Chem. Res. Chin. Univ., 2016, 32(2), 207—211 doi: 10.1007/s40242-016-5350-0

Synthesis and Bioactivity of a Novel Bismuthoxide Schiff-base Complex Derived from Salen-like Ligand and Bismuth(III) Nitrate

LI Chuanhua[1], JIANG Jianhong[1], LI Xu[1], XIAO Shengxiong[1], WEI Deliang[1], JIANG Chao[1], XIE Jinqi[1], PENG Mengna[1], GU Huiwen[2*] and LI Qiangguo[1*]

1. Hunan Provincial Key Laboratory of Xiangnan Rare-precious Metals Compounds and Applications, Department of Chemistry and Life Science, Xiangnan University, Chenzhou 423000, P. R. China;

2. State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P. R. China

Abstract In this paper, a novel bismuthoxide Schiff-base complex $[Bi_9O_8(vanen)_3(NO_3)_2(CH_3OH)_2(H_2O)\cdot 3NO_3\cdot 5.5H_2O]$(abbreviated as Bivanen) was synthesized with Salen-like ligand H_2vanen[H_2vanen=*N*,*N*′-ethylene bis(3-methoxysalicylideneimine)] and bismuth(III) nitrate. Its structure was characterized by IR spectra, NMR spectra and X-ray diffraction. In particular, the biology activities of the ligand and the complex against *Schizosaccharomyces pombe*(*S. pombe*) were studied using biological microcalorimetry. The metabolic thermogenic curves of *S. pombe* were measured at 32.00 °C. Then, some quantitative thermokinetic parameters of growth metabolism of *S. pombe* including the rate constant(*k*), inhibition ratio(*I*) and half inhibition concentration(IC_{50}) were calculated. Experimental results showed that the *k* values of *S. pombe* decreased while *I* values of *S. pombe* increased with the increase of concentrations of the ligand and the complex. The IC_{50} of the ligand and the complex were found to be 0.067 and 0.037 mmol/L, respectively.

Keywords Bismuthoxide Schiff-base complex; Microcalorimetriy; Thermokinetic property; *Schizosaccharomyces pombe*(*S. pombe*)

1 Introduction

Bismuth complexes, owning to the high effectiveness and low toxicity, have been applied in the treatment of various diseases for centuries[1,2]. In combination with antibiotics, basic bismuth salicylate(BSS), together with bismuth subcitrate (CBS) and ranitidine bismuth citrate, has been recommended as a standard treatment for ulcers and *H. pylori* infection in many countries[3]. Considerable attention has been directed towards the therapy of *H. pylori*, which related to gastritis and ulceration implicated in the development of gastric cancer and gastric lymphoma[4—9]. However, up to now, the action mechanism of bismuth complexes on *H. pylori* in the body, either in their interaction with bacteria, the urease *H. pylori* produces, or the localized environment around gastric lesions, have not been accurately determined[10]. There have also been attempts to model the structures of BSS(or CBS) through the formation and structural elucidation of a variety of bismuth carboxylates. The most important tris-substituted bismuth salicylates, $[Bi(Hsal)_3][H_2sal=(2\text{-}OH)C_6H_4COOH]$[11—14], require partial hydrolysis of the BiL_3 and accompany with hydroxide/oxide formation, resulting in the typical insolubility of these complexes, and thus affecting their compositions and structures.

Biological microcalorimetry, which provides a quantitative and continuous measurement of heat production, can be applied to directly determining the biological activities of a living system. Heat flux is an expression of overall metabolic flux, and the detection of small changes in heat production to respond to toxic insult will be a sensitive indicator of altered metabolism. Any substances that could modify cellular metabolism would change the power-time(*P-t*) curve obtained from the microcalorimeter and from the heat-output curves, not only thermodynamics data but also kinetic data could be derived[15,16]. Thus, microcalorimetry can offer a general analytical tool for the characterization of cell growth process and has been extensively employed to investigate the interaction between drug and cultured cell.

