Note

Zn(II) complexes with thiopyrimidine derivatives: solution study, synthesis and crystal structure of a zig-zag chain zinc(II) complex with the ligand 4,6-dimethyl-2-thiopyrimidine

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Abstract

The acid–base properties of the pyrimidine derivative 4,6-dimethyl-2-thiopyrimidine (HL) have been determined. The protonation constants of anionic L and neutral HL and the stability constants of the Zn(II) complexes formed with this ligand were determined by potentiometric measurements at 25 °C and 0.1 M KCl ionic strength. The molecular structure of the solid complex $[ZnL_2]_n$ has been established by single-crystal X-ray diffraction. The crystals of the compound are orthorhombic, of space group $P2_12_12_1$, with cell constants $a = 7.984(1)$, $b = 13.476(2)$, $c = 13.709(2)$ Å, $Z = 4$ and $D_c = 1.548$ g cm^{-3}. The structure was solved and refined to $R = 0.055$ ($R_w = 0.051$) and consists of infinite zig-zag chains running along the *a* axis. The geometry of each ZnN_3S_2 chromophore is almost an ideal trigonal bipyramid.

Key words: Crystal structures; Zinc complexes; Thiopyrimidine complexes; Solution study

Introduction

Pyrimidine bases, their nucleosides and nucleotides and pyrimidine metal complexes have important roles in living systems. Zn(II) is bound to several enzymes and proteins (e.g. carbonic anhydrase, carboxy peptidase A, glycolysis enzymes, DNA polymerase) [1]. Moreover, Zn(II) complexes could be directly implicated in the addition of a mononucleotide to the free end of the DNA molecule [2].

We have recently reported the synthesis and the crystal structure of the $Zn(HL)_2Cl_2$ complex (HL is 4,6-dimethyl-2-thiopyrimidine) [3]. Continuing with our work, we report here the acid–base equilibria of the HL ligand and its complexation with the Zn(II) ion. Our potentiometric study has been carried out in aqueous medium 0.1 M ionic strength KCl and 25 °C. We selected the pH conditions to obtain the solid species of $[ZnL_2]_n$ stoichiometry which has been characterized spectroscopically. Its molecular structure has been determined by single crystal X-ray diffraction.

Experimental

Reagents

Ligand HL (99%) and zinc(II) chloride were obtained from Aldrich and used without further purification. In the potentiometric measurements CO_2-free double distilled water was used as solvent. CO_2-free KOH solutions (Merck) were prepared by dilution and standardized against potassium hydrogenphthalate. The $ZnCl_2$ solutions were standardized complexometrically using EDTA, and HCl solutions were previously standardized using CO_2-free KOH as titrating agent. All the potentiometric measurements were carried out in 0.1 M KCl as background electrolyte.

Preparation of $[ZnL_2]_n$

To a stirred solution of HL (1 mmol) in water (20 ml), KOH (1 mmol) and $ZnCl_2$ (3 mmol) were added subsequently, the final volume reaching *c.* 45 ml. From the resulting solution (pH ≃ 7) a powdered precipitate of $[ZnL_2]_n$ was collected almost immediately. The mother liquor was then evaporated slowly on a water bath (at 40 °C) for 3 days after which colourless crystals of $[ZnL_2]_n$ were collected.

Apparatus

Microanalyses of C, H, N and IR spectra were performed as reported [3]. The potentiometric assembly was controlled with a Radiometer VIT90 video titrator unit connected to an ABU91 autoburette with a 25 ml exchanging unit (precision of ±0.005 ml). A calomel K4040 electrode and a glass G2040B electrode were used for the e.m.f. and pH measurements. The sample solutions were titrated in a double-walled vessel at 25.0 ± 0.1 °C under continuous flow of nitrogen, previously bubbled through ascarite.

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Procedure

Calibration of the electrodes (Gran method [4]) and the ionic product of the medium ($-\log Kw$) was through an acid–base titration (HCl against KOH) [5]. The pH dependence of the liquid junction potential was negligible throughout the pH working range.

