一种新型钌(Ⅱ)-组氨酸配合物[$RuCl(Me_2SO)_2(L\text{-}His)$]·$H_2O$的合成及其结构表征

柯晓康　张俊勇　涂　超　刘　琴　熊仁根　郭子建*

(南京大学配位化学国家重点实验室，南京　210093)

本文通过将抗癌活性化合物 *cis*-[$RuCl_2(Me_2SO)_4$]与 *L*-组氨酸在乙醇溶液中或在溶剂热条件下反应，均得到了配合物[$RuCl(Me_2SO)_2(L\text{-}His)$](1**)。X-射线单晶结构分析表明该配合物的晶体属变形八面体，空间群 $P3_121$，$a = b = 14.0575(16)$ Å，$c = 15.637(3)$ Å，分子中含一个结晶水。该配合物中 *L*-组氨酸配体分别通过氨基氮、咪唑氮、羧基氧与中心原子钌(Ⅱ)配位。**

关键词： 钌(Ⅱ)配合物　组氨酸　晶体结构　抗癌药物

分类号： O614.82$^+$1

Synthesis and Structural Characterization of a Novel Ruthenium (Ⅱ)-Histidine Complex

KE Xiao-Kang　ZHANG Jun-Yong　TU Chao　LIU Qing　XIONG Ren-Gen　GUO Zi-Jian*

(*State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing* 210093)

The reaction of anti-metastatic agent *cis*-[$RuCl_2(Me_2SO)_4$] with *L*-histidine in ethanolic solution or under solvothermal conditions results in the formation of [$RuCl(Me_2SO)_2(L\text{-}His)$] (**1**). The X-ray structure analysis shows that the Ru (Ⅱ) atom in the complex **1** has a distortedly octahedral coodination, $P3_121$, $a = b = 14.0575(16)$ Å, $c = 15.637(3)$ Å, with one crystallized water molecule. The histidine ligand coordinated to Ru (Ⅱ) in a facial tridentate mode through amino nitrogen, imidazole nitrogen and carboxylate oxygen, respectively.

Keywords: ruthenium complex　histidine　crystal structure　anticancer agent

0　Introduction

The great success of platinum-based anti-cancer drugs has stimulated wide interests in the search for more active and less toxic metallo-drugs as therapeutic agents[1~3]. Of these non-platinum transition metal anti-tumor agents, several ruthenium compounds have shown remarkable activities.

收稿日期：2001-05-16。**收修改稿日期**：2001-06-29。

国家自然科学基金资助项目（No. 29925102）。

*通讯联系人。E-mail: zguo@netra.nju.edu.cn

第一作者：柯晓康，男，29 岁，硕士生；研究方向：生物无机化学。

In particular, *trans*-[$RuCl_4(Me_2SO)(Im)]^-$ has entered clinic trials for the treatment of tumor metastases[4, 5].

The mechanism of action of Ru (Ⅲ) compounds appears to involve a reduction to Ru (Ⅱ), followed by the binding to some cellular target which is believed to be certain DNA[6] . Although direct correlation between cytotoxicity and DNA binding has been observed for several representative ruthenium anticancer complexes, other biological targets, such as DNA polymerase, topoisomerase II, and metrix metalloproteinase may also be involved[7].

Ruthenium compounds appear to be transported by transferrin and uptaken by tumor cells via transferrin receptor[8]. For example, crystallographic data show that *trans*-$[Ru(Im)_2Cl_4]^-$ binds to a histidine residue of iron binding site of lactoferrin[9]. However, there is scarce structural information available in the literature for Ru (Ⅱ) -histidine complex, except for those of [RuCl(*L*-His)(diene)][10] and [RuCl(*D*, *L*-His)$(PPh_3)_2$][10], where the histidine moiety coordinated to Ru (Ⅱ) in a tridentate fashion.

In this paper we report the synthesis and X-ray crystal structure of a chiral Ru (Ⅱ) complex, $[RuCl(Me_2SO)_2(L\text{-His})]$ (**1**), the reaction product of an anti-metastatic agent *cis*-$[Ru(DMSO)_4Cl_2]$ with *L*-histidine.