In this work, to further explore the coordination chemistry of the bismuth complexes and their structures, activities and behaviors in a biological environment, we designed and synthesizd a new polynuclear oxido-cluster structure of bismuth complex $[Bi_9O_8(vanen)_3(NO_3)_2(CH_3OH)_2(H_2O)\cdot 3NO_3\cdot 5.5H_2O]$ (abbreviated as Bivanen) derived from Salen-like ligand

*Corresponding authors. E-mail: liqiangguo@163.com; gruyclewee@hnu.edu.cn

Received September 10, 2015; accepted October 20, 2015.

Supported by the National Natural Science Foundation of China(Nos.21273190, 20973145) and the Science and Technology Plan Projects of Hunan Province, China(Nos.2014FJ3011, 2013FJ3033, 2014TT2026).

H_2vanen[H_2vanen=*N*,*N*′-ethylene bis(3-methoxysalicylideneimine)]. In particular, to get insight into the biological effect of the bismuth complex and to clarify its pharmacological mechanisms, *Schizosaccharomyces pombe*(*S. pombe*), which provides an ideal model to study cell morphogenesis[17] was used as study the material. The interactions of Salen-like ligand H_2vanen and bismuth complex Bivanen with *S. pombe* were investigated by means of microcalorimetry, respectively. The heat output power curves of metabolism of *S. pombe* were determined by a TAM Air calorimeter[18—20]. Moreover, we analyzed the relationship between the concentrations of Salen-like ligand and bismuth complex with the growth of *S. pombe* by the thermokinetic model.

2 Experimental

2.1 Instruments and Materials

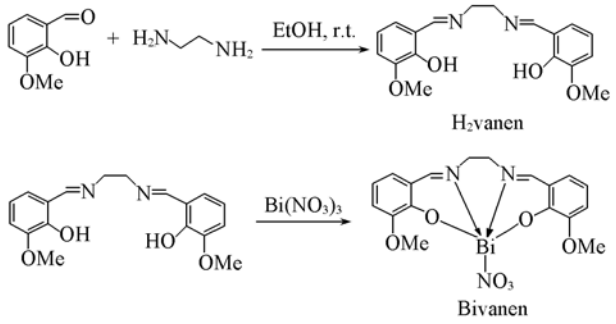
The microcalorimetric study was carried out on a 3116-2/3239 TAM Air calorimeter(Thermometric AB, Sweden), which was detailedly described in our previous work[18—20]. A U-3010 spectrophotometer(HITACHI, Japan) was used for scanning UV-Vis spectrum. FTIR spectra(4000—400 cm^{-1}) were recorded by an Avatar 360 spectrometer(Thermo Nicalet Corporation, USA), with a KBr pellet. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively using DMSO-d_6 as a solvent and Me_4Si(TMS) as an internal standard.

S. pombe(ACCC 20047) was obtained from the Agricultural Culture Collection of China. It was grown in the Edinburgh minimal medium(EMM), which contained 3 g of K_2HPO_4, 2.2 g of Na_2HPO_4, 5 g of NH_4Cl and 20 g of glucose per liter(natural pH).

All the chemicals used herein were of analytical grade and used as received.

2.2 Synthesis of the Ligand

The ligand, H_2vanen, was prepared by the 1:2(molar ratio) condensation of ethylenediamine with *o*-vanillin in ethanol after being stirred for 2 h at ambient temperature according to the reported literature[21](Scheme 1). The yellow product was further purified by recrystallization and dried at 60 °C in a vacuum oven.



