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### SYNTHESIS, MOLECULAR STRUCTURE AND TUMOR-INHIBITING PROPERTIES OF NICKEL(II) AND COBALT(II) COMPLEXES OF 2,2'-DIAMINO-4,4'-BITHIAZOLE. CRYSTAL STRUCTURE OF $[\text{NiL}_2(\text{SO}_4)(\text{MEOH})] \cdot 3\text{MEOH}$

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# SYNTHESIS, MOLECULAR STRUCTURE AND TUMOR-INHIBITING PROPERTIES OF NICKEL(II) AND COBALT(II) COMPLEXES OF 2,2'-DIAMINO-4,4'-BITHIAZOLE. CRYSTAL STRUCTURE OF $[\text{NiL}_2(\text{SO}_4)(\text{MeOH})] \cdot 3\text{MeOH}$

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Complexes of Ni(II) and Co(II) with 2,2'-diamino-4,4'-bithiazole (L) formulated as  $\text{ML}_2(\text{SO}_4) \cdot \text{XMeOH}$  (X = 0 or 4), were synthesized and characterized by elemental analysis, conductivity measurement, <sup>1</sup>H NMR, IR and electronic spectra. The structure of  $[\text{NiL}_2(\text{SO}_4)(\text{MeOH})] \cdot 3\text{MeOH}$  has been determined by single-crystal X-ray methods.

The nickel atom is octahedrally coordinated by two chelating organic ligands and two oxygen atoms of  $\text{SO}_4$  and MeOH in a *cis* arrangement. Ni—N bond lengths range from 2.076 to 2.100 Å; Ni—O( $\text{SO}_4$ ) is 2.118 Å and Ni—O(MeOH) is 2.128 Å. The effect of these complexes on DNA synthesis in Sarcoma 180 tumor cells has been investigated by the technique of isotopic liquid scintillation. Results indicate that the complexes inhibit DNA synthesis in the tumor cells.

**Keywords:** diaminobithiazole; cobalt (II); nickel (II); crystal structure; tumor-inhibiting properties

## INTRODUCTION

The bithiazole moiety, one domain of bleomycin, was shown to be responsible for binding of BLM to DNA.<sup>1</sup> This observation caused an explosion in research effort directed toward the design and synthesis of model compounds that can specifically recognize and cleave DNA.<sup>2</sup> Many of these bithiazole derivatives inhibit breakage of DNA by BLM.<sup>3</sup> The bithiazole derivatives examined only

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promote helix unwinding and overwinding (positive supercoiling). Recently, Sasaki found that the bithiazole derivative, 2,2'-bis(2-aminoethyl)-4,4'-bithiazole, demonstrates Co(II)-activated DNA cleaving activity.<sup>4</sup>

We thus became interested in designing coordination compounds of bithiazole derivatives and exploring their biological activity. Based on studies of interactions of *cis*-Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> with DNA,<sup>5</sup> and on covalent binding of *cis*-dichlorobis(1,10-phenanthroline)ruthenium(II) to the DNA duplex,<sup>6</sup> we have prepared the complexes NiL<sub>2</sub>(SO<sub>4</sub>)·XMeOH and CoL<sub>2</sub>(SO<sub>4</sub>)·XMeOH and investigated their effect on DNA synthesis in tumor cells. In this paper we report the synthesis, molecular structure and tumor-inhibiting properties of these complexes, and the crystal structure of [NiL<sub>2</sub>(SO<sub>4</sub>)(MeOH)]·3MeOH.

## EXPERIMENTAL

### Reagents and Methods

NiSO<sub>4</sub>·6H<sub>2</sub>O (A.R.) and CoSO<sub>4</sub>·7H<sub>2</sub>O (A.R.) were commercially available. <sup>3</sup>H-labelled thymidine was purchased from the Institute of Atomic Energy in China. Sarcoma 180 tumor cells were obtained from the Institute of Cancer Research in Shanxi. C, H and N microanalyses were carried out with a Perkin Elmer 2400 instrument. Molar conductance was measured with a DDS-12A conductivity meter made in China. Infrared spectra were recorded on a Shimadzu IR-435 spectrophotometer in KBr pellets in the range 4000–400cm<sup>-1</sup>. <sup>1</sup>H NMR spectra were recorded on a FX-80Q NMR spectrometer using TMS as internal standard in DMSO-d<sub>6</sub>. The electronic absorption spectra were measured on a Shimadzu 365 spectrophotometer. Radioactivity was determined on a PACKARD-Tir-Carb 2200CA liquid scintillation detector.

