Reduction-Promoted Sulfur–Oxygen Bond Cleavage in a Nickel Sulfenate as a Model for the Activation of [NiFe] Hydrogenase

Patrick J. Farmer,*,† Jean-Noël Verpeaux, and Christian Amatore*

Département de Chimie
Ecole Normale Supérieure URA CNRS 1679
24 rue Lhomond 75231 Paris Cedex 05, France

Marcetta Y. Darensbourg* and Ghezai Musie

Department of Chemistry, Texas A&M University
College Station, Texas 77843

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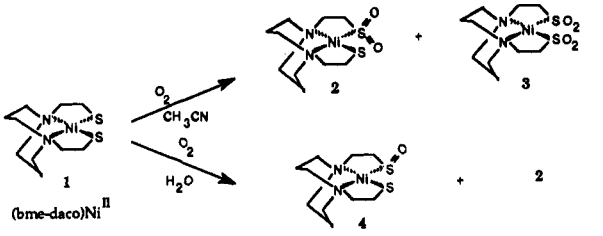
The air sensitivity of sulfur-rich metalloenzymes such as the [NiFe] hydrogenases[1,2] provides both a challenge toward establishing true catalytic activity[3] and a potential clue to the active site. As isolated in air the [NiFe] H_2ase enzymes, e.g., *Chromatium vinosum* and *Desulfovibrio gigas*, are activated by exposure to H_2 or chemical reductants in the absence of O_2, during which complicated changes in EPR spectra signal several different nickel-based redox states.[4,5] The possibility that nickel-bound sulfur oxygenates might exist in O_2-inactivated *C. vinosum* was inspired by an ^{17}O-label, EPR study, interpreted as a tightly-bound oxygen near, but not within, the first coordination sphere of the nickel center.[2] Nevertheless, comparisons with the typical products of O_2 oxygenations of nickel thiolate compounds, sulfinates ($Ni^{II}SO_2R$), were confuted by the fact that such moieties are resistant to deoxygenation.[6,7] The recently isolated examples of an intermediate sulfur-oxygenation state, sulfenates ($Ni^{II}S(=O)R$), have demonstrably greater reactivity toward oxygen transfer.[8,9] Unlike the inert sulfinates, the sulfenates were deoxygenated by SO_2 and PBu_3 producing SO_3 and $O{=}PBu_3$, respectively, and nickel products (thiolates).[9] However, no direct reaction was seen between $Ni^{II}S(=O)R$ and PPh_3 or H_2.[8,9] We now report a less sterically congested nickel(II) sulfenate which demonstrates that *reduction-promoted, intermolecular oxygen transfer* from a $Ni^{II}S(=O)R$ species could be consistent with the reductive activation seen in the enzymatic systems.

The N_2S_2 complex [*N*,*N*′-bis(mercaptoethyl)-1,5-diazacyclooctane]nickel(II), **1**, adds O_2 in a molecular fashion in nonaqueous solution to yield sulfinate compounds **2** and **3**, Scheme 1.[6d,7a] In H_2O/CH_3CN mixtures, **1** undergoes slow reaction with O_2 to produce different products: **4**, [*N*-(mercaptoethyl)-*N*′-(sulfenylethyl)-1,5-diazacyclooctane]nickel(II),[10] as well as **2**.

Scheme 1



Separated from **2** by alumina column chromatography, **4** was obtained crystalline from CH_3CN solvent and its molecular structure determined by X-ray crystallography (Figure 1).[11] The most critical metric parameter is the sulfenyl S–O bond length. Examination of the thermal ellipsoids for S(1) and O(1) indicated that the observed distance, 1.499(5) Å, could be significantly different from the true bond length. A recalculation based on the riding motion model of Busing and Levy[12] found an average S–O distance of 1.548 Å. This value is consistent with that of the previously isolated nickel sulfenate [S–O = 1.548(8) Å],[8] as well as those in such Co^{III} complexes as $[(en)_2Co(S(O)CH_2CH_2NH_2]^{2+}$, S–O = 1.552(5) Å,[13] and it suggests a weaker bond than in analogous sulfinates, $NiSO_2R$, where SO (average) = 1.45 Å.[6c,14]

Compound **4** is soluble in polar organic solvents and in water, where it is thermally stable. This stability extends to solutions prepared for electrochemistry experiments; however, repeated cyclic voltammetry scans generated changes. On first scanning in the cathodic direction, solutions of **4** display a reversible reduction wave ($E_{1/2}$ = –1.895 V vs NHE), and on reversal, an irreversible oxidation event (E_{pa} = +0.226 V), Figure 2A. Repeated scans through the reduction wave show new reduction events flanking that assigned to complex **4**, Figure 2B. The potentials of the two new waves correspond to those of compounds **1** and **2**,[14] respectively, i.e., the products of sulfenate disproportionation, eq 1. This was further confirmed by cathodic bulk electrolysis (at –2.00 V)[15] and subsequent spectroscopic (vis–UV)[16] characterization of the products. Products **1** and **2** were obtained in a ca. 1:1 molar ratio, with 50% conversion/equivalent of current passed.

$$\underset{\mathbf{4}}{2NiS(O)R} \xrightarrow{[e^-]} \underset{\mathbf{1}}{NiSR} + \underset{\mathbf{2}}{NiSO_2R} \qquad (1)$$

Chemical reduction with cobaltocene or $NaBH_4$ also induced disproportionation of **4**. For example, a solution of Cp_2Co (15.2

† Present address: Department of Chemistry, California Institute of Technology, Pasadena, CA 91125.

