

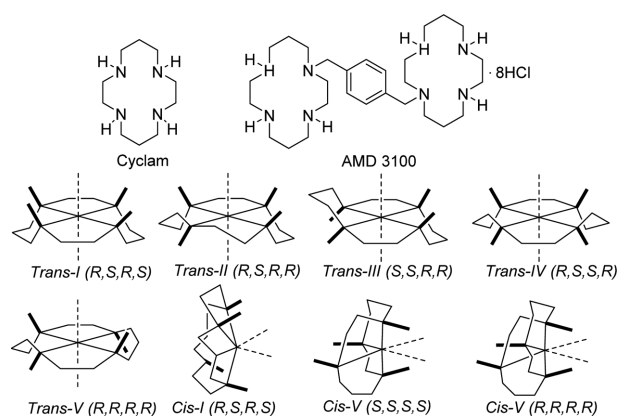
Oxometallate(VI) (M = Mo, W) Bridged Cadmium(II) Cyclam Dimers Bearing *Cis-V* Configurations

Chungsik Jang and Ju Chang Kim*

Department of Chemistry, Pukyong National University, Busan 608-737, Korea. *E-mail: kimjc@pknu.ac.kr
(Received February 22, 2014; Accepted March 3, 2014)

Key words: Anti-HIV, Cadmium(II) cyclam, Macrocycle, Oxometallate

The xylyl-bicyclam AMD 3100 was initially developed for potential use in the treatment of HIV, but the development was discontinued due to the lack of oral availability and problems of cardiac disturbances.¹⁻³ Instead, the development has been focused on the possible use of mobilizing hematopoietic stem cells for transplantation.³ The cyclam and bicyclam show enhanced anti-HIV activity in metal complexes compared to those of free macrocycles.^{4,5} It has been understood that the entry of HIV into cells by binding to the CXCR4 coreceptor is blocked by the metal complexes of macrocycles. The binding sites as well as the type of interactions between the CXCR4 coreceptor and macrocycles are well characterized.^{5,6} Although the metal complexes of macrocycles can show various configurations, the CXCR4 coreceptor recognizes the specific configurations and binds selectively to them.⁵ For instance, one of the metalocyclam units in the metalloxylyl-bicyclam is folded with *Cis-V* configuration, where the carboxylate groups (Asp 262 and Glu 288) of CXCR4 interact by coordination bond as well as hydrogen bonds. Another metalocyclam in the metalloxylyl-bicyclam takes a *Trans-I* configuration and the aspartate carboxylate (Asp 171) group of CXCR4 coreceptor is implicated in the binding site. Therefore, the understanding of the nature of interactions between specific metalocyclam configurations and carboxylate groups on a biological target is crucial for the development of potential anti-HIV drugs. Especially, the *Cis-V*, *Cis-I*, and *Trans-I* configurations of folded metalocyclams are a major concern for the development of potential anti-HIV agent. Nevertheless, isolation and characterization of metal cyclam complexes bearing folded cyclams are sparse (*Scheme 1*).⁷⁻⁹ In this context, investigations on expanding such examples of unusual configurations of metalocyclams are greatly required. Herein, we report two cadmium(II) complexes $[(\mu\text{-MoO}_4)_2\{\text{Cd}(\text{cyclam})\}_2]\cdot 9\text{H}_2\text{O}$ (**1**) and $[(\mu\text{-WO}_4)_2\{\text{Cd}(\text{cyclam})\}_2]\cdot 9\text{H}_2\text{O}$ (**2**) in which the cadmium(II) cyclams exhibit folded *Cis-V* (*S,S,S,S*) (in **1**) and *Cis-V* (*R,R,R,R*)



Scheme 1. Structures of cyclam and AMD 3100, and possible configurations in metal complexes of cyclam.¹⁰

(in **2**) configurations, respectively.