### Preparation of Complexes

The ligand, 2,2'-diamino-4,4'-bithiazole, was prepared according to a literature method.<sup>7</sup> Since the ligand is easily oxidizable in air, the following procedures were carried out under nitrogen.

[NiL<sub>2</sub>(SO<sub>4</sub>) (1). NiSO<sub>4</sub>·6H<sub>2</sub>O (1.0 mmol) was dissolved in oxygen-free anhydrous methanol (*ca* 40 cm<sup>3</sup>) in a Schlenk vessel (Solution A). The ligand (2.0 mmol) was dissolved in 160 cm<sup>3</sup> of boiling anhydrous methanol (Solution B). Solution B was filtered and added to solution A. After 2–5 days at room temperature, green crystals were obtained, which were filtered, washed with

methanol and dried *in vacuo* (yield 67%). Found: C, 26.1; H, 2.6; N, 19.9. Calc. for  $C_{12}H_{12}NiN_8O_4S_5$ (%): C, 26.1; H, 2.2; N, 20.3,  $\wedge_M = 9.8 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$  ( $1.0 \times 10^{-3} \text{ mol dm}^{-3}$  in DMSO). IR data ( $\text{cm}^{-1}$ ): 3400–3000br, 1609s, 1539s, 1515s, 1344s, 1273m, 1116m, 1054m, 990m, 952m.  $^1\text{H}$  NMR (ppm): 6.96(s, 2H), 6.60(s, 1H). Absorption spectra (maxima): 9615, 15385, 26316  $\text{cm}^{-1}$  (in DMSO); 10000, 16393  $\text{cm}^{-1}$  (in  $\text{H}_2\text{O}$ ).

[ $\text{CoL}_2(\text{SO}_4)$ ] (**2**). The preparation was the same as that for **1** and dark red crystals were obtained (yield 62%). Found: C, 25.9; H, 2.6; N, 20.1. Calc. for  $C_{12}H_{12}\text{CoN}_8O_4S_5$ (%): C, 26.1; H, 2.2; N, 20.3,  $\wedge_M = 10.6 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$  ( $1.0 \times 10^{-3} \text{ mol dm}^{-3}$  in DMSO). IR data ( $\text{cm}^{-1}$ ): 3400–3000br, 1617s, 1543s, 1515s, 1357s, 1277m, 1086m, 994m. Absorption spectra (maxima): 8333, 19048  $\text{cm}^{-1}$  (in DMSO); 8929, 20408  $\text{cm}^{-1}$  (in  $\text{H}_2\text{O}$ ).

Single crystals of the complex **1** were obtained from methanol; **1** crystallized as the  $[\text{NiL}_2(\text{SO}_4)(\text{MeOH})]\cdot 3\text{MeOH}$  solvate in the form of green polyhedron that effloresced immediately when isolated from its mother liquid in air. Samples of **1** obtained as green powders do not include any solvent according to elemental analysis data.

### X-ray Structure Determination

A crystal of dimensions  $0.50 \times 0.40 \times 0.30$  mm sealed in a glass capillary was used for X-ray diffraction data collection on a Rigaku AFC5R diffractometer at room temperature with graphite-monochromated  $\text{MoK}\alpha$  radiation ( $\lambda = 0.71069 \text{ \AA}$ ), using the  $\omega$ -2  $\theta$  scan mode. Details of crystal parameters, data collection and structure refinement are given in Table I.

