研究简报

一种新型 2,6-吡啶二甲酸镓(Ⅲ)配合物的合成、结构及抑菌活性研究

张秀英[1] 李书静*,[1,2] 杨 林[1]
([1] 河南师范大学化学与环境科学学院,河南省环境污染控制重点实验室,新乡 453007)
([2] 周口师范学院化学系,周口 466000)

关键词: 镓(Ⅲ)配合物; 2,6-吡啶二甲酸; 晶体结构; 抑菌活性
中图分类号: O614.37+1 **文献标识码**: A **文献编号**: 1001-4861(2005)07-1109-06

Synthesis, Structure and Antibacterial Studies of a Novel Gallium(Ⅲ) Complex with 2,6-pyridinedicarboxylate

ZHANG Xiu-Ying[1] LI Shu-Jing*,[1,2] YANG Lin[1]
([1]*Henan Key Laboratory for Environmental Pollution Control, College of Chemistry and Environmental Science, Henan Normal University, Xinxiang* 453007)
([2]*Department of Chemistry, Zhoukou Normal University, Zhoukou* 466000)

Abstract: A novel coordination polymer $[NaGa(dipic)_2\ (H_2O)_2]_n$ was synthesized by the reaction of gallium(Ⅲ) trichloride with Na-salt of 2,6-pyridinedicarboxylic acid and its crystal structure was determined by X-ray diffraction method. The crystal belongs to monoclinic, space group *Cc*; the unit cell parameters are *a*=1.502 9(3), *b*=1.228 1(3) and *c*=0.872 38(17) nm, β=92.85(3)°, and *Z*=4, *V*=1.608 2(6) nm^3, *F*(000)=920. Infrared, electronic absorption, ^{1}H NMR spectra, as well as the thermal behavior are reported. The antibacterial activity of the gallium (Ⅲ) complex has been studied against *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus* in order to check its potential for chemotherapy agent. The activity is notable and higher than that of the H_2L. CCDC: 240619.

Key words: gallium(Ⅲ) complex; 2,6-pyridinedicarboxyli acid; crystal structure; antibacterial activity

0 Introduction

The current interest in the crystal engineering of polymeric coordination networks stems from their potential application as zeolite-like materials for molecular selection, ion exchange and catalysis, as well as in the variety of architectures and topologies[1~4]. One of the basic strategies for crystal engineering utilizes metal-ligand bonding to create coordination polymers. In terms of molecular building blocks, coordination compounds have advantages over organic compounds, because metals have a variety of coordination geometries and a wide range of physical properties. In preparing coordination polymers, building blocks containing nitrogen donors and polycarboxylic acids have been frequently employed[5~8]. 2,6-pyridinedicarboxylic acid is also this kind of ligand and has biological activity too[9]. The heat resistance property of the spores of several gram-positive eubacteria during sporulation is attributed to the presence of the calcium salt of 2,6-

收稿日期:2004-12-06。收修改稿日期:2005-03-06。
国家自然科学基金资助项目(No.20371016)。
*通讯联系人。E-mail:shj_li@yahoo.com.cn
第一作者:张秀英,女,56 岁,教授;研究方向:稀有金属配合物。

pyridinedicarboxylic acid[10]. Its complexes of iron are found to play the role of electron carriers in some model biological systems[11,12] and are recognized as specific molecular tools in DNA cleavage[13].

On the other hand, the tumour-seeking and antineoplastic properties of gallium(Ⅲ) have been recognized 30 years ago. Gallium complexes such as tris(8-quinolato) gallium(Ⅲ) (KP46)[14,15] and tris(3-hydroxy-2-methyl-4H-pyran-4-onato) gallium(Ⅲ) (gallium maltolate)[16] for clinical. This leads us to prepare gallium(Ⅲ) complex with 2,6-pyridinedicarboxylic acid and study its structure and antibacterial activity. Here we report the synthesis, crystal structure, spectroscopic and antibacterial studies of the novel gallium(Ⅲ) complex. It exhibits interesting topology and potential properties as new materials. We hope our work will give important information not only for developing coordination theory, but also for seeking new chemotherapy agent.

1 Experimental

1.1 Materials

2,6-pyridinedicarboxylic acid was purchased from Aldrich. Ga_2O_3 (99.99 %) was purchased from the shanghai Reagent Industry. All other chemicals were of AR grade and used without further purification.