EXPERIMENTAL

Materials and Methods

All chemicals except solvents were purchased from Aldrich, and were used without further purification. Distilled water was used for all procedures. Infrared spectra of solid samples were recorded on a Perkin-Elmer Spectrum X spectrophotometer between 4000 cm^{-1} and 400 cm^{-1} as Nujol mulls on KBr discs. The elemental analyses (C, H, N) were performed on crystalline samples using a CE Instruments EA-1110 Elemental Analyzer at KRICT, Korea. Thermogravimetric analysis was performed on a Perkin-Elmer Model TGA-7 under N_2 sweep from 30 to 700 $^\circ\text{C}$ at a heating rate of 10 $^\circ\text{C}/\text{min}$. The starting material $\text{Cd}(\text{cyclam})(\text{ClO}_4)_2$ was prepared according to the literature procedures.⁷ *Caution! The perchlorate salts are potentially explosive and should be handled with care in small quantities.*

Synthesis of $[(\mu\text{-MoO}_4)_2\{\text{Cd}(\text{cyclam})\}_2]\cdot 9\text{H}_2\text{O}$ (**1**)

To a DMF (5 mL) solution of $\text{Cd}(\text{cyclam})(\text{ClO}_4)_2$ (126 mg,

0.2 mmol) was added an aqueous solution (10 mL) of K_2MoO_4 (48 mg, 0.2 mmole). The mixture was allowed to stand in an open beaker at room temperature. The colorless blocks of **1** were obtained in a day, which were collected for X-ray diffraction studies and other measurements. Yield > 90%. Found C, 21.56%; H, 5.87%; N, 10.09%. Anal. Calcd. for $C_{20}H_{66}Cd_2Mo_2N_8O_{17}$ (**2**): C, 21.67%; H, 5.96%; N, 10.11%. IR (Nujol, cm^{-1}): 3341 (ν O–H), 3214 (ν N–H), 1668 (δ H₂O), 846, 827, 814, 802 (ν Mo–O).

Syntheses of $[(\mu-WO_4)_2\{Cd(cyclam)\}_2]\cdot 9H_2O$ (**2**)

Color blocks of **2** were prepared according to a similar procedure described in the synthesis of **1** using K_2WO_4 instead of K_2MoO_4 . Yield > 90%. Found C, 18.81%; H, 5.11%; N, 8.75%. Anal. Calcd. for $C_{20}H_{66}Cd_2W_2N_8O_{17}$ (**2**): C, 18.70%; H, 5.14%; N, 8.72%. IR (Nujol, cm^{-1}): 3392 (ν O–H), 3216 (ν N–H), 1668 (δ H₂O), 847, 829, 814, 805 (ν W–O).

X-ray Crystallography

X-ray data were collected on a Nonius Kappa CCD diffractometer, using graphite monochromated Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). A combination of $1^\circ \phi$ and ω (with κ offsets) scans were used to collect sufficient data. The data frames were integrated and scaled using the Denzo-SMN package.¹¹ The structures were solved and refined using the SHELXTL\PC V6.1 package.¹² Refinement was performed by full-matrix least squares on F^2 , using all data (negative intensities included). For **1** and **2**, O5W was refined as a solvent water molecule. The O atom lies on a twofold rotation axis and the H atoms are not visible. The H atoms are most likely disordered and have not been included in the refinement but are included in the molecular formula. For **1** and **2**, hydrogen atoms were included in calculated positions. Crystal data and refinement details for **1** and **2** are listed in Table 1.

Table 1. Crystal data and structure refinement parameters for **1** and **2**

	1	2
Empirical formula	$C_{20}H_{66}Cd_2Mo_2N_8O_{17}$	$C_{20}H_{66}Cd_2W_2N_8O_{17}$
Formula weight	1107.49	1283.31
Temperature (K)	150 (1)	150 (1)
Wavelength (\AA)	0.71073	0.71073
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12$	$P2_12_12$
a (\AA)	14.124 (3)	14.142 (3)
b (\AA)	15.682 (3)	15.712 (3)
c (\AA)	8.9220 (18)	8.9256 (18)
V (\AA^3)	1976.1 (7)	1983.3 (7)
Z	2	2
D_{calcd} (Mg/m^3)	1.861	2.149
Absorption coefficient (mm^{-1})	1.755	6.912
F (000)	1116	1244
Crystal size (mm)	$0.20 \times 0.14 \times 0.12$	$0.16 \times 0.15 \times 0.10$
θ range for data collection	2.60 to 27.51°	2.59 to 27.50°
Index ranges	$-17 \leq h \leq 18$ $-20 \leq k \leq 20$ $-11 \leq l \leq 11$	$-18 \leq h \leq 18$ $-20 \leq k \leq 20$ $-11 \leq l \leq 11$
Reflections collected	14581	17540
Independent reflections	4434 [R(int) = 0.0523]	4487 [R(int) = 0.0856]
Completeness to θ	99.8% ($\theta = 27.51^\circ$)	99.6% ($\theta = 27.50^\circ$)
Absorption correction	Semi-empirical from equiv.	Semi-empirical from equiv.
Max. and min. transmission	0.816 and 0.722	0.506 and 0.334
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	4434/0/222	4487/0/222
Goodness-of-fit on F^2	1.119	1.101
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0422$, $wR_2 = 0.0906$	$R_1 = 0.0436$, $wR_2 = 0.0886$
R indices (all data)	$R_1 = 0.0610$, $wR_2 = 0.1032$	$R_1 = 0.0561$, $wR_2 = 0.0951$
Largest diff. peak and hole	1.700 and $-1.405 \text{ e. \AA}^{-3}$	1.688 and $-1.815 \text{ e. \AA}^{-3}$

