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Synthesis, spectroscopic and structural characterization of methyl pyruvate- and pyridoxal-hydrazinopyruvoylthiosemicarbazones

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Abstract

Two new thiosemicarbazones, methyl pyruvate-hydrazinopyruvoylthiosemicarbazone (H_2mpipt), pyridoxal-hydrazinopyruvoylthiosemicarbazone (H_2piript), and their common reaction intermediate, pyruvic acid thiosemicarbazone hydrazide (Hipt), have been synthesized and characterized using IR and NMR spectroscopic methods. The crystal structures of H_2mpipt and Hipt·H_2O have been determined by X-ray crystallographic methods. Both compounds form monoclinic crystals belonging to the space group $P2_1/c$ with $Z=4$ ($a=11.050(2)$, $b=10.386(2)$, $c=11.468(2)$ Å, $\beta=114.87(3)°$ and $a=7.476(1)$, $b=15.359(3)$, $c=8.367(1)$ Å, $\beta=114.43(3)°$, respectively). The ligand H_2mpipt reacts with $[Cu(PPh_3)Cl]_4$ and forms the Cu(I) complex $[Cu(PPh_3)_2(H_2mpipt)Cl]\cdot CH_3OH$ whose structure has been determined by X-ray crystallographic methods. The copper atom has a distorted tetrahedral coordination sphere involving a chlorine atom, the phosphorus atoms of the two PPh_3 molecules and a sulfur atom of the H_2mpipt moiety. The crystals of the complex are triclinic, space group $P\bar{1}$, $Z=2$, $a=18.331(2)$, $b=10.025(2)$, $c=13.697(2)$ Å, $\alpha=72.17(2)$, $\beta=97.77(2)$, $\gamma=87.42(2)°$. The configuration of H_2mpipt in the complex is different from that of the free ligand. The ^1H, ^{13}C and ^{15}N NMR spectra for H_2piript are also discussed.

Keywords: Crystal structures; Copper complexes; Thiosemicarbazone complexes

1. Introduction

We have recently reported the synthesis and the structural investigation of a series of metal complexes of pyridoxal and methyl pyruvate thiosemicarbazones [1–4], whose ligand behaviour is S-monodentate or SNO-terdentate depending upon the nature of the metal ion and the experimental conditions.

In order to extend the knowledge of the relation between the structure and the biological activity in thiosemicarbazones and their metal complexes, we have now modified the nature and the geometry of this kind of ligand. So, two new more flexible thiosemicarbazones, methyl pyruvate-hydrazinopyruvoylthiosemicarbazone (H_2mpipt), pyridoxal-hydrazinopyruvoylthiosemicarbazone (H_2piript), and their common reaction intermediate, pyruvic acid thiosemicarbazone hydrazide (Hipt) are now isolated and investigated.

Following our interest concerning the chemical and structural investigation into the chemistry of Cu(I) and Cu(II) complexes [5–7] we here also report the synthesis and structural characterization of a Cu(I) complex, $[Cu(PPh_3)_2(H_2mpipt)Cl]\cdot CH_3OH$, obtained by reaction of $[Cu(PPh_3)Cl]_4$ [8] with H_2mpipt. An interesting feature of this research is to investigate the transformation of the pseudo-cubane stereochemistry [9–11] in connection with different factors such as the oxidation state of the metal and the experimental conditions employed in the synthesis. Our intention is to extend our studies on the stereochemistry of Cu(I) and Cu(II) complexes, as possible models for the coordination geometries of the Cu(I)–Cu(II) redox couple in copper enzymes, and on the ligand configuration related to

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the biological activity of the ligand and the above copper complexes.

2. Experimental

2.1. Synthesis of ligands and complexes

Three separate steps were involved in the synthesis of two new polyfunctional ligands as reported in Scheme 1 with the abbreviations for the definition of the nomenclature used throughout.

The first step was the synthesis of methyl pyruvate thiosemicarbazone Hmpt, according to the procedure previously reported [2].

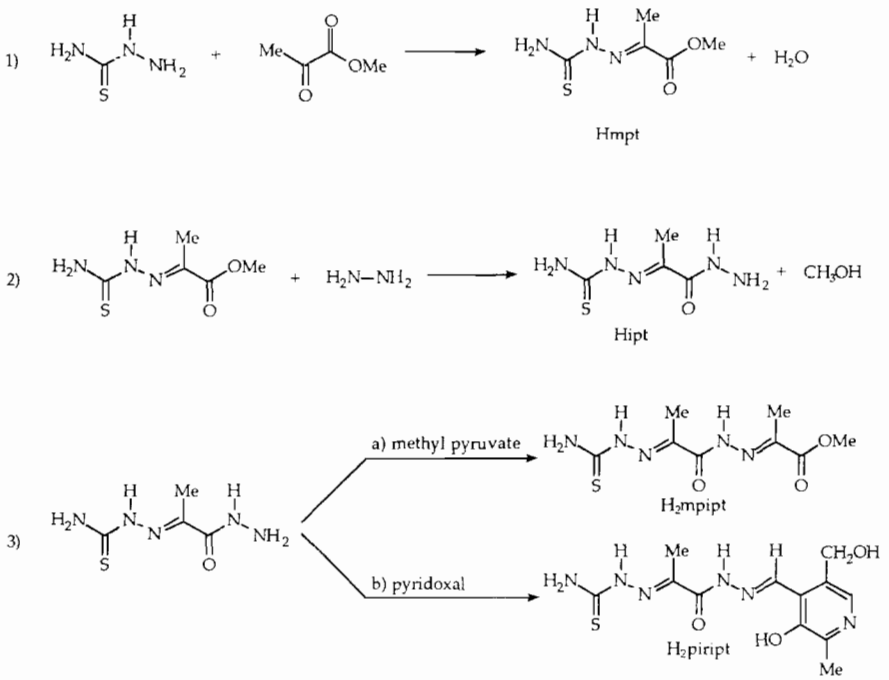
The second step was the synthesis of pyruvic acid thiosemicarbazone hydrazide Hipt (**A**): 1.06 ml (21.7 mmol) of hydrazine hydrate were added dropwise to solid Hmpt·0.5H_2O (4.0 g, 21.7 mmol). The resulting slurry was diluted with 10 ml of abs. EtOH, stirred at room temperature for another 25 min, and finally heated under reflux for 20 min. After cooling, the crude product was filtered, air-dried, and then dissolved in 200 ml of 2:1 vol./vol. mixture of water and ethanol by stirring for 1.5 h at 25 °C and then refluxing for 30 min. The resultant solution, slowly evaporated at room temperature, yielded white crystals of hydrazide Hipt·H_2O (m.p. = 160 °C). *Anal.* Found: C, 24.4; H, 5.7; N, 36.5. Calc. for $C_4H_{11}N_5O_2S$: C, 24.9; H, 5.7; N, 36.3%. MS, *m/e* (%): 175 (M^+, 18.0), 158 (5.0), 143 (8.0), 116 (100.0), 99 (3.0), 75 (46.0), 59 (24.0), 57 (32.0). ^1H NMR: δ 10.38 (s, 1H, NHCS), 9.81 (s, 1H, NHCO), 8.56 (d, $^2J(HH) = 10$ Hz, 2H, NH_2CS), 4.36 (s, 2H, NH_2), 2.06 (s, 3H, CH_3). FT-IR (cm^{-1}): ν(NH), ν(OH) = 3451m, 3379m, 3277s, 3252ms, 3168m(br), ν(CO) = 1674s, 1642vs, ν(CN) = 1619s, ν(NCS) = 1421s, ν(CS) = 964m, ν(NCS) = 711ms.

