Inorg. Chem. **2005**, *44*, 8–10

Inorganic Chemistry
Communication

Tetranuclear Copper(II) Complex with Glucose-1-phosphate and Its Phosphate Ester Exchange with ATP

Merii Kato and Tomoaki Tanase*

Department of Chemistry, Faculty of Science, Nara Women's University,
Kitauoya-higashi-machi, Nara 630-8285, Japan

Received September 3, 2004

The novel tetranuclear copper(II) complexes with α-D-glucose-1-phosphates, $[Cu_4(\mu\text{-OH})(\alpha\text{-D-Glc-1P})_2(L)_4(H_2O)_2](NO_3)_3$ (L = bpy (**1**), phen (**2**)), were prepared and characterized by X-ray crystallography. Complex **1** was further transformed into the ATP stabilized tetracopper(II) complex of $[Cu_4(ATP)_2(bpy)_4]$ (**4**), where ATP is adenosine 5′-triphosphate.

Carbohydrates are indispensable to living organisms as energy source, and in their metabolism and biosyntheses, sugar phosphate esters are known to play crucial roles as intermediate compounds in regulating biosystems.[1] Recent biological studies have revealed that many enzymes, which promote transformations of sugar phosphates, require metal ions with their functions, examples being fructose-1,6-bisphosphatase (dinuclear Mg^{II}, Mn^{II}, Co^{II}, Zn^{II}),[2] phosphomannose isomerase (Zn^{II}),[3] phosphoglucose isomerase (Fe^{II}),[4] phosphoglucomutase (Mg^{II}),[5] and ribulose bisphosphate carboxylase (Mg^{II}, Mn^{II}, Ca^{II}).[6] In this regard, studies on interaction of sugar phosphate esters with metal ions are of significant importance in the field of bioinorganic chemistry; however, no structurally characterized transition metal complex has been reported thus far. We have studied synthesis and characterization of transition metal complexes with *N*-glycosides, in which aldoses such as D-glucose and D-mannose, having very weak affinity to metal ions under neutral conditions by themselves, were tethered onto metal centers through *N*-glycosidic bond formation with polyamine ligands.[7] In the present study, we have focused on α-D-glucose-1-phosphate (α-D-Glc-1P), since it acts as critical intermediate in the first step of glycolysis and glycogen synthesis, and we have successfully prepared and characterized discrete tetranuclear copper(II) complexes bridged by α-D-Glc-1P with the help of diimine ligands. Further, the bridging sugar phosphates were readily replaced by adenosine 5′-triphosphate (ATP) through a structural change of tetranuclear copper(II) framework. Cu^{II} complexes with diimine-type ligands, notably, have been studied in relevance to artificial nuclease activity.[8]

Reaction of $Cu(NO_3)_2 \cdot 3H_2O$ with $Na_2[\alpha\text{-D-Glc-1P}]$ in the presence of 2,2′-bipyridyl (bpy) or 1,10-phenanthroline (phen) afforded blue crystals of $[Cu_4(\mu\text{-OH})(\alpha\text{-D-Glc-1P})_2(L)_4(H_2O)_2](NO_3)_3$ (L = bpy (**1**), phen (**2**)).[9] The electronic absorption (UV−vis) and circular dichroism (CD) spectra exhibited conspicuous positive Cotton effects (λ_{max} ($\Delta\epsilon$) = 647 nm (0.370) (**1**), 651 nm (0.233) (**2**)) in the range of the d−d transition of Cu^{II} ions, and suggested that the chiral sugar phosphate esters directly coordinated to the metal centers. In the ESI-MS spectra for methanolic solutions of **1** and **2**, divalent parent peaks corresponding to $\{Cu_4(\alpha\text{-D-Glc-1P})_2(L)_4 - 2H\}^{2+}$ were observed at m/z = 694.97 (**1**) and 743.23 (**2**). The distributions of the different isotopes, observed in the range of m/z 695−699 (**1**) and 743−748 (**2**),

---

* Author to whom correspondence should be addressed. E-mail: tanase@cc.nara-wu.ac.jp.

(1) (a) Voet, D.; Voet, J. G. *Biochemistry*; John Wiley & Sons: NewYork, 1995; pp 443−512. (b) He, X.; Agnihotri, G.; Liu, H.-H. *Chem. Rev.* **2000**, *100*, 4615. (c) Wilcox, D. E. *Chem. Rev.* **1996**, *96*, 2435. (d) Westheimer, F. H. *Science* **1987**, *235*, 1173.