TABLE I Summary of crystallographic data and data collection parameters for  $[\text{NiL}_2(\text{SO}_4)(\text{MeOH})]\cdot 3\text{MeOH}$

Formula	$C_{16}H_{28}Ni_2N_8O_8S_5$
Formula weight	679.45
Crystal system	monoclinic
Space group	$P2_1/n$
$a$ ( $\text{\AA}$ )	14.270 (3)
$b$ ( $\text{\AA}$ )	14.794 (4)
$c$ ( $\text{\AA}$ )	14.313 (4)
$\beta$ ( $^\circ$ )	108.81 (2)
$V$ ( $\text{\AA}^3$ )	2860 (1)
$D_{\text{calc}}$ ( $\text{Mg m}^{-3}$ )	1.58
$Z$	4
$F(000)$	1408
$\mu$ ( $\text{mm}^{-1}$ )	1.083
Temperature (K)	297
Data collection index range	$h, k, l$ (0, 16; 0, 15; -16, 16)

TABLE I (Continued)

No. of independent reflections	4733
No. for refinement [ $I > 3 \sigma(I)$ ]	3394
Largest residue ( $\text{e} \text{ \AA}^{-3}$ )	0.42
$R$	0.049
$R_w$	0.065

Cell dimensions were obtained from 25 reflections with  $2\theta \leq 48^\circ$ . All reflections were corrected for Lp effects and absorption using DIFABS.<sup>8</sup> Data reduction and structure refinement was performed using the TEXSAN package. The structure was solved by direct methods and refined by least-squares. The hydrogen atoms of the hydroxyl groups in four methanol atoms could not be located, others were located by a combination of difference Fourier syntheses and calculation and added to structure factor calculations, but positions were not refined.

### Biological activity

DNA syntheses were assessed by monitoring cellular incorporation of  $^3\text{H}$ -labelled thymidine. Sarcoma 180 cells were diluted with PRMI 1640 medium to  $1.4 \times 10^7$  cells per  $\text{cm}^3$  of cell suspension. Three concentrations of complex ( $5 \times 10^{-6}$ ,  $5 \times 10^{-5}$ ,  $5 \times 10^{-4}$  mol  $\text{cm}^{-3}$ ) were selected, then equal amounts ( $0.1 \text{ cm}^3$ ) of complex solution and cell suspension were transferred to each well of a 96-well plate. The plates were incubated at  $37^\circ\text{C}$  under  $\text{CO}_2$  for 3 hr, and for another 1.5 hr after addition of  $^3\text{H}$ -thymidine ( $15.0 \mu\text{Ci/nmol}$ ). The cells were washed with salt water and then filtered through Millipore AP filters. The filters were dried under vacuum at  $80^\circ\text{C}$ , and associated radioactivity was determined after addition of scintillation mixture. Every sample was triplicated in parallel and an average value obtained. Rates of incorporation were calculated from the values of counts per minute, indicated by (T/C)% (CPM of complex/CPM of complex free mixtures). Rates of inhibition are indicated by (1-T/C)%.

## RESULTS AND DISCUSSION

### Preparation

Interaction of Ni(II) and Co(II) with 2,2'-diamino-4,4'-bithiazole result in the formation of complexes with the formula  $\text{NiL}_2\text{SO}_4$  and  $\text{CoL}_2\text{SO}_4$ . According to analytical data, the stoichiometry for the metal and L is 1:2, which differs from

previous 2,2'-bithiazole complexes with a ratio of 1:3<sup>9-10</sup>. Even when the metallic salt and ligand were added in the ratio 1:3 during synthesis, the same complexes were obtained. Molar conductance values for the nickel and cobalt complexes indicate non-electrolyte nature.<sup>11</sup> The complexes are soluble in water; this is markedly different from the ligand, which is not soluble in water.

### Spectroscopic Studies

<sup>1</sup>H NMR of complex **1** was measured in DMSO-*d*<sub>6</sub> solvent. A peak at  $\delta = 6.96$  ppm is assigned to protons of the amino group and a peak at  $\delta = 6.60$  ppm is assigned to the proton of thiazole, indicating the presence of ligands in the complex **1**. <sup>1</sup>H NMR of complex **2** could not be observed due to the paramagnetism of Co(II).