The final step was the synthesis of:

(*a*) *H_2mpipt, methyl pyruvate-hydrazinopyruvoylthiosemicarbazone* (***B***)

Hipt·H_2O (2.0 g, 10.4 mmol) was refluxed and stirred for 90 min in methanol (250 ml). Methyl pyruvate (0.94 ml, 10.4 mmol) was placed in a dropping funnel with 40 ml of methanol and added to the above warm solution. This addition caused the immediate formation of a white rather voluminous solid (**1a**). After an hour, heating was stopped, and the suspended solid was removed by filtration. The filtrate afforded, upon slow evaporation of the solvent at room temperature, first pale yellow crystals (**2a**) as the major product, then a small amount of white crystalline material (**3a**). The analytical composition of the two white compounds (crystalline material, **3a**, and solid filtered off, **1a**) was in good agreement with that of the pale yellow crystals (**2a**) suitable for X-ray diffraction studies (decomp. > 205 °C). *Anal.* Found: C, 37.2; H, 5.1; N, 27.4. Calc. for $C_8H_{13}N_5O_3S$: C, 37.1; H, 5.1; N, 27.0%.

Recrystallization of the crude voluminous solid product (**1a**) from ethanol or methanol at room temperature gave again yellow crystals (**2a**) and white crystalline material (**3a**) as confirmed by comparison of microanalyses and IR and NMR spectral patterns (Table 1). The spectral differences are due to the presence of different isomeric forms, two of them are most probably



Scheme 1.

Table 1
^{1}H NMR (ppm) and IR (cm^{-1}) spectral data for H_2mpipt (**2a** and **3a**)

	δ	Integration	Signal	Attributed to
2a	10.7	2	s	NHCS, CONH
	8.8	1	[a]	H_2NCS
	8.5	1	[a]	H_2NCS
	3.8	3	s	OCH_3
	2.1	6	s	CH_3
3a	13.1	1	s	CONH
	11.0	1	s	NHCS
	8.9	1	[a]	H_2NCS
	7.7	1	[a]	H_2NCS
	3.8	3	s	OCH_3
	2.1	6	s	CH_3

	ν(NH) ν(OH)	ν(CO)	ν(CN)	ν(NCS)	ν(NCS) + ν(C–C(=O)–O)	ν(CS)	ν(NCS)
2a	3440ms	1730s	1600vs	1440s	1270s(br)	950vw	740m
	3340s	1680s	1520s		1200ms	910ms	720m
	3300ms				1160s(br)	850ms	
	3180mw				1120(sh)	830m	
3a	3420s	1700s	1600vs	1430ms	1280s	980vw	760m
	3300ms	1680s	1570w	1415ms	1200ms	960mw	
	3220m				1160s	900m	
	3180ms				1120ms	835m	
					1035m		

[a]Broad pseudo-singlet.

bounded together via hydrogen bonds in compound **1a**. As H_2mpipt can assume different configurations (*EE*, *EZ*, *ZE*, *ZZ*) depending on the relative position of the CH_3 and NH groups, the ligand probably exists in solution as an equilibrium of rotamers which are potentially temperature dependent. Compound **2a** is in *EE* configuration as demonstrate by X-ray crystallographic studies.

(b) H_2piript, pyridoxal-hydrazinopyruvoylthiosemicarbazone

A 1.0 g (6.00 mmol) sample of pyridoxal obtained in its neutral form was stirred in 50 ml of methanol for 30 min at 55 °C; 1.16 g (6.00 mmol) of Hipt·H_2O were dissolved in 60 ml of the same solvent by heating at reflux for 45 min. Both solutions were cooled to room temperature, and then mixed. The mixture was stirred for 30 min at the same temperature and was then allowed to evaporate slowly. Within a few hours deep yellow microcrystals of H_2piript·MeOH·0.5H_2O, unsuitable for X-ray crystallographic analysis were isolated (m.p. = 241 °C). *Anal.* Found: C, 42.8; H, 5.7; N, 23.7. Calc. for $C_{13}H_{21}N_6O_{4.5}S$: C, 42.7; H, 5.8; N, 23.0%. FAB-MS, *m/e* (%): 347 ($[M+Na]^+$, 12.0), 325 ($[M+H]^+$, 100.0), 307 (11.5), 289 (12.0), 253 (15.0), 217 (10.0), 191 (17.5), 183 (30.0), 177 (56.0), 166 (50.0), 165 (49.0). ^{1}H, ^{13}C, and ^{15}N NMR data are reported below (see Results and discussion). FT-IR (cm^{-1}): ν(NH), ν(OH) = 3430m(br), 3279ms(br), 3173s, ν(CO) = 1677vs, ν(CN) = 1621s, ν(CS) = 906m, ν(NCS) = 757mw.

2.2. Reaction of $[Cu(PPh_3)Cl]_4$ with H_2mpipt

Under a nitrogen atmosphere, the ligand H_2mpipt (0.26 g, 1.0 mmol) was dissolved in methanol (150 ml) by heating at reflux for about 1 h. To this solution was added solid $[Cu(PPh_3)Cl]_4$ (0.36 g, 0.25 mmol; molar ratio H_2mpipt: metal = 1:1). After a few minutes of stirring, the tetramer was completely reacted as evidenced by the colour change. The resultant solution (pH = 6) was heated at reflux for another 2 h, and left to cool at room temperature in a nitrogen atmosphere. When the solvent was partially evaporated in vacuo, the solution gave an extensive formation of bright yellow crystals of $[Cu(PPh_3)_2(H_2mpipt)Cl]\cdot CH_3OH$ (**C**) stable towards air. A single crystal for X-ray crystallographic analysis was selected from this batch (m.p. = 140 °C). *Anal.* Found: C, 59.2; H, 5.2; N, 7.6. Calc. for $C_{45}H_{47}ClCuN_5O_4P_2S$: C, 59.1; H, 5.2; N, 7.7%. IR (cm^{-1}): ν(NH), ν(OH) = 3420ms, 3360m, 3260m, 3160m, ν(CO) = 1700s, ν(CN) = 1600ms, br, 1585(sh), ν(NCS) = 1435vs, ν(CS) = 980mw, 910mw, 840mw, ν(NCS) = 740ms. However: (i) when the same synthesis was attempted by the reaction of H_2mpipt and $[Cu(PPh_3)Cl]_4$ with a 1:2 ligand–metal molar ratio, compound **C** was obtained together with a small amount of unreacted $[Cu(PPh_3)Cl]_4$; (ii) when the reaction was performed strictly by the same procedure as reported above (1:1 molar ratio), but in the presence of air, a mixture of different types of crystals was obtained upon