(2) (a) Zhang, Y.; Liang, J.-Y.; Huang, S.; Ke, H.; Lipscomb, W. N. *Biochemistry* **1993**, *32*, 1844. (b) Xue, Y.; Huang, S.; Liang, J.-Y.; Zhang, Y.; Lipscomb, W. N. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 12482.

(3) (a) Cleasby, A.; Wonacott, A.; Skarzynski, T.; Hubbard, R. E.; Davies, G. J.; Proudfoot, A. E. I.; Bernard, A. R.; Payton, M. A.; Wells, T. N. C. *Nature Struct. Biol.* **1996**, *3*, 470. (b) Wells, T. N. C.; Coulin, F.; Payton, M. A.; Proudfoot, A. E. I. *Biochemistry* **1993**, *32*, 1294.

(4) (a) Swan, M. K.; Solomons, J. T. G.; Beeson, C. C.; Hansen, T.; Schonheit, P.; Davies, C. *J. Biol. Chem*. **2003**, *278*, 47261. (b) Berrisford, J. M.; Akerboom, J.; Turnbull, A. P.; Geus, de D.; Sedelnikova, S. E.; Staton, I.; McLeod, C. W.; Verhees, C. H.; Oost, van der J.; Rice, D. W.; Baker, P. J. *J. Biol. Chem.* **2003**, *278*, 33290.

(5) Lahiri, S. D.; Zhang, G.; Dunaway-Mariano, D.; Allen, K. N. *Science* **2003**, *299*, 2067.

(6) (a) Andersson, I.; Knight, S.; Schneider, G.; Lindqvist, Y.; Lundqvist, T.; Branden, C.-I.; Lorimer, G. H. *Nature* **1989**, *337*, 229. (b) Mizohata, E.; Matsumura, H.; Okano, Y.; Kumei, M.; Takuma, H.; Onodera, J.; Kato, K.; Shibata, N.; Inoue, T.; Yokota, A.; Kai, Y. *J. Mol. Biol*. **2002**, *316*, 679. (c) Karkehabadi, S.; Taylor, T. C.; Andersson, I. *J. Mol. Biol*. **2003**, *334*, 65.

(7) (a) Tanase, T.; Inukai, H.; Onaka, T.; Kato, M.; Yano, S.; Lippard, S. J. *Inorg. Chem*. **2001**, *40*, 3943. (b) Tanase, T.; Tamakoshi, S.; Doi, M.; Mikuriya, M.; Sakurai, H.; Yano, S. *Inorg. Chem*. **2000**, *39*, 692. (c) Tanase, T.; Onaka, T.; Nakagoshi, M.; Kinoshita, I.; Shibata, K.; Doe, M.; Fujii, J.; Yano, S. *Inorg. Chem*. **1999**, *38*, 3150 and references cited therein.

(8) (a) Sigman, D. S.; Mazumder, A.; Perrin, D. M. *Chem. Rev.* **1993**, *93*, 2295. (b) Humphreys, K. J.; Karlin, K. D.; Rokita, S. E. *J. Am. Chem. Soc.* **2002**, *124*, 6009. (c) Humphreys, K. J.; Karlin, K. D.; Rokita, S. E. *J. Am. Chem. Soc.* **2002**, *124*, 8055. (d) Dhar, S.; Senapati, D.; Das, P. K.; Chattopadhyay, P.; Nethaji, M.; Chakravarty, A. R. *J. Am. Chem. Soc*. **2003**, *125*, 12118.

10.1021/ic0487631 CCC: $30.25

were in agreement with the simulated peak patterns (as shown in Supporting Information). These spectral similarities indicated that the tetranuclear structures of **1** and **2** are analogous to each other, and the detailed structure of **2** was determined by X-ray crystallography.[10]