1.2 Physical measurements

Elemental analysis was performed with a Perkin-Elmer 2400 elemental analyser. Infrared spectra (4 000~400 cm^{-1}) were recorded on a Bio-Rad FTS-40 IR spectrophotometer (as KBr pellets). Electronic absorbance spectra were measured on a Perkin-Elmer Lambda 17 UV/VIS spectrophotometer. ^1H NMR spectra were obtained in DMSO-d_6 on a Bruker Avane 400 FT-NMR spectrometer with TMS as an internal standard. Thermal analysis (in static air, heating rate of 10 °C·min^{-1}) was carried out in a DT-40 thermobalance (TG and DTA curves were recorded).

1.3 Synthesis of complex

$GaCl_3$ was prepared by the dissolving of Ga_2O_3 (0.094 g, 0.5 mmol) into 1 mL of hot 6 mol·L^{-1} HCl. Na-salt of 2,6-pyridinedicarboxylic acid was prepared by the reaction of NaOH (0.160 g, 4 mmol) with 2,6-pyridinedicarboxylic acid (0.334 g, 2 mmol) in water. Then to the solution of Na-salt of 2,6-pyridinedicarboxylic acid, $GaCl_3$ was added drop by drop. The reaction mixture was stirred for 6 h and then left undisturbed in darkness at room temperature. Colorless crystals suitable for X-ray study were obtained and washed with 3×10 mL of ethanol after 20 days. Yield: 0.378 g, 82.4 %. Anal. Calcd. for $NaGaC_{14}H_{10}N_2O_{10}$ (%) (M_r=458.95): C, 36.64; H, 2.20; N, 6.11. Found (%): C, 36.59; H, 2.30; N, 6.08.

1.4 Crystallography

A single crystal of dimensions 0.20 mm × 0.18 mm × 0.18 mm was chosen for diffraction study. Determination of unit cell and data collection were made at room temperature on a Rigaku-AXIS-IV X-ray area detector, using graphite-momochromatised Mo $K\alpha$ ra-

Table 1 Crystal data and structure refinement for $[NaGa(dipic)_2(H_2O)_2]_n$

Empirical formula	$C_{14}H_{10}GaN_2NaO_{10}$
Formula weight	458.95
Temperature / K	291(2)
Wavelength / nm	0.071 073
Crystal system	Monoclinic
Space group	*Cc*
a / nm	1.502 9(3)
b / nm	1.228 1(3)
c / nm	0.872 38(17)
β / (°)	92.85(3)
Volume / nm^3	1.608 2(6)
Z	4
D_c / (Mg·m^{-3})	1.896
Absorption coefficient / mm^{-1}	1.803
F(000)	920
Crystal size / mm	0.20 × 0.18 × 0.18
θ range for data collection / (°)	2.14 to 24.98
Index ranges	$-10 \leqslant h \leqslant 17$, $-14 \leqslant k \leqslant 11$, $-10 \leqslant l \leqslant 10$
Reflections collected / unique	2 529 / 1 411 [*R*(int)=0.066 1]
Completeness to θ=24.98° / %	99.2
Absorption correction	None
Max. and min. transmission	0.737 3 and 0.714 4
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1 411 / 7 / 270
Goodness-of-fit on F^2	1.062
Final *R* indices [$I>2\sigma(I)$]	R_1=0.039 4, wR_2=0.090 9
R indices (all data)	R_1=0.041 9, wR_2=0.092 3
Absolute structure parameter	0(10)
Extinction coefficient	0.016 8(15)
Largest diff. peak and hole / (e·nm^{-3})	978 and −638

diation (λ=0.071 073 nm), θ_{min}=2.14°, θ_{max}=24.98°. A total of 2 529 reflections were collected, of which 1 411 reflections were unique. The crystal structure was solved using direct methods (program SHELXS 97)[17] and refined by Full-matrix Least-squares methods on F^2 (using SHELXL 97 system)[18]. All non-hydrogen atoms were refined anisotropically, while all hydrogen atoms were added according to theoretical model. For additional data collection and refinement details see Table 1.

CCDC: 240619.

