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Tridentate N₂S ligand from 2,2'-dithiodibenzaldehyde and N,N-dimethylethylenediamine: Synthesis, structure, and characterization of a Ni(II) complex with relevance to Ni Superoxide Dismutase

Joshua R. Zimmerman, Bradley W. Smucker[†], Ryan P. Dain, Michael J. VanStipdonk, and David M. Eichhorn

Department of Chemistry, Wichita State University, Wichita, KS 67260-0051

Abstract

Nickel Superoxide Dismutase (NiSOD) and the A-cluster of Carbon Monoxide Dehydrogenase/Acetyl Coenzyme A Synthase (CODH/ACS) both feature active sites with Ni coordinated by thiolate and amide donors. It is likely that the particular set of donors is important in tuning the redox potential of the Ni center(s). We report herein an expansion of our efforts involving the use of 2,2'-dithiodibenzaldehyde (DTDB) as a synthon for metal-thiolate complexes to reactions with Ni complexes of N,N-dimethylethylenediamine (dmen). In the presence of coordinating counterions, these reactions result in monomeric square-planar complexes of the tridentate N₂S donor ligand derived from the Schiff-base condensation of dmen and DTDB. In the absence of a coordinating counterion, we have isolated a Ni(II) complex with an asymmetric N₂S₂ donor set involving one amine and one imine N donor in addition to two thiolate donors. This latter complex is discussed with respect to its relevance to the active site of NiSOD.

Keywords

X-ray crystal structure; Nickel complex; N and S containing ligand

1. Introduction

Interest in the bioinorganic chemistry of nickel has increased recently, with the discovery of two new metalloenzymes known to contain Ni at their active sites, bringing to six the number of established Ni-containing enzymes. [1] Ni Superoxide Dismutase (NiSOD) [2] and the bifunctional enzyme Carbon Monoxide Dehydrogenase/Acetyl Coenzyme A Synthase (CODH/ACS) [3], distinguish themselves by the unusual use of deprotonated amide donors from the peptide backbone and with the presence of thiolate donation to the active site metal. CODH/ACS is a tetrameric $\alpha_2\beta_2$ enzyme which catalyzes reversible CO₂

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Correspondence to: David M. Eichhorn.

[†]current address, Department of Chemistry, Austin College, Sherman, TX 75090

5. Supplementary Information. CCDC 811845 – 811853 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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reduction in the β domain and, in the α domain, assembly of acetyl CoA from CoA, a methyl group delivered by a corrinoid FeS protein, and CO delivered from the β domain. The active site cluster of the α domain, known as the A-cluster (Figure 1a), is comprised of an Fe_4S_4 cubane bridged by a cysteine thiolate to an asymmetric dinuclear Ni cluster. Three crystal structures of CODH/ACS have been reported [4], leading ultimately to a consensus structure for the A-cluster. The square-planar Ni_2S_2 coordination geometry of the distal Ni atom (Ni_d) comes from a Cys-Gly-Cys section of the peptide, with coordination of two of the backbone amide N atoms and the two cysteine thiolates, which bridge to the proximal Ni atom (Ni_p). The S_3X coordination of Ni_p consists of the three cysteine thiolates which bridge to the FeS cube and Ni_d and a diatomic exogenous N or O donor ligand.

NiSOD is the most recently discovered superoxide dismutase, a class of enzymes which catalyze the disproportionation of superoxide to dioxygen and hydrogen peroxide. Unlike FeSOD, MnSOD, and Cu/ZnSOD, NiSOD contains an active-site metal whose aqueous reduction potential is far outside the range necessary to catalyze superoxide disproportionation, implicating the unusual donor set in tuning the potential for this process. As established by two crystal structures, the active site of reduced NiSOD (Figure 1b) has a geometry related to that of Ni_d in the CODH/ACS A-cluster – the square-planar Ni(II) center is coordinated by two cysteine thiolates and the deprotonated amide of Cys2, with the N-terminal amine of His1 providing the fourth donor. During the catalytic cycle, the Ni center is oxidized to Ni(III), accompanied by coordination of the imidazole N of His1 to create a five-coordinate square-pyramidal site [5].

One interesting feature shared by these two active sites is coordination of the Ni by deprotonated amide donors from the polypeptide chain. While it is common for metalloproteins to have N donation to the active site metal, the vast majority utilize the imidazole N atom of the histidine side chain for this purpose – only a handful of examples have been documented with amide coordination. In order to shed some light on this unusual donor, we have been pursuing an effort to synthesize active site models for enzymes containing mixed N/S coordination which includes amide N donors [6]. Our approach is to synthesize two sets of models – one containing imine N coordination, which would represent the “normal” imidazole coordination, and a second containing amide coordination, but otherwise identical to the first set. Comparison of these two sets will yield information about the function of the amide ligands in the enzyme systems.

