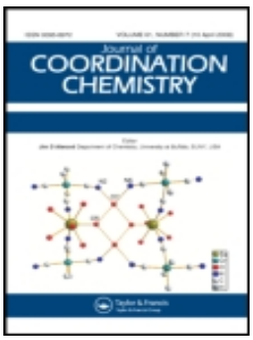

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Supramolecular lead(II) azide complex of 2,6-diacetylpyridine dihydrazone: synthesis, molecular structure, and biological activity

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The complex of 2,6-diacetylpyridinedihydrazone (L) with lead(II) and azide has been characterized by elemental analyses, FTIR, and single-crystal X-ray analysis. The $Pb(C_9H_{13}N_{11})$ (**1**) crystallized in the monoclinic space group *C2/c*. The coordination of **1** exhibits a gap around the lead(II), possibly occupied by a stereochemically active electron lone pair on lead(II) resulting in a *hemidirected* complex. Antimicrobial activity of the complex is higher than the free ligand.

Keywords: Biological activity; Schiff base; Dihydrazone; Lead complex; Azido bridge

1. Introduction

Interest in hydrazone-based Schiff-base ligands lies in their versatility in coordinating metals, pharmacological, and biological activity [1]. The Schiff base used in this study is a planar tridentate analog to terpy, prepared by condensation of 2,6-diacetylpyridine and hydrazine hydrate precursors in a template reaction. Lead(II) has stereoactive lone pair electrons which can be used to design complexing agents for controlling the toxicity toward biological systems. Shimoni-Livny *et al.* [2] discussed stereochemical activity of the lone pair in divalent lead compounds. Lead coordination geometry is classified as "holodirected" if the bonds to ligands are directed throughout the surface of an encompassing sphere, and as "hemidirected" if the bonds to ligands are directed to only part of an encompassing globe, leaving a gap in the distribution of bonds to ligands. Coordination chemistry of lead(II) has been studied with macrocycles [3] and chelating ligands [4]. Due to explosive properties of lead azide compound, lead(II) azide chemistry is less studied than lead(II) thiocyanate complexes. Morsali *et al.* [5], reported the structural influence of counter-ions in some lead(II) complexes, $[Pb(\mu\text{-}SCN)_2\,\mu\text{-ebp})_{1.5}]_n$

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where ebp is 4,4′-[(1E)-ethane-1,2-diyl]*bis*[pyridine], [Pb(phen)(CH_3COO)(NCS)] [6], [Pb(phen)$_2$(CH_3COO)](NCS) [7], [Pb(phen)$_n$(NO_2)(NCS)] [8], and [Pb(BTZ)($SCN)_2$] [9], where BTZ is 4,4′-bithiazole. Lead(II) thiocyanate complexes have also been synthesized to understand the coordinating ability of bibracchial ethers and density functional theory (DFT) of these complexes was reported to predict the structural features and electronic properties [10].

In this study, we report the synthesis and X-ray crystal structure characterization of hemidirected mononuclear lead(II) azide complex of 2,6-diacetylpyridinedihydrazone, whose chemical structure is shown in figure 1. As Schiff-base complexes exhibit antimicrobial activity, we also investigate the antibacterial and antifungal activities of the free ligand and its complex *in vitro*.

2. Materials and methods

All reagents and solvents were purchased from Merck, Aldrich, or Carlo Erba and are used without purification. Elemental analyses for the ligand and complex were carried out at the Eurovector 3018 CHNS analyzer. A Hitachi 8200 atomic absorption spectrometer was used for lead analysis. IR spectra were obtained using IR grade KBr disks on a Perkin–Elmer 1600 Series FTIR spectrophotometer from 4000 to 400 cm^{-1}.

2.1. *Synthesis of the ligand*

2,6-Diacetylpyridinedihydrazone was prepared by reacting 2,6-diacetylpyridine and hydrazine hydrate in ethanol as described previously [11].

Caution! Although not encountered in our experiments, azido complexes of metal ions in the presence of organic ligands are potentially explosive. Only a small amount of material should be prepared, and should be handled with care.