RESULTS AND DISCUSSION

Description of Structures

The dimeric structure of **1**, as illustrated in Fig. 1, consists of two cadmium(II) cyclam units and two bridging molybdate ligands. Each molybdate ligand bridges cadmium(II) cyclams in monodentate fashion. The coordination environment around the cadmium(II) ion can be described as a distorted octahedron with four Cd–N and two Cd–O bonds, where the bond distances are Cd–N = 2.312(6), 2.344(5), 2.337(5), 2.325(6) Å and Cd–O = 2.310(4), 2.271(4) Å. The Cd–N and Cd–O distances are comparable to those found in the folded cadmium(II) cyclam complex.⁷ The Mo–O bond distances of 1.773(4), 1.747(5), 1.758(4), 1.748(4) are observed in **1**. A list of selected bond distances and angles is given in Table 2. Since the macrocycle in the cadmium(II) cyclam unit is folded, one of the oxygen atoms from the molybdate ligand occupies an axial position and the other one resides on the equatorial position in the distorted octahedron. The configuration of four nitrogen atoms in **1** shows a *Cis-V* (*S,S,S,S*) configuration. The isolation and the understanding of metal cyclams bearing the *Cis-V* (*S,S,S,S*) configuration are important to design and develop the drugs exhibiting anti-HIV activity.⁵ It has been reported that one of the zinc cyclam unit in the Zn₂-AMD 3100 complex is folded, showing the *Cis-V* configuration.⁹ Under such configuration, the carboxylate group of aspartate residue of CXCR4 coreceptor effectively interacts by covalent bond as well as hydrogen bonds. Two factors are believed to affect the configuration in the metallocyclam. One is the metal ion radius of metal ion which is coordinated to a cyclam and the other is the nature of an

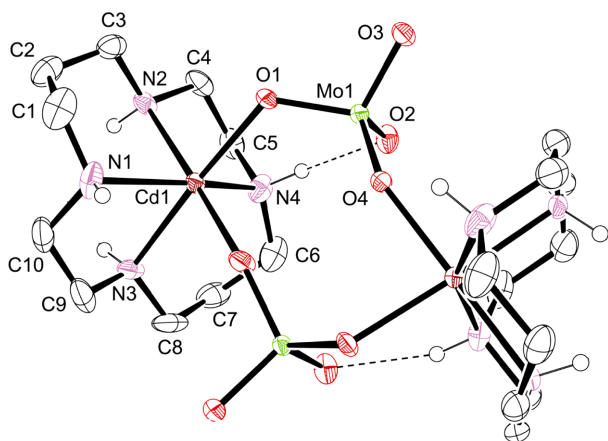


Figure 1. Molecular structure of **1** with atom-labeling scheme. Hydrogen atoms other than those on nitrogen atoms are omitted for clarity.