1.5 Procedure for antibacterial study

The antibacterial activity of the ligand and its complex was studied using the K-B method[19]. The strains chosen included G(+) *Staphylococcus aureus*, G(−) *Escherichia coli* and G(+) *Bacillus subtilis*. The culture media are beef cream peptone solid medium and liquid medium[20]. The bacterial strains were picked with inoculating loop and inoculated in 2 mL of liquid medium at 35 ℃ for 12 h, then adjusted with physiological saline (0.5 Mc Farland Standard). 0.2 mL of the liquid containing strains were coated uniformly on the surface of the solid medium plate, after 5 min, paper discs (6 mm diameter) soaked in 20 μL different concentration of the compounds (in DMSO) were struck on the already seeded Petri plates and incubated at 35 ℃ for 18 h. Every sample was paralleled three times. The diameter (mm) of inhibition zone around each disc was measured with calipers after 18 h.

2 Results and discussion

2.1 Description of the crystal structure of $[NaGa(dipic)_2(H_2O)_2]_n$

X-ray diffraction analysis revealed that the complex is a three-dimensional network structure, which constitutes from the asymmetric unit $NaGa(dipic)_2 \cdot 2H_2O$ (Fig.1). Every Ga(Ⅲ) ion is hexacoordinated by two deprotonated 2,6-pyridinedicarboxylic acids. The Ga center is surrounded by an approximately octahedral arrangement of two pyridine N [N(1) and N(2)] and four carboxylate O atoms [O(1), O(3), O(5), O(7)] from the two ligands. There are four five-membered rings (C-O-Ga-N-C) in each unit, so the structure is very stable. The mean Ga-O and Ga-N bond lengths are 0.202 1 and 0.197 3 nm, respectively (Table 2).

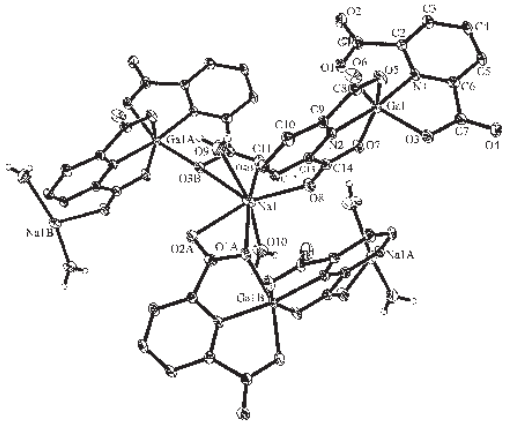

Fig.1 A stereoview of the $[NaGa(dipic)_2(H_2O)_2]_n$ complex, showing the coordination environment of gallium and sodium ions (pyridine H atoms are omitted for clarity)

Table 2 Selected bond lengths(nm) and angles (°) for the complex

Ga(1)-N(1)	0.197 3(5)	Na(1)-O(4)#1	0.242 2(5)	O(6)-C(8)	0.122 9(7)
Ga(1)-N(2)	0.197 2(5)	Na(1)-O(8)	0.242 7(5)	O(7)-C(14)	0.129 7(7)
Ga(1)-O(1)	0.203 6(5)	Na(1)-O(9)#2	0.237 8(6)	O(8)-C(14)	0.122 5(7)
Ga(1)-O(3)	0.199 8(4)	Na(1)-O(10)	0.234 0(6)	O(9)-H(9A)	0.085(2)
Ga(1)-O(5)	0.203 1(5)	O(1)-C(1)	0.128 4(8)	O(9)-H(9B)	0.085(2)
Ga(1)-O(7)	0.201 9(4)	O(2)-C(1)	0.125 0(7)	O(10)-H(10B)	0.084(2)
Na(1)-O(1)#2	0.261 9(5)	O(3)-C(7)	0.129 7(7)	O(10)-H(10C)	0.085(2)
Na(1)-O(2)#2	0.249 9(5)	O(4)-C(7)	0.123 0(7)		
Na(1)-O(3)#1	0.301 8(5)	O(5)-C(8)	0.128 4(7)		
N(2)-Ga(1)-N(1)	171.8(2)	N(2)-Ga(1)-O(1)	93.82(19)	O(4)#1-Na(1)-O(3)#1	47.35(14)
N(1)-Ga(1)-O(1)	78.72(18)	O(5)-Ga(1)-O(7)	157.99(15)	O(4)#1-Na(1)-O(8)	93.45(18)
N(1)-Ga(1)-O(3)	79.46(19)	O(2)#2-Na(1)-O(1)#2	51.98(14)	O(8)-Na(1)-O(1)#2	84.08(16)
N(2)-Ga(1)-O(3)	108.02(19)	O(2)#2-Na(1)-O(3)#1	86.00(14)	O(10)-Na(1)-O(9)	161.9(2)

Symmetry transformations used to generate equivalent atoms: #1: $x-1/2$, $y-1/2$, z; #2: x, $-y+1$, $z-1/2$; #3: x, $-y+1$, $z+1/2$; #4: $x+1/2$, $y+1/2$, z.