2.2. *Synthesis of lead(II) azide complex of 2,6-diacetylpyridinedihydrazone (1)*

To a boiling solution of $Pb(NO_3)_2 \cdot 6H_2O$ (1 mmol) in ethanol (25 mL) and 2,6-diacetylpyridinedihydrazone (2 mmol) in acetonitrile (30 mL), the NaN_3 (2 mmol) in water (5 mL) was added slowly. The mixture was stirred for additional time of 10 min and then left to stand for 2 or 3 days. The light brown crystalline precipitate was filtered off and dried in open air. Yield: 73%, Anal. Calcd for $C_9H_{13}N_{11}Pb$: C, 22.40; H, 2.69;

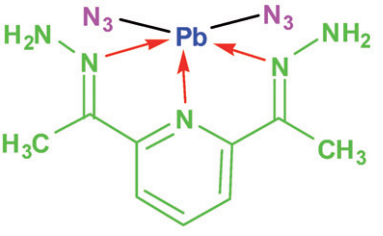

Figure 1. Structural drawing of 2,6-diacetylpyridinedihydrazone lead(II) diazide mononuclear complex.

N, 31.92; Pb, 42.94. Found: C, 22.13; H, 2.35; N, 31.23; Pb, 42.28. Crystals were suitable for XRD.

2.3. *X-ray crystal structure*

The data collection was performed at 293 K on a Stoe-IPDS-2 diffractometer equipped with graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods using SHELXS-97 and refined by full-matrix least-squares using SHELXL-97 [12]. All non-hydrogen atoms were found from the difference Fourier map and refined anisotropically. All hydrogens on carbon were included using a riding model. Molecular graphics were prepared using ORTEP3 [13].

2.4. *Biological activity assays*

Agar Disc Diffusion Method, Microdilution Broth Susceptibility Assay [14, 15], and Single Spore Culture Technique (for filamentous fungi) [16] were employed for determination of antibacterial and antifungal activities. The compounds L and **1** were screened for antibacterial and antifungal activities using *Staphylococcus aureus* ATCC6538, *Escherichia coli* ATCC25292, *Pseudomonas aeruginosa* ATCC27853, *Enterobacter aerogenes* NRRL3567, *Proteus vulgaris* NRLLB123, *Listeria monocytogenes* ATCC7644, *Serretia marcescens* (clinic isolate), *Candida albicans* (clinic isolate), *Aspergillus flavus*, *Aspergillus niger*, *Penicillium expansum*, and *Alternaria brassicola*. The tested microfungi were isolated from soil in our laboratory [17].

The Agar Disc Diffusion Method was employed for determination of antimicrobial properties of the free ligand and its metal complex [15]. Suspensions of the tested microorganisms (10^8 CFU μL^{-1}) were spread on solid media plates. Stock solutions (10^{-3} M) were prepared by dissolving the compounds (L) or (**1**) in DMF. Filter paper discs (6 mm in diameter) were soaked with 20 µL of the stock solutions and placed on the inoculated plates. After keeping for 2 h at 2°C, they were incubated at 37°C for 24 h for bacteria and *C. albicans*. The diameters of the inhibition zones were measured in millimeters.

For the determination of minimum inhibitory concentration (MIC) the Microdilution Broth Susceptibility Assay was used [15]. Serial dilutions of compounds were prepared in sterile distilled water in 96-well microtiter plates. Freshly grown bacterial suspensions in double strength Mueller Hinton Broth and yeast suspension of *C. albican*s in Saboroud Dextrose Broth were standardized with 10^8 CFU mL^{-1} (McFarland No. 0.5). Sterile distilled water served as growth control in a separate plate. A total of 100 µL of each tested compound was then added to each well. The last row containing only serial dilutions of the title compounds without microorganisms was used as negative control. After incubating at 37°C for 24 h, the first well without turbidity was determined as the minimal inhibitory concentration.

The antifungal activities were evaluated against *A. flavus*, *A. niger*, *P. expansum*, and *Al. brassicola* by the Disc Diffusion method. The test solutions were prepared in DMF. In order to obtain conidia, the fungi were cultured on Czapex Dox Agar and/or Malt Extract Agar medium in 9 cm petri dishes at 25°C for 10 days. Harvesting was carried out by suspending the conidia in a 1% (w/v) NaCl solution containing 5% (w/v) DMF. The spore suspension was then filtered and transferred into tubes and stored at −20°C,

according to the method of Hadecek and Greger [18]. The inhibition of fungal growth expressed in percentage was determined from the growth in test plates compared to the respective control plates as follows [19].

$$\text{Inhibition } \% = 100(C - T)/C$$

where C = diameter of fungal growth on the control and T = diameter of fungal growth on the test plate. The activities were compared with the activity of the standard fungicide ketoconazol obtained from Carlo Erba.