Table 2. Selected bond distances (Å) and angles (°) for **1**

Cd1–O1	2.310(4)	Cd1–O4#1	2.271(4)
Cd1–N1	2.312(6)	Cd1–N2	2.344(5)
Cd1–N3	2.337(5)	Cd1–N4	2.325(6)
Mo1–O1	1.773(4)	Mo1–O2	1.747(5)
Mo1–O3	1.758(4)	Mo1–O4	1.748(4)
O4#1–Cd1–O1	86.73(16)	O4#1–Cd1–N1	88.8(2)
O1–Cd1–N1	104.2(2)	O4#1–Cd1–N4	107.2(2)
O1–Cd1–N4	93.23(9)	N1–Cd1–N4	157.1(2)
O4#1–Cd1–N3	90.40(17)	O1–Cd1–N3	176.72(18)
N1–Cd1–N3	77.3(3)	N4–Cd1–N3	86.1(2)
O4#1–Cd1–N2	175.95(19)	O1–Cd1–N2	92.38(17)
N1–Cd1–N2	87.6(2)	N4–Cd1–N2	76.8(2)
N3–Cd1–N2	90.60(18)	Mo1–O1–Cd1	120.3(2)
Mo1–O4–Cd1#1	150.2(3)		

Symmetry transformations used to generate equivalent atoms: #1 $-x+1, -y+1, z$

additional ligand involving in the coordination to the metallocyclam. The most stable *Trans III* (*S,S,R,R*) configuration is commonly observed in many cases.¹³ However, other configurations such as *Trans-I* (*R,S,R,S*), *Cis-I* (*R,S,R,S*), and *Cis-V* (*S,S,S,S*) are rarely found in the metal complexes of cyclam in the solid state.^{7–9,13} The solid state structures of folded cadmium(II) cyclam complexes with *Cis-I* configuration have also been reported.^{7–9} The present molybdate bridged cadmium cyclam dimer **1** is another type of a folded cadmium(II) cyclam, but the configuration is *Cis-V*. The difference between the *Cis-I* and *Cis-V* configuration is that all four hydrogen atoms on nitrogen atoms point to the same direction in the *Cis-I* configuration, whereas two of the four hydrogen atoms on nitrogen atoms face the opposite directions in the *Cis-V* configuration.

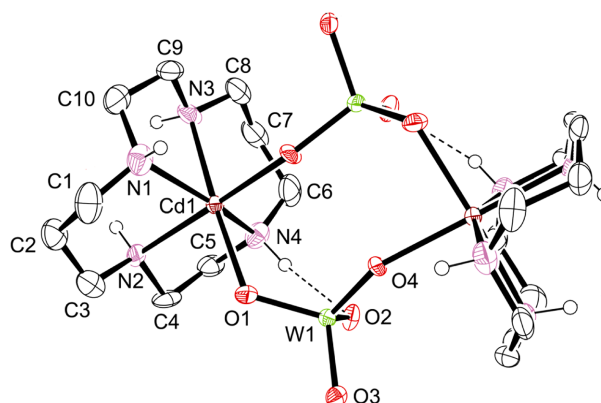


Figure 2. Molecular structure of **2** with atom-labeling scheme. Hydrogen atoms other than those on nitrogen atoms are omitted for clarity.

Table 3. Selected bond distances (Å) and angles (°) for **2**

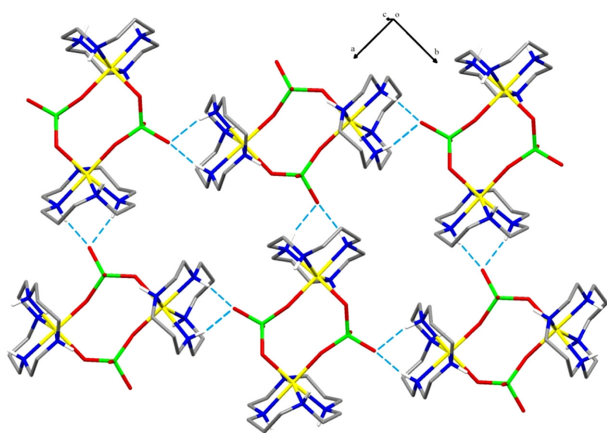
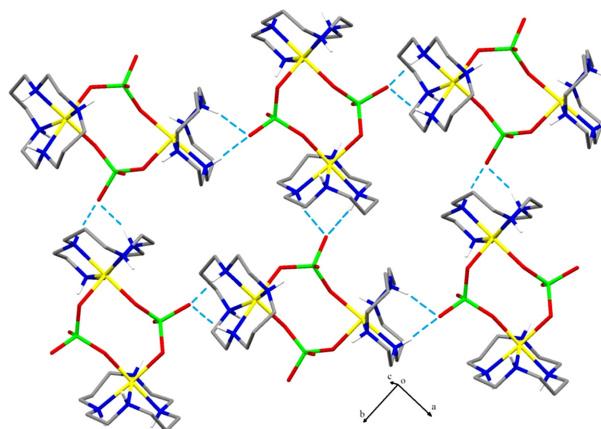
Cd1–O1	2.312(7)	Cd1–O4#1	2.260(6)
Cd1–N1	2.315(10)	Cd1–N2	2.322(8)
Cd1–N3	2.352(9)	Cd1–N4	2.330(10)
W1–O1	1.795(7)	W1–O2	1.733(6)
W1–O3	1.783(7)	W1–O4	1.773(6)
O4#1–Cd1–O1	86.1(3)	O4#1–Cd1–N1	88.6(3)
O1–Cd1–N1	103.6(3)	O4#1–Cd1–N2	176.3(3)
O1–Cd1–N2	92.7(3)	N1–Cd1–N2	88.2(3)
O4#1–Cd1–N4	107.5(3)	O1–Cd1–N4	93.8(3)
N1–Cd1–N4	157.2(3)	N2–Cd1–N4	76.1(3)
O4#1–Cd1–N3	90.7(3)	O1–Cd1–N3	176.6(3)
N1–Cd1–N3	77.4(4)	N2–Cd1–N3	90.6(3)
N4–Cd1–N3	86.2(4)	W1–O1–Cd1	120.0(3)
W1–O4–Cd1#1	149.7(4)		