1 Experimental

1.1 Chemicals

All solvents were of analytical grade and were used without further purification. $RuCl_3 \cdot 3H_2O$ was supplied by the Analytical Center of Tongji University (P. R. China). *L*-Histidine was purchased from Shanghai Bo-Ao Biological Technology Ltd. *Cis*-$[Ru(DMSO)_4Cl_2]$ was prepared and recrystallized according to the literature method[11, 12].

1.2 Measurement

Electronic absorption spectra were recorded on Shimadzu UV-3100 UV-VIS-NIR recording spectrophotometers with 1cm path length cells. 1H NMR spectra were recorded on a Bruker AMX-500 spectrometer, and the chemical shifts internally referenced to TSP. IR spectra were collected on a Shimadzu 440 spectrometer with KBr pellets.

1.3 X-Ray Crystallographic Analysis

The single crystal X-ray diffraction experiment was performed at room temperature using a SMART CCD diffractometer equipped with monochromated Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å). A suitable crystal was quickly chosen from the mother liquid and coated with epoxy. The unit cell parameters were obtained based on the least-squares refinement of three dimension centroids of 12311 reflections, the intensity data were collected using a narrow frame method. Frames were integrated with the Siemens SAINT program[13] . The SADABS program absorption correction based upon redundant reflections was applied to the data set. For chiral space group, the correctness of the selected space group was confirmed by a reasonable Flack value of $-0.04(3)$. The crystal data for **1** are listed in Table 1.

1.4 Synthesis of $[RuCl(Me_2SO)_2(L\text{-His})] \cdot H_2O$ (1)

Table 1　Crystal Data, Data Collection, Solution and Refinement for 1

empirical formula	$C_{10}H_{22}ClN_3O_5RuS_2$
formula weight	464. 94
crystal habit, colour	cubic, green-yellow
crystal size/mm	0. 2 × 0. 2 × 0. 2
crystal system	hexagonal
space group	$P3_121$
a/Å	14. 0575(16)
b/Å	14. 0575(16)
c/Å	15. 637(3)
volume/Å^3	2676. 1(6)
Z	6
density(calc.)/(Mg · m^{-3})	1. 731
absorption coefficient/mm^{-1}	1. 285
F(000)	1416
data collection	
diffractometer	bruke SMART platform CCD
wavelength/Å	0. 71073
temperature/K	293(2)
θ range for data collection/(°)	3. 90 ~ 30. 00
index ranges	$-19 \leqslant h \leqslant 19$, $-19 \leqslant k \leqslant 19$, $-20 \leqslant l \leqslant 8$
No. reflections collected	12311
No. independent reflections	4924(R_{int} = 0. 0255)
solution and refinement	
system used	SHELXTL 97
solution	direct methods
refinement method	full-matrix least-squares on F^2
absorption correction	SADABS(Sheldrick, 1996)
max. and min. Transmission	1. 000 and 0. 735
data/restraints/parameters	4924/0/203
R indices ($I > 2\sigma(I)$)	R_1 = 0. 0280, wR_2 = 0. 0645
R indices (all data)	R_1 = 0. 0441, wR_2 = 0. 0707
goodness-of-fit on F^2	1. 014
largest difference peak and hole/(e · Å^{-3})	0. 832 and −0. 974

Complex **1** was first prepared via solvothermal synthesis in ethanol solution. *cis*-[$RuCl_2(DMSO)_4$] 100mg(0. 21mmol) and *L*-histidine 32mg(0. 20mmol) were carefully introduced into a thick-walled Pyrex tube. After addition of 1mL of ethanol, the mixture was frozen in liquid N_2, evacuated in vacuo and sealed with a torch. The tube is kept at 90℃ in an electric oven for ca. 7 days, giving rise to a dark brown solution. Dark-yellow cubic crystals, suitable for X-ray analysis, are obtained when cooling slowly to room temperature(yield, 40%). Anal. Calc. For $C_{10}H_{22}ClN_3O_5RuS_2$: C, 25. 83; H, 4. 77; N, 9. 04. Found: C, 25. 75; H, 4. 61; N, 8. 84. ^{1}H NMR(D_2O): δ = 3. 05, 3. 31, 3, 32, 347, 4. 08, 7. 17, 8. 14. Selected IR absorptions (cm^{-1}): 1720(ν_{CO}), 1600(ν_{NH_2}), 1070(ν_{SO}). Electronic spectra (λ_{max}, nm): in H_2O: 360, 296.

