Cationic and Anionic Dinuclear Nickel Complexes $[Ni(N_2S_2)Ni(dtc)]^n$ ($n = -1, +1$) Modeling the Active Site of Acetyl-CoA Synthase

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Two dinuclear nickel complexes $(Et_4N)[Ni(mbpa)Ni(dtc^{Et})]$ (**1**) (dtc^{Et} = diethyldithiocarbamate) and $[Ni(dadt^{Et})Ni(dtc^{Me})](BPh_4)$ (**2**) (dtc^{Me} = dimethyldithiocarbamate) have been synthesized as models for the active site of acetyl-CoA synthase (ACS). Cyclic voltammograms show that each complex exhibits a reduction wave, in which the reduction potential of the anion **1** exhibits a significant negative shift from that of the cation **2**.

Acetyl-CoA synthase (ACS)/carbon monoxide dehydrogenases (CODH) are bifunctional metalloenzymes, playing significant roles for CO_2 fixation in various microorganisms.[1,2] Crystallographic results reported for ACS from *Moorella themoacetia* and *Carboxydothermus hydrogenoformans* have revealed that the A-cluster, the active site of ACS, is composed of a $[Fe_4S_4]$ cluster and a dinuclear Ni_d–Ni_p unit as shown in Figure 1,[3,4] where the two nickels designated as Ni_d and Ni_p occupy *distal* and *proximal* positions to the $[Fe_4S_4]$ cluster, respectively. The geometry around Ni_d is square planar composed of two cysteine sulfurs and two carboxyamide nitrogens of the tripeptide Cys–Gly–Cys from the protein backbone. The proximal nickel ion, Ni_p, carries an unidentified ligand X and the three bridging cysteine sulfurs, two from the aforementioned tripeptide, and one from the $[Fe_4S_4]$ cluster.[5–9]

Since the elucidation of the ACS crystal structure, several thiolate-bridged dinuclear nickel complexes modeling the active site of ACS have been reported.[10] However, among these, only a single complex $[Ni^{II}(dadt^{Et})Ni^{II}(SCH_2CH_2PPh_2)]^+$ reported by Holm and co-workers ($dadt^{Et}$ = *N*,*N*′-diethyl-3,7-diazanonane-1,9-dithiolate) has a third thiolate ligand at the Ni_p site.[10a] Recently, we have found that the trinuclear cluster, $[\{Ni(dadt^{Et})\}_2Ni](NiBr_4)$, serves as a useful precursor of dinuclear nickel complexes of the type, $Ni(dadt^{Et})Ni(X)_2$ and $[Ni(dadt^{Et})Ni(L)_2]^{2+}$ (X = arenethiolates, L = tmtu, *t*-BuNC).[11] To improve insight into the function of the dinuclear nickel site in the A-cluster, we have extended our studies to the dianionic dicarboxyamido–dithiolato nickel(II), $[Ni(mbpa)]^{2-}$ (H_4mbpa = [*N*,*N*′-bis-(3-methyl-3-sulfanylbutyryl)-*o*-phenylenediamine]),[12] as a Ni_p site model (see Scheme 1). The mbpa ligand has two properties superior to the $dadt^{Et}$ ligand; (1) carboxyamido nitrogens of the mbpa ligand structurally more closely resemble the donors found in the A-cluster than the amino donors of the $dadt^{Et}$ ligand, (2) the mbpa ligand carries a 4^- charge as does the Cys–Gly–Cys ligand in the A-cluster, whereas the $dadt^{Et}$ ligand is dianionic. Herein we report the synthesis of $(Et_4N)[Ni(mbpa)Ni(dtc^{Et})]$ (**1**) (dtc^{Et} = diethyldithiocarbamate) and $[Ni(dadt^{Et})Ni(dtc^{Me})](BPh_4)$ (**2**) (dtc^{Me} = dimethyldithiocarbamate), and discuss their structures and redox properties.

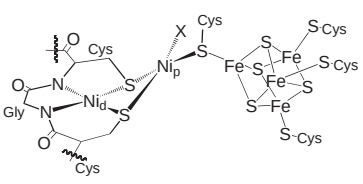
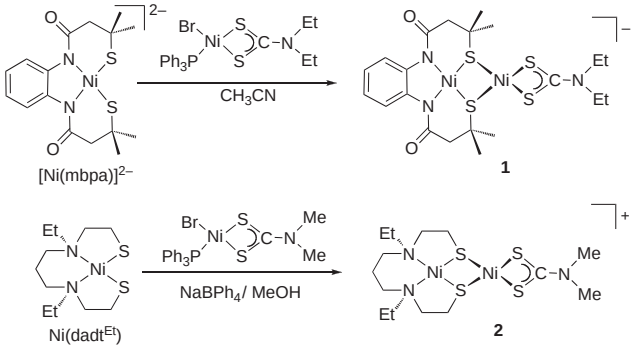


Figure 1. Drawing of the active site of ACS.



Scheme 1.

