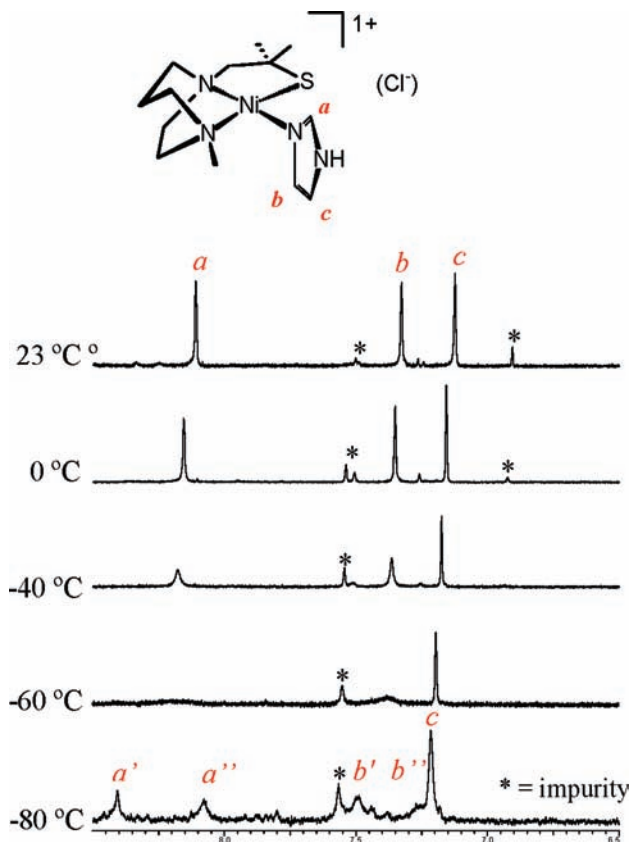


Figure 12. Variable Temperature 400-MHz ^1H NMR spectra of complex **3** in MeOH.

coalescence temperature (213 K), eq 2 gives ΔG^\ddagger equal to $8.9 \text{ kcal mol}^{-1}$.

There are four possible isomers of **3** (Figure 13). Isomer **A** depicts the molecular structure as determined by X-ray crystallography. Isomer **B** leaves the imidazole orientation unchanged but the NiN_2C_3 metallocyclooctane ring is converted from chair to boat conformation. Isomers **C** and **D** are analogous to **A** and **B**, respectively, but with the imidazole ring inverted. While the lowest energy gas phase DFT-calculated structure is isomer **C**, solvent correction indicates that in MeOH isomer **A**, the experimentally found structure, is of lowest energy (more stable than **C** by 0.68 kcal/mol). The stability of **A** in polar solvent over **C** is attributed to the differences of the dipole moments of the two complexes; the dipole moment in **A** is calculated to be 6.59 and in **B** it is 6.11 . In both the gas phase and in solvent, the calculated difference in energy between the two complexes is relatively small. DFT calculations were used to examine activation barriers to proton site equilibration due to the ring flip in the diazacycle backbone (**A** vs **B** or **C** vs **D**) or to rotation of the coordinated imidazole (**A** vs **C** or **B** vs **D**).

Note that the calculated ΔG° value of isomers **A** versus **B** and **C** versus **D** would correspond to an isomer ratio of $\sim 33,000:1$ and $\sim 700:1$, respectively. At these ratios, only one set of signals in the NMR spectra would be observable at low temperatures. On the basis of these values, the fluxional process that most likely corresponds to the signals seen in the NMR spectra is the rotation of the imidazole ring that equilibrates isomers **A** and **C**.

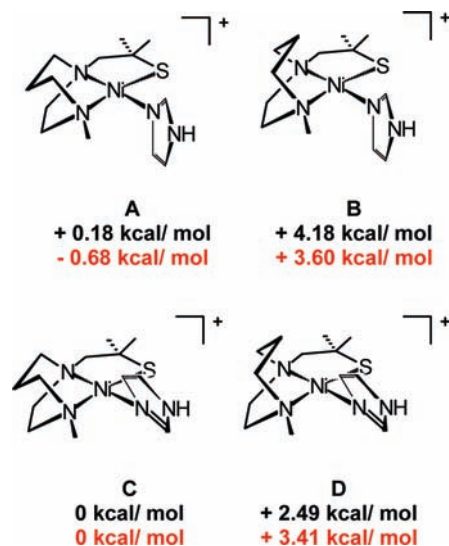


Figure 13. Four possible conformational isomers of **3** and their DFT calculated relative energies (ΔG°). Black: gas phase; red: solvent correction in MeOH.