The results reported herein were motivated by an effort to synthesize imine-containing models for the dinuclear Ni portion of the CODH/ACS A-cluster. There are many examples in the literature of *symmetric* Ni dimers with two thiolate bridges. However, there are very few reports of asymmetric bis(thiolate)-bridged Ni dimers [7], and none in which all the donors are biologically relevant. A minimal requirement for a structural model of the A-cluster is an asymmetric dinuclear Ni species with NS_3 donation at one Ni and N_2S_2 donation at the other. We have been developing, for the past decade, a methodology for the synthesis of metal complexes with mixed N/S donation using 2,2'-dithiodibenzaldehyde (DTDB) as an air-stable reactant to provide the thiolate donation without the need for cumbersome protection and deprotection steps [6,8]. This methodology (Scheme 1) involves the reaction of DTDB with metal complexes containing coordinated primary amines, resulting in Schiff-base condensation with the aldehyde functionality of DTDB and concomitant cleavage of the disulfide to provide the thiolate donor. Among the complexes we have reported using this methodology is a symmetric bis(thiolate)-bridged Ni dimer using $\text{Ni}(\text{aet})_2$ as a reactant (Haet = 2-aminoethanethiol). Both Ni atoms in this product have NS_3 coordination environments, reminiscent of Ni_p in CODH/ACS. We have also reported reactions involving ethylenediamine (en). With Fe(III) and Co(III), these resulted in a tridentate N_2S -donor ligand formed by reaction of DTDB at only one of the primary amines

– two of these ligands complete the octahedral coordination environment [8a]. With Cu(II) and Ni(II), however, DTDB condensed with both amines to give M(tsalen), complexes with the metal in an N₂S₂ coordination environment [8b]. A possible route to a first-generation model for the dinuclear Ni portion of the A-cluster would combine these two coordination environments, using the tridentate NS₂ ligand derived from Haet and a tridentate N₂S ligand derived from en. In order to prevent formation of the tetradentate tsalen ligand, we envision using N,N-dimethylethylenediamine (dmen), which has only one primary amine available for Schiff-base formation. We report herein investigations into the reactivity of dmen, DTDB, and nickel, producing complexes of the tridentate ligand 2-[(2-dimethylamino-ethylimino)-methyl]-benzenethiol (NNS). As a result of this investigation, we have isolated the first complex of Ni(II) with one amine, one imine and two thiolate donors - a complex with relevance to the active site of NiSOD.

2. Experimental

2.1. General Experimental

Unless otherwise stated, all solvents and reagents were used as received from Aldrich, Acros, and Fisher Scientific without further purification. 2,2'-dithiodibenzaldehyde was synthesized by literature methods [9]. When dry methanol is specified, it was distilled from NaOMe. IR spectra were recorded on a Nicolet Avatar 360 FTIR. Electrospray mass spectra were obtained on a Finnigan LCQ DECA spectrometer. UV-Vis data was collected on a Hitachi U-2010 spectrophotometer. Electrochemical data was collected on an EG & G Princeton Applied Research potentiostat model 263A with a Pt working electrode, Pt counter electrode, and Ag/AgCl reference electrode. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ. For the X-ray structures, crystals were selected under a polarizing microscope, affixed to a nylon cryoloop (Hampton Research) or glass filament using oil (Paratone-n, Exxon), and mounted in the cold stream of a Bruker Kappa – ApexII area detector diffractometer. The temperature at the crystal was maintained at 150 K using a Cryostream 700 EX low – temperature apparatus (Oxford Cryosystems). The unit cells were determined from the setting angles of the reflections collected in 36 frames of data. Data were measured using graphite monochromated molybdenum K_α radiation ($\lambda = 0.71073 \text{ \AA}$) collimated to a 0.6 mm diameter and a CCD detector at a distance of 50 mm from the crystal with a combination of phi and omega scans. A scan width of 0.5 degrees and scan time of 10 seconds were employed. Data collection, reduction, structure solution, and refinement were performed using the Bruker Apex2 suite (v2.0-2) [10]. All available reflections to $2\theta_{\text{max}} = 52^\circ$ were harvested and corrected for Lorentz and polarization factors with Bruker SAINT (v6.45) [11]. Reflections were then corrected for absorption, interframe scaling, and other systematic errors with SADABS 2004/1 [12]. The structures were solved (direct methods) and refined (full-matrix least-squares against F^2) with the Bruker SHELXTL package (v6.14-1) [13]. All non-hydrogen atoms, except the disordered C atoms in **7**, were refined using anisotropic thermal parameters. Hydrogen atoms were included at ideal positions (except on the disordered C atoms in **7**) and were not refined. X-ray data collection and structure solution parameters for all structures are listed in Table 1.

2.2. [Ni(NNS)Cl] (**1**)

A solution of 2,2'-dithiodibenzaldehyde (100 mg, 0.37 mmol) in 50 mL of MeOH is heated to reflux. To the refluxing solution is added dropwise a solution of N,N-dimethylethylenediamine (64 mg, 0.73 mmol) in 10 mL of methanol. The solution turns orange within 1 min, and NiCl₂·6 H₂O (173 mg, 0.73 mmol) is added. The solution immediately turns brown and is degassed by bubbling N₂ gas. The solution is then heated at reflux under nitrogen for 30 min. The methanol is removed by rotary evaporation, resulting in a brown solid, which is washed with CH₂Cl₂ to give **1** as a brown solid (210 mg, 0.70

mmol, 96%). X-ray quality crystals were formed by slow evaporation of a methanol solution. Elem. Anal. Found (Calculated for $C_{11}H_{15}N_2SnCl$): C, 43.58 (43.83); H, 5.12 (5.02); N, 9.10 (9.29). IR (KBr pellet, cm^{-1}) 1604, 1587, 1533, 1460, 1406, 1221, 1126, 1071, 1055, 1028, 1004, 957, 784, 756, 723. UV/Vis (acetonitrile); $\lambda_{max} = 449$ nm; $\epsilon = 1660$ $M^{-1}cm^{-1}$. ESI – MS (positive mode, MeOH, m/z): 265 $[Ni(NNS)]^+$, 283 $[Ni(NNS)(H_2O)]^+$, 297 $[Ni(NNS)(MeOH)]^+$. Electrochemistry (acetonitrile; 0.1M NEt_4ClO_4 ; E_c/E_a (mV) vs Ag/AgCl): 780, 1084/1192, -1072/-996, -1320.