Oxygen atoms O(1), O(3), O(5), O(7) are coordinated while O(2), O(4), O(6), O(8) are not, in this case, it generally results in the C-O (1, 3, 5, 7) distance longer than C-O (2, 4, 6, 8), indicating conjugation of the double bond after deprotonation[21]. The dihedral angle between the planes of the two ligands is equal to 80.1°, almost perpendicular. And the bond angle of N(1)-Ga(1)-N(2) is 171.8°.

The linearity of the N(1)-Ga-N(2) group in the complex seems to indicate a significant strain in the bond angles and bond lengths of the pyridine groups as compared with those in 2,6-pyridinedicarboxylic acid itself[22]. This strain is relieved in the complex through N-Ga-N angle contraction; the pyridine rings retain their approximate C_{2v} symmetry within experimental error.

The unit cell contains four $NaGa(dipic)_2 \cdot 2H_2O$ units with the Na^+ located in interstitial positions. Every Na^+ ion is surrounded by seven O atoms in a pseudo-pentagonal bipyramid orientation. Three of these O atoms [O(2), O(4), O(8)] are provided by non-coordinating carboxylate O atoms, with an average Na-O distance of 0.244 9(5) nm. The fourth and fifth atoms [O(1), O(3)] share coordination with Ga(Ⅲ) and the bond lengths are 0.261 9(5) and 0.301 8(5) nm respectively. The coordination sphere is completed by two trans water O atoms [O(9), O(10)] with an average Na-O distance of 0.235 9(6) nm.

The structure can also be viewed as consisting of two building blocks [Ga(dipic)$_2$] and [Na(dipic)$_3$(H$_2$O)$_2$]. They are linked together through Na-O bonding and a set of hydrogen bonds[O(8)⋯O(9) 0.281 7(7) nm, O(8)⋯H(9A)–O(9) 142(52)°; O(5)⋯O(9) 0.322 1(8) nm, O(5)⋯H(9B)–O(9) 172(8)°; O(4)⋯O(10) 0.303 0(7) nm, O(4)⋯H(10B)–O(10) 162(5)°; O(6)⋯O(10) 0.292 5(7) nm, O(6)⋯H(10C)–O(10) 152(12)°], generating the final three-dimensional network structure. The pyridine rings are orderly packed along *c* axis, and π-π stacking interactions are found between them with face-to-face separation of *ca.* 0.334 nm, the distance is similar to the standard distance for a strong π-π stacking interaction between two aryl rings. The existence of π-π stacking interactions and hydrogen bonds further stabilizes the structure.

Viewed from the point of topology, the network can be represented using the (n, p) notation (where n is the number of nodes in the shortest circuit, and p is the connectivity of the nodes). Fig.2 exhibits a three dimensional (10,3)-b network[23], in which the Na(I) and Ga(Ⅲ) atoms act as three-connected nodes. The nodes have 120° angles. Each node is connected to two neighbors in a 1D planar zigzag strip. The third connection at every node is to a node belonging to a zigzag strip running perpendicular to the first.

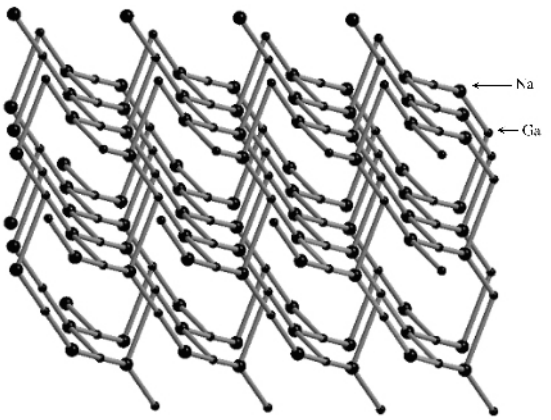

Fig.2 Topology structure of the complex

2.2 Infrared spectra

The IR spectrum of the free ligand (2,6-pyridinedicarboxylic acid) exhibits the $\nu_{(C=O)}$ stretch of the -COOH group in 1 700 cm^{-1}. In the Ga(Ⅲ)-Na(I) complex, this absorption band disappears and bands at 1 682 and 1 343 cm^{-1} are observed and assigned to the asymmetrical and symmetrical stretching of the carboxylate groups O-C-O. The considerable difference between νas and νs indicates strong coordination of the carboxylate oxygen to the Ga(Ⅲ) acceptor center[24].