3. Results and discussion

3.1. *Crystal structure of 1*

The molecular structure of the title complex is illustrated in figure 2. Crystal structure parameters and conditions of data collection are given in table 1 and the final atomic coordinates are presented in "Supplementary material". Selected bond distances and angles are listed in table 2. As shown in figure 2, the central Pb(II) is surrounded by seven nitrogens from three 2,6-diacetylpyridinedihydrazones and four azides, resulting in a seven-coordinate complex; the coordination sphere could be described as capped octahedron [20]. The azido group is almost linear with an N3–N2–N1 bond angle of 178.5(12)°. Figure 3 displays a 1-D supramolecular polymeric network structure constructed by μ-azido in which every two units are linked into a linear chain of –[LPb–$(N_3)_2$–LPb–$(N_3)_2$–LPb–$(N_3)_2$–LPb–$(N_3)_2$]$_n$.

The ligand is almost planar and mean deviation from planarity for all the non-H atoms of the 2,6-diacetylpyridinedihydrazone is 0.021 Å, except for methyl

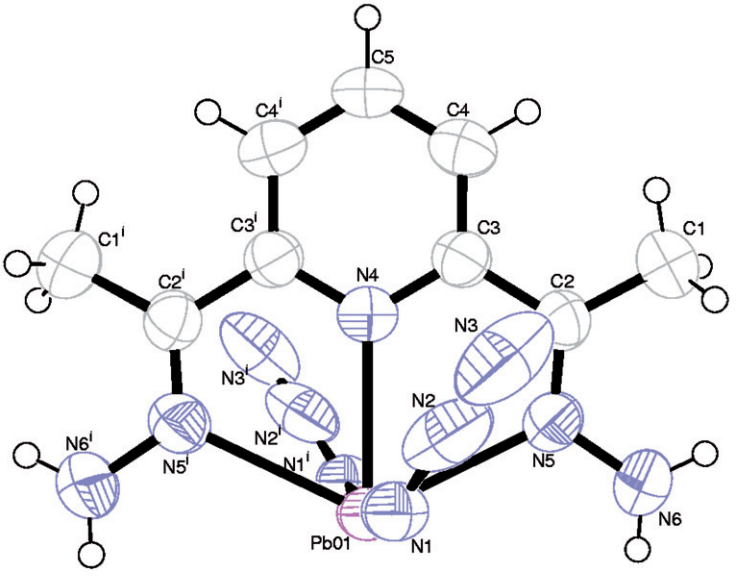

Figure 2. The structure of the title compound, showing 50% probability displacement ellipsoids and the atom-numbering scheme.

carbons and nitrogens of hydrazine that were not fitted. The Pb–N (from pyridine, two from hydrazone, and two from azide) bond distances range from 2.484(9) to 2.582(8) Å [Pb(1)–N(5)$_{hydrazone}$ = 2.582(8), Pb(1)–N(4)$_{pyridine}$ = 2.484(9), and Pb(1)–N(1)$_{azide\ ion}$ = 2.524(8) Å]. These values are bigger than those observed in *bis*(2,6-diacetylpyridine dioximato)nickel(IV) [21].

The crystal structure of **1** (figure 3) was stabilized by two types of interaction. One is the strong intermolecular bonding between nitrogens N6 and N3 with symmetry code $(1/2-x, 1/2-y, 1-z)$ [N6 $\cdots$ N3 = 3.45(2) Å and N6–H6A $\cdots$ N3 = 174°]. There is also weak hydrogen bonding between N6 and N1 with symmetry code $(1/2-x, 1/2-y, 1-z)$

Table 1. Crystal data and experimental details of the title compound.