The DFT calculated barriers for the processes that interconvert the four isomers are given in Figure 14. As shown in Figure 14a, starting from the structure of **3** determined crystallographically, isomer **A**, the DFT calculated ΔG^\ddagger for the ring flip in the diazacycle backbone from the chair to the boat conformation, achieving a transition state where the C_3N to N linker is fairly flat, is $7.02 \text{ kcal mol}^{-1}$. Calculations carried out for the ring flip of the isomer with the imidazole rotated 180° as compared to the solid state structure, isomer **B**, resulted in a ΔG^\ddagger of $6.59 \text{ kcal mol}^{-1}$ (Figure 14(b)). The DFT-calculated ΔG^\ddagger of $8.86 \text{ kcal mol}^{-1}$ for the conversion of isomer **A** to **C**, that is, rotation of the imidazole as seen in Figure 14c, passing through a transition state where the imidazole plane is roughly within the NiN_2S plane, is strikingly similar to the experimental value obtained from the VT NMR study. Thus, the DFT calculations that aid interpretation of experimental results suggest that the separate isomers seen at low temperature are due to cessation of imidazole rotation about the $\text{Ni}-\text{N}$ bond. Furthermore, the calculations suggest there is little difference in energy between the two rotational isomers of **3** ($< 0.2 \text{ kcal mol}^{-1}$), and this is also indicated in the experimental ^1H NMR data which by the ratio of isomers is about 1 at -80°C .

Reactivity Studies with Small Molecules (O_2^- , O_2 , and H_2O_2). Complexes **3–5** have been examined for superoxide reactivity using the nitroblue tetrazolium (NBT) assay. This qualitative test based on the reduction of NBT by O_2^- is detected by the change of colorless NBT to the blue formazan ($\lambda_{\text{max}} = 580 \text{ nm}$, $\sim 30,000 \text{ M}^{-1} \text{ cm}^{-1}$; Figure 15).⁴⁴ The presence of an active SOD inhibits the color formation by scavenging the O_2^- radical. Figure 16 shows the results of addition of solid K_2O_2 (100 equiv per mole of NBT) to a ($61 \mu\text{M}$) aqueous NBT solution (phosphate buffer, pH 7.4). Note that the limited solubility of formazan in aqueous solution causes a decrease in the absorbance over time.

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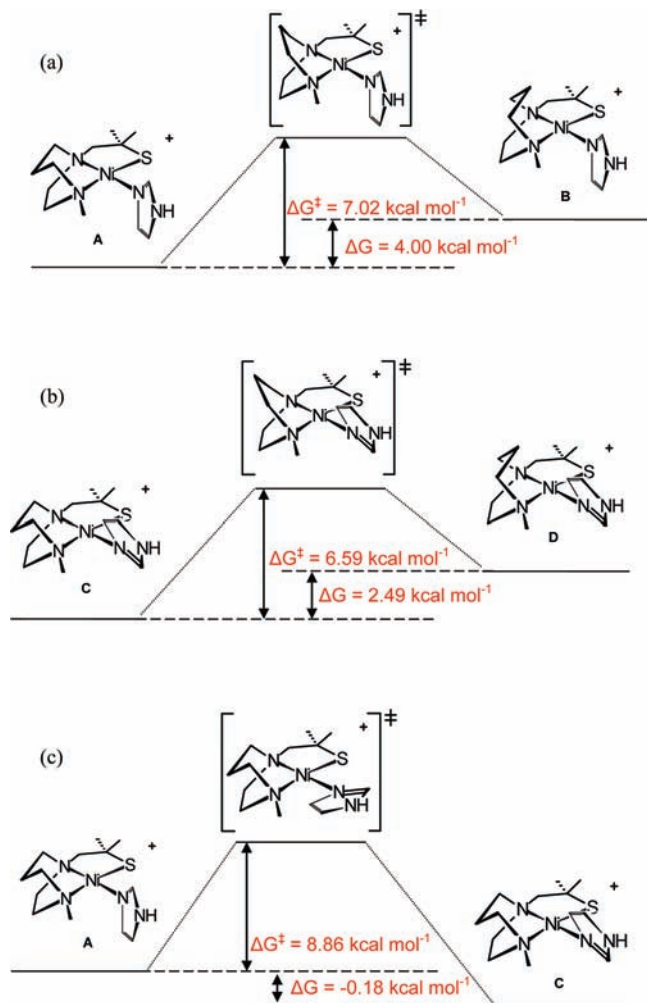


Figure 14. DFT calculated energies (kcal mol^{-1}): (a) Ring flip calculated with imidazole orientation same as in solid state structure; (b) Ring flip calculated with imidazole orientation 180° rotated as compared to (a); (c) imidazole rotation calculated with NiN_2C_3 ring in chair conformation.