Complex **1** was also prepared in methanol solution by reacting *cis*-[$RuCl_2(DMSO)_4$] with histidine in the presence of NaOEt. A mixture of *cis*-[$RuCl_2(DMSO)_4$] (50 mg, 0. 103mmol) and *L*-histidine(17 mg, 0. 110 mmol) was refluxed in 10mL of MeOH in presence of NaOEt(7. 84 mg,

0. 110mmol) under N_2 for 4 hours. The color of the solution turned to dark-yellow. The resulting white precipitates were filtered. The volume of the solution was then reduced to ca 2mL. The dark yellow crystalline solid was obtained by acetone slowly diffusing to the solution(yield, 50%). Anal. Calc. For $C_{10}H_{22}ClN_3O_5RuS_2$: C, 25. 83; H, 4. 77; N, 9. 04. Found: C, 25. 70; H, 4. 65; N, 8. 74. The IR and ^1H NMR data of the product is identical to complex **1**.

2 Results and Discussion

2. 1 X-ray crystal structure of $[RuCl(Me_2SO)_2(L\text{-His})]\cdot H_2O$(1)

The molecular structure of 1 is shown in Fig. 1. The histinate anion in the molecule is present as a facial tridentate ligand coordinating to Ru(Ⅱ) via amino nitrogen N(1), imidazole nitrogen N(2) and carboxylate oxygen O(6). The remaining coordination sites are occupied by two sulfur atoms S(1) and S(2) of two Me_2SO, and a chlorine atom Cl(1) . The Ru(Ⅱ) is situated in a slightly distorted octahedral geometry, with the N1 being positioned trans to Cl(1) while N(2) and O(6) trans to S(1) and S(2), respectively, as shown in Fig. 2.

The selected bond distances and angles are listed in Table 2. As can be seen, the bond length of Ru(1)-S(1) (trans to N(2)) is comparable to those found in *cis*-$[Ru(Ⅱ)Cl_2(DMSO)_4]$, the average value of 2. 267(1)Å[12] and 2. 25(1)Å[13] in $[Ru(DMSO)_6]^{2+}$, however, it is longer than that of Ru(1)-S(2) (trans to O(6)). The bond length of S(2)-O(4) (1. 495(8)Å) is longer than that of S(1)-O(5) (1. 485(9)Å), so the short bond length of Ru(1)-S(2) probably arises from a stronger π-back bonding from d(orbital of Ru to a p_π^* orbital of S = O with carboxylate group being a strong π-donor. The bond lengths of Ru(1)-N(1), Ru(1)-N(2) and Ru(1)-O(6) are very close to those (2. 114(8), 2. 120(8) and 2. 114(8)Å[10], respectively) found in [RuCl(*L*-his)(diene)]. The bond angles of N(1)-Ru(1)-O(6) and N(2)-Ru(1)-O(6) are significantly smaller than 90°, which may be due to the formation of histidinate chelate rings. The bond angles of O(6) -Ru(1) -S(2), N(2) -Ru(1) -S(1) and N(1) -Ru(1) -Cl(1) are smaller than 180° which may be attributed to the steric effect of the imidazole ring and the ring strain of histidinate metallocycle.