Chemical formula	$C_9H_{13}N_{11}Pb$
Formula weight	482.49
Crystal system	Monoclinic
Space group	*C2/c*
Unit cell dimensions (Å, °)	
a	19.5324(13)
b	11.0083(8)
c	7.2190(4)
β	112.325(5)
Unit cell volume V (Å^3)	1435.87(16)
Z	4
Calculated density D_x (mg m^{-3})	2.232
Electron number (F_{000})	904
Linear absorption coefficient μ (mm^{-1})	11.764
Crystal color, shape	Yellow, prism
Crystal dimensions (mm^3)	0.170 × 0.147 × 0.120
X-ray and wavelength	Mo-Kα, 0.71073
Data collection temperature, T (K)	293(2)
R_{int}	0.0966
h, k, l intervals (°)	−24/24, −14/14, −9/9
θ_{max} (°)	27.19
Data collection device	STOE IPDS II
Data collection method	ω-scan
Reflections with ($I > 2\sigma(I)$)	1304
Measured reflections	10491
Independent reflections	1593
Used programs	Wingx, SHELXS-97, SHELXL-97
Structure refinement	For full matrix (F^2)
Weight function	$1/[\sigma^2(F_o^2)+(0.0618P)^2+2.3633P]$, $P=(F_o^2+2F_c^2)/3$
Parameter number	93
R, $R_W(I > \sigma(I))$	0.0451, 0.11
S	1.087
$\Delta\rho_{min}$, $\Delta\rho_{max}$ (e Å^{-3})	−2.725, 0.797

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

Pb01–N1	2.524(8)	N2–N1	1.181(15)
Pb01–N4	2.484(9)	N3–N2	1.161(18)
Pb01–N5	2.582(8)		
N4–Pb01–N1	84.82(15)	N6–N5–Pb01	119.5(6)
N1–Pb01–N1	169.6(3)	N2–N1–Pb01	123.1(7)
N4–Pb01–N5	63.87(15)	C3–N4–Pb01	120.8(5)
N1–Pb01–N5	82.0(2)	C2–N5–Pb01	120.3(6)
N5–Pb01–N5	127.7(3)	N3–N2–N1	178.5(12)

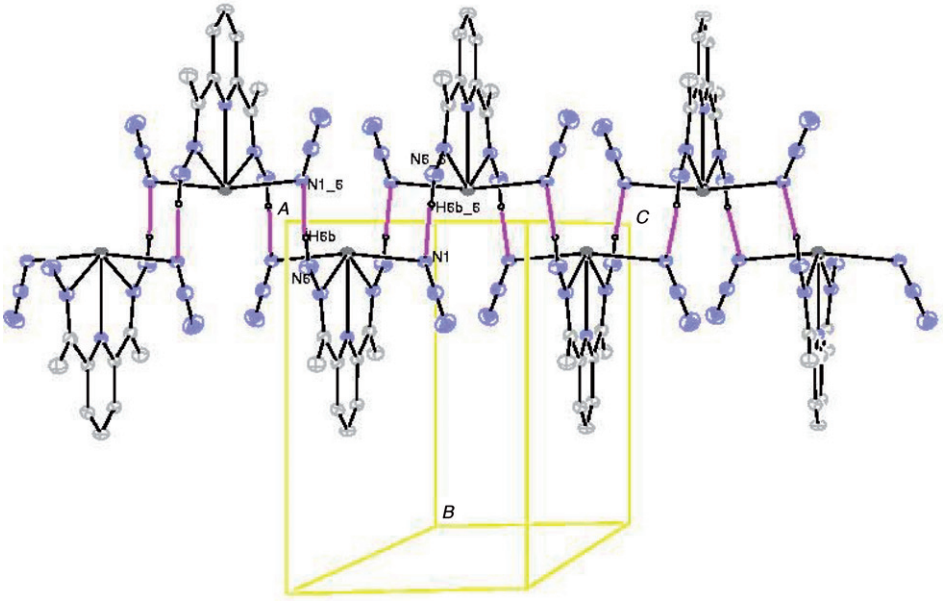

Figure 3. The crystal packing diagram of the title compound viewed parallel to the sheets. Pink lines between the layers show hydrogen bonds.

[N6 $\cdots$ N1 = 3.034(12) Å and N6–H6B $\cdots$ N1 = 142°] and C4 and N3 with symmetry code $(x, 1-y, -1/2+z)$ [C4 $\cdots$ N3 = 3.182(19) Å and C4–H4 $\cdot$ N3 = 147°]. The crystal structure also has π–π stacking. This slipped π–π interaction occurs between Cg1 (the centroid of the N4–C3 ring) and its symmetry equivalent at $(x, 1-y, -1/2+z)$, with a centroid to centroid distance of 3.854 Å.