Scheme 1 Synthesis of ligand and its bismuth complex

2.3 Synthesis of the Complex

$Bi(NO_3)_3·5H_2O$(0.4 mmol, 0.194 g) and mannitol (0.4 mmol, 0.0728 g) were ground into a smooth paste in an appropriate mortar. Then 3 mL of deionized water and 5 mL of methanol were added in turn to the mortar and the mixture was stirred. Subsequently, the mixed solution was slowly added dropwise to a stirred methanol solution(25 mL) of H_2vanen(0.8 mmol, 0.2624 g) at 45—60 °C for 30 min. After 2 h of continuously stirring, the product was collected by filtration after being concentrated by rotary evaporation to a small volume and washed with dichloromethane. Single crystals were obtained by slow diffusion of diethylether into the filtrate in two weeks(the synthetic procedure of the bismuth complex was illustrated in Scheme 1). IR(KBr), $\tilde{\nu}$/cm^{-1}: 3421.1, 2918.6, 1635.4, 1449.8, 1384.0, 1265.3, 1216.9, 1083.6. ^{1}H NMR(DMSO-d_6, 400 MHz), δ: 8.49(s, 6H), 6.82—7.24(m, 18H), 4.00—4.41(m, 12H), 2.82(s, 18H). ^{13}C NMR(DMSO-d_6, 100 MHz), δ: 166.9, 150.8, 150.7, 127.2, 124.2, 117.9, 115.6, 62.2, 53.2.

2.4 Microcalorimetric Measurement

The microcalorimetric measurements of *S. pombe* were carried out on a TAM air isothermal microcalorimeter at 32.00 °C. Baselines were taken before each measurement and the calorimeter was calibrated electrically. More details about the performance and structure of the instrument are available in the literatures[18—20].

When the system obtained a stable baseline, 5 mL of EMM-sterilized culture medium was added into the sterilized sample ampoules. *S. pombe* was inoculated with an initial density of 1×10^6 cell/mL. Then, the ligand H_2vanen and bismuth complex Bivanen at different concentrations were added to the cell suspension, respectively. All the ampoules containing the cell suspension of *S. pombe* and drugs were shaken, numbered, covered with caps and pressed with special pliers. The ampoules in turn were hanged into the 8-channel calorimeter block. When the temperature of ampoules reached 32.00 °C, the thermogenic curves were recorded until the recorder returned to the baseline. A computer equipped with dedicated software package linked to the TAM Air calorimeter was used to continuously monitor and record the power-time curves. All the microcalorimetric experiments were repeated three times and the results were identical.

2.5 X-Ray Crystallographic Analysis

Crystal data were collected on a Bruker smart CCD area-detector diffractometer[graphite-monochromated Mo *Kα* X-ray radiation(λ=0.071073 nm)] and corrected for absorption using the SADABS. Structural solution and refinements were carried out using the SHELX suite of programs with the graphical interface X-Seed. The crystal structures were severely affected by the large heavy-atom content, and therefore data were not as precise as preferred. However, the connectivity of the structure is unambiguous. In the refined process, some restriction was performed with optimal geometries. A few hydrogen atoms were not added in the crystal structure. Crystallographic data and structure refinement parameters for the complex are presented in Table 1. Crystallographic data (without structure factors) for the structure(s) reported in this

paper have been deposited at the Cambridge Crystallographic Data Centre with supplementary publication No. CCDC-961392.

Table 1 Crystal data and structure refinement parameters for the complex

Empirical formula	$C_{56}H_{75}Bi_9N_{11}O_{43.5}$
Formula weight	3479.07
Temperature/K	173(2)
Wavelength/nm	0.071073
Crystal system	Triclinic
Space group	$P\bar{1}$
a/nm	1.49741(15)
b/nm	1.68900(17)
c/nm	1.85248(19)
α/(°)	80.769(2)
β/(°)	84.451(2)
γ/(°)	71.208(2)
V/nm^3	4.37289
Z	2
D_c/(g·cm^{-3})	2.63139
Absorption coefficient/mm^{-1}	18.135
Crystal size/mm^3	0.32×0.24×0.18
Reflections collected	35927
Independent reflections(R_{int})	14938
Completeness to θ=25.02°(%)	96.5
Maximum and minimum transmission	0.1388 and 0.0682
F(000)	3152
Goodness-of-fit on F^2	1.072
Final R indices[$I>2\sigma(I)$]	R_1=0.0501, wR_2=0.1502
R indices(all data)	R_1=0.0693, wR_2=0.1615