The computer program BEST [6] was used to process data and calculate the basicity of the ligand and the stability constants of the complexes. The program minimizes the sum of the square residuals between the observed and calculated pH values given by $U = \Sigma w_i([\text{pH}]_{\text{obs}} - [\text{pH}]_{\text{calc}})^2$ where w_i is a weighting factor defined by $w_i = 1/(\text{p[H]}_{i+1} - \text{p[H]}_{i-1})^2$. The standard deviation, in pH units, is given by $\sigma_{\text{fit}} = (U/N)^{1/2}$, where $N = \Sigma w_i$.

Protonation equilibria were studied at ionic strength 0.1 M KCl and analytical ligand concentration between 1.0×10^{-3} and 2.5×10^{-3} M. The complex formation equilibria were studied at $\text{HL} = 1.0 \times 10^{-3}$ M and [HL]/[Zn(II)] ratios from 4:1 to 1:1, at ionic strength 0.1 M KCl.

X-ray data collection and structure determination

Single crystal data collection was performed at 293 K with a Siemens R3m/V diffractometer using graphite monochromatized Mo Kα ($\lambda = 0.71069$ Å) radiation. A prismatic colourless crystal was used with dimensions $0.30 \times 0.30 \times 0.25$ mm. The complex crystallizes in the orthorhombic system, space group $P2_12_12_1$ (No. 19) with $a = 7.984(1)$, $b = 13.476(2)$, $c = 13.709(2)$ Å, $V = 1475.0(2)$ Å^3, $Z = 4$, $D_c = 1.548$ g cm^{-3}, $F(000) = 704$, μ(Mo Kα) $= 1.94$ mm^{-1}.

The unit cell parameters were calculated by least-squares refinement of 25 well centred reflections in the range $15 < 2\theta < 45°$. The data were collected by $\omega/2\theta$ scan mode in the range $3 < 2\theta < 70°$. Intensities of three check reflections measured after every 120 min showed only statistical variation. A total of 2997 reflections (with 172 parameters) was considered as observed with $I > 3\sigma(I_o)$. The data were corrected for Lorentz and polarization effects and for absorption.

The structure of $[\text{ZnL}_2]_n$ was solved by Patterson methods and subsequent Fourier syntheses with the SHELXTL PLUS program [7]. All non-hydrogen atoms were refined anisotropically in the final refinements. The positions of the hydrogen atoms were calculated with isotropic temperature factors ($U = 0.08$) and were not refined. Neutral atomic scattering and dispersion factors were those included in the SHELXTL package. The function minimized was $\Sigma w(\Delta F)^2 (1/w = \sigma^2(F_o))$, resulting in a final $R = \Sigma|F_o - F_c|/\Sigma|F_o|$ value of 0.055 and $R_w = [(\Sigma w|F_o - F_c|)^2/\Sigma w|F_o|^2]^{1/2}$ value of 0.051.

Results and discussion

Protonation equilibria

The protonation equilibria of HL have been studied potentiometrically by titrating acidified aqueous solutions (HCl) of the ligand (c_L from 1.0×10^{-3} to 2.5×10^{-3} M and ionic strength 0.1 M KCl) with KOH 0.1 M. Protonation constants were obtained from 50 experimental points in the pH range 2.5–8.5. The values obtained for processes (1) and (2), corresponding to the N(1)–C(2)–N(3) protonations, are given in Table 1 (statistical parameter $\sigma_{\text{fit}} = 0.0073$). The species formed in the equilibria are labelled by the (*pqr*) parameters. These define the number of metal ions, deprotonated ligands and protons, respectively, forming the species.

$$\text{H}^+ + \text{L} \rightleftharpoons \text{HL} \qquad (\beta_{011}) \tag{1}$$

$$2\text{H}^+ + \text{L} \rightleftharpoons \text{H}_2\text{L}^+ \qquad (\beta_{012}) \tag{2}$$

The first protonation constant ($\log \beta_{011} = 8.47$) (eqn. (1)) is slightly lower than that for protonation of the monoanion uracil in water (8.926 at 37 °C and ionic strength 0.15 M KNO_3 [8] and 9.40 at 25 °C and ionic strength 0.1 M KNO_3 [9]). This indicates a lower basicity of the thione anion than that of the oxo anion from uracil and the inductive effect of the two CH_3 exocyclic substituents of HL that enhance the electronic density of the ring.