Under the same conditions employed in the control experiment and in the presence of complex **3** ($69 \mu\text{M}$), a 40% decrease in the intensity of the band centered at 580 nm was observed, indicating a decrease in formazan production (Figure 17a). This result suggests that **3** possesses superoxide scavenging properties that prevent a portion of the NBT from reacting with O_2^- and at a rate competitive with NBT. In addition, intense bubble formation, much more than with formazan in the absence of **3**, was observed within the first 30 s following KO_2 addition. It should be noted that there is no indication of catalytic O_2^- decomposition. The addition of solid KO_2 to concentrated solutions of complex **3**, resulted in a shift in the d-d band from 464 to 471 nm and a new band appeared at 350 nm (Figure 17b), suggesting that a new nickel species is formed.

The ability of complexes **4** and **5**, and (bme-dach)Ni, as well as NiCl_2 , to inhibit NBT superoxide reactivity was screened by identical experiments. Under both low and high concentrations, none inhibited the production of formazan.

Complex **3** was screened for reactivity with the products of superoxide dismutation, O_2 and H_2O_2 .

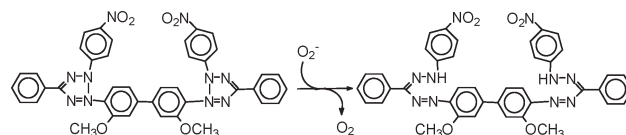


Figure 15. Nitroblue tetrazolium (NBT) reaction with superoxide to produce formazan.

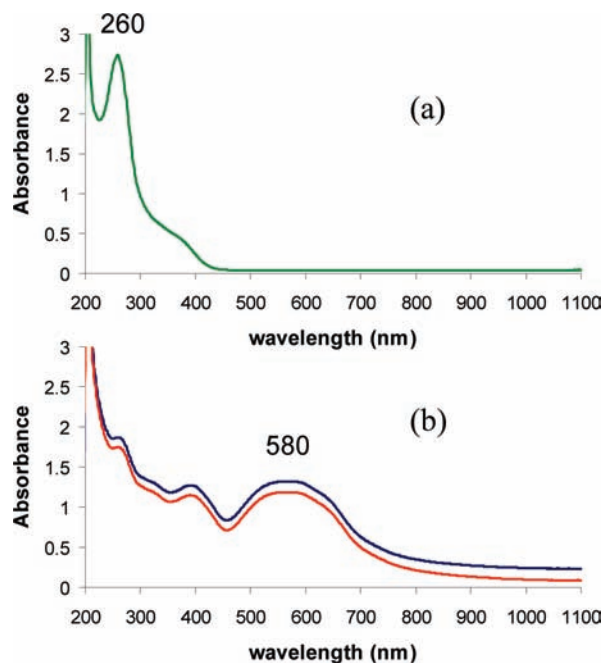


Figure 16. Electronic spectra of (a) NBT in aqueous phosphate buffer (pH 7.4). (b) Blue, addition of 100 equiv of KO_2 ; red, 5 min after addition (formation of insoluble formazan decreases intensity).

Molecular oxygen was bubbled through a MeOH solution of complex **3**. No oxygenation products were observed, and only the starting material was recovered. Upon addition of H_2O_2 (10 mM) to complex **3** dissolved in MeOH, an immediate color change from orange to yellow was observed. The molecular formulas and predicted isotope envelopes for both the mono-oxygenated and bis-oxygenated derivatives of complex **3** were observed in the ESI-MS spectrum (Supporting Information, Figure S10). These results indicate that complex **3** is stable to aerobic oxidation, and only strong oxidants are capable of oxidizing the Ni-bound $\text{N}_2\text{N}'\text{S}$ ligand.