3 Results and Discussion

3.1 Description of the Structure of the Complex

The complex $[Bi_9O_8(vanen)_3(NO_3)_2(CH_3OH)_2(H_2O)\cdot 3NO_3\cdot 5.5H_2O]$ crystallizes in a triclinic crystal system with space group $P\bar{1}$. It consists of three ligands and nine bismuth atoms[as shown in Fig.1(A)]. Each ligand is attached to the bismuth(III) through its two imino N^- atoms, two phenolic oxygen atoms and two methoxyl oxygen atoms. The nine bismuth atoms and eight oxygen atoms consists of the shrouding of the Bi_9O_8 core, which can be described as a monocapped square anti-prism[22], with Bi1/Bi2/Bi3/Bi4 forming one square face and Bi5/Bi6/Bi7/Bi8 constructing the other one[Fig.1(B)]. The dihedral angle between the two mean planes is 0.348(2)°. The ninthbismuth atom locates in the crown, resulting from the extension of the two surfaces mentioned above. The coordination number of bismuth is seven and the coordination environments of bismuth can be divided into two different types: one is the bismuth ion linked by seven oxygen atoms; the other is bismuth ion bonded to two nitrogen atoms except for five oxygen atoms[Fig.1(C)]. Partially selected bond lengths for the complex are listed in Table 2.

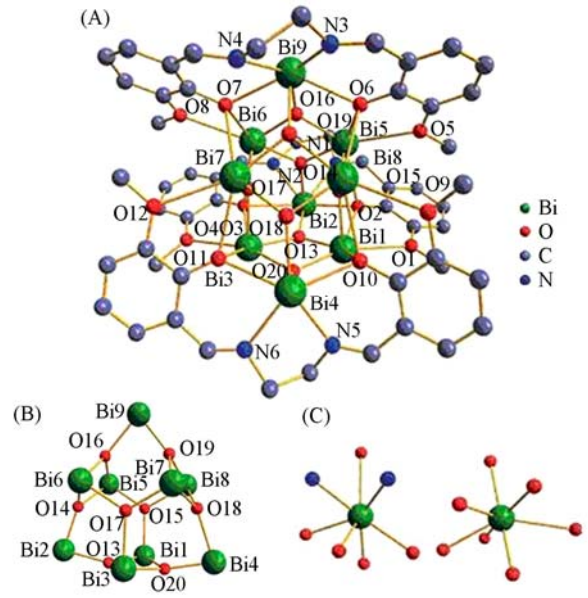


Fig.1 Crystal structure of the complex(A), perspective views of the Bi_9O_8 core(B) and the coordination modes of bismuth atoms(C)