The ligand shows bands around 1 570, 650, and 420 cm^{-1} which maybe assigned to 8a or 8b (ring deformation), 6a (in-plane deformation) and 16b (out-of-plane deformation) vibrations, respectively. In the complex, these bands show upward shifts (–40~20 cm^{-1}) to 1 602, 684 and 457 cm^{-1}, and the splitting of 6a band has also been observed. The upward shift and splitting of 6a band are consistent with the pyridine nitrogen coordination to gallium atom[25].

2.3 Electronic absorption spectra

The electronic absorption spectrum of the complex in H_2O is similar to that of the ligand. Only one band (270.4 nm) is observed in the UV region in the spectrum of the ligand, which is attributed to π-π^* in-

traligand transitions (K band). In the complex, the band exhibits a hypsochromic shift of 4.8 nm to 265.6 nm. This is because the electron cloud transferred from the oxygen atoms to gallium ion via coordination, the electron cloud of the conjugated system rearranged.

2.4 ^{1}H NMR spectra

The ^{1}H NMR spectra of the free ligand and the gallium(Ⅲ) complex were obtained in DMSO-d_6 and the chemical shift data are given in Table 3. The positions of the H protons of the ligand are shown in Fig.3. The proton signals of -COOH disappears after coordination, the signals of the pyridine protons show a slight downfield shift due to increased conjugation on coordination[26], which supports the conclusion derived from their electronic absorbance spectra.

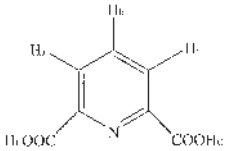

Fig.3　Positions of the H protons of the ligand

Table 3　^{1}H NMR data of the ligand and complex (δ ppm in DMSO-d_6)

Compounds	H_a	H_b	H_c
H_2L	8.233, 8.250, 8.254 (2H, t)	8.160, 8.176, 8.183, 8.198 (1H, m)	13.260 (2H, br)
	^3J=7.6 Hz, ^4J=0.8 Hz	^3J=6.4 Hz, ^3J=6.0 Hz	
$[NaGa(L)_2(H_2O)_2]_n$	8.445, 8.464 (2H, d)	8.690, 8.709, 8.728 (1H, t)	—
	^3J=7.6 Hz	^3J=7.6 Hz, ^3J=7.6 Hz	

2.5 Thermal behavior

The complete dehydration of hydrated gallium complex is a single-step process which takes place in a temperature range from 160 to 220 ℃. The complex gradually loses 7.414 % of its mass (cal: 7.853 %) and the dehydration is connected with a strong endothermic peak in the DTA curve. A horizontal stage corresponding to anhydrous compound is observed in the TG curve, which extends over a temperature range from 220~350 ℃. The ligand decomposition takes place in 350~600 ℃, loses 64.65 % of its mass (cal: 64.97 %). Stable oxides Na_2O, Ga_2O_3 are the final products[27].

2.6 Study of biological activity

Inhibition of cell division (associated with cell elongation) is a characteristic property of anticarcinogenic compounds[28]. The gallium complex reported here was tested against *Staphylococcus aureus*, Escherichia coli and *Bacillus subtilis* to find out whether it can significantly inhibit the bacterial growth with the final objective of testing it against selected tumor models. The result of the bacterial grow inhibition study is reported in Table 4 in terms of the average diameter of inhibition zone. As a whole, the gallium complex shows better activity than the free ligand, and they are more sensitive to gram-positive *Staphylococcus aureus* and *Bacillus subtilis*. Generally, the sensitivity to bacteria can be judged by measuring the diameter of inhibition zone. For $d \geqslant 18$ mm, its highly sensitive, while 15 mm $\leqslant d \leqslant$ 17 mm is intermediately sensitive and $d \leqslant 14$ mm is active. From the result, we can see the antibacterial effect of complex is very notable. The diameter of inhibition zone at 20 mg·mL^{-1} for *Staphylococcus aureus* and *Bacillus subtills* are 42.00 and 31.00 mm, which are much larger than 18 mm. Further studies of examining it against selected tumor models both in vitro and vivo will be gone on.

