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

Yumei Song, Mikinao Ito, Mai Kotera, Tsuyoshi Matsumoto,* and Kazuyuki Tatsumi*
Research Center for Materials Science, and Department of Chemistry, Graduate School of Science,
Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8602

(Received October 24, 2008; CL-081022; E-mail: i45100a@nucc.cc.nagoya-u.ac.jp)

Two dinuclear nickel complexes (Et$_4$N)[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$_4$S$_4$] 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$_4$S$_4$] 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$_4$S$_4$] 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$_2$CH$_2$PPh$_2$)]$^+$ 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})}$_2$-Ni](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$_4$mbpa = [*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$_4$N)[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.

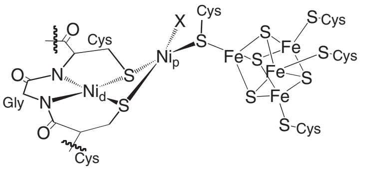
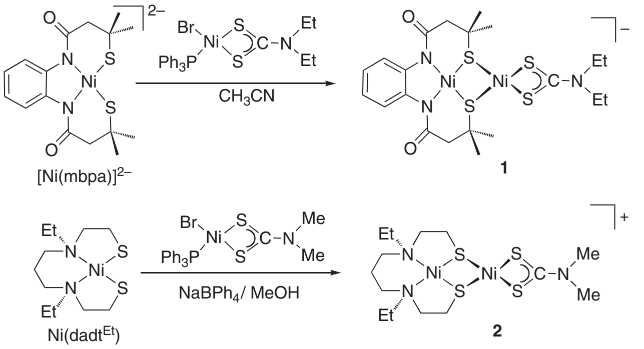


Figure 1. Drawing of the active site of ACS.



Scheme 1.

(Et$_4$N)$_2$[Ni(mbpa)] was synthesized by the reaction of H$_4$mbpa and Ni(OAc)$_2$•4H$_2$O in the presence of KOH followed by cation exchange with Et$_4$NCl.[13] The X-ray crystallography reveals that the geometry and metric parameters around the nickel of (Et$_4$N)$_2$[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$_4$N)$_2$[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$_2$S$_2$ ligand to form a folded Ni$_2$S$_2$ quadrangle; the dihedral angles along μS(1)–μS(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

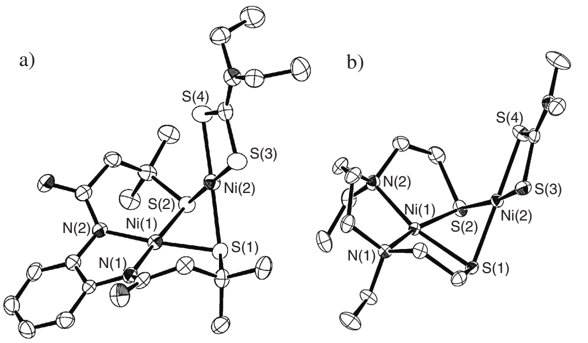


Figure 2. Molecular structures of (a) the anion in **1** and (b) the cation in **2** (50% thermal ellipsoids).

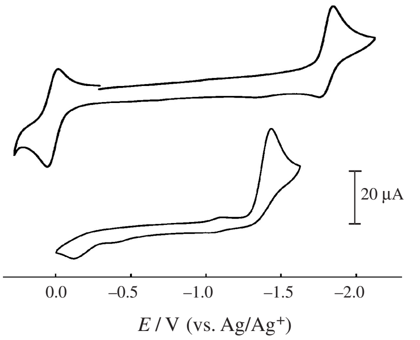


Figure 3. Cyclic voltammograms of **1** (top) and **2** (bottom).

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.

This research was supported by Grant-in-Aids for Scientific Research (Nos. 18GS0207 and 18065013) and Nagoya Global COE Program from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We are grateful to Prof. Roger E. Cramer for discussions and careful reading of the manuscript.

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.