3.2. *IR spectrum of ligand and 1*

FTIR spectra of 2,6-diacetylpyridinedihydrazone has 3358 and 3199 cm^{-1} amine N–H stretching, 3024 and 3079 cm^{-1} aromatic Ar–H, 2933 and 2906 cm^{-1} methyl hydrogens, 1568 imine C=N and pyridine ring 1457 and 1369 cm^{-1}. The complex has two azides coordinating with lead, with characteristic and very intense FTIR peaks at 2023 cm^{-1}. Shift of the amine N–H peaks from 3358 and 3199 cm^{-1} to 3347 and 3177 cm^{-1}, the 1567 cm^{-1} imine to 1544 cm^{-1} and the peak due to the pyridine ring from 1457 to 1317 cm^{-1} support the ligand coordination to lead. The single azide peak at 2023 cm^{-1} for two azides indicates similarity or equality of the azide coordination in the complex.

3.3. *Biological activity of ligand and 1*

The antimicrobial activities of the ligand and its lead(II) complex have been screened against seven pathogenic bacteria, four fungi, and yeast by the Agar Disc Diffusion Method and Microdilution Broth Susceptibility Assay (table 3) and Single Spore Culture Technique (table 4). The lead(II) complex has higher activity than the corresponding free ligand against the tested microorganisms except gram positive bacterium *S. aureus* ATCC 6538.

Table 3. Antimicrobial screening and activity of the ligand and its complex according to disc diffusion method (mm) and microdilution broth susceptibility assay (MIC) ($\mu g\,mL^{-1}$).

	Disc diffusion			MIC ($\mu g\,mL^{-1}$)		
Microorganisms	**1**	L	Standard	**1**	L	Standard
E. aerogenes NRRL 3567	10	8	22[a]	125	250	250[a]
E. coli ATCC 25292	11	9	22[a]	62.5	125	125[a]
L. monocytogenes ATCC 7644	10	7	24[a]	125	250	125[a]
P. aeruginosa ATCC 27853	10	8	23[a]	62.5	250	250[a]
P. vulgaris NRRL 123	10	8	24[a]	62.5	250	125[a]
S. marcescens (Klinik izolat)	9	8	24[a]	125	250	250[a]
S. aureus ATCC 6538	10	9	22[a]	125	125	125[a]
C. albicans (Klinik izolat)	11	7	27[b]	62.5	250	250[b]

[a]Chloramphenicol; [b]Ketoconazol.

Table 4. Antifungal activity data for **1** and L.

	1			L			Standard		
Microfungi	T	C	%Inh	T	C	%Inh	T	C	%Inh
Al. brassicola	42.5	50	15	45	50	10	11	50	78
A. flavus	48	55	13	49	55	11	9	55	84
A. niger	38.5	50	23	40	50	20	28	50	40
P. expansum	–	20	100	14	20	30	7	20	65

C: diameter of fungal growth on the control.
T: diameter of fungal growth on the test plate.
Inh: inhibition.

Inhibition of the complex against *E. coli* ATCC 2529, *P. aeruginosa* ATCC 27853, *P. vulgaris* NRRL 123, and *C. albicans* were more effective ($62.5\,\mu g\,mL^{-1}$) than the reference substances chloramphenicol and ketoconazol. Also, the sensitivity of *S. aureus* ATCC 6538 and *L. monocytogenes* ATCC 7644 against the complex were the same as the references substances ($125\,\mu g\,mL^{-1}$) (table 3).

Such increased activity of the complex can be explained on the basis of Overtone's concept and chelation theory [22] according to which chelation reduces the polarity of the central metal atom, mainly because of partial sharing of its positive charge with the ligand. Consequently this favors the penetration of the complex through the lipid layer of cell membrane and blocking of the metal binding sites in the enzymes of microorganisms. This complex may disturb the respiration process of the cell and thus block the synthesis of proteins [23].

4. Conclusions

Synthesis, X-ray structure analysis, and biological activity of the hemidirected mononuclear lead(II) compound of 2,6-diacetylpyridinedihydrazone with two azides are described. FTIR spectra show azide ligands in coordination with the lead(II). Antibacterial and antifungal activities of L and 1 show the complex to be more active than the free ligand.

Supplementary material

CCDC-636084 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; Email: deposit@ccdc.cam.ac.uk).

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