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(10) FTIR ν(SO) absorptions (KBr pellet), **4**: 925 cm^{-1}. UV–vis, MeOH solution, λ_{max} (ϵ), **4**: 355 (3132), 472 (475), 267 (>9000) nm. Elemental anal. Calcd (found) for $C_{10}H_{21}N_2S_2O_{1.5}Ni$: C, 37.97 (38.12); H, 6.64 (6.62); N, 9.14 (8.86).

(11) X-ray diffraction data were collected on a Nonius CAD4 diffractometer at 296 K. The structure was solved by standard procedures; crystallographic data are given as follows: for $C_{10}H_{21}N_2O_{1.5}S_2Ni$, fw = 316.12; monoclinic, space group $C2/c$, a = 16.081(2) Å, b = 7.813(4) Å, c = 22.059(2) Å, V = 2628(2) Å^3, and Z = 8, d_{calc} = 1.60 g cm^{-3}, μ(Mo Kα) = 17.75 cm^{-1}, 2θ range from $4 < 2\theta < 50$. Using 2299 unique reflections with $F > 4\sigma(F)$, R = 0.036 and R_w = 0.037. The compound crystallizes with two molecules of **4** hydrogen-bonded through sulfenate oxygens to a common water molecule. The sulfenate moiety is oriented on the same side of the plane as the chair form of the metallodiazacyclohexane ring and shows disorder in the placement of the sulfenyl unit between the two sulfur positions. The minor form (10%), not shown in Figure 1, has the sulfenyl oxygen on S(2), away from the lattice water.

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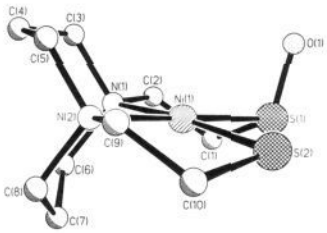

Figure 1. Molecular structure of [*N*-(mercaptoethyl)-*N'*-(sulfenylethyl)-1,5-diazacyclooctane]nickel(II), **4**·$^1/_2H_2O$; hydrogen atoms have been omitted for clarity. Selected bond lengths (Å): Ni(1)–S(1) 2.153(1), Ni(1)–S(2) 2.153(2), Ni(1)–N(1) 1.991(4), Ni(1)–N(2) 1.990(4), S(1)–O(1) 1.499(5) (riding model[12] correction, S(1)–O(1) = 1.549 Å, see text), S(1)–C(1) 1.809(8) [$O_{sulfenyl}$–O_{water} distance 2.696(6) Å]. Selected *bond angles (deg): S(1)–Ni(1)–S(1A)* 88.43(7), *N(1)–Ni(1)–N(2)* 89.7-(2), N(1)–Ni(1)–S(1) 91.0(1), N(1)–Ni(1)–S(2) 175.3(1), Ni(1)–S(1)–C(1) 93.6(2), Ni(1)–S(1)–O(1) 107.4(2).

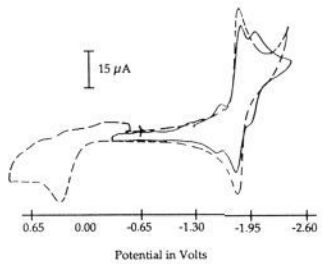

Figure 2. Cyclic voltammograms of **4** (2.5 mM) in 0.3 M $TBABF_4$-CH_3CN: (- - -) fresh solution, scanning in cathodic direction; (—) after repetitive scanning in the reversible reduction region only.

mg, 0.08 mmol, in 10 mL of MeOH) was added in aliquots to a solution of **4** (23.6 mg, 0.076 mmol, in 10 mL of dry, degassed MeOH) and stirred overnight. Following the elution of cobaltocene from an alumina column (MeOH as eluant), the products were obtained: **1**, 4.4 mg (18%); **2**, 3.8 mg (16%); unreacted **4**, 15.1 mg (64%).