2.3. $[Ni(NNS)NO_3]$ (2)

Under nitrogen, $Ni(NO_3)_2 \cdot 6H_2O$ (212 mg, 0.73 mmol) in 40 mL of methanol is added dropwise to a solution of 2,2'-dithiodibenzaldehyde (100 mg, 0.365 mmol) in 50 mL of CH_2Cl_2 . N,N-dimethylethylenediamine (64 mg, 0.73 mmol) in 10 mL of methanol is added by dropping funnel to the stirring solution at room temperature. The solution slowly turns red while continuously stirring under nitrogen for 24 hrs. A brown solid is formed as the solvents are removed by rotary evaporation. The product is dissolved in CH_2Cl_2 , to which diethyl ether is added, resulting in a brown precipitate (181 mg, 0.55 mmol, 76%). X-ray quality crystals were formed by diffusion of diethyl ether into a CH_2Cl_2 solution. Elem. Anal. Found (Calculated for $C_{11}H_{15}N_3O_3Sn$): C, 40.39 (40.29); H, 4.82 (4.61); N, 12.64 (12.81). IR (KBr pellet, cm^{-1}) 1613, 1588, 1538, 1491, 1451, 1384, 1287 (NO_3^-), 1219, 1130, 1083, 1067, 906, 786, 754, 719. UV/Vis (acetonitrile); $\lambda_{max} = 419$ nm; $\epsilon = 2800$ $M^{-1}cm^{-1}$. ESI MS (positive mode, MeOH, m/z): 265 $[Ni(NNS)]^+$, 283 $[Ni(NNS)H_2O]^+$, 297 $[Ni(NNS)(MeOH)]^+$. Electrochemistry (acetonitrile; 0.1M NEt_4ClO_4 ; E_c/E_a (mV) vs Ag/AgCl): 888, 1232, -1046/-968.

2.4. $[Ni(NNS)NO_2]$ (3)

Under nitrogen, a solution of 2,2'-dithiodibenzaldehyde (250 mg, 0.91 mmol) in 25 mL of dry methanol is heated to reflux. To the refluxing solution is added dropwise a solution of N,N-dimethylethylenediamine (161 mg, 1.83 mmol) in 5 mL of dry methanol. The solution turns orange within 5 min, and $Ni(NO_3)_2 \cdot 6H_2O$ (530 mg, 1.82 mmol) dissolved in 25 mL of dry methanol is added. The solution is heated at reflux for 30 min. and the solvent is removed by rotary evaporation. The resulting brown solid is extracted with CH_2Cl_2 . Filtration and removal of the CH_2Cl_2 by rotary evaporation gives **3** as a red solid (450 mg, 1.44 mmol, 80%). X-ray quality crystals were formed by slow evaporation of a 1:1 acetonitrile, toluene solution. Elem. Anal. Found (Calculated for $C_{11}H_{15}N_3O_2Sn \cdot H_2O$): C, 39.18 (40.04); H, 5.11 (5.19); N, 12.58 (12.73). IR (KBr pellet, cm^{-1}) 1611, 1587, 1536, 1456, 1406, 1376, 1330 (NO_2^-), 1130, 901, 819 (NO_2^-), 784, 760. UV/Vis (acetonitrile); $\lambda_{max} = 425$ nm; $\epsilon = 1210$ $M^{-1}cm^{-1}$. ESI – MS (positive mode, CH_3CN , m/z): 265 $[Ni(NNS)]^+$, 306 $[Ni(NNS)(CH_3CN)]^+$. Electrochemistry (acetonitrile; 0.1M NEt_4ClO_4 ; E_c/E_a (mV) vs Ag/AgCl): 832, 1296, -1104/-972, -1336.

2.5. $[Ni(dmen)_2(H_2O)_2](NO_3)_2$ (4)

N,N-dimethylethylenediamine (608 mg, 6.9 mmol) in 5 mL of acetonitrile is added dropwise to a solution of $Ni(NO_3)_2 \cdot 6H_2O$ (1.0 g, 3.4 mmol) in 50 mL of acetonitrile. After stirring for 10 min, the solvent is removed by rotary evaporation, leaving **4** as a blue solid (1.24 g, 3.13 mmol, 92%). X-ray quality crystals were formed by slow evaporation of an acetonitrile solution. Elem. Anal. Found (Calculated for $C_8H_{24}N_6O_6Ni \cdot 2H_2O \cdot CH_3CN$): C, 27.54 (26.58); H, 7.16 (6.42); N, 22.48 (22.04). IR (KBr pellet, cm^{-1}) 1599, 1475, 1394, 1325, 1293, 1190, 1117, 1146, 1062, 1029, 1006, 934, 884, 825, 782. ESI – MS (positive mode, MeOH, m/z): 208 $[Ni(dmen)(NO_3)]^+$, 296 $[Ni(dmen)_2(NO_3)]^+$

2.6. [Ni(dmen)₂(H₂O)(CH₃CN)](BF₄)₂ (5)

N,N-dimethylethylenediamine (518 mg, 5.8 mmol) in 5 mL of methanol is added dropwise to a solution of Ni(BF₄)₂·6H₂O (1.0 g, 2.9 mmol) in 50 mL of methanol. The solution turns blue and is stirred for 10 min, after which the solvent is removed by rotary evaporation, yielding **5** as a blue solid (1.5 g, 2.8 mmol, 98%). X-ray quality crystals were formed by slow evaporation from acetonitrile. Elem. Anal. Found (Calculated for C₈H₂₄N₄B₂F₈Ni·2H₂O): C, 22.02 (21.61); H, 6.03 (6.35); N, 11.87 (12.60). IR (KBr pellet, cm⁻¹) 1598, 1476, 1293, 1112, 1062, 1036, 935, 885, 783, 630. ESI – MS (positive mode, MeOH, m/z): 177 [Ni(dmen)(MeOH)]⁺, 233 [Ni(dmen)₂]⁺, 351 [Ni(dmen)₂(BF₄)(MeOH)]⁺.