Table 4　Antibacterial data for the ligand and the complex

Agent	Concentration / (mg·mL^{-1})	Average value of diameter of inhibition zone / mm		
		Staphylococcus aureus	*Escherichia coli*	*Bacillus subtilis*
H_2L	10	9.00	6.73	6.83
	20	9.67	8.17	10.17
	40	8.33	9.23	12.07
$[NaGa(L)_2(H_2O)_2]_n$	10	9.33	10.33	8.00
	20	42.00	16.03	31.00
	40	27.00	7.83	22.87

References:

[1] Zaworotko M J. *Chem. Soc. Rev.*, **1994**,**23**(4):283~288

[2] Braga D, Grepioni F, Desiraju G R. *Chem. Rev.*, **1998**,**98**(4): 1375~1405

[3] Hagrman P J, Hagrman D, Zubieta J. *Angew. Chem. Int. Ed.*, **1999**,**38**(18):2638~2684

[4] Swieger G F, Malefetse T J. *Chem. Rev.*, **2000**,**100**(9):3483~3537

[5] Seo J S, Whang D, Lee H, et al. *Nature*, **2000**,**404**(6781):982~986

[6] Withersby M A, Blake A J, Champness N R, et al. *J. Am. Chem. Soc.*, **2000**,**122**(17):4044~4046

[7] Cui Y, Evans O R, Ngo H L, et al. *Angew. Chem. Int. Ed.*, **2002**,**41**(7):1159~1162

[8] Horikoshi R, Mochida T, Moriyama H. *Inorg. Chem.*, **2002**, **41**(11):3017~3024

[9] Setlow B, Setlow P. *Appl. Environ. Microbiol.*, **1993**,**59**(2): 640~643

[10]Hasimoto T, Black S H, Gerhardt P. *Can. J. Microbiol.*, **1960**, **6**(2):203~212

[11]Laine P, Gourdon A, Launay J P. *Inorg. Chem.*, **1995**,**34**(21): 5129~5137

[12]Mauk A G, Coyle C L, Bardingnon E, et al. *J. Am. Chem. Soc.*, **1979**,**101**(17):5054~5056

[13]Groves J T, Kady I O. *Inorg. Chem.*, **1993**,**32**(18):3868~3872

[14]Collery P, Domingo J L, Keppler K. *Anticancer Res.*, **1996**, **16**(2):687~691

[15]Thiel M, Schilling T, Grey D C, et al. *Contrib. Oncol.*, **1999**, **54**:439~443

[16]Bernstein L R, Tanner T, Godfrey C, et al. *Metal-Based Drugs*, **2000**,**7**(1):33~47

[17]Sheldrick G M. *SHELXS* 97, *Program for Solution of Crystal Structures*. Germany: University of Göttinger, **1997**.

[18]Sheldrick G M. *SHELXL* 97, *Program for Crystal Structure Refinement*. Germany: University of Göttinger, **1997**.

[19]LI Zong-Yi(李宗义), LIU Guo-Sheng(刘国生), LI Xue-Mei(李学梅). *Laboratory Techniques in Microbiology*(微生物学实验技术). Beijing: Weather Press, **1997**.

[20]LIU Yun-De(刘运德). *Microbial Assay*, 2*nd ed*(微生物学检验, 第二版). Beijing: People Sanitation Press, **2004**.

[21]Brouca-Cabarrecq C, Fernandes A, Jaud J, et al. *Inorg. Chim. Acta*, **2002**,**332**:54~60

[22]Takusagawa F, Hirotsu K, Shimada A. *Bull. Chem. Soc. Jpn*, **1973**,**46**(7):2020~2027

[23]Batten S R, Robson R. *Angew. Chem. Int. Ed.*, **1998**,**37**(11): 1460~1494

[24]Kumari V, Sahni S K, Kher S, et al. *Synth. React. Inorg. Met. Org. Chem.*, **1979**,**9**(5):409~418

[25]Gill N S, Nuttall R H, Scaife D E, et al. *J. Inorg. Nucle. Chem.*, **1961**,**18**:79~87

[26]Pasto D J, Johnson C R. *Organic Structure Determination*. London: Prentice Hall International, **1969**.

[27]Cui Y, Zhang X, Huang J S. *Polyhedron*, **1999**,**18**(26):3411~3416

[28]Williams D R. *Inorg. Chim. Acta Rev.*, **1972**,**6**:123~133