$(Et_4N)_2[Ni(mbpa)]$ was synthesized by the reaction of H_4mbpa and $Ni(OAc)_2 \cdot 4H_2O$ in the presence of KOH followed by cation exchange with Et_4NCl.[13] The X-ray crystallography reveals that the geometry and metric parameters around the nickel of $(Et_4N)_2[Ni(mbpa)]$ compare well with those of $Ni(dadt^{Et})$ reported previously.[14] Although the bond angles around the nickels of $[Ni(mbpa)]^{2-}$ and $Ni(dadt^{Et})$ are somewhat different owing to the different chelate ring-size, the nickels of both $[Ni(mbpa)]^{2-}$ and $Ni(dadt^{Et})$ assume a regular square-planar geometry.

Treatment of $(Et_4N)_2[Ni(mbpa)]$ with $Ni(PPh_3)(dtc^{Et})Br$ in acetonitrile afforded the dinuclear nickel anion **1** in 87% yield as green crystals (Scheme 1). A similar reaction using $Ni(dadt^{Et})$ in methanol and successive anion-exchange with $NaBPh_4$ gave the analogous dinuclear nickel cation **2** in 90% yield as brown crystals.

X-ray crystallographic analysis confirms the formation of the dinuclear nickel complexes **1** and **2** as shown in Figure 2.[15] Their structures compare well with that of the dinuclear nickel site in the A-cluster of ACS shown in Figure 1. The two square-planar nickels of each complex are bridged by the two thiolato sulfurs of the N_2S_2 ligand to form a folded Ni_2S_2 quadrangle; the dihedral angles along $\mu S(1)$–$\mu S(2)$ vectors are 102.6 and 105.5° for **1** and **2**, respectively, whereas the corresponding angle for the dinuclear nickel site in the A-cluster is somewhat larger, 138°. Accordingly, Ni(1)–Ni(2) distances for **1** (2.6839(8) Å) and **2** (2.6706(3) Å) are shorter than the value

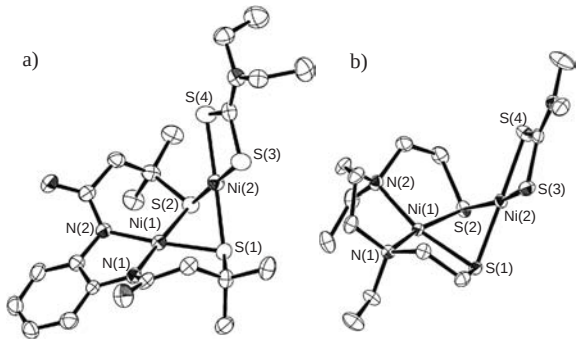


Figure 2. Molecular structures of (a) the anion in **1** and (b) the cation in **2** (50% thermal ellipsoids).

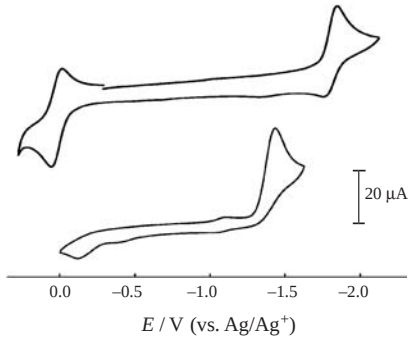


Figure 3. Cyclic voltammograms of **1** (top) and **2** (bottom).

for the A-cluster (3.0 Å). Such structural differences would be ascribed to the geometrical difference of the N_2S_2 ligands.

The redox behavior of **1** and **2** is of interest, because the activation process of ACS involves a one- or two-electron reduction of the A-cluster although the mechanism has not been elucidated. The cyclic voltammogram of the cation **2** recorded in MeCN exhibits an irreversible reduction process at $E_a = -1.42$ V (vs. Ag/Ag^+) (Figure 3).[16] Because Ni($dadt^{Et}$) does not show any redox event in the $+0.3$–-1.8 V range, this wave would correspond to the reduction of the nickel located at the model Ni_p site. The reduction wave for **1** was observed at $E_a = -1.84$ V in MeCN as a quasi-reversible reduction process, which is negatively shifted from **2**. This negative shift is understandable, considering that **1** is anionic while **2** is cationic.[17] As for **1**, an additional reversible oxidation event was observed at $E_{1/2} = +0.10$ V, which probably corresponds to the oxidation of the nickel sitting in the mbpa ligand. This oxidation potential is shifted positively by 0.7 V from that of mononuclear $[Ni(mbpa)]^{2-}$ observed at $E_p = -0.6$ V, because of the coordination of the electrophilic $[Ni(dtc^{Et})]^+$ unit to the $[Ni(mbpa)]^{2-}$ of **1**.

In summary, we have synthesized two dinuclear nickel complexes **1** and **2** modeling the ACS active site structure. These are rare examples carrying S-donor ligands at the model Ni_p site. Their structural features compare well with that of the ACS dinuclear nickel site, as confirmed by X-ray crystallographic analysis. Both **1** and **2** show a cyclic voltammogram reduction wave, and their reduction potentials exhibit different values, reflecting their relative net charges.