The species distribution diagram shows that deprotonation of HL starts at pH 6.5. L is the predominant species from pH 8.5 to pH 9.5. The neutral HL species predominates in the 4–7 pH range and the doubly protonated H_2L^+ species predominates at pH below 2.5.

Zn(II) complexation equilibria

Previously acidified solutions of Zn(II) chloride and HL with $c_{\text{HL}}/c_{\text{M}}$ from 1/1 to 4/1 ($c_{\text{HL}} = 1.0 \times 10^{-3}$ M) were titrated with 0.1 M KOH at ionic strength 0.1

TABLE 1. Equilibrium data for protonation of L and complex formation of Zn(II) with protonated and unprotonated species (25 °C in 0.1 M KCl)[a]

Species (*pqr*)	Process	log β	
		HL	Uracil[b]
(011)	$\text{H}^+ + \text{L} \rightleftharpoons \text{HL}$	8.47(4)	8.926 9.40
(012)	$2\text{H}^+ + \text{L} \rightleftharpoons \text{H}_2\text{L}^+$	10.95(9)	
(110)	$\text{Zn}^{2+} + \text{L} \rightleftharpoons \text{ZnL}^+$	5.06(2)	2.39
(120)	$\text{Zn}^{2+} + 2\text{L} \rightleftharpoons \text{ZnL}_2$	8.54(3)	
(111)	$\text{Zn}^{2+} + \text{L} + \text{H}^+ \rightleftharpoons \text{ZnHL}^{2+}$	11.93(3)	
(10-4)	$\text{Zn}^{2+} \rightleftharpoons \text{Zn(OH)}_4{}^{2-} + 4\text{H}^+$	$-32.03(9)$	

[a] Values in parentheses are the standard deviation corresponding to the last significant digit. [b] From refs. 8 and 9.

KCl in order to study the formation of the complexes. The titrations were extended to pH 8.5 before the onset of precipitation. Equilibrium constants, obtained from 50 experimental points, are summarized in Table 1. The distribution plots as a function of the pH for the system Zn(II)/HL appear in Fig. 1.

$$Zn^{2+} + L \rightleftharpoons ZnL^{+} \qquad (\beta_{110}) \tag{3}$$

$$Zn^{2+} + 2L \rightleftharpoons ZnL_2 \qquad (\beta_{120}) \tag{4}$$

$$Zn^{2+} + L + H^{+} \rightleftharpoons Zn(HL)^{2+} \qquad (\beta_{111}) \tag{5}$$

$$Zn^{2+} \rightleftharpoons Zn(OH)_4^{2-} + 4H^{+} \qquad (\beta_{10-4}) \tag{6}$$

The experimental data indicate the existence of ZnL^+, ZnL_2, $Zn(HL)^{2+}$ and $Zn(OH)_4^{2-}$ species ($\sigma_{fit} = 0.0084$). The stability of the ZnL^+ species (eqn. (3)) (log $\beta_{110} = 5.06$) is two order of magnitude larger than that of the ZnU^+ complex (U is uracil) (log $\beta = 2.39$) [8]. In ZnU^+, monodentate coordination of U^- occurs through the negatively charged N_{cyclic} atom of the uracil ring whereas in the former there is a chelating N_{cyclic}–S coordination of the L anion.

The overall stability constant of monomer ZnL_2 (where L is S–N coordinated, see Fig. 3), is log $\beta_{120} = 8.54$; thus log K for $ZnL^+ + L \rightleftharpoons ZnL_2$ is smaller (3.48) than log β_{110}. This would indicate steric hindrance between L molecules in the ZnL_2 units, as suggested by the $[ZnL_2]_n$ crystal structure, see below.

On the other hand, the difference between log β_{111} and log β_{011} (eqns. (5) and (1)) gives a log K value of 3.46 for the HL complexation process. This value is much smaller than that of the ZnL^+ species (Table 1), as expected from the different coordination patterns of the ligand in ZnL^+ and $Zn(HL)^{2+}$, bidentate and monodentate, respectively [3].