Table 2 Partially selected bond lengths(nm) for the complex

Bi1—O1	0.2758(1)	Bi5—O15	0.2184(9)
Bi1—O13	0.2124(8)	Bi6—O7	0.2573(9)
Bi1—O25	0.2724(2)	Bi6—O14	0.2196(9)
Bi2—O2	0.2425(9)	Bi6—O41	0.2610(1)
Bi2—O14	0.2072(9)	Bi7—O12	0.2785(8)
Bi3—O4	0.2781(9)	Bi7—O19	0.2187(7)
Bi3—O17	0.2212(8)	Bi8—O10	0.2633(8)
Bi4—N5	0.2430(9)	Bi8—O19	0.2165(7)
Bi4—O11	0.2590(7)	Bi9—N4	0.2492(1)
Bi5—O2	0.2789(2)	Bi9—O16	0.2276(9)
Bi5—O14	0.2213(8)	Bi1—O10	0.2705(8)
Bi6—O3	0.2842(1)	Bi1—O20	0.2170(8)
Bi6—O7	0.2573(9)	Bi2—N2	0.2540(1)
Bi6—O17	0.2229(9)	Bi2—O13	0.2242(9)
Bi7—O11	0.2621(8)	Bi3—O3	0.2571(9)
Bi7—O18	0.2100(7)	Bi3—O13	0.2110(8)
Bi8—O9	0.2815(7)	Bi3—O63	0.2581(1)
Bi8—O18	0.2114(8)	Bi4—O10	0.2396(7)
Bi9—N3	0.2462(9)	Bi4—O20	0.2105(9)
Bi9—O7	0.2517(8)	Bi5—O6	0.2586(8)
Bi1—O2	0.2601(1)	Bi5—O16	0.2134(8)
Bi1—O15	0.2189(8)	Bi6—O8	0.2812(8)
Bi2—N1	0.2401(1)	Bi6—O16	0.2098(8)
Bi2—O3	0.2511(8)	Bi7—O7	0.2750(8)
Bi2—O61	0.2878(2)	Bi7—O17	0.2139(9)
Bi3—O11	0.2834(9)	Bi8—O6	0.2751(8)
Bi3—O20	0.2193(8)	Bi8—O15	0.2214(9)
Bi4—N6	0.2535(1)	Bi8—O21	0.2719(9)
Bi4—O18	0.2285(8)	Bi9—O6	0.2526(8)
Bi5—O5	0.2812(9)	Bi9—O19	0.2127(8)

The eighteen Bi—O bonds involve the deprotonated phenol oxygen atoms[from 0.2396(7) nm to 0.2842(1) nm]. The six Bi—O(methoxy) distances cover a narrow range, 0.2758(1)—0.2815(7) nm. The six Bi—N distances are in the range of 0.2401(1)—0.2540(1) nm. The range of twenty-four Bi—O_{core} is 0.2072(9)—0.2285(8) nm.

3.2 Thermogenic Curves for the Growth of *S. pombe* Cells

The thermogenic curves(power-time curves) for growth of *S. pombe* cells treated by different concentrations of ligand H_2vanen and bismuth complex Bivanen were determined by the ampoule method at 32.00 °C, respectively. All the

microcalorimetric experiments were repeated three times. The results are illustrated in Fig.2. From Fig.2 we can find that the thermogenic curves are similar to that of *S. pombe* treated without any drugs. In addition, Fig.2 obviously revealed that ligand H_2vanen and bismuth complex Bivanen possessed the bidirectional biological effect and Hormesis effect, *i.e.*, they stimulated the growth of the *S. pombe* at low concentration, but inhibited the growth of *S. pombe* at high concentration.

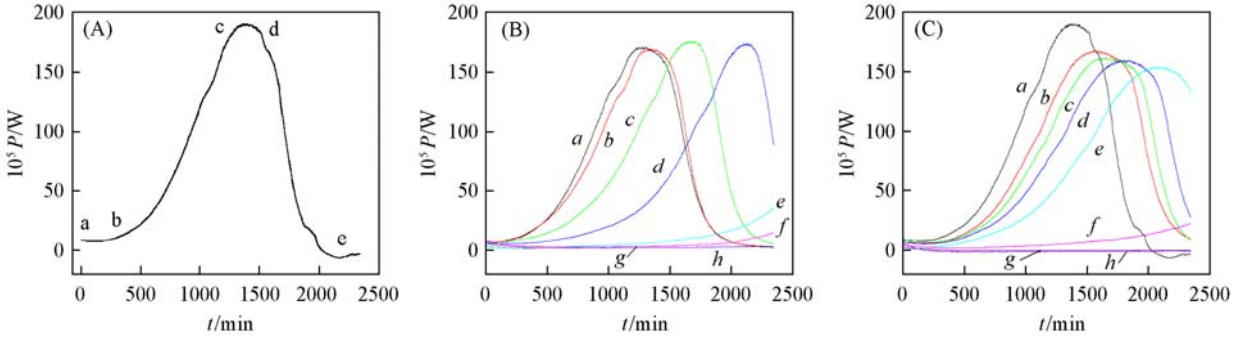


Fig.2 Metabolism thermogenic curves of *S. pombe* cells affected by the tested drugs at 32.00 °C