2.7. [Ni(dmen)₂(CH₃CN)₂](PF₆)₂ (6)

A solution of KPF₆ (0.93 g, 5.0 mmol) in 50 mL of acetonitrile is added dropwise to a solution of **4** (1.0 g, 2.5 mmol) in 50 mL of acetonitrile. The solution turns purple and a white precipitate is deposited. After stirring for 5 min, the solution is filtered and the filtrate condensed to 25 mL. Addition of 100 mL of diethyl ether results in the deposition of **6** as a purple solid (1.3 g, 2.3 mmol, 93%). Elem. Anal. Found (Calculated for C₈H₂₇N₄P₂F₁₂Ni·CH₃CN): C, 22.04 (21.22); H, 4.54 (4.81); N, 12.53 (12.37). IR (KBr pellet, cm⁻¹) 1636, 1597, 1476, 1292, 1134, 1108, 1063, 1028, 1006, 935, 834, 782, 558. ESI – MS (positive mode, MeOH, m/z): 177 [Ni(dmen)(MeOH)]⁺, 233 [Ni(dmen)₂]⁺.

2.8. [Ni(dmen)₂(CH₃CN)₂](BPh₄)₂ (7)

A solution of NaBPh₄ (1.7 g, 5.0 mmol) in 50 mL of acetonitrile is added to a solution of **4** (1.0 g, 2.5 mmol) in 50 mL of acetonitrile. The solution turns purple and a white precipitate is deposited. After stirring for 5 min, the solution is filtered and the solvent removed by rotary evaporation, leaving **7** as a light purple solid (2.4 g, 2.4 mmol, 97%). X-ray quality crystals were formed by slow evaporation from acetonitrile. Elem. Anal. Found (Calculated for C₅₆H₆₄N₂B₂Ni·2 H₂O·2 CH₃CN): C, 73.38 (72.68); H, 7.07 (7.52); N, 8.60 (8.48). IR (KBr pellet, cm⁻¹) 1953, 1889, 1829, 1578, 1477, 1383, 1286, 1268, 1182, 1154, 1058, 1032, 998, 931, 836, 778, 734, 708, 612. ESI – MS (positive mode, MeOH, m/z): 147 [Ni(dmen)]⁺, 177 [Ni(dmen)(MeOH)]⁺, 233 [Ni(dmen)₂]⁺.

2.9. [Ni(NNS)(Im⁺S)]BPh₄ (8)

A 250 mL round bottom flask is charged with 2,2'-dithiodibenzaldehyde (100 mg, 0.365 mmol), **7** (320 mg, 0.365 mmol), and NaOH (100 mg, 2.5 mmol), to which 100 mL of CH₂Cl₂ is added. Nitrogen is bubbled through the solution for 15 min, then the flask is stoppered and the solution stirred for 24 hrs. The solution is filtered and the solvent is removed by rotary evaporation to give **8** as a red solid (154 mg, 0.195 mmol, 53%). X-ray quality crystals were formed by slow evaporation of a CH₂Cl₂ solution. Elem. Anal. Found (Calculated for C₄₄H₄₉N₄BS₂Ni · 2 CH₂Cl₂): C, 60.07 (59.97); H, 5.29 (5.56); N, 5.59 (5.83). IR (KBr pellet, cm⁻¹) 1699, 1608, 1590, 1579, 1533, 1458, 1425, 1406, 1247, 1221, 1128, 1068, 1030, 1009, 954, 927, 753, 734, 707. UV/Vis (acetonitrile); λ_{max} = 435 nm; ε = 1620 M⁻¹cm⁻¹. ESI – MS (positive mode, CH₃CN, m/z): 265 [Ni(NNS)]⁺, 306 [Ni(NNS)(CH₃CN)]⁺, 471 [Ni(NNS)(Im⁺S)]⁺. Electrochemistry (acetonitrile; 0.1M NEt₄ClO₄; E_c/E_a (mV) vs Ag/AgCl): 756, 976, 1184/1296, -1268.

2.10. 2-(2-Dimethylamino-ethyl)-benzo[d]isothiazol-2-ium tetraphenylborate (9)

To a 250 mL round bottom flask containing a solution of DTDB (100 mg, 0.37 mmol) in 100 mL of dry CH₂Cl₂ was added 319 mg (0.37 mmol) of solid **7**. The slurry was stirred and degassed with nitrogen. After stirring for 3 days at room temperature under a N₂ atmosphere, a portion of the solution was transferred to an Erlenmeyer flask. Slow evaporation of the solvent resulted in the formation of X-ray quality crystals.