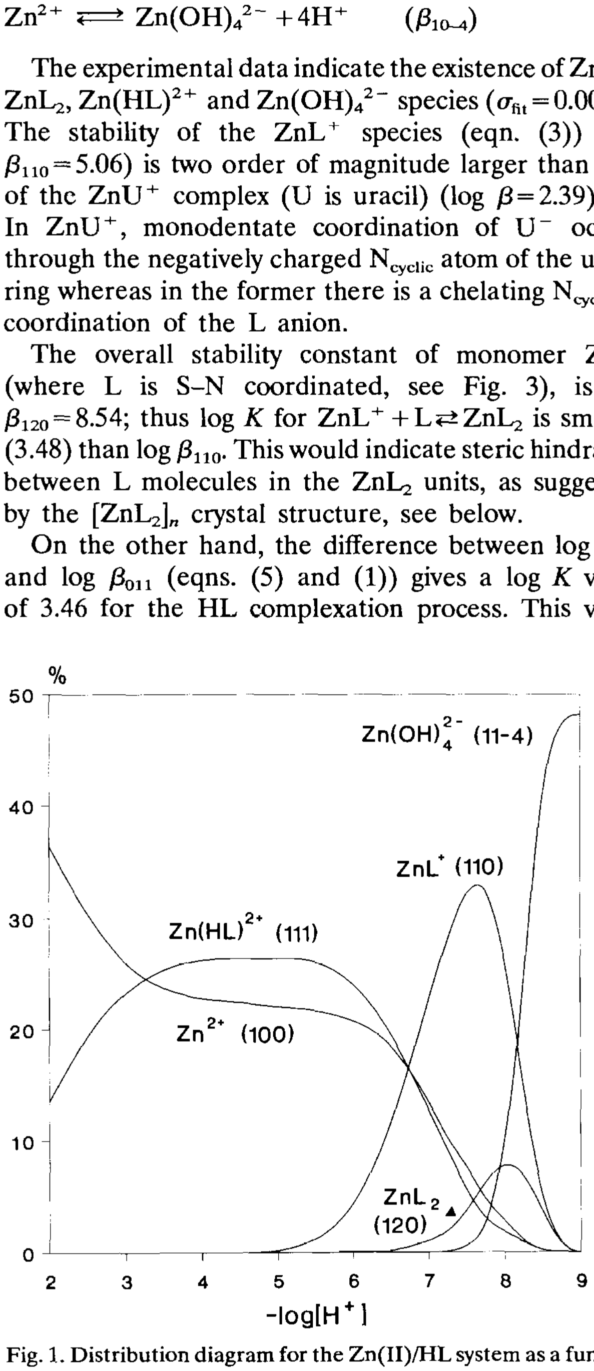

Fig. 1. Distribution diagram for the Zn(II)/HL system as a function of pH.

From Fig. 1 it becomes evident that the complex species with the neutral HL predominate at pH values below 5.5, whereas the ones in which the ligand is anionic predominate in the 7–8 pH range. At the working reagent concentrations and pH ranges the $Zn(HL)_2^{2+}$ species has not been detected, which can be related to the formation of precipitates observed in the media. A monomeric species of $Zn(HL)_2^{2+}$ stoichiometry has been obtained and characterized by X-ray diffraction methods from solutions containing an $HL/ZnCl_2$ mixture at pH 4.5 [3], whereas solutions of the HL/Zn system at pH $\simeq$ 7 yielded $[ZnL_2]_n$, which, is probably formed by polymerization of the monomeric ZnL_2 species according to the following process: $nZnL_2 \rightleftharpoons [ZnL_2]_n$.

IR spectrum

The absence of the broad band of the HL ligand (at 2912 cm^{-1}) in the IR spectrum of $[ZnL_2]_n$ indicates coordination of the monoanion L to the Zn(II) ions and its anhydrous character. The strong ν(C=C) and ν(C=N) stretching vibration bands of the ligand are shifted from 1624 and 1568 cm^{-1} to 1578 and 1533 cm^{-1}, respectively. This supports the existence of Zn–N_{cyclic} bonds in $[ZnL_2]_n$, as found in the Pd(II) and Pt(II) complexes of neutral N-coordinated HL [3].