Table 2
Experimental data for the crystallographic analyses[a]

Compound	Hipt·H_2O (**A**)	H_2mpipt (**B**)	$[Cu(PPh_3)_2(H_2mpipt)Cl]\cdot CH_3OH$ (**C**)
Formula	$C_4H_{11}N_5O_2S$	$C_8H_{13}N_5O_3S$	$C_{45}H_{47}ClCuN_5O_4P_2S$
Molecular weight	193.2	259.3	914.9
Crystal symmetry	monoclinic	monoclinic	triclinic
Space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$
a (Å)	7.476(1)	11.050(2)	18.331(2)
b (Å)	15.359(3)	10.386(2)	10.025(2)
c (Å)	8.367(1)	11.468(2)	13.697(2)
α (°)	90.0	90.0	72.17(2)
β (°)	114.43(3)	114.87(3)	97.77(2)
γ (°)	90.0	90.0	87.42(2)
V (Å^3)	874.7(3)	1194.1(5)	2364.2(7)
Z	4	4	2
D_{calc} (g/cm^3)	1.46	1.44	1.28
$F(000)$	408	544	952
Crystal size (mm)	0.13×0.05×0.33	0.10×0.10×0.23	0.06×0.23×0.23
μ (cm^{-1})	30.6	24.5	25.9
θ Range (°)	3 to 70	3 to 70	3 to 70
h Range	−9 to 70	−13 to 12	−22 to 22
k Range	0 to 18	0 to 12	−11 to 12
l range	0 to 10	0 to 13	0 to 15
Standard reflections	1 2 3	1 0 2	4 4 0
Intensity variation	none	none	none
No. measured reflections	1863	2529	8987
Conditions for observed reflections	$I>2\sigma(I)$	$I>2\sigma(I)$	$I>2\sigma(I)$
Max./min. height in final difference synthesis	0.16, −0.25	0.12, −0.14	0.65, −0.23
No. refined parameters	109	206	527
No. unique reflections	1477	1892	3271
R	0.052	0.039	0.064
R'	0.061	0.045	0.071

[a]Data common to three compounds: Cu Kα radiation (λ = 1.54178 Å); Siemens-AED diffractometer: $T=293\pm1$ K; unit weights are used.

evaporation of the resultant green–blue solution (pH = 3–4). These compounds were separated and identified as triphenylphosphine oxide, $[Cu(PPh_3)_2Cl]_4$, $\{[Cu(Hpt)Cl]\cdot 2H_2O\}_n$ (H_2pt = pyruvic acid thiosemicarbazone) blue crystals [2] and $[Cu(PPh_3)_2(H_2mpipt)Cl]\cdot CH_3OH$ (**C**) yellow crystals, by analytical and IR data.

The blue compound, $\{[Cu(Hpt)Cl]\cdot 2H_2O\}_n$, was also obtained when a solution of $CuCl_2\cdot 2H_2O$ (0.9 g, 5.2 mmol) was made to react with Hipt·H_2O (1.0 g, 5.2 mmol) in absolute ethanol. In both cases it is probable that the reaction induced Cu(II) complexation with the hydrolysis products of H_2mpipt and Hipt, respectively.

2.3. Reaction of $[Cu(PPh_3)Cl]_4$ with H_2piript

An equimolar amount of solid $[Cu(PPh_3)Cl]_4$ was added to a stirred suspension of H_2piript in methanol. No reaction took place at room temperature and at reflux, as shown by the IR data of the solids isolated from the clear solution over several hours.

2.4. Physical measurements

Elemental analyses for C, H and N were performed on a Perkin-Elmer 240 automatic instrument. The Hipt mass spectrum was registered on a Varian CH-5 spectrometer (70 eV ($\sim 1.12\times10^{-17}$ J)). The positive ions FAB H_2piript mass spectrum (*m*-nitrobenzyl alcohol, Xe, 8 eV) was recorded on a Kratos MS 25 spectrometer at low resolution. ^{1}H NMR of Hipt and H_2mpipt spectra were recorded on a Bruker AC 100 apparatus. ^{1}H, ^{13}C, and ^{15}N spectra of H_2piript were recorded on a Bruker 400 AMX apparatus. All the NMR spectra were obtained by dissolution of the ligands in DMSO-d_6 (pH = 7) and present two signals at 2.5 and at about 3.4 ppm due to DMSO and water, respectively. IR data (KBr discs) were recorded on either a Nicolet 5PC FT-IR or a Perkin-Elmer 283 B spectrophotometer.

2.5. X-ray structure determination

Crystal data and information pertinent to the data collection and structural determination are given in Table 2. The absorption correction was neglected in view of small or almost isotropic crystals dimensions. The structures were solved by direct methods for compounds **A** and **B**, and by the heavy-atom technique starting from the three-dimensional Patterson analysis for compound **C**, using the SHELX-86 system of computer programs [12]. For all compounds successive Fourier syntheses gave the coordinates of all non-

hydrogen atoms, which were refined first by means of isotropic, and then anisotropic (except C(45) of the methanolic group in **C**) least-squares calculations [13]. The hydrogen atoms, located by ΔF syntheses, were not refined for **A** but isotropically refined for **B**. In **C** the hydrogen atoms of the ligand and that of methanolic oxygen were located from a ΔF synthesis, but those of the PPh_3 phenyl groups and of the methanolic methyl group were calculated with standard geometries. None of the hydrogen atoms in **C** were refined. The final atomic fractional coordinates are given in Table 3 for **A** and **B** and in Table 4 for **C**. Atomic scattering factors were taken from Ref. [14]. All calculations were performed on a GOULD 6440 Powernode computer of the Centro di Studio per la Strutturistica Diffrattometrica del C.N.R. (Parma) using the PARST [15] program for the geometrical description of the structure, ORTEP [16] and PLUTO [17] for the structure drawings.