Symmetry transformations used to generate equivalent atoms: #1 $-x+1, -y+1, z$

In the structure **2**, two cadmium cyclam units are linked by bridging of two tungstate ligands, forming a dimer (*Fig. 2*). The complex also shows a folded cadmium cyclam unit with a *Cis-V* configuration. But, interestingly enough the absolute configuration of four nitrogen atoms in **2** are all inverse compared to those found in **1**, resulting in *Cis-V* (*R,R,R,R*) configuration. The selective isolation of *Cis-V* (*R,R,R,R*) is unexpected, and it is under current investigation for the possible presence and isolation of a *Cis-V* (*S,S,S,S*) enantiomer. A list of selected bond distances, angles and hydrogen bonds for complexes **2** is given in *Table 3*. The dimeric complexes **1** and **2** extend their structures in the solid state by hydrogen bonds to form 2D supramolecules, respectively (*Figs. 3* and *4*).

Analytical, Spectroscopic and Thermal Properties

The microanalytical results for **1** and **2** were consistent

**Figure 3.** Extended structure of **1** by hydrogen bonds.**Figure 4.** Extended structure of **2** by hydrogen bonds.

with the structures determined by X-ray diffraction methods. The solid state infrared spectrum of **1** shows strong absorptions at 846, 827, 814, 802 cm^{-1} ($\nu\text{Mo-O}$) due to bridging molybdate ligands.¹⁴ In addition, bands at 3341 cm^{-1} ($\nu\text{O-H}$), 3214 cm^{-1} ($\nu\text{N-H}$) and 1668 ($\delta\text{H}_2\text{O}$) are observed, indicating the presence of the macrocycle and the lattice water molecules. Similarly, the infrared spectrum of **2** shows bands at 847, 829, 814, 805 ($\nu\text{W-O}$),¹⁵ 3392 cm^{-1} ($\nu\text{O-H}$), 3216 cm^{-1} ($\nu\text{N-H}$), and 1668 ($\delta\text{H}_2\text{O}$) in **2**. In the infrared spectra of **1** and **2**, no strong absorptions associated with perchlorate ions due to the remaining of starting materials are observable.

TGA curves for complexes **1** and **2** further support the structures. Complex **1** shows weight losses of 14.54% (calculated 14.64%) over $\sim 54\text{--}280$ °C by three endothermic processes, corresponding to the loss of nine lattice water molecules. On further heating, significant weight loss accompanies due to the loss of macrocyclic ligand. Finally, the CdO and MoO₃ residues (observed 51.04%, calculated 49.18%) remain above 700 °C. For complex **2**, the TGA curve shows the loss of nine solvated water molecules (12.63%, calculated 12.63%) over $\sim 74\text{--}235$ °C by two endothermic processes. Subsequent loss of the macrocycle is also observed on further heating. Finally, the CdO and WO₃ residues (observed 54.82%, calculated 56.14%) remain above 630 °C.