On the other hand the strong ν(C=S) band at 1187 cm^{-1} in HL weakly appears at 1165 cm^{-1}, indicating a coordinated S atom in $[ZnL_2]_n$. This feature is found in the compounds $Zn(HL)_2Cl_2$ and $Cd(HL)_2Cl_2$, where the neutral HL is monodentately coordinated through the S atom [3]. Nevertheless, in the last two compounds the ν(C=C) and ν(C=N) bands are unaffected.

Comparison of the HL and $[ZnL_2]_n$ IR spectra in the 600–180 cm^{-1} range reveals two new bands centred at 195 (wide and strong) and 304 (medium) cm^{-1} which are assigned to ν(Zn–N) and ν(Zn–S) stretching vibration bands, respectively. These low values are evidently due to the S,N chelation [10].

Description of the structure of $[ZnL_2]_n$

The Zn(II) centres in $[ZnL_2]_n$ are bridged sequentially by pyrimidine rings to form infinite chains. These zigzag chains extend along the crystallographic *a* axis (Fig. 2). A perspective view of the mononuclear fragment together with the atomic labelling scheme is given in Fig. 3. Selected bond distances and angles are listed in Table 2.

The zinc(II) ion is pentacoordinated within each mononuclear unit. Four of these bonds are formed with the sulfur and the nitrogen atoms belonging to two monoanionic ligands. The remaining bond is formed

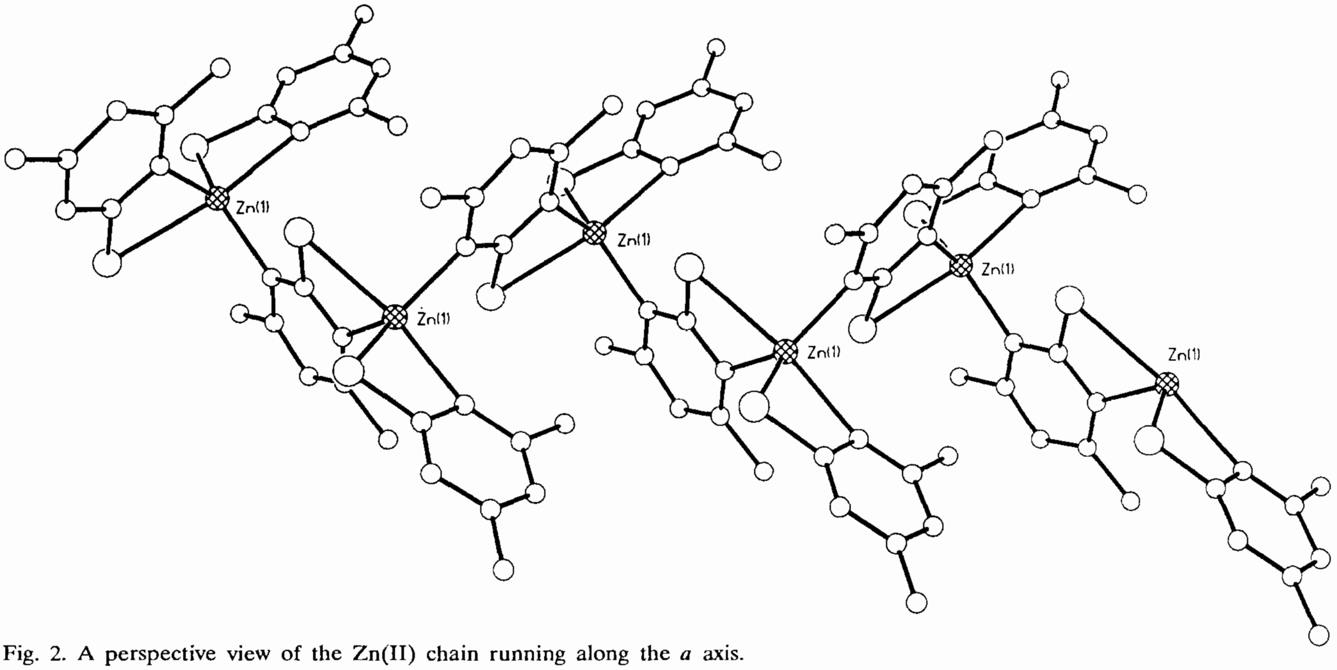

Fig. 2. A perspective view of the Zn(II) chain running along the *a* axis.