3. Results and Discussion

Our previous studies with DTDB involved two different reaction paradigms – (i) reaction of DTDB with a preorganized complex of the metal and the reagent ligand (i.e., DTDB + Ni(aet)₂) or (ii) a ternary reaction of DTDB, the appropriate reagent ligand, and a metal salt. In either case, the reaction results in cleavage of the DTDB disulfide bond to produce a thiolate ligand – the reductant for this process has yet to be identified. The studies involving DTDB and dmen were initiated using method (ii) with NiCl₂ and Ni(NO₃)₂ (Scheme 1). In both cases, the desired N₂S ligand is formed. However, instead of forming a dimeric product, as was the case with the NS₂ ligand derived from Haet, a monomeric product is formed with the anion occupying the fourth coordination site. Mercury [14] thermal ellipsoid drawings of [Ni(NNS)Cl] (**1**) and [Ni(NNS)NO₃] (**2**) are shown in Figure 2, with X-ray data collection and structure solution parameters given in Table 1 and selected bond distances and angles in Table 2. Complex **1** crystallizes on a general position in the orthorhombic space group Pna2₁, while **2** crystallizes on a general position in the monoclinic space group P2₁/n. The tridentate ligand binds, as expected through the amine and imine N atoms and the thiolate S atom, forming 5- and 6-membered chelate rings, with the square-planar coordination completed by a chloride and a monodentate nitrate ion, respectively. The phenyl ring makes an angle of 12.48° and 18.52° with respect to the mean plane of the coordination sphere for **1** and **2**, respectively, and the nitrate ligand in **2** extends below the coordination plane in the same direction as the phenyl ring. All bond distances and angles are unexceptional for Ni(II) complexes.

Complex **1** was synthesized, under nitrogen, by first adding dmen in MeOH to a refluxing solution of DTDB in MeOH and then adding NiCl₂·6H₂O to this solution and continuing the reflux for 30 min. Complex **2** was synthesized, at room temperature under nitrogen, by combining a solution of DTDB in CH₂Cl₂ with a solution of Ni(NO₃)₂·6H₂O in MeOH, followed by a slow addition of dmen in MeOH. An alternate synthesis using Ni(NO₃)₂·6H₂O, but with the procedure used to form **1**, resulted in the isolation of [Ni(NNS)NO₂] (**3**), in which the nitrate ion has been reduced to nitrite. A thermal ellipsoid diagram of **3** is shown in Figure 3, with X-ray data collection and structure solution parameters given in Table 1 and selected bond distances and angles in Table 2. Complex **3** crystallizes on a general position in the monoclinic space group P2₁/c, with a structure similar to those of **1** and **2**. The nitrite ion is coordinated *via* the N atom.

As indicated above, we expected that the reactions with dmen would result in a dimeric species similar to that realized with Haet, but with the Ni atoms in N₂S₂ coordination environments. In such a [Ni(NNS)₂]X₂ dimer, the two Ni atoms would be bridged by the phenylthiolate S atoms derived from the DTDB synthon (Scheme 1, bottom left). Clearly, the coordinating anion, X, prevents this from happening, resulting instead in monomeric species in which X completes the square-planar coordination sphere. In order to avoid this pathway, chloride and nitrate were replaced with less coordinating anions. The approach adopted for this purpose was to first synthesize preorganized [Ni(dmen)₂]X₂ complexes (X = BF₄, PF₆, and BPh₄). The NO₃ (**4**) and BF₄ (**5**) complexes were prepared by reaction of dmen with Ni(NO₃)₂·6H₂O and Ni(BF₄)₂·6H₂O, respectively. The PF₆ (**6**) and BPh₄ (**7**) complexes were then synthesized by anion-exchange reactions with **4**. X-ray quality crystals of all four complexes were isolated – thermal ellipsoid diagrams of the molecules are shown in Figures 4 (**4** and **5**) and S1 (**6** and **7**). X-ray data collection and structure solution parameters are given in Table 1 and selected bond distances in Table 3. The molecules in **4** and **6** crystallize on inversion centers in the space groups P2₁/c and C2/c, respectively – there are two molecules in the asymmetric unit of **4**. The molecules in **5** and **7** crystallize on general positions in the space groups P2₁2₁2₁ and P2₁/c, respectively. All four complexes feature octahedral Ni dications with coordination of two molecules of dmen and two solvent

molecules – water in **4**, acetonitrile in **6** and **7** and one molecule each of water and acetonitrile in **5**. This is in concert with other reported crystal structures of Ni with dmen [15] – all have two molecules of dmen coordinated to Ni and all except one are octahedral with two other ligands completing the coordination sphere (one structure [15d] has been reported of square-planar $\text{Ni}(\text{dmen})_2^{2+}$). In contrast, structures have been reported with ethylenediamine with either two or three en ligands bound to Ni [16]. One of the dmen ligands in **7** is slightly disordered, with two positions modeled for the methylene C atoms and one of the methyl C atoms. In **4** and **6**, the two dmen ligands form the equatorial plane, with solvent ligands occupying axial positions – the molecule displays crystallographically imposed inversion symmetry with the NMe_2 groups *trans* to each other. In **5** and **7** the solvent molecules are *cis* to each other in the coordination sphere, each solvent molecule being *trans* to a NH_2 group from a dmen ligand. Of the six previously reported structures of the type $\text{Ni}(\text{dmen})_2\text{X}_2$, only two display a *cis*- dmen_2 geometry [15a,b] – both of these structures have a geometry similar to those of **5** and **7**. As with the other $\text{Ni}(\text{dmen})_2\text{X}_2$ structures, Ni-N bond lengths in **4–7** are longer for the methylated N atoms than for the unmethylated N atoms.