To our knowledge, IR data for complexes including bithiazole have never been reported. Here, the significant change observed was that the band at 1290 cm<sup>-1</sup> in the the ligand was shifted to 1344–1357 cm<sup>-1</sup> in the complexes. The ligand band might be due to skeletal vibration of the imino tautomer<sup>12</sup> of 2-amino-thiazole. Due to coordination, the imino tautomer no longer exists. Electronic absorption spectra of the complexes were studied in DMSO and H<sub>2</sub>O solution. The bands at 9615, 15385 and 26316 cm<sup>-1</sup> in **1** are attributed to <sup>3</sup>A<sub>2g</sub> → <sup>3</sup>T<sub>2g</sub>(F), <sup>3</sup>A<sub>2g</sub> → <sup>3</sup>T<sub>1g</sub>(F) and <sup>3</sup>A<sub>2g</sub> → <sup>3</sup>T<sub>1g</sub>(P) in DMSO. Bands at 8333 and 19048 cm<sup>-1</sup> in **2** are attributed to <sup>4</sup>T<sub>1g</sub> → <sup>4</sup>T<sub>2g</sub>(F) and <sup>4</sup>T<sub>1g</sub> → <sup>4</sup>T<sub>1g</sub>(P) in DMSO. The positions of the bands suggest octahedral geometry for the complexes.<sup>13</sup> Because of the obvious blue shift in water, the <sup>3</sup>A<sub>2g</sub> → <sup>3</sup>T<sub>1g</sub>(P) band of **1** might overlap with strong bands from L in the ultraviolet range and not be observed. Although the complexes are non-electrolytes in DMSO, they dissolve in H<sub>2</sub>O. It is possible that two H<sub>2</sub>O molecules substitute for SO<sub>2</sub><sup>2-</sup> and methanol to give [NiL<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]<sup>2+</sup> and [CoL<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]<sup>2+</sup>. In contrast to [Ni(H<sub>2</sub>O)<sub>6</sub>]<sup>2+</sup>, the bands of [NiL<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]<sup>2+</sup> were blue-shifted, indicating that 2,2'-diamino-4,4'-bithiazole has a stronger ligand field than H<sub>2</sub>O.

### Crystal Structure

Selected bond distances and angles of [NiL<sub>2</sub>(SO<sub>4</sub>)(MeOH)]·3MeOH are given in Table II. The X-ray crystal structure is shown in an ORTEP view in Figure 1 and in the unit cell in Figure 2. A comparison of related structural data is given in Table III. Positional parameter for the non-hydrogen atoms are listed in Table IV.

TABLE II Selected bond lengths (Å) and angles (°) for  $[\text{NiL}_2(\text{SO}_4)(\text{MeOH})] \cdot 3\text{MeOH}$ 

Ni—N(6)	2.100(4)	Ni—N(2)	2.089(4)
Ni—N(5)	2.086(4)	Ni—N(1)	2.076(4)
Ni—O(1)	2.118(3)	Ni—O(5)	2.128(3)
S(1)—C(2)	1.719(6)	S(1)—C(1)	1.741(5)
S(2)—C(5)	1.715(6)	S(2)—C(6)	1.729(5)
N(1)—C(1)	1.319(6)	N(1)—C(3)	1.398(6)
N(2)—C(6)	1.310(6)	N(2)—C(4)	1.396(6)
N(3)—C(1)	1.332(7)	N(4)—C(6)	1.340(7)
C(2)—C(3)	1.347(7)	C(3)—C(4)	1.425(7)
C(4)—C(5)	1.345(7)	C(9)—C(10)	1.458(7)
N(1)—Ni—N(5)	97.4(2)	N(1)—Ni—N(2)	79.3(2)
N(1)—Ni—N(6)	176.9(2)	N(1)—Ni—O(1)	92.3(1)
N(1)—Ni—O(5)	91.9(1)	N(5)—Ni—N(2)	96.8(2)
N(5)—Ni—N(6)	80.2(1)	N(5)—Ni—O(1)	86.5(1)
N(5)—Ni—O(5)	168.2(1)	N(2)—Ni—N(6)	99.1(1)
N(2)—Ni—O(1)	171.3(1)	N(2)—Ni—O(5)	92.0(1)
N(6)—Ni—O(1)	89.4(2)	N(6)—Ni—O(5)	90.8(1)
O(1)—Ni—O(5)	85.9(1)	C(1)—N(1)—Ni	133.7(3)
C(3)—N(1)—Ni	114.1(3)	C(6)—N(2)—Ni	135.4(3)
C(4)—N(2)—Ni	113.8(3)	C(7)—N(5)—Ni	136.0(4)
C(9)—N(5)—Ni	112.6(3)	C(12)—N(6)—Ni	135.6(3)
C(10)—N(6)—Ni	111.8(3)	S(5)—O(1)—Ni	132.1(2)
C(13)—O(5)—Ni	123.2(3)		