3. Results and discussion

3.1. Description of the structure

The structure of **A**, the common intermediate in the preparation of the ligands H_2mpipt and H_2piript, consists

Table 3
Fractional atomic coordinates ($\times 10^4$) for non-hydrogen atoms for **A** and **B**

Atom	x/a	y/b	z/c
Compound **A**			
S	7536(2)	5577(1)	2025(1)
O(1)	557(4)	8172(2)	−5134(3)
O(2)	6428(5)	9071(2)	456(4)
N(1)	7325(5)	7310(2)	1692(4)
N(2)	5054(5)	6516(2)	−575(4)
N(3)	4262(4)	7292(2)	−1377(4)
N(4)	2770(5)	8810(2)	−2679(4)
N(5)	2115(5)	9672(2)	−3212(4)
C(1)	6621(5)	6543(2)	1027(5)
C(2)	2769(6)	7250(2)	−2874(5)
C(3)	1922(6)	8117(3)	−3644(5)
C(4)	1788(7)	6440(3)	−3820(6)
Compound **B**			
S	8639(1)	2300(1)	8976(1)
O(1)	8505(2)	7953(2)	12631(2)
O(2)	5125(2)	11557(2)	8282(2)
O(3)	6244(2)	11585(2)	10435(2)
N(1)	7409(3)	4529(3)	8117(3)
N(2)	8702(3)	4402(2)	10278(2)
N(3)	8330(2)	5632(2)	10393(2)
N(4)	7723(3)	8095(2)	10443(2)
N(5)	7154(2)	9276(2)	10411(2)
C(1)	8212(3)	3823(3)	9098(3)
C(2)	8820(3)	6142(3)	11525(3)
C(3)	9762(4)	5531(3)	12750(3)
C(4)	8347(3)	7478(3)	11601(3)
C(5)	6540(3)	9795(3)	9295(3)
C(6)	6362(5)	9269(4)	8018(3)
C(7)	5895(3)	11064(3)	9268(3)
C(8)	5724(4)	12861(3)	10466(4)

Table 4
Fractional atomic coordinates ($\times 10^4$) for non-hydrogen atoms for **C**

Atom	x/a	y/b	z/c
Cu	2437(1)	525(2)	3091(1)
S	2836(2)	2827(3)	2782(2)
Cl	3400(2)	−935(3)	2846(2)
P(1)	2363(1)	−32(3)	4822(2)
P(2)	1463(1)	479(3)	1864(2)
N(1)	3921(5)	2142(9)	1874(8)
N(2)	3976(4)	4203(8)	2274(7)
N(3)	4625(4)	4352(8)	1868(7)
N(4)	5838(5)	4453(9)	1043(8)
N(5)	6464(5)	4391(10)	653(8)
O(1)	6064(4)	6465(9)	1431(7)
O(2)	5539(4)	2121(8)	591(7)
O(3)	6490(5)	1192(9)	48(7)
O(4)	3418(5)	5765(7)	3494(7)
C(1)	3621(5)	3034(10)	2265(8)
C(2)	4969(6)	5447(10)	1860(8)
C(3)	4715(7)	6633(12)	2226(10)
C(4)	5658(6)	5538(12)	1416(10)
C(5)	6642(6)	3359(12)	329(10)
C(6)	7348(7)	3348(15)	−111(12)
C(7)	6143(6)	2181(12)	367(10)
C(8)	6079(8)	−9(15)	−3(11)
C(9)	3203(6)	212(11)	5614(8)
C(10)	3870(6)	−350(14)	5502(9)
C(11)	4524(7)	−201(16)	6090(11)
C(12)	4505(8)	491(17)	6812(11)
C(13)	3858(8)	1091(16)	6912(11)
C(14)	3188(7)	962(14)	6326(10)
C(15)	1652(5)	1001(10)	5137(7)
C(16)	1516(7)	2389(12)	4614(9)
C(17)	984(9)	3247(13)	4802(10)
C(18)	571(8)	2669(17)	5591(12)
C(19)	693(8)	1291(16)	6106(12)
C(20)	1233(8)	434(13)	5895(11)
C(21)	2198(6)	−1847(11)	5530(8)
C(22)	2544(7)	−2632(13)	6469(10)
C(23)	2376(8)	−3995(15)	6967(11)
C(24)	1793(9)	−4509(14)	6477(13)
C(25)	1433(8)	−3740(15)	5535(13)
C(26)	1597(7)	−2371(12)	5010(9)
C(27)	629(6)	1615(11)	1715(8)
C(28)	221(8)	2345(15)	783(10)
C(29)	−409(8)	3213(16)	716(10)
C(30)	−656(7)	3273(14)	1627(13)
C(31)	−262(7)	2546(14)	2552(11)
C(32)	373(6)	1695(11)	2614(9)
C(33)	1124(5)	−1271(11)	2023(7)
C(34)	384(6)	−1460(11)	1836(8)
C(35)	187(7)	−2862(14)	1993(9)
C(36)	697(8)	−3945(13)	2213(10)
C(37)	1439(7)	−3769(12)	2408(10)
C(38)	1644(6)	−2408(12)	2274(9)
C(39)	1695(5)	978(10)	554(7)
C(40)	1528(6)	230(12)	−149(9)
C(41)	1737(8)	658(15)	−1122(10)
C(42)	2110(9)	1825(17)	−1422(10)
C(43)	2269(7)	2582(15)	−750(11)
C(44)	2081(7)	2163(13)	242(9)
C(45)	3408(10)	5093(20)	4660(14)

of pyruvic acid thiosemicarbazone hydrazide (Hipt) (Fig. 1(a)) and water molecules. The packing is generated by hydrogen bonds. The geometry around the water molecule is a distorted tetrahedron involving three organic molecules through the following hydrogen bonds: $N(1)-H\cdots O(2)_w = 2.874(4)$, $N(4)-H\cdots O(2)_w = 2.930(4)$, $O(2)_w-H\cdots S(x, \frac{3}{2}-y, z-\frac{1}{2}) = 3.344(4)$, and $O(2)_w-H\cdots N(5)(1-x, 2-y, -z) = 2.856(4)$ Å (Fig. 1(b)). Weak N–H···S hydrogen bonds across centres of symmetry form dimer-like molecules similar to those found in other thiosemicarbazones [2].