With the $\text{Ni}(\text{dmen})_2$ complexes with non-coordinating anions in hand, reactions with DTDB were undertaken, but still failed to produce a dimeric Ni species. However, reaction of **7** with DTDB in the presence of excess NaOH produced a surprising monomeric four-coordinate Ni(II) species (Scheme 1). As with **1–3**, the tridentate NNS ligand occupies three of the coordination sites. With no coordinating anion present to complete the coordination sphere, the fourth coordination site is occupied by a thiolate ligand that is derived from a second equivalent of NNS – 1,1-dimethyl-2-(2-mercaptophenyl)-4,5-dihydroimidazolium (Im^+S^-). Attack of the dimethylamine N atom of NNS on the imine C atom would produce this quaternary ammonium heterocyclic species. A thermal ellipsoid diagram of $[\text{Ni}(\text{NNS})(\text{Im}^+\text{S})]\text{BPh}_4$ (**8**) is shown in Figure 5, with X-ray data collection and structure solution parameters given in Table 1 and selected bond distances and angles in Table 2. The complex crystallizes on a general position in the monoclinic space group $\text{P}2_1/\text{c}$ with two molecules of CH_2Cl_2 per Ni complex. As with **1–3**, the NNS ligand coordinates in a tridentate fashion and the Im^+S ligand occupies the fourth coordination site, binding through the thiolate S atom. The phenyl group of the NNS ligand is bent slightly out of the plane of the coordination sphere, with a dihedral angle of 15.26° . The phenyl group of the Im^+S ligand is essentially perpendicular to the plane of the coordination sphere, with a dihedral angle of 80.15° . As with the nitrate ligand in **2**, the phenyl group of the Im^+S ligand is situated on the same side of the plane of the coordination sphere as is the phenyl group of the NNS ligand.

Compound **8** is the first reported $\text{Ni}^{\text{II}}\text{N}_2\text{S}_2$ complex with an amine and an imine donor. It joins only six other species which, like the active site of reduced NiSOD, feature Ni^{2+} in an asymmetric $\text{NN}'\text{S}_2$ square-planar coordination site with two *cis* thiolate S donors and two *cis* N donors of different types. Like the NiSOD active site, one of the N donors in **8** is an amine N. The second N donor is an imine N in **8**, as compared to an amide N in NiSOD. The other complexes reported in the literature with $\text{NN}'\text{S}_2$ coordination geometries are two complexes reported by Harrop and coworkers with amide N and pyridyl N donors [17] and one complex reported by Shearer and coworkers with amide N and amine N donors [18]. Shearer and coworkers [19], Weston and coworkers [20], and Jackson and Laurence and coworkers [21] have also reported peptide-based complexes which, although not crystallographically characterized, likely have amide N and amine N donors to the Ni center. The crystallographically characterized complexes, like NiSOD, all feature a shorter (ca. $1.87 \text{ \AA}$) and a longer ($1.95 - 2.00 \text{ \AA}$) Ni-N bond distance. Table 4 lists the crystallographically determined coordination bond distances. In all the synthetic complexes, the longer distance is to the amine or pyridyl N donor, while the shorter distance is to the amide or, in the case of **8**, imine donor. In NiSOD, on the other hand, the shorter (albeit by only $0.034 \text{ \AA}$) distance

is to the amine donor. In all cases, the longer Ni-S distance is to the S donor *trans* to the imine or amide N.

Formation of a cyclized product from the NNS ligand is not unprecedented, although formation of the imidazolium ring was unexpected. There are many examples in the literature where phenylthiolates with *ortho*-imine substituents undergo reactions in which the thiolate S and imine N atoms form a bond, resulting in substituted benzisothiazoles. An example in a system related to the current one is found in the reaction of [Ni(tsalen)] with FeCl₃, in which a crystalline product containing the dication of 1,2-bis(1,2-benzisothiazol-2-yl)ethane (BBITE) was isolated [22]. During the synthesis of **8**, a byproduct was isolated and crystallographic analysis identified it as 2-(2-Dimethylamino-ethyl)-benzo[d]isothiazol-2-ium tetraphenylborate (**9**). A thermal ellipsoid diagram of **9** is shown in Figure 6 and X-ray data collection and structure solution parameters are given in Table 1. The cation crystallizes on a general position in the orthorhombic space group P2₁2₁2₁ with two molecules per asymmetric unit. As with BBITE, the structure of **9** features a trigonal planar geometry around the imine N atom, resulting in a formal positive charge on the N – the formation of **9** would require a two-electron oxidation of the NNS ligand.

3.1. Electrochemistry

As the function of NiSOD is to catalyze a redox process, the reduction potential of the Ni center is of profound importance. As indicated above, the requisite potential for catalysis of superoxide dismutation is far from the normal aqueous potential for the Ni^{III/II} couple. Therefore, the unusual ligand set must tune the potential of the Ni center in NiSOD, making it important to understand the effect of the component ligands on the reduction potential. The electrochemistry of **1**, **2**, **3**, and **8** was studied by cyclic voltammetry. These all show very similar features. A quasi-reversible anodic potential at about -1.0 V vs. Ag/AgCl is assigned to the Ni^{II/I} couple and a quasi-reversible cathodic potential around 1.2 V vs. Ag/AgCl is assigned to the Ni^{III/II} couple. The remaining features are assigned to ligand-based redox events. Previous studies have shown that Ni(II) complexes with N₂S₂ coordination geometries show very low Ni^{III/II} potentials with bis(amide) coordination, relatively higher potentials with bis(amine) coordination and still higher potentials with bis(imine) coordination. The one complex with amide/amine coordination displays a Ni^{III/II} couple between those of bis(amide) and bis(amine) complexes. On the other hand, **8** displays a Ni^{III/II} couple at a higher potential than for most of the bis(imine) complexes. This could be explained by the presence of the positively charged imidazolium moiety on the pendant thiolate ligand.