TABLE III Comparison of bond distances (Å)\*

	<i>Free 4,4'</i> - <i>bithiazole</i>	$[\text{Fe}(4\text{bt})_3](\text{ClO}_4)_2$	$[\text{Ni}(4\text{bt})_3](\text{ClO}_4)_2$	$[\text{NiL}_2(\text{SO}_4)(\text{MeOH})] \cdot$ $3\text{MeOH}$
C—C	1.469(7)	1.461(4)	1.471(4)	1.458(7)
(between rings)		1.456(6)	1.464(5)	1.425(7)
N(1)—C(3)	1.383(4)	1.383(4)	1.381(3)	1.398(6)
N(1)—C(1)	1.300(5)	1.320(4)	1.321(3)	1.319(6)
C(2)—C(3)	1.360(5)	1.341(4)	1.345(4)	1.347(7)
S(1)—C(2)	1.704(4)	1.711(4)	1.711(3)	1.719(6)
S(1)—C(1)	1.710(4)	1.696(3)	1.696(3)	1.741(5)
ref.	10	9	9	this work

\*4bt = 4,4'-bithiazole, L = 2,2'-diamino-4,4'-bithiazole

TABLE IV Positional parameters and  $B(\text{eq})$  for  $[\text{NiL}_2(\text{SO}_4)(\text{MeOH})] \cdot 3\text{MeOH}$ 

Atom	$x/a$	$y/b$	$z/c$	$B(\text{eq})$
N1	0.78203(4)	0.32889(4)	0.56681(4)	2.38(3)
S1	0.5565(1)	0.3217(1)	0.7375(1)	5.17(7)
S2	0.9592(1)	0.1090(1)	0.7852(1)	5.29(7)
S3	0.5822(1)	0.1455(1)	0.3216(1)	6.20(8)
S4	0.9794(1)	0.3647(1)	0.3687(1)	3.79(6)
S5	0.72883(8)	0.52479(8)	0.45056(9)	2.71(5)
O1	0.6991(2)	0.4357(2)	0.4804(2)	2.9(1)
O2	0.8161(3)	0.5583(3)	0.5290(3)	4.5(2)
O3	0.6472(3)	0.5874(3)	0.4365(3)	4.8(2)

TABLE IV (Continued)

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>B(eq)</i>
O4	0.7568(3)	0.5167(3)	0.3629(3)	5.3(2)
O5	0.8697(2)	0.4321(2)	0.6573(2)	2.9(1)
O6	0.6376(4)	0.4565(3)	0.1840(4)	6.4(2)
O7	0.3796(4)	0.1143(5)	0.4768(5)	8.5(3)
O8	0.8035(3)	0.2637(3)	0.0689(4)	6.5(2)
N1	0.6899(3)	0.3223(3)	0.6531(3)	2.9(2)
N2	0.8528(3)	0.2277(3)	0.6676(3)	3.1(2)
N3	0.5557(3)	0.4198(3)	0.5793(3)	3.8(2)
N4	0.9865(4)	0.1738(3)	0.6216(4)	4.6(2)
N5	0.7008(3)	0.2427(3)	0.4545(3)	3.0(2)
N6	0.8737(3)	0.3282(2)	0.4778(3)	2.4(1)
N7	0.5722(4)	0.1800(4)	0.5012(4)	5.5(2)
N8	1.0207(3)	0.4041(3)	0.5611(3)	2.9(2)
C1	0.6043(4)	0.3598(4)	0.6470(4)	3.3(2)
C2	0.6577(4)	0.2524(5)	0.7831(4)	4.9(3)
C3	0.7210(4)	0.2609(4)	0.7313(4)	3.4(2)
C4	0.8105(4)	0.2131(4)	0.7417(4)	3.5(2)
C5	0.8584(5)	0.1522(4)	0.8102(4)	4.8(3)
C6	0.9310(4)	0.1766(3)	0.6813(4)	3.4(2)
C7	0.6212(4)	0.1947(4)	0.4371(4)	3.7(2)
C8	0.6792(5)	0.1941(5)	0.2974(4)	5.4(3)
C9	0.7345(4)	0.2429(4)	0.3738(3)	3.3(2)
C10	0.8256(3)	0.2925(3)	0.3846(3)	2.8(2)
C11	0.8712(4)	0.3066(4)	0.3174(4)	3.7(2)
C12	0.9559(3)	0.3673(3)	0.4804(3)	2.5(2)
C13	0.8571(4)	0.4615(4)	0.7477(4)	4.7(3)
C14	0.6101(8)	0.5344(8)	0.1339(8)	10.3(6)
C15	0.334(1)	0.0388(8)	0.482(1)	16(1)
C16	0.7032(5)	0.2793(5)	0.0517(5)	5.4(3)