In conclusion, by the reaction of Cd(cyclam)(ClO₄)₂ and oxometallate ligands, two new cadmium(II) cyclam dimers **1** and **2** in which each cadmium(II) cyclam unit shows a folded structure. Both complexes show a *Cis-V* configuration. However, the absolute configuration of nitrogen atoms is different from each other, showing (*S,S,S,S*) in **1** and (*R,R,R,R*) in **2**. The identification of folded macrocycles in **1** and **2** by the interactions between cadmium(II) cyclams and bridg-

ing oxometallate ligands may provide insights into the design and development of macrocyclic metal complexes in potential anti-HIV agents.

Acknowledgments. This work was supported by a Research Grant of Pukyong National University (2013). We also acknowledge the Department of Chemistry at the University of Toronto for providing the crystal structure results.

Supporting Information. TGA curves, IR spectra and CIF files for **1** and **2** (Figs. S1-S3, Tables S1 and S2). Crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC) under deposition numbers CCDC 986998 (for **1**) and 986999 (for **2**), respectively. Data Acquisition - the Cambridge Crystallographic Data Centre deposit@ccdc.cam.ac.uk <http://www.ccdc.cam.ac.uk/deposit> Telephone: (44) 01223 762910 Facsimile: (44) 01223 336033 Postal Address: CCDC, 12 Union Road, CAMBRIDGE CB2 1EZ, UK.

REFERENCES

- Ross, A.; Choi, J.-H.; Hunter, T. M.; Pannecouque, C.; Moggach, S. A.; Parsons, S.; De Clercq, E.; Sadler, P. J. *Dalton Trans.* **2012**, 41, 6408.
- De Clercq, E. *Nature Rev. Drug Discov.* **2003**, 2, 581.
- Davies, S. L.; Serradell, N.; Bolos, J.; Bayes, M. *Drugs Fut.* **2007**, 32, 123.
- Paisey, S. J.; Sadler, P. J. *Chem. Commun.* **2004**, 306.
- Gerlach, L.-O.; Jakobsen, J. S.; Jensen, K. P.; Rosenkilde, M. M.; Skerlj, R. T.; Ryde, U.; Bridger, G.; Schwartz, T. W. *Biochemistry* **2003**, 42, 710.
- Rosenkilde, M. M.; Gerlach, L.-O.; Jakobsen, J. S.; Skerlj, R. T.; Bridger, G. J.; Schwartz, T. W. *J. Biol. Chem.* **2004**, 279, 3033.
- Liang, X.; Parkinson, J. A.; Parsons, S.; Weishäupl, M.; Sadler, P. J. *Inorg. Chem.* **2002**, 41, 4539.
- Kwag, J. S.; Jeong, M. H.; Lough, A. J.; Kim, J. C. *Bull. Korean Chem. Soc.* **2010**, 31, 2069.
- Liang, X.; Parkinson, J. A.; Weishäupl, M.; Gould, R. O.; Paisey, S. J.; Park, H.-s.; Hunter, T. M.; Blindauer, C. A.; Parsons, S.; Sadler, P. J. *J. Am. Chem. Soc.* **2002**, 124, 9105.
- Hunter, T. M.; McNae, I. W.; Liang, X.; Bella, J.; Parsons, S.; Walkinshaw, M. D.; Sadler, P. J. *Proc. Natl. Acad. Sci. USA* **2005**, 102, 2288.
- Otwinowski, Z.; Minor, W. *Methods in Enzymol.* **1997**, 276, 307.
- Sheldrick, G. M. *SHELXTL/PC V6.1, Bruker Analytical X-ray Systems*, Madison, WI, USA, 2001.
- Hunter, T. M.; McNae, I. W.; Simpson, D. P.; Smith, A. M.; Moggach, S.; White, F.; Walkinshaw, M. D.; Parsons, S.; Sadler, P. J. *Chem. Eur. J.* **2007**, 13, 40.
- Kim, J. C.; Lough, A. J.; Fetting, J. C.; Choi, K.-Y.; Kim, D.; Pyun, S.-Y.; Cho, J. *Inorg. Chim. Acta* **2000**, 303, 163.
- Choi, K.-Y.; Ryu, H.; Suh, I.-H. *Inorg. Chim. Acta* **2000**, 299, 268.