Summary and Remarks

Complexes **3** and **4** presented above are, to our knowledge, the first molecular structures of compounds containing both an S-thiolate and N-imidazole donor atom in the first coordination sphere of Ni^{II} . The use of the (bme-dach)Ni complex and the dimeric dithiolate bridged Ni^{II} dication as precursor reagents in the preparation of the $\text{Ni}(\text{N}_2\text{N}'\text{S})$ complexes resulted in similar solid state structures for complexes containing both tethered and untethered imidazole ligands. That the diazacycloheptane N_2 “backbone” plays a stabilizing role in these complexes is highly reasonable. The following salient points are to be noted.

Imidazole Ligand Geometrical Orientation in Square Planar Ni^{II} Complexes. While severe ligand restrictions

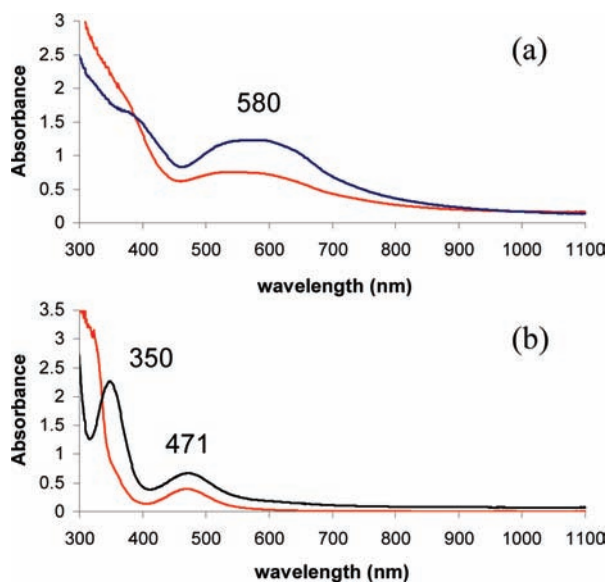


Figure 17. Electronic spectra of **3** in phosphate buffer (pH 7.4). (a) Blue, addition of 100 equiv of KO_2 to NBT ($61 \mu\text{M}$); red, addition of 100 equiv of KO_2 to NBT ($61 \mu\text{M}$)/complex **3** ($69 \mu\text{M}$). (b) Red, complex **3** (2.75 mM); black, addition of KO_2 to Complex **3** (0.46 mM)/NBT buffer solution (0.18 mM).

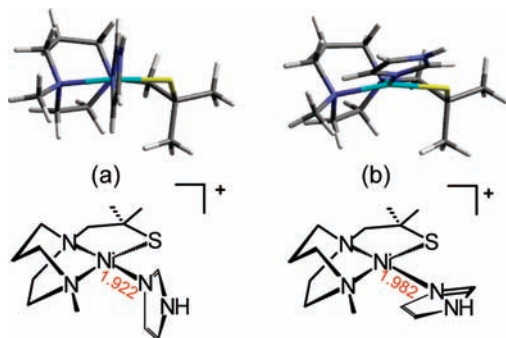


Figure 18. (a) DFT calculated ground state structure. (b) DFT calculated transition state structure.

position the imidazole ligand coplanar with the $\text{N}_2\text{N}'_2\text{Ni}^{\text{II}}$ plane of complex **5**, the solid state structures of complexes **3** and **4** revealed a preferred orientation of the imidazole donor ligand perpendicular to the $\text{N}_2\text{N}'\text{S}\text{Ni}^{\text{II}}$ plane. The solution phase VT ^1H NMR study of complex **3** demonstrated that the imidazole ligand freely rotates about the $\text{Ni}-\text{N}_{\text{imid}}$ bond at $22 \text{ }^\circ\text{C}$, with static structures appearing between -60 and $-80 \text{ }^\circ\text{C}$. Both the experimental and the DFT computed barriers to rotation are found to be $\sim 9 \text{ kcal mol}^{-1}$. The lowest energy DFT-calculated gas phase structure also found the imidazole plane to orient perpendicular to the $\text{N}_2\text{N}'\text{S}$ plane, but rotated 180° with respect to the crystallographically determined structure. Applying solvent corrections, the DFT lowest energy structure was calculated to be the same orientation as observed in the solid state. Thus, the built-in asymmetry of the diazacycloheptane ring provides subtle tuning of ligand orientation preferences.