Molecules contain a six-coordinate nickel atom chelated by four nitrogen atoms of two bidentate organic ligands and two oxygen atoms of  $\text{SO}_4^{2-}$  and  $\text{CH}_3\text{OH}$  in a *cis* arrangement with bite angles  $\text{N}(1)\text{--Ni--N}(2) = 79.3(2)^\circ$  and  $\text{N}(5)\text{--Ni--N}(6) = 80.2(1)^\circ$ . The distorted octahedral geometry can be rationalized after considering the small bite angles, which are significantly diminished and similar to those found in the complexes  $[\text{Ni}(4\text{bt})_3](\text{ClO}_4)_2$  and  $[\text{Fe}(4\text{bt})_3](\text{ClO}_4)_2$  (4bt = 4,4'-bithiazole).<sup>9</sup> Distances within the coordination sphere are normal.<sup>14</sup> Ni–N distances are slightly unequal. Ni–N(1) and Ni–N(5) are slightly longer than Ni–N(2) and Ni–N(6). Ni–O distances are similar to those of  $[\text{Ni}(1,3\text{-pdda})(\text{H}_2\text{O})_2]$ .<sup>14</sup> (1,3-pdda = 1,3-propanediamine-*N,N'*-diacetate). Comparison of the structure of free 4,4'-bithiazole<sup>10</sup> with its complexes shows that coordination results in shorter bond distances between the two adjacent carbon atoms of the thiazole rings (Table III). The carbon-carbon bridge determined in the present work is considerably shorter than that in  $[\text{Fe}(4\text{bt})_3](\text{ClO}_4)_2$  and  $[\text{Ni}(4\text{bt})_3](\text{ClO}_4)_2$ , although this is a comparison between two different ligands. This is probably an indication of the greater delocalization



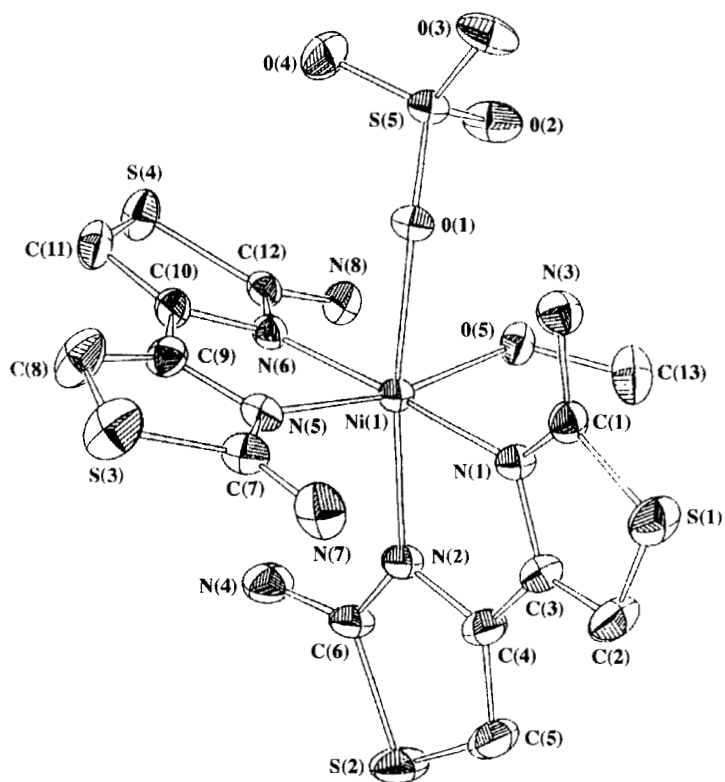


FIGURE 1 Molecular structure and atom numbering scheme for  $[\text{NiL}_2(\text{SO}_4)(\text{MeOH})] \cdot 3\text{MeOH}$ .