The structure of **B**, H_2mpipt, consists of molecules linked through N–H···O hydrogen bonds to form ribbons along the *z* axis (Fig. 2). Intramolecular hydrogen bonds to N(3) are favoured by the orientation of N(1) and N(4) placed *cis* to N(3) ($N(1)\cdots N(3) = 2.632(4)$; $N(4)\cdots N(3) = 2.651(3)$ Å). In this compound the presence of numerous intramolecular interactions seems to prevent formation of N–H···S intermolecular bonds which appear to be important for biological activity and which were present in the crystal structure of methyl pyruvate thiosemicarbazone (Hmpt) [2] and of Hipt (**A**). The whole system is not completely planar and considering the torsion angles (see Table 7) it can

Table 5
Bond distances (Å) and angles (°) for **A** and **B**

Compound **A**			
S–C(1)	1.702(4)	O(1)–C(3)	1.234(4)
N(1)–C(1)	1.316(5)	N(4)–C(3)	1.335(5)
N(2)–N(3)	1.377(4)	N(4)–N(5)	1.419(4)
N(2)–C(1)	1.368(4)	C(2)–C(3)	1.505(5)
N(3)–C(2)	1.290(4)	C(2)–C(4)	1.494(6)
S–C(1)–N(1)	124.3(3)	N(3)–C(2)–C(3)	114.8(3)
S–C(1)–N(2)	117.5(3)	C(3)–C(2)–C(4)	118.6(3)
N(1)–C(1)–N(2)	118.3(3)	N(4)–C(3)–C(2)	115.4(3)
N(3)–N(2)–C(1)	118.1(3)	N(5)–N(4)–C(3)	122.4(3)
N(2)–N(3)–C(2)	117.0(3)	O(1)–C(3)–C(2)	121.5(3)
N(3)–C(2)–C(4)	126.5(4)	O(1)–C(3)–N(4)	123.1(4)
Compound **B**			
S–C(1)	1.672(3)	N(4)–C(4)	1.370(4)
N(1)–C(1)	1.323(4)	N(4)–N(5)	1.372(3)
N(2)–C(1)	1.368(4)	N(5)–C(5)	1.287(3)
N(2)–N(3)	1.366(3)	C(5)–C(6)	1.498(5)
N(3)–C(2)	1.291(4)	C(5)–C(7)	1.492(4)
C(2)–C(3)	1.493(4)	O(2)–C(7)	1.206(3)
C(2)–C(4)	1.498(4)	O(3)–C(7)	1.342(4)
O(1)–C(4)	1.223(4)	O(3)–C(8)	1.451(4)
S–C(1)–N(1)	124.4(2)	O(1)–C(4)–N(4)	123.8(3)
S–C(1)–N(2)	119.3(2)	N(5)–N(4)–C(4)	118.9(2)
N(1)–C(1)–N(2)	116.2(3)	N(4)–N(5)–C(5)	116.5(2)
N(3)–N(2)–C(1)	119.8(2)	N(5)–C(5)–C(7)	116.0(2)
N(2)–N(3)–C(2)	117.7(2)	N(5)–C(5)–C(6)	128.1(3)
N(3)–C(2)–C(3)	127.1(3)	C(6)–C(5)–C(7)	115.9(2)
C(3)–C(2)–C(4)	117.4(2)	O(3)–C(7)–C(5)	113.6(2)
N(3)–C(2)–C(4)	115.4(2)	O(2)–C(7)–C(5)	122.5(2)
N(4)–C(4)–C(2)	115.0(2)	O(2)–C(7)–O(3)	123.9(3)
O(1)–C(4)–C(2)	121.2(2)	C(7)–O(3)–C(8)	116.2(2)

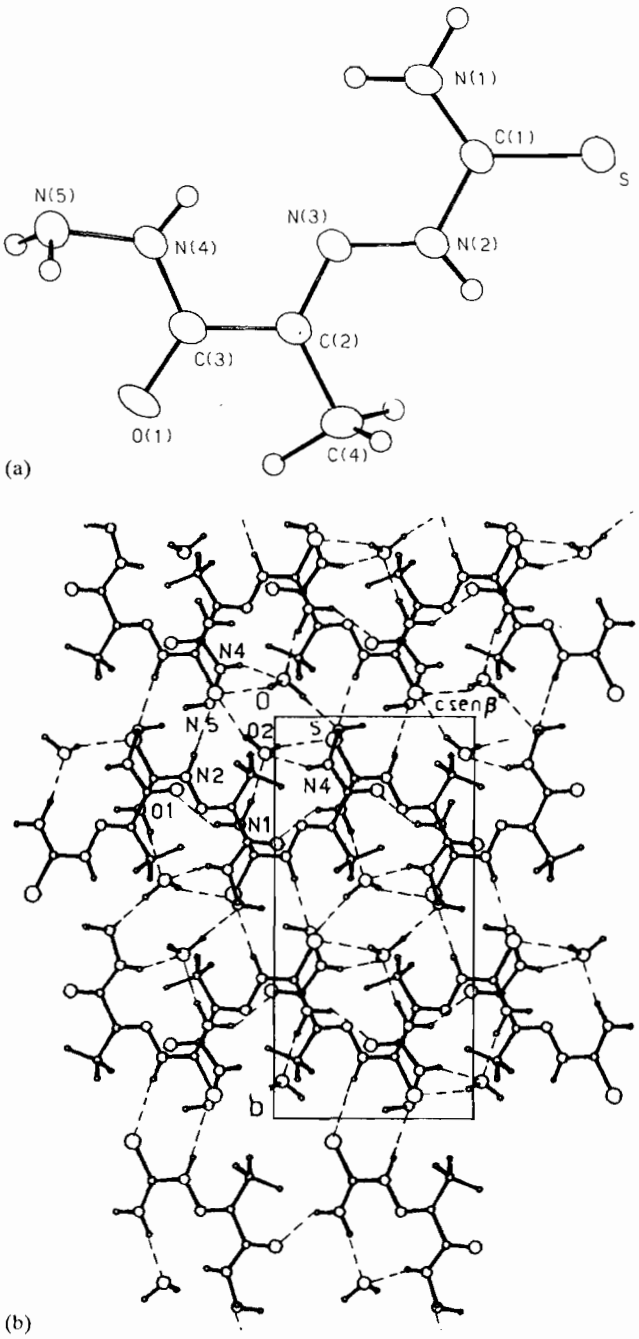


Fig. 1. (a) Single molecule of A. (b) Projection of compound **A** on the (1 0 0) plane.

be observed that two rotations of nearly 15 and 11°, respectively, about the C(2)–C(4) and C(5)–C(7) bonds, are present. Both compounds **A** and **B** show an *E* configuration about the C(2)–N(3) bond and **B** also about C(5)–N(5) bond (Fig. 3). The bond distances for **B** are reported in Table 5.