The orientation of imidazole ligands in metalloenzyme active sites is well recognized to influence structure/function relationships such as midpoint redox potentials, electronic structure, spin states, electron transfer rates, and the coordination of substrates.⁴⁵ Furthermore, ligand rotational properties have been shown to contribute to significant factors affecting antitumor properties in ruthenium antitumor compounds.⁴⁶ The DFT computed transition state structure for imidazole rotation about the $\text{Ni}-\text{N}_{\text{imid}}$ bond in complex **3** positions the imidazole ligand roughly coplanar with the NiN_2S plane. In fact, elongation of the $\text{N}_{\text{imidazole}}-\text{Ni}$ bond distance by 0.06 \AA (from 1.922 in the DFT calculated ground state to 1.982 \AA in the transition state) is accompanied by distortion (a Td twist defined by the intersection of the N_2Ni and $\text{SN}_{\text{imid}}\text{Ni}$ planes, of 21.2°), Figure 18. The preferred orientation may be a product of steric and/or electronic effects, studies of which are currently in progress.

Superoxide Reactivity. The nickel-imidazole complexes described above are all water-soluble and thus their potential for superoxide reactivity could be assessed in aqueous buffer via the NBT assay. Only complex **3** competed with the NBT scavenging of superoxide; complexes **4**, **5**, and $(\text{bme-dach})\text{Ni}$ did not and neither did simple salts such as NiCl_2 . As the NBT assay gives little information regarding the nature of interference from the coordination complex, we can regard these results as preliminary. This suggests the need for further examination of nickel complexes of various charge and redox properties such as we have in a catalog of such square planar Ni complexes.

Implications to Nickel Containing Biomolecules. An unsuccessful attempt was made to synthesize a NiSOD enzyme active site model complex from alkylation of a thiolate within an $\text{N}_2\text{S}_2\text{Ni}^{\text{II}}$ framework by chloromethylimidazole to thus incorporate a dangling imidazole (His mimic) with the capability of shifting into an axial binding position on oxidation of Ni^{II} to Ni^{III} . The resulting $\text{N}_2\text{N}'\text{S}_{\text{thiolate}}$ binding motif found for complex **4**, which matched that of complex **3**, was impressive of the good binding ability of imidazole nitrogen and its preference for the square plane of Ni^{II} . In the NiSOD enzyme active site, the axial His binding is governed by the protein superstructure, the position of the His residue next to the N-terminus that provides the amine ligation, the coordination of the strong carboxyamido N and S donors of one cysteine unit, and a second distal S-cysteine donor. This square planar coordination environment creates two favorable 5-membered rings, whereas the His ligand binding in the square plane in place of the N-terminus amine would result in one 5-membered ring and a less-favored 7-membered ring.

Interestingly, the $(\text{N}_{\text{imid}})_3\text{NiS}_{\text{cys}}$ “plane” of NikR, Figure 1, finds a range of N_{imid} plane orientations, canted so as to best accommodate the steric requirements.¹⁰ As nickel binding or release, with concomitant long-range protein structural changes, is an important feature of this site, specific orientations of the imidazole ligands are likely suspects as triggers of release and binding.

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Drennan, Zamble, and co-workers have demonstrated that other metal ions may bind in this site; however, the nickel form is reported to be $250\times$ more active.^{11b,47} Our $(\text{N}_2\text{N}'\text{S})\text{Ni}$ complexes are suitable as first coordination sphere molecular models of the Ni-binding site of the Nik-R protein and are expected to be useful for selectivity and relative binding affinity studies of physiologically relevant metal ions.

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Note Added in Proof: During the review of this manuscript, Harrop and co-workers reported a similar $(\text{N}_2\text{S})_2\text{Ni}_2$ dimer cleavage reaction as a versatile route to NiSOD biomimetics. (Gale, E. M.; Patra, A. K.; Harrop, T. C. *Inorg. Chem.* **2009**, *ASAP*.)

Supporting Information Available: Summary of crystallographic data for complexes **1–5**, packing diagram of complex **4**, electrochemical data, experimental and optimized parameters for complexes **3** and **4**, DFT calculated energies and compositions of frontier molecular orbitals of complexes **3** and **4**, DFT predicted ^1H NMR predictions for the imidazole protons of complex **3**, ESI-MS data for oxygenated derivatives of complex **3**, and full citation for the Gaussian 03 program (ref 30). This material is available free of charge via the Internet at <http://pubs.acs.org>.