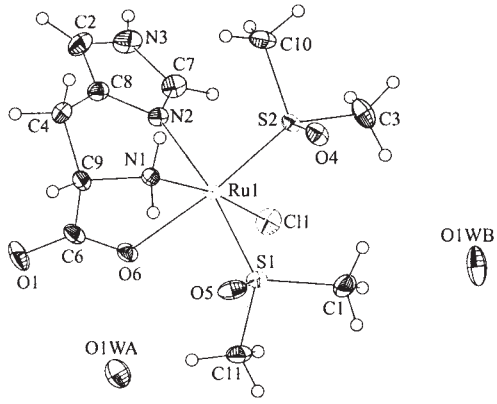

Fig. 1 ORTEP drawing of $[RuCl(Me_2SO)_2(L\text{-His})]\cdot H_2O$(**1**) showing the atom numbering scheme (thermal ellipsoids at 30% probability level)

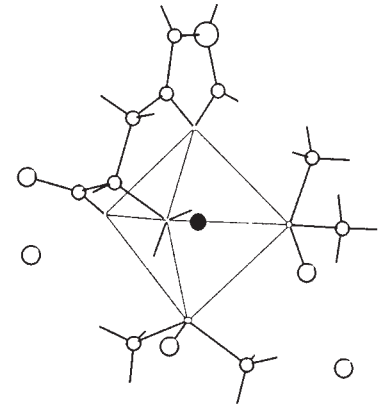

Fig. 2 A plot highlighting central Ru atom with a slightly distorted octahedron (dark circle stands for Ru atom)

Table 2　Selected Bond Lengths(Å) and Angles(°) for 1

Ru(1)-N(1)	2.100(4)	Ru(1)-S(2)	2.2090(11)	Ru(1)-N(2)	2.123(4)
Ru(1)-O(6)	2.145(3)	S(2)-O(4)	1.495(8)	Ru(1)-S(1)	2.2454(11)
Ru(1)-Cl(1)	2.4178(13)	S(1)-O(5)	1.485(9)		
N(1)-Ru(1)-N(2)	87.38(14)	N(1)-Ru(1)-O(6)	77.81(13)	N(2)-Ru(1)-O(6)	83.42(13)
N(1)-Ru(1)-S(2)	94.89(9)	N(2)-Ru(1)-S(2)	93.55(10)	O(6)-Ru(1)-S(2)	172.18(10)
N(1)-Ru(1)-S(1)	88.49(10)	N(2)-Ru(1)-S(1)	171.81(11)	O(6)-Ru(1)-S(1)	88.79(10)
S(2)-Ru(1)-S(1)	93.865(4)	N(1)-Ru(1)-Cl(1)	169.96(9)	N(2)-Ru(1)-Cl(1)	91.26(11)
O(6)-Ru(1)-Cl(1)	92.15(10)	S(2)-Ru(1)-Cl(1)	95.12(5)	S(1)-Ru(1)-Cl(1)	91.58(5)

In the molecular structure of **1** there are two histidinate metallocycles: a five-membered metallocycle with Ru(1), O(6), C(6), C(9), C(1) and a six membered metallocycles with Ru(1), N(1), C(9), C(4), C(8), N(2). The torsion angles of the two metallocycles are listed in Table 3. The five-membered metallocycle can be considered as an envelope conformation, with N(1) being slightly away from the approximate plane defined by the remaining atoms. A half-chair conformation is observed for the adjacent six-membered metallocycle with N(1) displaced 0.2041Å from the approximate plane through the remaining five atoms. Take hydrogen bonding into account as shown in Fig. 3, the four water molecules in the crystal form a quadrangle shape with a dimension of 2.807 × 2.861 × 2.861 × 1.933Å. There is a strong hydrogen bond(1.976Å) between H10 and O1A .

Table 3　Selected Torsion Angles(°) for 1

Ru(1)-O(6)-C(6)-C(9)	-8.8(5)	O(6)-C(6)-C(9)-N(1)	-19.4(5)	Ru(1)-N(1)-C(9)-C(6)	37.1(4)
N(1)-Ru(1)-O(6)-C(6)	23.5(3)	Ru(1)-N(1)-C(9)-C(4)	-84.3(3)	C(8)-C(4)-C(9)-N(1)	65.7(4)
C(9)-C(4)-C(8)-N(2)	-19.5(5)	Ru(1)-N(2)-C(8)-C(2)	-179.8(3)	N(1)-Ru(1)-N(2)-C(8)	-14.0(3)
N(2)-Ru(1)-N(1)-C(9)	51.8(2)				

2.2　Solution Behavior of [RuCl(Me$_2$SO)$_2$(*L*-His)]·H$_2$O(1)

Complex **1** is very soluble in water, in methanol, but insoluble in non-polar solvents. Due to the air-sensitive nature, the color of the aqueous solution of complex **1** in air changes slowly from yellow to red and to pink. The UV spectra show that the bands at 300nm and 360nm decreased in intensity and disappeared after 3 days.