An appealing mechanistic possibility for the reduction-initiated, disproportionation or O-atom transfer is based on the radical chain process of eqs 2–5. Initial electron transfer produces the reactive Ni(I) sulfenyl radical anion complex, eq 2, which acts as an O-atom donor in reaction with the parent Ni(II) sulfenyl complex, eq 3. The resulting Ni(I) thiolate radical anion can then propagate the chain by electron transfer to another sulfenyl complex, eq 4, resulting in the overall products of eq 1.

initiation

$$Ni^{II}S(O)R + e^- \rightarrow Ni^{I}S(O)R^{\bullet -} \quad (2)$$

propagation

$$Ni^{I}S(O)R^{\bullet -} + Ni^{II}S(O)R \rightarrow Ni^{II}SO_2R + Ni^{I}SR^{\bullet -} \quad (3)$$

$$Ni^{I}SR^{\bullet -} + Ni^{II}S(O)R \rightarrow Ni^{I}S(O)R^{\bullet -} + Ni^{II}SR \quad (4)$$

termination

$$Ni^{I}SR^{\bullet -} + Ni^{II}SO_2R \rightarrow Ni^{I}SO_2R^{\bullet -} + Ni^{II}SR \quad (5)$$

Electron transfer between $\mathbf{1}^{\bullet -}$ and the sulfinate **2**, as in eq 5, is a likely candidate for the termination step, given the thermodynamic stability of Ni^I in the sulfinates as compared to thiolates. On the basis of the $E_{1/2}$ values of the $Ni^{II}/^I$ couple for complexes **1** (–1.94 V vs NHE),[14] **2**, (–1.63 V),[14] and **4** (–1.89 V), the equilibrium constant of the electron transfer reaction (4) is calculated to be 6.7; for reaction 5, 1.95×10^5. In the absence of any fast irreversible chemical step following electron transfer, it is unlikely that radical anion $\mathbf{2}^{\bullet -}$ could reduce **4** (a process with an equilibrium constant of 3.4×10^{-5}). This competing electron transfer reaction accounts for lack of efficiency in the electrocatalysis. A common hypothesis in cases such as this is that $\mathbf{2}^{\bullet -}$ ultimately transfers its electron to solvent.

As a test of the reduction-induced, O-atom transfer mechanism for disproportionation expressed in eqs 2–5, reductive electrolysis (–2.0 V) of **4** was carried out in the presence of PPh_3 as a competitive O-atom acceptor (10-fold excess PPh_3, degassed CH_3CN, under N_2 at 22 °C). Since PPh_3 is unreactive with **4**, *vide supra*, the production of $O{=}PPh_3$ under electrolysis conditions, as confirmed by ^{31}P NMR, and the observed absence of **2** (with ca. 98% conversion of **4** to **1**) were consistent with the reduction-activated O-atom transfer mechanism.

$$\underset{\mathbf{4}}{Ni^{II}S(O)R} + PPh_3 \xrightarrow{[e^-]} \underset{\mathbf{1}}{Ni^{II}SR} + O{=}PPh_3 \quad (6)$$

Two points of relevance to [NiFe] hydrogenases arise from these results:

First, the reaction of Ni^{II} thiolates with O_2 in aqueous solution results in O-atom (peroxidic) activity, producing monooxygenated sulfenates, as opposed to the well-documented pairwise, molecular O_2-addition products, sulfinates, that are formed in nonaqueous solutions. An analogous reversible oxygen atom addition reaction in H_2ase enzymes should occur at a Ni^{II}–SR site, accessible both to oxygen and water. In fact, indications that the Ni–SI (EPR-silent Ni^{II}) form is H^+-accessible include its pH dependent redox potentials and its involvement in the catalytic cycle via H^+ uptake.[17] Thus, the conditions for production of the sulfenate moiety are possible in the enzymatic systems.

Secondly, reduction of such Ni-bound sulfenates initiates O-atom transfer which, in the presence of a suitable trap, *regenerates the thiolate complexes. The slow, reductive activation* of O_2-exposed enzymatic systems may require the presence of such an O-atom acceptor.[2]

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Supplementary Material Available: Crystallographic packing diagram, an ORTEP representation, tables of atomic coordinates and equivalent isotropic displacement parameters, and complete listing of bond lengths and angles for **4** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) In a typical electrolysis experiment, 20 mg of **4** was dissolved in 10 mL of degassed 0.3 M $TBABF_4$ in CH_3CN. Controlled-potential electrolysis experiments were performed at 25 °C, in an H-cell where the two compartments were separated by a fine glass frit. The Pt working electrode (6.00-mm diameter) was placed in one compartment while Pt-wire auxiliary and Ag/Ag^+ reference electrodes were placed in the second compartment. A potential of –2.00 V was applied while the solution was continuously stirred under an N_2 atmosphere until the current ratio dropped to 0.10%.

(16) λ_{max} (ϵ) (CH_3CN solvent): **1**, 506 (640) and 602 (sh) nm; **2**, 446 (300) and 554 (sh) nm. Farmer, P. J. Ph.D. Dissertation, Texas A&M, 1993.

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