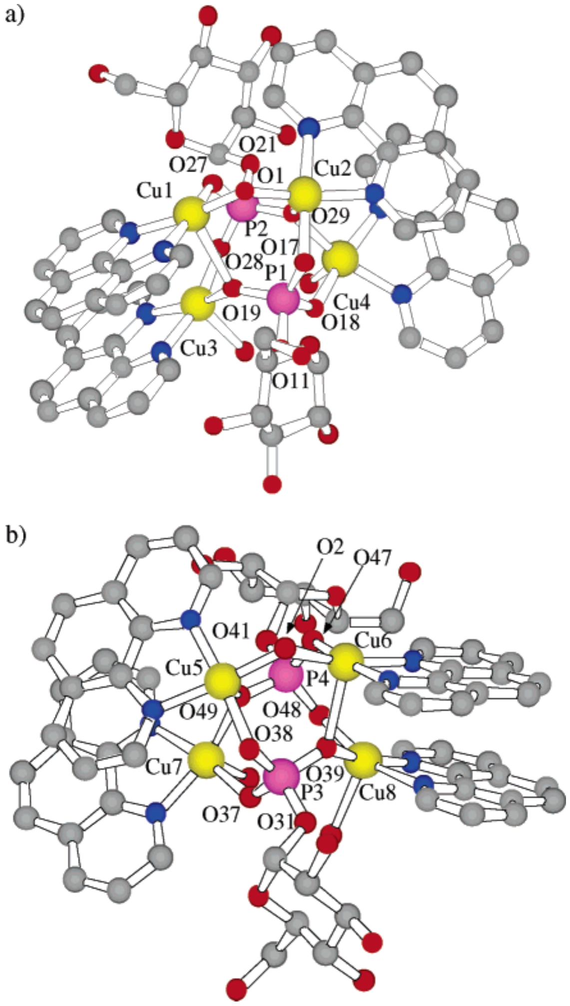
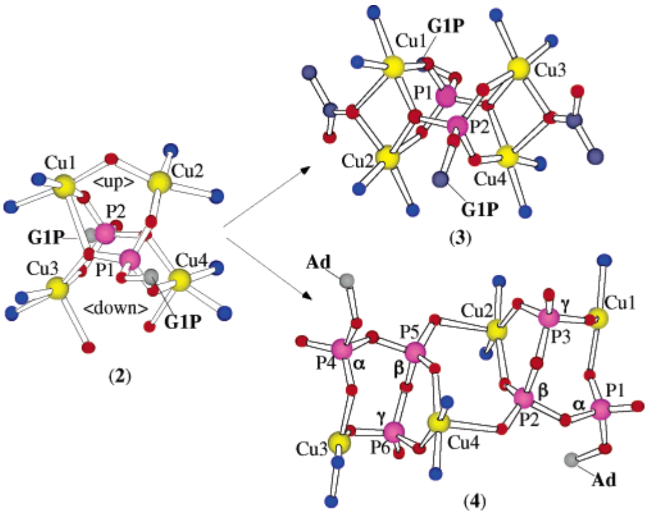


Figure 1. Perspective drawings for the complex cations of **2**: (a) cation **A** and (b) cation **B**; Cu (yellow), P (violet), O (red), N (blue), and C (gray).

Scheme 1. Structural Changes of the Tetranuclear Copper(II) Core of Complex **2** (Cation A) to Those of Complexes **3** and **4**[a]



[a] Color scheme: Cu (yellow), P (violet), O (red), N (blue), and C (gray).

The asymmetric unit of complex **2** contains two independent complex cations, abbreviated as **A** and **B** (Figure 1). Both cations contain tetranuclear copper(II) ions bridged by two phosphate groups of α-D-Glc-1P and a hydroxo group with four auxiliary phen and two water molecules. To our knowledge, this is the first example of transition metal complexes containing free sugar phosphate esters.[11] Each copper ion is ligated by two N atoms of phen and three O atoms of phosphate, hydroxo, and/or water units, and adopts $[N_2O_3]$ square pyramidal geometry with axial bond distance significantly elongated (2.212(4)−2.697(4) Å). The phosphate group of α-D-Glc-1P bridges three Cu atoms at equatorial sites and additionally attaches to the fourth Cu atom at its axial site, resulting in a trapezoidal tetracopper core with the upper side clipped by the hydroxo bridge ($\mathrm{Cu_{up}}\cdots\mathrm{Cu_{up}}$ = 3.254(1) Å (**A**), 3.409(1) Å (**B**); average $\mathrm{Cu_{up}}\cdots\mathrm{Cu_{down}}$ = 3.562 Å (3.425(1)−3.669(1) Å); $\mathrm{Cu_{down}}\cdots\mathrm{Cu_{down}}$ = 4.258(1) Å (**A**), 4.234(1) Å (**B**); average $\mathrm{Cu{-}O_{OH}}$ = 1.928 Å; average $\mathrm{Cu{-}O_{OH}{-}Cu}$ = 119.6°) (Scheme 1). The $\{\mathrm{Cu_4}(\mu\text{-OH})(\mu_4\text{-PO_4})_2\}$ core structures of cations **A** and **B** are chemically similar and approximately enantiomeric to each other, and in contrast, the orientations of the D-glucose moieties are entirely different, although the sugar parts with a stable $^4C_1$-chair conformation are away from the tetranuclear core without any interaction with $\mathrm{Cu^{II}}$ ions. In cation **A**, C-6 hydroxymethyl parts of D-glucose