(A) Control; ab: lag phase; bc: log phase; cd: stationary phase; de: decline phase. (B) with the ligand; c(ligand)/(mmol·L^{-1}): *a*. 0; *b*. 0.02; *c*. 0.04; *d*. 0.06; *e*. 0.08; *f*. 0.10; *g*. 0.12; *h*. 0.014; (C) with the complex. c(complex)/(mmol·L^{-1}): *a*. 0; *b*. 0.008; *c*. 0.01; *d*. 0.02; *e*. 0.03; *f*. 0.04; *g*. 0.06; *h*. 0.10.

3.3 Growth Rate Constant(k) of *S. pombe* Cells

Since *S. pombe* metabolic process was monitored under the isothermal and isochoric conditions, the oxygen and nutrient consumed by cells were supplied limitedly. The thermogenic curves for the growth of *S. pombe* cells could be divided into four phases: a lag phase(ab), a log phase(bc), a stationary phase(cd) and a decline phase(de). During the log phase, the power-time curves obeyed the following equation:

$$n_t = n_0 \exp[k(t-t_0)] \quad (1)$$

where t indicates the time after the start of exponential growth phase, t_0 indicates the start time of exponential growth phase, n_t and n_0 are the cell number at time t and t_0, respectively. k is the growth rate constant of *S. pombe* under specified conditions, whose size represents growth speed. If the power output of each *S. pombe* cell is w, then

$$n_t w = w n_0 \exp[k(t-t_0)] \quad (2)$$

If $P_t = n_t w$; $P_0 = n_0 w$, then

$$P_t = P_0 \exp[k(t-t_0)] \quad (3)$$

or

$$\ln P_t = \ln P_0 - kt_0 + kt \quad (4)$$

where P_0 is the heat-output power at the beginning of baseline and P_t represents that at time t.

The thermogenic curves of the exponential phase of growth obeyed Eq.(4), while the growth rate constants could be obtained by fitting $\ln P_t$ and t to a linear equation. As shown in Table 3, the growth rate constants of *S. pombe* at different concentrations of drugs were calculated. All the correlation coefficients were greater than 0.9955, indicating a good reproducibility and correlation. From Fig.2 and Table 3, it could be seen that the peak time of maximum heat-output power t_p delayed and the growth rate constants decreased with the increase of concentrations of the tested drugs. In comparison, the bismuth complex possessed the better inhibitory activity on the growth metabolism of *S. pombe*.

Relationships between growth rate constant of *S. pombe* and the concentrations of the ligand and the complex are shown in Fig.3.

Table 3 Thermokinetic parameters of the growth of *S. pombe* affected by inhibitors at different concentrations at 32.00 °C

Inhibitor	c/(mmol·L^{-1})	k^a/min^{-1}	I^b(%)	IC_{50}^c/(mmol·L^{-1})
H_2vanen	0	0.0035±4.4212×10^{-6}	0	0.067
	0.02	0.0030±4.7054×10^{-6}	14.3	
	0.04	0.0025±1.8940×10^{-6}	28.6	
	0.06	0.0021±1.6927×10^{-6}	40	
	0.08	0.0012±2.1767×10^{-6}	65.7	
	0.10	0.00023±3.993×10^{-6}	84.3	
	0.12	0.00002±2.965×10^{-6}	94.3	
	0.14	—	100	
Bivanen	0	0.0036±2.9289×10^{-6}	0	0.037
	0.008	0.0034±3.2407×10^{-6}	5.6	
	0.01	0.0030±3.3155×10^{-6}	17.6	
	0.02	0.0027±2.5502×10^{-6}	25	
	0.03	0.0029±3.7249×10^{-6}	39.4	
	0.04	0.0013±4.4363×10^{-6}	63.9	
	0.06	—	100	
	0.10	—	100	

a. The values are mean±S.D., n=3; *b*. inhibition ratio; *c*. half inhibition concentration.