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This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

References and Notes

1 a) S. W. Ragsdale, *Crit. Rev. Biochem. Mol. Biol.* **2004**, *39*, 165. b) S. W. Ragsdale, M. Kumar, *Chem. Rev.* **1996**, *96*, 2515.
2 P. A. Lindahl, *Biochemistry* **2002**, *41*, 2097.
3 T. I. Doukov, T. M. Iverson, J. Seravalli, S. W. Ragsdale, C. L. Drennan, *Science* **2002**, *298*, 567.
4 C. Darnault, A. Volbeda, E. J. Kim, P. Legrand, X. Vernede, P. A. Lindahl, J.-C. Fontecilla-Camps, *Nat. Struct. Biol.* **2003**, *10*, 271.
5 M. R. Bramlett, X. Tan, P. A. Lindahl, *J. Am. Chem. Soc.* **2003**, *125*, 9316.
6 J. Seravalli, Y. Xiao, W. Gu, S. P. Cramer, W. E. Antholine, V. Krymov, G. J. Gerfen, S. W. Ragsdale, *Biochemistry* **2004**, *43*, 3944.
7 a) T. Funk, W. Gu, S. Friedrich, H. Wang, S. Gencic, D. A. Grahame, S. P. Cramer, *J. Am. Chem. Soc.* **2004**, *126*, 88. b) S. Gencic, D. A. Grahame, *J. Biol. Chem.* **2003**, *278*, 6101.
8 C. E. Webster, M. Y. Darensbourg, P. A. Lindahl, M. B. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 3410.
9 a) T. C. Brunold, *J. Biol. Inorg. Chem.* **2004**, *9*, 533. b) R. P. Schenker, T. C. Brunold, *J. Am. Chem. Soc.* **2003**, *125*, 13962.
10 a) P. V. Rao, S. Bhaduri, J. Jiang, R. H. Holm, *Inorg. Chem.* **2004**, *43*, 5833. b) P. V. Rao, S. Bhaduri, J. Jiang, D. Hong, R. H. Holm, *J. Am. Chem. Soc.* **2005**, *127*, 1933. c) M. L. Golden, M. V. Rampersad, J. H. Reibenspies, M. Y. Darensbourg, *Chem. Commun.* **2003**, 1824. d) Q. Wang, A. J. Blake, E. S. Davies, E. J. L. McInnes, C. Wilson, M. Schröder, *Chem. Commun.* **2003**, 3012. e) R. C. Linck, C. W. Spahn, T. B. Rauchfuss, S. R. Wilson, *J. Am. Chem. Soc.* **2003**, *125*, 8700. f) R. Krishnan, C. G. Riordan, *J. Am. Chem. Soc.* **2004**, *126*, 4484. g) W. G. Dougherty, K. Rangan, M. J. O'Hagan, G. P. A. Yap, C. G. Riordan, *J. Am. Chem. Soc.* **2008**, *130*, 13510. h) T. C. Harrop, M. M. Olmstead, P. K. Mascharak, *Inorg. Chem.* **2006**, *45*, 3424.
11 a) M. Ito, Y. Song, T. Matsumoto, K. Tatsumi, *Inorg. Chem.*, in press. b) T. Matsumoto, M. Ito, K. Tatsumi, *J. Biol. Inorg. Chem.* **2007**, *12*, S121.
12 a) E. Galardon, E. Bourles, I. Artaud, J.-C. Daran, P. Roussel, A. Tomas, *Inorg. Chem.* **2007**, *46*, 4515. b) S. Ito, A. Ota, H. Suhara, K. Tabashi, Y. Kawashima, *Chem. Pharm. Bull.* **1993**, *41*, 1066. c) M. Rat, R. Alves de Sousa, J. Vaissermann, P. Leduc, D. Mansuy, I. Artaud, *J. Inorg. Biochem.* **2001**, *84*, 207.
13 Recently Tomas et al. have reported the synthesis of $(Et_4N)_2$-[Ni(mbpa)] independently from our research. See ref 12a.
14 F. Osterloh, W. Saak, S. Pohl, *J. Am. Chem. Soc.* **1997**, *119*, 5648.
15 Crystallographic data for $(Et_4N)_2$[Ni(mbpa)], **1**, and **2** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-709677, 709678, and 709679, respectively.
16 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
17 a) M. V. Rampersad, S. P. Jeffery, J. H. Reibenspies, C. G. Ortiz, D. J. Darensbourg, M. Y. Darensbourg, *Angew. Chem., Int. Ed.* **2005**, *44*, 1217. b) M. V. Rampersad, S. P. Jeffery, M. L. Golden, J. Lee, J. H. Reibenspies, D. J. Darensbourg, M. Y. Darensbourg, *J. Am. Chem. Soc.* **2005**, *127*, 17323.

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