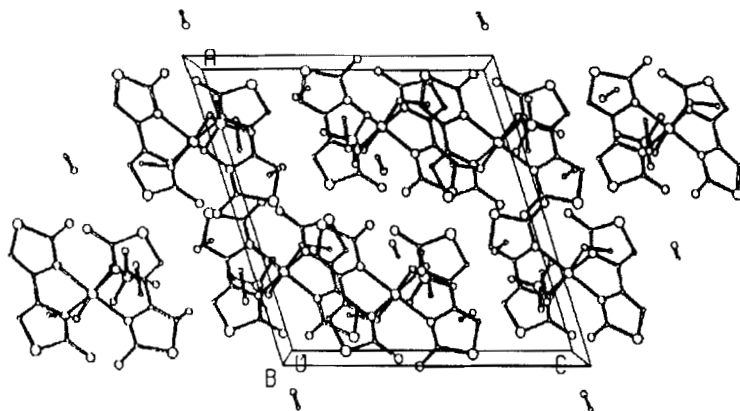


FIGURE 2 Unit cell contents of  $[\text{NiL}_2(\text{SO}_4)(\text{MeOH})] \cdot \text{MeOH}$ .

of the  $\pi$ -electrons between the rings in 2,2'-diamino-4,4'-bithiazole<sup>10</sup> and more extensive  $\pi$ -interactions between the metal ion and the ligand.

The importance of p-electronic delocalization in the bonding description of 2,2'-diamino-4,4'-bithiazole can be inferred not only from the short C—C single bond which connects the rings, but also from the other bond distances in the rings (Table III). In addition, N(3)—C(1) is shorter than a the normal N—C single bond, indicating the nitrogen of the amino group is included in the delocalization system.

As discussed above, changes in the coordination sphere may occur due to coordination of CH<sub>3</sub>OH and SO<sub>4</sub><sup>2-</sup>. First, powder samples of the complexes do not include CH<sub>3</sub>OH molecules. Secondly, the configurations of the complex may change in solution. Complex **1** should have a *trans* configuration in DMSO solution according to the <sup>1</sup>H NMR spectrum. If the *cis* configuration were maintained in solution, the bithiazole protons would become distinguishable as two sets. Finally, the solvent molecules would come into the coordination sphere when dissolved. For example, complexes may exist as [ML<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]<sup>2+</sup> complex ions in H<sub>2</sub>O. In spite of such changes of the coordination sphere, the essential features of crystal structure would be maintained, as far as metal bithiazole parameter are concerned.

### Biological Activity

<sup>3</sup>H-Labelled thymidine is a precursor of DNA synthesis. S<sub>180</sub> cells were incubated with incubation solution alone and with addition of complexes, respectively. The effects of complexes on the DNA biosynthesis can be determined by the incorporation rate of thymidine into cells.<sup>15</sup> Results are shown in Table V. Incorporation of <sup>3</sup>H-TdR is inhibited by these complexes. The structure of the complexes in this paper is closely related to those of other *cis* species<sup>5-6</sup> with biological activity. Their tumor-inhibiting properties are also shown by experiment. Efforts are also being made to study detailed biochemical mechanisms in order to understand these findings.

TABLE V Effect of complexes on the incorporation of <sup>3</sup>H-TdR into S<sub>180</sub> cells expressed as (1-T/C) %

Complex	Concentration (mol dm <sup>-3</sup> )		
	5×10 <sup>-6</sup>	5×10 <sup>-5</sup>	5×10 <sup>-4</sup>
<b>1</b>	23.14	52.42	92.50
<b>2</b>	54.15	69.98	93.01

### Supplementary Data

Full lists of H atom positions, anisotropic thermal parameter, bondlengths and angles, and observed and calculated structure factors are available from the authors on request.

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