The structure of **C**, reported in Fig. 4, is composed of discrete molecular units of $[Cu(PPh_3)_2(H_2mpipt)Cl]$ and methyl alcohol of crystallization. The geometry around Cu(I) is a distorted tetrahedron and includes, as previously found in $[Cu(PPh_3)_2(dto)Cl]$ [11] and in

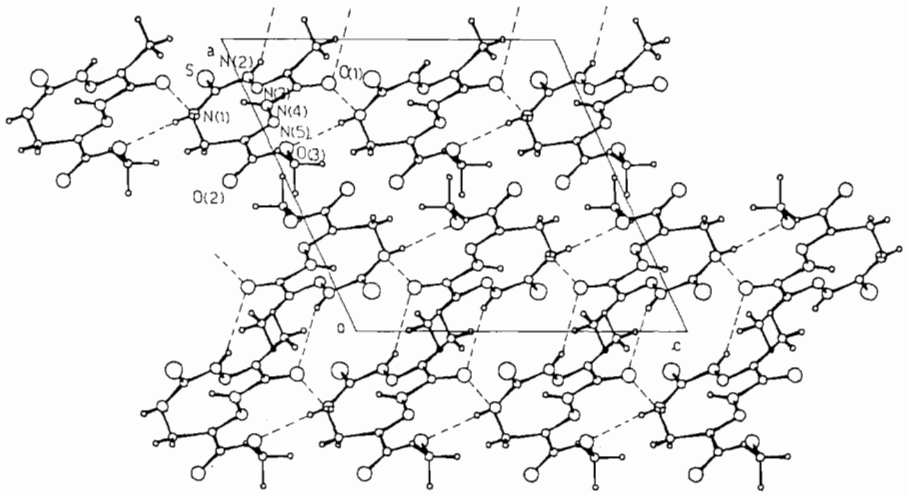


Fig. 2. The packing arrangement of compound **B** projected on the (0 1 0) plane.

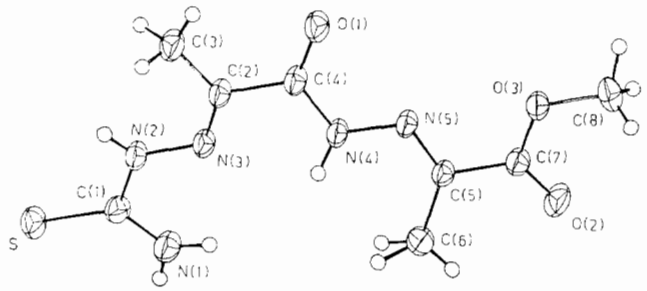


Fig. 3. ORTEP drawing of the molecule of H_2mpipt (**B**) with thermal ellipsoids at 50% probability level.

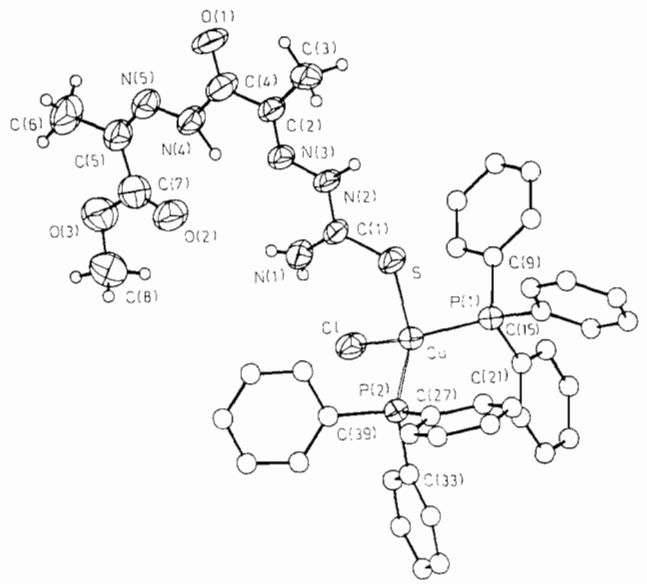


Fig. 4. Perspective view of complex **C** with thermal ellipsoids at 40% probability level.

$[Cu(PPh_3)_2(Hmpt)Cl]\cdot 0.5C_7H_8$ [3], a chlorine atom, the phosphorus atoms of the two PPh_3 molecules and a sulfur atom of the H_2mpipt moiety. This stoichiometry and coordination geometry, involving two triphenylphosphine molecules, seems to be favoured when rigid and nearly planar ligands such as dto (dithioxamide), Hmpt and H_2mpipt are employed, while it appears that using as ligand the bulky phenylpyridylthiourea [11], a different stoichiometry and coordination geometry (trigonal planar) is observed, and the complexes obtained are dimeric or polymeric.

The Cl–Cu–S, S–Cu–P, Cl–Cu–P angles show deviations (max. 9.3°) from the tetrahedral value, while the P–Cu–P angle is much larger (by 13.7°) owing to the interactions between the two bulky phosphine ligands. The dihedral angle between the CuPP and CuSCl planes is 96.0(1)°. The coordination distances (Cu–Cl = 2.365(3); Cu–S = 2.383(3); Cu–P(1) = 2.288(3); Cu–P(2) = 2.294(3) Å) agree well with the values found in other similar Cu(I) complexes containing two phosphine ligands [18].

Geometries within the phosphine ligands are standard [18]. The phosphorus–carbon bond lengths fall in the range 1.81–1.85 Å. The Cu–P–C angles are greater than tetrahedral, and the C–P–C angles, smaller.

The thiosemicarbazone moiety is neutral, monodentate and bonds through the sulfur atom. The configuration is *Z* about the C(5)–N(5) bond, while the uncoordinated molecule **B** shows an *E* configuration. This fact suggests that in solution two isomeric forms are present. The bond distances (Table 6) are similar to those found in the free ligand (compound **B**, Table 5) in spite of the change of configuration and confirm the presence of an extended π delocalization. The ligand conformation places O(2) close to N(4) and also in a suitable position for a further intramolecular hydrogen bond (N(4)–H···O(2) = 2.66(1) Å) which is not present in the free H_2mpipt. This increases the planarity of the whole system as compared to the uncoordinated molecule **B**. This can also be observed in Table 7 where the torsion angles of **B** and **C** are reported and compared. Other intramolecular hydrogen bonds are