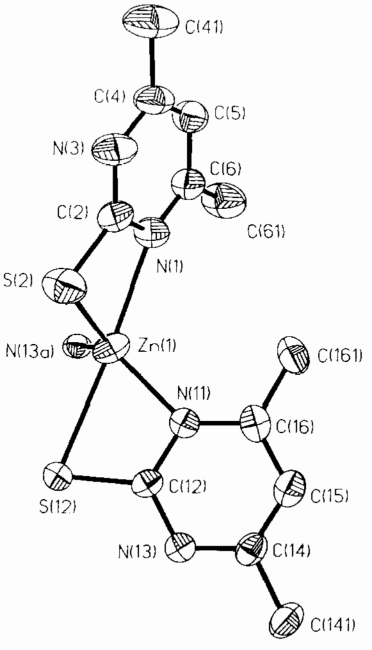

Fig. 3. Labelling scheme of the asymmetric complex unit of the structure.

with a different N(13)^{I} nitrogen atom from an adjacent symmetry related fragment (I$=x-\frac{1}{2}$, $1\frac{1}{2}-y$, $2-z$) at a distance of 2.040(5) Å. This pentacoordination mode is compatible with two idealized geometries: square pyramidal and trigonal bipyramidal. The procedure proposed by Muetterties ad Guggenberg [11] locates the coordination polyhedron at 10.9% towards C_{4v} of the $D_{3h}\rightarrow C_{4v}$ deformation pathway. In a trigonal bipyramidal description, the ligands are not equivalent. Thus, the first ligand coordinates in a bidentate mode through the deprotonated N(1) atom in an axial position at 2.369(6) Å and the S(2) atom in an equatorial position at 2.319(2) Å, while the second ligand bridges in a tridentate fashion, through the deprotonated N(11) atom in an equatorial site at 2.061(5) Å, the S(12) atom in the remaining axial position at a longer distance of 2.679(2) Å (but well within the S–Zn bond distance [12]) and the N(13) atom in an equatorial position of a neighbour Zn(II)^{I} ion, to form infinite chains. This longer Zn–S(12) distance seems to be a consequence of two factors. First, the S(2)···S(12) contact value of 3.875(3) Å is very close to the S···S van der Waals contact distance of 3.70 Å [13]; a shortening of this contact would lead to increased steric crowding in the compound. A second factor responsible for the longer Zn–S(12) distance is the bridging coordination mode of this ligand. Thus, the ligands are not coplanar but

TABLE 2. Selected bond lengths (Å) and angles (°)

Zn(1)–N(1)	2.369(6)	Zn(1)–N(13)^{I}	2.040(5)
Zn(1)–S(2)	2.319(2)	S(2)–C(2)	1.730(7)
Zn(1)–N(11)	2.061(5)	S(12)–C(12)	1.704(6)
Zn(1)–S(12)	2.679(2)		
N(1)–Zn(1)–N(13)^{I}	98.0(2)	S(2)–Zn(1)–N(13)^{I}	128.0(2)
N(11)–Zn(1)–N(1)	114.9(2)	S(12)–Zn(1)–N(1)	168.6(1)
N(11)–Zn(1)–N(13)^{I}	118.7(2)	S(12)–Zn(1)–S(2)	101.4(1)
S(2)–Zn(1)–N(1)	67.6(1)	S(12)–Zn(1)–N(11)	65.3(1)
S(2)–Zn(1)–N(11)	112.4(2)	S(12)–Zn(1)–N(13)^{I}	91.3(2)

$^{I}=x-\frac{1}{2}$, $1\frac{1}{2}-y$, $2-z$.

twisted 113.3(1)° to each other, which results in a displacement of the S(12) atom to a longer distance with respect to the Zn(II) ion. These two factors lead to a delicate balance between the bridging coordination mode, to form the zig-zag chains, and the Zn–S(12) distance, to form a real Zn–S bond, without steric crowding due to the S(2)···S(12) contact. Nevertheless, the formation of chains and the coordination through two four-membered chelating rings, Zn–N–C–S, indicates steric hindrance in the structure.