The ^{1}H NMR spectrum of a freshly prepared solution of **1** in D$_2$O show that the four methyl groups of the two Me$_2$SO are magnetically inequivalent, and exhibits four sharp singlets at 3.47, 3.32, 3.31, 3.05ppm, respectively. This is due to the the lack of symmetry of **1** and restricted rotation of Ru-S bonds. The α-CH and imidazole protons of histindine gave rise to three well-resolved resonances at 4.08, 7.17 and 8.14ppm, respectively.

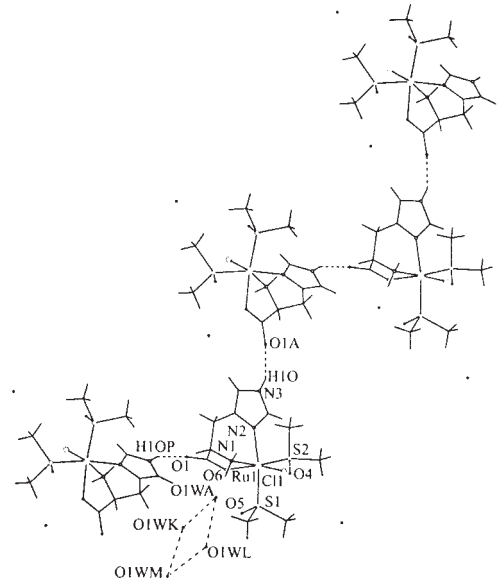

Fig. 3　A perspective view of **1** showing 3-D hydrogen-bonding interactions (the dotted lines stand for them)

3 Conclusions

In summary, we have synthesized and structurally characterized a novel Ru (Ⅲ) -histidine complex. The ruthenium anticancer compounds are likely transported by transferrin, and the histidine residues in the metal-binding site play an important role in the coordination[9]. The current data provide detailed structural information for the Ru (Ⅲ) -His center, which could be potentially useful in the design of novel Ru-based anticancer agents.

References

[1] Guo Z., Sadler P. J. *Angew. Chem. Int. Ed.*, **1999**, **38**, 1513.
[2] Guo Z., Sadler P. J. *Adv. Inorg. Chem.*, **2000**, **49**, 183.
[3] Orvig C., Abroms M. J., Guest Ed *Chem. Rev.*, **1999**, **99**(9), 2201.
[4] Sava G., Alessio E., Bergamo E., Mestroni G. *Top. Biol. Inorg. Chem.*, **1999**, **1**, 143.
[5] Bergamo A., Zorzet S., Gava B. *Anti-Cancer Drug.*, **2000**, **11**, 665.
[6] Zhao M., Clarke M. J. *J. Biol. Inorg. Chem.*, **1999**, **4**, 318.
[7] Clarke M. J., Zhu F., Frasca D. R. *Chem. Rev.*, **1999**, **99**, 2511.
[8] Frasca D., Ciampa J., Emerson J., Umans R. S., Clarke M. J. *Metal-Based Drugs*, **1996**, **3**, 197.
[9] Smith C. A., Sutherland-Smith A. J., Keppler B. K., Kratz F., Baker E. N. *J. Biol. Inorg. Chem.*, **1996**, **1**, 424.
[10] Sheldrick W. S., Exner R. *Inorg. Chim. Acta*, **1992**, **195**, 1.
[11] Evans I. P., Spencer A., Wilkinson G. J. *J. Chem. Soc., Dalton Trans.*, **1973**, 1770.
[12] Alessio E., Mestroni G., Nardin G., Attia W. M., Calligaris M., Sava G., Zorzet S. *Inorg. Chem.*, **1988**, **27**, 4099.
[13] Davies A. R., Einsstein F. W. B., Farrell N. P., James B. R., McMillian R. S. *Inorg. Chem.*, **1978**, **17**, 1965.