Table 6
Selected bond distances (Å) and angles (°) for **C**

Cu–Cl	2.365(3)	N(2)–N(3)	1.37(1)
Cu–S	2.383(3)	N(3)–C(2)	1.29(1)
Cu–P(1)	2.288(3)	C(2)–C(3)	1.50(2)
Cu–P(2)	2.294(3)	C(2)–C(4)	1.47(2)
P(1)–C(9)	1.83(1)	O(1)–C(4)	1.22(2)
P(1)–C(15)	1.81(1)	N(4)–C(4)	1.38(2)
P(1)–C(21)	1.84(1)	N(4)–N(5)	1.34(1)
P(2)–C(27)	1.82(1)	N(5)–C(5)	1.29(2)
P(2)–C(33)	1.85(1)	C(5)–C(6)	1.50(2)
P(2)–C(39)	1.82(1)	C(5)–C(7)	1.52(2)
S–C(1)	1.68(1)	O(2)–C(7)	1.19(2)
N(1)–C(1)	1.31(2)	O(3)–C(7)	1.36(2)
N(2)–C(1)	1.37(1)	O(3)–C(8)	1.46(2)
		O(4)–C(45)	1.54(2)
P(1)–Cu–P(2)	123.2(1)	S–C(1)–N(1)	124.5(8)
Cl–Cu–P(2)	104.2(1)	S–C(1)–N(2)	117.4(8)
Cl–Cu–P(1)	109.8(1)	N(1)–C(1)–N(2)	118.0(9)
S–Cu–P(2)	111.5(1)	N(3)–N(2)–C(1)	117.2(8)
S–Cu–P(1)	99.7(1)	N(2)–N(3)–C(2)	118.5(9)
Cl–Cu–S	107.8(1)	N(3)–C(2)–C(3)	126.0(1.0)
Cu–S–C(1)	113.7(4)	C(3)–C(2)–C(4)	118.4(1.0)
Cu–P(1)–C(21)	118.4(4)	N(3)–C(2)–C(4)	115.6(1.0)
Cu–P(1)–C(15)	115.1(4)	N(4)–C(4)–C(2)	115.4(1.0)
Cu–P(1)–C(9)	114.0(4)	O(1)–C(4)–C(2)	122.1(1.1)
C(15)–P(1)–C(21)	102.5(5)	O(1)–C(4)–N(4)	122.4(1.1)
C(9)–P(1)–C(21)	101.6(5)	N(5)–N(4)–C(4)	121.1(1.0)
C(9)–P(1)–C(15)	103.1(5)	N(4)–N(5)–C(5)	121.2(1.0)
Cu–P(2)–C(39)	112.8(4)	N(5)–C(5)–C(7)	121.1(1.1)
Cu–P(2)–C(33)	114.8(3)	N(5)–C(5)–C(6)	119.0(1.2)
Cu–P(2)–C(27)	118.0(4)	C(6)–C(5)–C(7)	119.9(1.1)
C(33)–P(2)–C(39)	102.8(5)	O(3)–C(7)–C(5)	108.5(1.0)
C(27)–P(2)–C(39)	103.0(5)	O(2)–C(7)–C(5)	127.4(1.2)
C(27)–P(2)–C(33)	103.7(5)	O(2)–C(7)–O(3)	124.0(1.1)
		C(7)–O(3)–C(8)	116.4(1.0)

Table 7
Comparison of torsion angles (°) for **B** and **C**

	B	**C**
N(3)–N(2)–C(1)–N(1)	1.3(4)	0.1(1.4)
C(1)–N(2)–N(3)–C(2)	−179.7(3)	179.6(1.0)
C(4)–N(4)–N(5)–C(5)	−177.6(3)	178.2(1.3)
N(3)–C(2)–C(4)–N(4)	−15.0(4)	1.4(1.5)
N(3)–C(2)–C(4)–O(1)	164.1(3)	−174.5(1.1)
C(3)–C(2)–C(4)–O(1)	−14.1(4)	7.5(1.8)
C(3)–C(2)–C(4)–N(4)	166.8(3)	−176.6(1.0)
N(5)–C(5)–C(7)–O(3)	10.9(4)	−175.7(1.1)
N(5)–C(5)–C(7)–O(2)	−168.5(3)	7.0(2.1)
C(6)–C(5)–C(7)–O(2)	10.1(5)	−171.7(1.3)
C(6)–C(5)–C(7)–O(3)	−170.6(3)	5.5(1.6)
N(2)–N(3)–C(2)–C(4)	−178.3(3)	180.0(0.9)
N(4)–N(5)–C(5)–C(7)	178.5(2)	0.7(1.8)

N(4)–H···N(3) = 2.62(1), N(1)–H···N(3) = 2.61(1) and N(1)–H···Cl = 3.21(1).

The orientation of the thiosemicarbazone molecule relative to CuPP plane appears to be determined by hydrogen-bonding interaction between N(1) and the chlorine atom, typical of such Cu(I) compounds with sulfur containing ligands [3,11].

The packing is governed by the presence of a solvent molecule which forms hydrogen bonds involving a nitrogen atom of the same asymmetric unit N(2)–H···O(4) = 2.87(1) Å and a chlorine atom of an adjacent molecule O(4)–H···Cl (x, $y+1$, z) = 3.149(8) Å stacked in the b direction, forming chains running along this axis. The connection between the chains is ensured by two weak interactions C–H···O (C(43)–H···O(1) ($1-x$, $1-y$, $-z$) = 3.41(2); C(8)–H···O(1) (x, $y-1$, z) = 3.48(2) Å) and by van der Waals contacts.

3.2. Proton, carbon and nitrogen NMR spectra of H_2piript

The signals shown in ^{1}H, ^{13}C and ^{15}N NMR spectra of H_2piript ligand are listed in Table 8 and in Scheme 2 the corresponding atomic labels are reported.

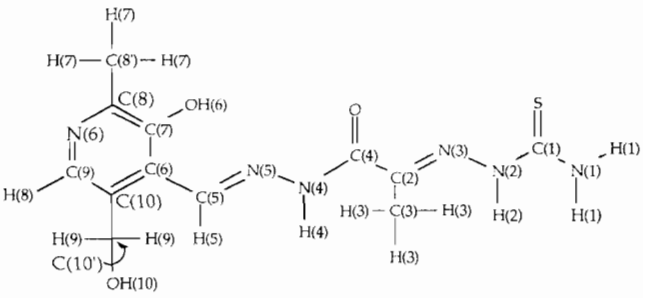
At room temperature, the resonances of the O–H(6) and N(4)–H(4) groups are identical (12.24 ppm) while the signal due to N(2)–H(2) is at 10.70 ppm downfield with respect to that of the same proton in Hipt (10.38 ppm). All these three singlets disappear when D_2O is added to the sample.

In Fig. 5(a, b, c) is shown a series of variable temperature ^{1}H NMR spectra which were recorded for

Table 8
^{1}H, ^{13}C and ^{15}N NMR data of the ligand H_2piript

Label	Integral	δ (ppm)	Label	δ (ppm)	Label	δ (ppm)
H(4)	1	12.24(s, br)	C(1)	179.49	N(6)	212(s)
H(6)	1	12.24(s, br)	C(4)	160.36	N(5)	207(s)
H(2)	1	10.70(s)	C(7)	150.47	N(3)	191(s)
H(5)	1	8.87(s)	C(5)	147.38	N(4)	57(d)
H(1)	1	8.82[a]	C(8)	145.97	N(2)	52(d)
H(1)	1	8.75[a]	C(2)	140.16	N(1)	4(t)
H(8)	1	7.94(s)	C(9)	138.49		
H(10)	1	5.44(t)	C(10)	132.13		
H(9)	2	4.62(d)	C(6)	120.13		
H(7)	3	2.41(s)	C(10′)	58.80		
H(3)	3	2.16(s)	C(8′)	18.72		
			C(3)	11.46		

[a]Broad pseudo-singlet.



Scheme 2.