The bond lengths and angles in the ligands are like those found in related complexes [3, 14]. Planarity characterizes both pyrimidine rings, the maximum deviation from the mean-squares planes being *c.* 0.04 Å. The equatorial coordinated atoms S(2), N(11), N(13)^{I} and the Zn(II) ion are practically coplanar in the coordination polyhedron, the maximum deviation being less than 0.09 Å for the Zn(II) ion, which is displaced toward the N(1) atom. This plane forms an angle of 69.3(1)° with respect to that defined by the N(1), Zn(1) and S(12) atoms.

Although a ZnN_3S_2 chromophore has been described as an approximate trigonal bipyramid [15], this bis(2-thiobenzaldimino)-2,6-diacetylpyridine zinc(II) complex might be better described as intermediate between square pyramid and trigonal bipyramid. To the best of our knowledge, this is the first structure containing trigonal bipyramidal ZnN_3S_2 chromophores [12, 15, 16]. The bridging coordination mode of the thiopyrimidine ligand through the N(13)^{I} atom to a metal of a neighbouring unit is quite unusual and has only been previously observed in the complex $[Li(L^1)(hmpa)]_n$ (HL^1 is 2-mercaptopyridine and hmpa is hexamethylphosphoramide) [17].

Supplementary material

Atomic coordinates, anisotropic thermal parameters, full listing of bond lengths and angles, and observed and calculated structure factors are available from the authors on request.

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References

1 H. Sigel (ed.), *Metal Ions in Biological Systems,* Vol. 15, Marcel Dekker, New York 1983.
2 M.J. Kendrick, M.T. May, M.J. Plishka and K.D. Robinson, *Metals in Biological Systems,* Ellis Horwood, Chichester, UK, 1992.
3 R. López-Garzón, M.D. Gutiérrez-Valero, M.L. Godino-Salido, B.K. Keppler and B. Nuber, *J. Coord. Chem., 30* (1993) 111.
4 G. Gran, *Analyst, 77* (1952) 661.
5 A. Liberti and T.S. Light, *J. Chem. Educ., 39* (1962) 236.
6 A.E. Martell and R.J. Motekaitis, *The Determination and Use of Stability Constants,* VCH, New York, 1988.
7 *SHELXTL-PLUS program,* X-ray Instrument Group, Nicolet Instrument Corp., Madison, WI, 1990.
8 E. Casassas, A. Izquierdo and R. Tauler, *J. Inorg. Biochem., 39* (1990) 327.
9 R.B. Martin and Y.H. Mariam, *Metal Ions in Biological Systems,* Vol. 8, Marcel Dekker, New York, 1979, Ch. 2.
10 J.R. Ferraro, *Low Frequency Vibrations of Inorganic and Coordination Compounds,* Plenum, New York, 1971.
11 E.L. Muetterties and L.J. Guggenberg, *J. Am. Chem. Soc., 96* (1974) 1748.
12 P.G. Harrison, M.J. Begley, T. Kikabhai and F. Miller, *J. Chem. Soc., Dalton Trans.,* (1986) 929.
13 L. Pauling, *The Nature of the Chemical Bond,* Cornell University Press, Ithaca, NY, 3rd edn., 1960.
14 M.A. Romero-Molina, M.D. Gutiérrez-Valero, R. López-Garzón, J.M. Salas-Peregrín, M.I. Arriortua and F.J. Zúñiga, *Inorg. Chim. Acta, 136* (1987) 87, and refs. therein.
15 V.L. Goedken and G.G. Christopf, *Inorg. Chem., 12* (1973) 2316.
16 G. Davies, A. El-Toukhy, K.D. Onan and M. Veidis, *Inorg. Chim. Acta, 84* (1984) 41.
17 D.R. Armstrong, R.E. Mulvey, D. Barr, R.W. Porter, P.R. Raithby, T.R.E. Simpson, D.S. Wright, K. Gregory and P. Mikulcik, *J. Chem. Soc., Dalton Trans.,* (1991) 765.