3.2. Electronic Spectroscopy

Complexes **1** – **3** all display electronic spectra which feature a distinct maximum in the 400 – 450 nm range and a shoulder in the 340 – 370 nm range. Both of these transitions can be assigned as ligand-to-metal charge transfer by comparison to similar complexes and are in the range reported for NiSOD. In complex **8**, both features appear as shoulders on the higher energy ligand-based transitions, and are still at energies (ca. 435 and 385 nm) consistent with the spectra of NiSOD.

4. Conclusions

The use of N,N-dimethylethylenediamine with DTDB has proven to be an effective method for the synthesis of a tridentate N₂S donor ligand without relying on protection and deprotection of the thiolate. In the presence of coordinating anions, straightforward complexes of the form [Ni(NNS)X] were isolated. In the absence of a coordinating anion, an unusual zwitterionic thiolate is formed by the apparent cyclization of an equivalent of the

NNS ligand. This resulted in the isolation of **8**, which is the first reported Ni complex containing two thiolates, one amine, and one imine in the coordination sphere. Compound **8** will serve as an entry into the synthesis of model complexes for the active site of NiSOD. Although **8** does not display the required reduction potential to act as a catalyst for superoxide dismutation, further adaptations of this methodology to (a) replace the cationic thiolate donor with those derived from neutral thiols, (b) incorporate amide rather than imine N donors, and (c) include a potential fifth ligand as a model for the labile imidazole will provide valuable insight into the unusual active site of NiSOD.

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Figure 2. Mercury [14] drawings of (a) **1** and (b) **2** showing the 50% thermal ellipsoids. H atoms omitted for clarity

Figure 3. Mercury [14] drawing of **3** showing the 50% thermal ellipsoids. H atoms omitted for clarity.

Figure 4. Mercury [14] drawings of the cations in (a) **4** and (b) **5** showing the 50% thermal ellipsoids. H atoms have been omitted for clarity. For **4**, one of the two similar molecules in the asymmetric unit is represented.

Figure 5. Mercury [14] drawing showing the cation in **8** as 50% thermal ellipsoids. H atoms have been omitted for clarity.

Figure 6. Mercury [14] drawing of the cation in **9** showing the 50% thermal ellipsoids. H atoms omitted for clarity.

Scheme 1.

Table 1

X-ray Data Collection and Structure Solution Parameters for 1–9

	1	2	3	4H ₂ O	5	6	7	8·2CH ₂ Cl ₂	9
Empirical formula	C ₁₁ H ₁₅ ClN ₂ NiS	C ₁₁ H ₁₅ N ₃ NiO ₃ S	C ₁₁ H ₁₅ N ₃ NiO ₂ S	C ₈ H ₃₀ N ₆ NiO ₉	C ₁₀ H ₂₇ B ₂ F ₈ N ₅ Ni O	C ₁₂ H ₃₀ F ₁₂ N ₄ NiP ₂	C ₆₀ H ₇₀ B ₂ N ₆ Ni	C ₄₈ H ₃₈ BCl ₄ N ₄ NiS ₂	C ₃₅ H ₃₅ BN ₂ S
Formula weight	301.47	328.03	312.03	395.07	465.7	579.55	955.55	966.42	526.52
Temperature, K	150	150	150	150	150	150	150	150	150 K
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Triclinic	Monoclinic	Orthorhombic
Space group	Pna2 ₁	P2 ₁ /n	P2 ₁ /c	P2 ₁ /c	P2 ₁ 2 ₁ 2 ₁	C2/c	P1	P2 ₁ /c	P2 ₁ 2 ₁ 2 ₁
a, Å	15.0154(12)	6.519(3)	10.4931(6)	14.3278(6)	7.8854(4)	8.4068(16)	12.1833(7)	15.8724(4)	16.5825(9)
b, Å	12.4728(9)	17.938(6)	9.5272(6)	8.3122(4)	15.849(8)	17.973(4)	18.3930(11)	18.5204(5)	18.533(10)
c, Å	6.5038(5)	11.851(4)	13.0770(8)	16.1968(7)	16.194(8)	15.987(3)	23.1254(15)	16.4307(4)	18.763(11)
α, deg	90	90	90	90	90	90	89.184(4)	90	90
β, deg	90	104.14(2)	97.918(3)	112.087(2)	90	90.487(11)	90	103.9830(10)	90
γ, deg	90	90	90	90	90	90	90	90	90
Volume	1218.06(16)	1343.9(8)	1294.84(14)	1787.41(14)	2023.98(18)	2415.5(8)	5181.6(5)	4686.9(2)	5766.6(6)
Z	4	4	4	4	4	4	4	4	8
d _{calc} , Mg/m ³	1.644	1.621	1.601	1.468	1.528	1.592	1.225	1.37	1.213
μ, mm ⁻¹	1.956	1.605	1.656	1.132	1.039	1.034	0.42	0.77	0.139
F(000)	624	680	648	840	960	1184	2040	2028	2240
Dimensions (mm)	.128×.04×.04	.236×.145×.043	.29×.126×.088	.53×.37×.34	.57×.176×.124	.221×.121×.115	.27×.17×.10	.48×.15×.12	.47×.20×.15
θ range collected	3.17 – 26.00	2.88 – 25.99	2.90 – 26.00	2.80 – 26.00	2.82 – 26.00	2.67 – 26.00	1.67 – 26.00	2.20 – 26.00	1.54 – 26.00
Index ranges	–18 ≤ h ≤ 17 –15 ≤ k ≤ 15 –8 ≤ l ≤ 7	–8 ≤ h ≤ 7 –21 ≤ k ≤ 22 –14 ≤ l ≤ 12	–12 ≤ h ≤ 12 –11 ≤ k ≤ 11 –16 ≤ l ≤ 16	–17 ≤ h ≤ 17 –8 ≤ k ≤ 10 –19 ≤ l ≤ 19	–9 ≤ h ≤ 9 –19 ≤ k ≤ 19 –19 ≤ l ≤ 19	–10 ≤ h ≤ 10 –21 ≤ k ≤ 22 –19 ≤ l ≤ 19	–15 ≤ h ≤ 15 –22 ≤ k ≤ 22 –28 ≤ l ≤ 28	–19 ≤ h ≤ 19 –22 ≤ k ≤ 22 20 ≤ l ≤ 19	–18 ≤ h ≤ 20 –22 ≤ k ≤ 22 –23 ≤ l ≤ 22
Refl. collected	18407	20275	82348	40426	57775	13250	96125	134381	154194
Ind. Refl. (R _{int})	2384 (0.1060)	2626 (0.2755)	2542 (0.0626)	3516 (0.0220)	3969 (0.0347)	2373 (0.1500)	33915 (0.2688)	9210 (0.0748)	11332 (0.0625)
Complt to θ = 26.00°	99.80%	99.70%	99.90%	99.90%	99.90%	99.80%	99.10%	99.90%	99.90%
Data/restr/param	2384/1/147	2626/0/175	2542/0/174	3516/0/224	3969/0/249	2373/0/154	33915/3/2451	9210/0/545	11332/0/707
gof on F ²	1.009	1.06	0.93	1.065	1.055	1.043	0.958	1.091	1.028
R1, wR2 [I>2σ(I)]	0.0408, 0.0532	0.1140, 0.2679	0.0316, 0.0660	0.0340, 0.1048	0.0334, 0.0901	0.1114, 0.2747	0.1211, 0.2518	0.0560, 0.1306	0.0462, 0.1166