---

(9) Complex **1**·10.5H_2O: Anal. Calcd for $C_{52}H_{79}O_{40}N_{11}P_2Cu_4$: C, 34.42; H, 4.39; N, 8.49. Found: C, 34.47; H, 4.16; N, 8.45. Yield: 63%. IR (KBr pellet): $\tilde{\nu}$ 3411br, 1602w, 1384s, 1139m, 1032w, 944w, 774w $\mathrm{cm^{-1}}$. UV/vis (CH_3OH): λ_{max} (ϵ) 667 nm (172). CD (CH_3OH): λ_{max} ($\Delta\epsilon$) 647 nm (3.70×10^{-1}). Complex **2**·6H_2O: Anal. Calcd for $C_{60}H_{71}O_{36}N_{11}P_2Cu_4$: C, 39.20; H, 3.89; N, 8.38. Found: C, 39.10; H, 3.85; N, 8.49. Yield: 11%. IR (KBr pellet): $\tilde{\nu}$ 3394br, 1629w, 1385s, 1141m, 941w, 722m $\mathrm{cm^{-1}}$. UV/vis (CH_3OH): λ_{max} (ϵ) 673 nm (205). CD (CH_3OH): λ_{max} ($\Delta\epsilon$) 651 nm (2.33×10^{-1}). Complex **3**·4H_2O: Anal. Calcd for $C_{56}H_{68}O_{32}N_{10}P_2Cu_4$: C, 39.35; H, 4.01; N, 8.19. Found: C, 39.12; H, 3.89; N, 8.24. Yield: 23%. IR (KBr pellet): $\tilde{\nu}$ 3403br, 1603s, 1576m, 1385s, 1132s, 1107s, 1032s, 941m, 773w $\mathrm{cm^{-1}}$. UV/vis (CH_3OH): λ_{max} (ϵ) 657 nm (225). CD (CH_3OH): λ_{max} ($\Delta\epsilon$) 640 nm (2.87×10^{-1}). Complex **4**·15H_2O: Anal. Calcd for $C_{60}H_{90}O_{41}N_{18}P_6Cu_4$: C, 33.37; H, 4.20; N, 11.67. Found: C, 33.62; H, 4.15; N, 11.49. Yield: 55%. IR (KBr pellet): $\tilde{\nu}$ 3409br, 1653w, 1603m, 1448w, 1250s, 1105s, 908m $\mathrm{cm^{-1}}$. UV/vis (H_2O): λ_{max} (ϵ) 680 nm (194). CD (H_2O): λ_{max} ($\Delta\epsilon$) 744 (-1.28×10^{-1}), 597 nm (8.17×10^{-2}).

(10) Crystal data for **2**·15H_2O: $C_{60}H_{89}N_{11}O_{45}P_2Cu_4$, $M_r = 2000.52$, monoclinic, space group $P2_1$ (No. 4), $a = 15.454(1)$ Å, $b = 31.618(2)$ Å, $c = 16.698(1)$ Å, $\beta = 101.660(3)°$, $V = 7990.5(9)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.663$ g cm^{-3}, $2\theta_{max} = 55°$, $\mu = 12.00$ cm^{-1}, $T = -120$ °C, $R_1 = 0.052$ (31336 refs, $I > 2\sigma(I)$, $6° < 2\theta < 55°$) and $wR2 = 0.136$ (all refs) for 2199 variables. Crystal data for **3**·2CH_3OH·0.5H_2O: $C_{58}H_{69}N_{10}O_{30.5}P_2Cu_4$, $M_r = 1710.36$, triclinic, space group $P1$ (No. 1), $a = 11.6421(2)$ Å, $b = 12.9269(1)$ Å, $c = 13.2228(1)$ Å, $\alpha = 64.151(6)°$, $\beta = 82.562(9)°$, $\gamma = 73.240(8)°$, $V = 1714.8(1)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.656$ g cm^{-3}, $2\theta_{max} = 51°$, $\mu = 13.67$ cm^{-1}, $T = -120$ °C, $R_1 = 0.050$ (5037 refs, $I > 2\sigma(I)$, $6° < 2\theta < 51°$) and $wR2 = 0.144$ (all refs) for 642 variables. Crystal data for **4**·20.5H_2O: $C_{60}H_{97}N_{18}O_{46.5}P_6Cu_4$, $M_r = 2254.55$, triclinic, space group $P1$ (No. 1), $a = 10.9106(2)$ Å, $b = 12.7652(4)$ Å, $c = 17.4061(2)$ Å, $\alpha = 76.852(6)°$, $\beta = 72.075(6)°$, $\gamma = 84.895(7)°$, $V = 2245.7(1)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.667$ g cm^{-3}, $2\theta_{max} = 55°$, $\mu = 11.49$ cm^{-1}, $T = -120$ °C, $R_1 = 0.037$ (9142 refs, $I > 2\sigma(I)$, $6° < 2\theta < 55°$) and $wR2 = 0.100$ (all refs) for 1112 variables. All data were collected with a Rigaku AFC8R/Mercury CCD diffractometer with graphite monochromated Mo $K\alpha$ radiation ($\lambda = 0.71070$ Å).