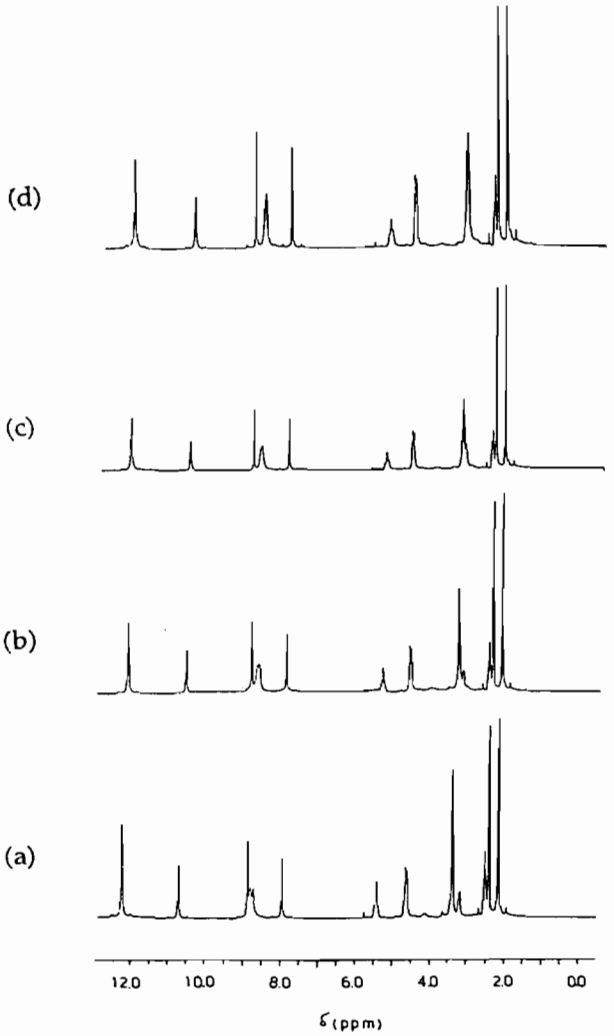


Fig. 5. ^{1}H NMR spectra of H_2piript at (a) 298, (b) 308, (c) 315 and (d) 323 K. (d) Shows the spectrum at the coalescence temperature for the NH_2 signals.

the H_2piript ligand in DMSO-d_6 solution. These exhibited two broadened pseudo-singlets for the NH_2 protons indicating hindered rotation about the C(1)–N(1) bond [19–24], due to its partial double-bond character; the coalescence temperature for these NH_2 signals is at 323 K (see Fig. 5(d)). The chemical shift of NH_2 protons was dependent on concentration, suggesting the absence of intramolecular hydrogen bonding.

The triplet at 5.44 ppm (^2J(HH) = 5.3 Hz) is due to a coupling of the O–H(10) group with the two protons H(9) whose resonance is at 4.62 ppm. The methyl groups show resonance at different fields: the methyl group bonded to the aromatic ring of the ligand is at 2.41 ppm, while the other one is at 2.16 ppm.

In the ^{13}C NMR spectrum the signals relative to carbons from C(6) to C(10) of the aromatic ring of the ligand are difficult to assign, because they all fall in a very narrow region of the spectrum and are substantially pH dependent [25,26]. The resonances at

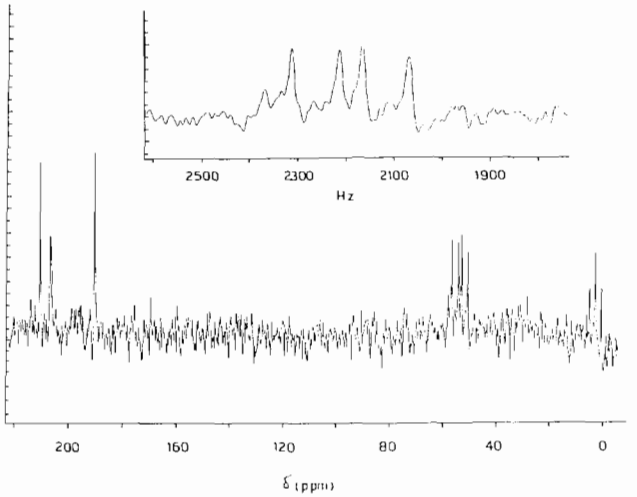


Fig. 6. ^{15}N NMR spectrum obtained in natural abundance of H_2piript. The insert shows a detail of the spectrum where the resonances of the N(4)–H(4) (^1J(NH) = 100 Hz) and N(2)–H(2) (^1J(NH) = 93 Hz) groups, respectively, are compared.

11.46 and 18.72 ppm are assignable to C(3) and C(8′), respectively, while the carbon C(10′) is at 58.80 ppm.

In the ^{15}N NMR spectrum, not decoupled from the proton of the ligand, and obtained in natural abundance (see Fig. 6), the resonances are shown in the range 0–220 ppm. The external reference is formamide.

The N(2)–H(2) (resonant at 52 ppm, ^1J(NH) = 93 Hz) and the C(5)=N(5) groups (at a lower field than C(2)=N(3)) behave similarly to the N–H and C=N groups of a series of polyfunctional molecules containing the fragment $R^1HC{=}N{-}NH{-}C(=O){-}R^2$ (R^1 = 2-(5-formyl)pyrrolyl and 2-(5-formyl)furanyl, R^2 = 2-furanyl, 2-pyridyl, 2-hydroxyphenyl and 2-thienyl) [27] which show the nitrogen of the NH group in the range 50–60 ppm with ^1J(NH) = 93–95 Hz. The other doublet at 57 ppm (^1J(NH) = 100 Hz) is attributable to N(4)–H(4). The N(6) nitrogen of the pyridinic ring shows a resonance at 212 ppm.

The presence of the signal H(6) at 12.24 ppm in the ^{1}H NMR of the phenolic group and the single resonance of the pyridine N(6) in the ^{15}N NMR is in agreement with the neutral form of the ligand.

4. Conclusions

It is important to note that the pyridoxal moiety has been found in the zwitterion form in the crystalline free pyridoxal thiosemicarbazone [28] and its metal complexes [1,4], while the ^{1}H NMR spectrum of H_2piript, dissolved in DMSO, reveals the existence of the neutral form. This fact could be attributed to the aprotic nature of DMSO with respect to that of the other solvents (H_2O, CH_3OH or C_2H_5OH) employed in the isolation of the above-mentioned crystalline compounds.

The biological activity of the above-mentioned thiosemicarbazones is a function of the parent aldehyde or ketone and of the metal coordination type [2]. At this moment induction differentiation experiments on Friend erythroleukemia cells (FLC), involving the free ligands and the complexes studied here, are in progress at the Istituto di Patologia Speciale Medica dell'Università di Parma. Preliminary results indicates that only the Cu(I) complex **C** acts as a cellular differentiation modulator.

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