	1	2	3	4·H ₂ O	5	6	7	8·2CH ₂ Cl ₂	9
R1, wR2 (all data)	0.0779, 0.0619	0.2468, 0.3357	0.0405, 0.0701	0.0367, 0.1074	0.0439, 0.0963	0.2122, 0.3422	0.3978, 0.3985	0.0896, 0.1485	0.0849, 0.1560
$\rho_{\max}$, $\rho_{\min}$, e/Å ³	0.392, -0.399	1.755, -0.938	0.958, -0.502	0.873, -0.981	0.381, -0.500	1.521, -0.903	0.527, -0.675	1.336, -1.268	0.443, -0.524

Table 2Selected bond distances ($\text{\AA}$) and angles (deg) for $[\text{Ni}(\text{NNS})\text{X}]$

	1 (X=Cl)	2 (X=NO₃)	3 (X=NO₂)	8 (X=RS)
Ni – N _{amine}	1.989(3)	2.002(9)	1.975(2)	2.002(3)
Ni – N _{imine}	1.866(4)	1.836(10)	1.865(2)	1.879(3)
Ni – S	2.142(13)	2.145(3)	2.143(8)	2.1392(10)
Ni – X	2.196(14)	1.862(8)	1.903(3)	2.2265(9)
N _{amine} -Ni-N _{imine}	87.10(15)	86.4(5)	87.27(9)	86.72(12)
N _{amine} -Ni-S	174.54(11)	175.3(4)	174.41(7)	175.29(9)
N _{amine} -Ni-X	92.18(10)	91.3(4)	90.49(10)	91.85(9)
N _{imine} -Ni-S	96.14(12)	97.0(4)	96.99(7)	95.86(9)
N _{imine} -Ni-X	176.68(12)	173.8(5)	171.61(13)	171.92(10)
S-Ni-X	84.84(5)	85.0(3)	85.80(8)	86.14(4)

Table 3Selected average bond distances ($\text{\AA}$) for $[\text{Ni}(\text{dmen})_2(\text{Solv})_2]\text{X}_2$

	4 (X=NO₃)	5 (X=BF₄)	6 (X=PF₆)	7 (X=BPh₄)
Ni – NH ₂	2.087	2.106	2.035	2.127
Ni – NMe ₂	2.165	2.188	2.181	2.183
Ni – NCCH ₃		2.058	2.100	2.061
Ni-OH ₂	2.112	2.115		

Table 4

Comparison of bond distances (Å) for NiSOD and model complexes.

	Ni-N (min)	Ni-N (max)	Ni-S (min)	Ni-S (max)	reference
8					this work
[Ni(nmp)(SC ₆ H ₄ -p-Cl)] ⁻	1.879(3)	2.002(3)	2.1392(10)	2.2265(9)	17
[Ni(nmp)(SiBu)] ⁻	1.8638(14)	1.9470(14)	2.1492(5)	2.2139(4)	17
[Ni(BEAMM)] ⁻	1.882(2)	1.9635(19)	2.1629(7)	2.1938(7)	18
NiSOD	1.858(6)	1.989(7)	2.137(2)	2.177(2)	5