(11) Characterized structures, to date, of unprotected sugar phosphates with metal ions have been reported only as alkali and alkaline earth metal salts; for example, sodium, potassium, and barium salts of D-glucose-1- or -6-phosphate and sodium salts of D-fructose-1- or -6-phosphate and D-fructose-1,6-diphosphate.

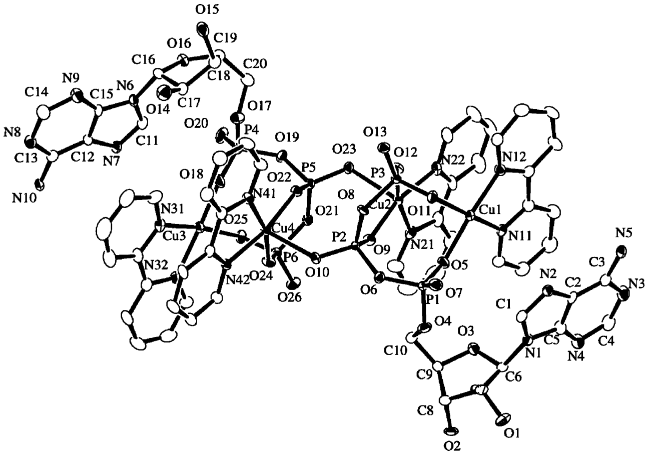


Figure 2. ORTEP plot of complex **4**; thermal ellipsoids set at 40% probability.

moieties are directed upward, near to the hydroxo bridge, and in cation **B**, those parts are directed downward, far from the hydroxo unit. These structures implied that the sugar residues are easily rotated around the α anomeric C−O and P−O single bonds depending on the configurational switch of the tetracopper cluster core. It should be noted that the hydrophobic stacking between two phen units attached to the $\mathrm{Cu_{up}}$ and $\mathrm{Cu_{down}}$ centers may stabilize the tetranuclear structure.

When complex **1** was treated with CH_3COOH, the bridging hydroxo group was dissociated to afford another blue complex of $[\mathrm{Cu_4}(\alpha\text{-D-Glc-1P})_2(\mathrm{CH_3COO})_2(\mathrm{bpy})_4](\mathrm{NO_3})_2$ (**3**).[9,10] The phosphate-bridged tetracopper framework of **1** was converted into a symmetrical rectangular core (Cu1···Cu2 = 3.341(1) Å, Cu3···Cu4 = 3.254(1) Å, Cu1···Cu3 = 4.254(1) Å, Cu2···Cu4 = 4.062(1) Å), in which the hydroxo group disappeared and, instead, two acetate anions bridge another pair of $\mathrm{Cu^{II}}$ ions ($\mathrm{Cu_{up}Cu_{down}}$) with μ_2-oxygen atoms (Scheme 1).