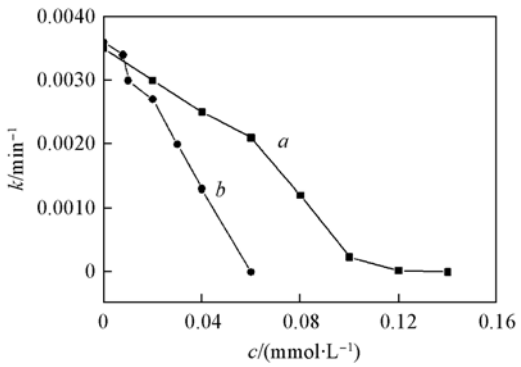


Fig.3 Relationships between growth rate constant of *S. pombe* and concentrations of the ligand(a) and the complex(b)

As can be seen from Fig.3, the growth rate constant of *S. pombe* decreases with the increase of the concentration of the

ligand and the bismuth complex. The relationships between k with c_{ligand} and $c_{complex}$ could be described as follows, respectively:

$$k=0.00353–0.0280c(0.00\ mmol/L\leqslant c_{ligand}\leqslant 0.14\ mmol/L) \quad (5)$$

$$k=0.00375–0.0161c(0.00\ mmol/L\leqslant c_{complex}\leqslant 0.06\ mmol/L) \quad (6)$$

3.4 Inhibition Ratio(I) and Half Inhibition Concentration(IC_{50})

The inhibiton ratio(I, %) can be defined as:

$$I=(k_0–k_c)/k_0\times 100\% \quad (7)$$

where k_0 was the growth rate constant of the control and k_c was the growth rate constant of the *S. pombe* cells when they were treated by drugs at concentration(c). When the inhibition ratio was 50%, the drug concentration was the half inhibition concentration(IC_{50}). Based on the above definition, we calculated the inhibition ratio(see Table 3) of *S. pombe* cells at different drug concentrations.

By plotting inhibition ratio against concentration of the ligand and the complex, Fig.4 can be obtained.

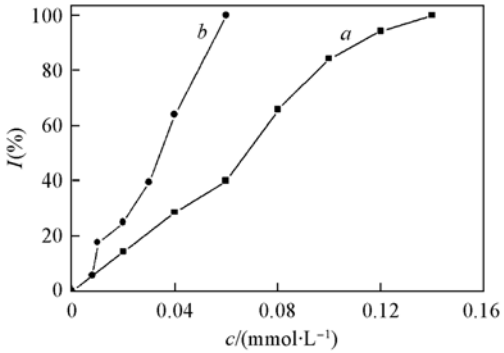


Fig.4 Relationships between inhibition ratio(I) of *S. pombe* and concentrations of the ligand(a) and the complex(b)

It could be seen that inhibition ratio gradually increases with the increase of concentration of the ligand and the complex. The relationship between I and c_{ligand} or $c_{complex}$ could be described as follows, respectively:

$$I=–0.4667+769.5238c$$
$$(0\ mmol/L\leqslant c_{ligand}\leqslant 0.14\ mmol/L) \quad (8)$$

$$I=–4.4009+1680.3951c$$
$$(0\ mmol/L\leqslant c_{complex}\leqslant 0.06\ mmol/L) \quad (9)$$

4 Conclusions

In summary, we described the synthesis, structure and biological activity of a novel synthetic bismuthoxide Schiff-base complex. The quantitative relationships of the k and I values of *S. pombe* with concentrations of the ligand and the complex were obtained. IC_{50} values of the ligand and the complex were found to be 0.067 and 0.037 mmol/L, respectively, which demonstrate that the biology activities of the bismuth complex on *S. pombe* are much better than those of the free ligand.

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