In some attempts to explore reactions of sugar phosphate esters, complex **1** was revealed to readily undergo phosphate-ester-exchange reaction by ATP. Reaction of **1** with $\mathrm{Na_2[H_2\text{-}ATP]}$ in a 1:2 ratio afforded the tetracopper(II) complex formulated as $[\mathrm{Cu_4(ATP)_2(bpy)_4}]$ (**4**).[9] The structure was determined by X-ray crystallographic analysis to consist of four linearly dispersed $\{\mathrm{Cu^{II}(bpy)}\}$ fragments bridged by two ATP tetravalent anions as illustrated in Figure 2(Cu1···Cu2 = 3.444(1) Å, Cu3···Cu4 = 3.4523(8) Å, Cu2···Cu4 = 5.0613(7) Å).[10] Two dinuclear, square pyramidal $\mathrm{Cu^{II}}$ units supported by the triphosphate group of ATP, $\{\mathrm{Cu_2(ATP)(bpy)_2}\}$, are further connected through the axial coordination of β-phosphate oxygen atoms (Cu2−O23 = 2.263(4) Å, Cu4−O10 = 2.247(4) Å), resulting in a characteristic eight-membered puckered ring of the central part (Scheme 1). Whereas metal complexes with ATP could provide useful insights to elucidate bioenergetic processes, characterized examples have still been rare and most are mononuclear species and its sodium salts.[12] In particular, those containing multimetallic centers have strictly been limited; the only available structures with multinuclear transition metal ions are $[\mathrm{Zn(H_2ATP)(bpy)}]_2$ (**5**)[13] and $[\mathrm{Cu(H_2ATP)(phen)}]_2$ (**6**),[14] both possessing an essentially identical structure with the triphosphate group chelating to a metal and its γ-phosphate oxygen atom attaching to the other metal ion. In contrast, the bridging behavior of the ATP triphosphate groups in the dimeric units of complex **4** is remarkably different as two $\mathrm{Cu^{II}}$ ions are held together by the bridges from α- and β-phosphate oxygen atoms and from two oxygen atoms of γ-phoshate unit. The adenosine residues take the *anti*-C2′-*endo* conformation without any direct interaction with metal ions, but weak intramolecular stacking between the purine ring and two bpy ligands is observed as in complexes **5** and **6**.[13,14] The stacking may be responsible for the considerable stability of **4**. It should be noted that complex **4** was not obtained just by mixing $\mathrm{Cu^{II}}$ ions with $\mathrm{Na_2[H_2ATP]}$ and bpy, demonstrating that the tetranuclear $\mathrm{Cu^{II}}$ centers of **1** provide a suitable platform to stabilize the triphosphate unit of ATP.

In conclusion, the tetracopper(II) complexes with α-D-glucose-1-phosphates were prepared and characterized as the first example of transition metal complexes fixing free sugar phosphates, in which α-D-Glc-1P moieties are anchored exclusively by the phosphate group and the orientation of sugar parts is delicately influenced by the structure of the core framework. Further, complex **1** was revealed to be a good precursor of the ATP stabilized tetranuclear $\mathrm{Cu^{II}}$ complex **4**. These molecules could provide useful information in elucidation of phosphate-dependent bioprocesses and in development of biomimetic reactions.

Acknowledgment. This work is partly supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, and Science and Technology, Japan.

Supporting Information Available: X-ray crystallographic files in CIF format and ORTEP plots of complexes **2** and **3**, tables of crystallographic data for complexes **2**−**4**, ESI-MS spectra of **1** and **2**, and UV−vis and CD spectra of complexes **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

IC0487631

---

(12) For example: (a) Cini, R.; Pifferi, C. *J. Chem. Soc., Dalton Trans.* **1999**, 699. (b) Sugawara, Y.; Kamiya, N.; Iwasaki, H.; Ito, T.; Satow, Y. *J. Am. Chem. Soc.* **1991**, *113*, 5440. (c) Cini, R.; Marzilli, L. G. *Inorg. Chem.* **1988**, *27*, 1855. (d) Sabat, M.; Cini, R.; Haromy, T.; Sundaralingam, M. *Biochemistry* **1985**, *24*, 7827. (e) Cini, R.; Burla, M. C.; Nunzi, A.; Polidori, G. P.; Zanazzi, P. F. *J. Chem. Soc., Dalton Trans.* **1984**, 2467. (f) Cini, R.; Sabat, M.; Sundaralingam, M.; Burla, M. C.; Nunzi, A.; Polidori, G.; Zanazzi, P. F. *J. Biomol. Struct. Dyn.* **1983**, *1*, 633.

(13) (a) Orioli, P.; Cini, R.; Donati, D.; Mangani, S. *Nature* **1980**, *283*, 691. (b) Orioli, P.; Cini, R.; Donati, D.; Mangani, S. *J. Am. Chem. Soc.* **1981**, *103*, 4446.

(14) Sheldrick, W. S. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 460.