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New Zinc Complexes bearing κ^2-Heteroscorpionate Ligands: Influence of Second-Sphere Bonding Interactions on Reactivity and Properties

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New zinc complexes (LOMe)$ZnCl_2$ (**1**) and (LOH)$ZnCl_2$(**2**) of the heteroscorpionate ligands 1-[(3,5-di-*tert*-butyl-2-methoxyphenyl)(3,5-dimethyl-pyrazol-1-yl)methyl)]-3,5-dimethyl-pyrazole (LOMe) and 2,4-di-*tert*-butyl-6-[bis(3,5-dimethyl-pyrazol-1-yl)methyl]phenol (LOH) have been synthesized. The X-ray molecular structure of **2** was reported and compared with the one of the iron(II) complex (LOH)FeI_2 (**3**). The complexes **2**−**3** adopt a tetrahedral structure in the solid state in which the LOH ligand is κ^2-coordinated to the metal via the imino nitrogens of the two pyrazolyl rings. The hydroxyl phenyl group is not coordinated to the metal but found to be involved in an intermolecular hydrogen bond. The solution structures of **1** and **2** are consistent with this tetrahedral C_S symmetric geometry. Dilution and $^1H-^1H$ Nuclear Overhauser Effect Spectroscopy (NOESY) experiments revealed that the free ligands LOMe and LOH are involved in intra- and intermolecular hydrogen bonding interactions. Coordination of LOMe and LOH to $ZnCl_2$ was investigated by NMR titration methods. Association constants (K_a) of $(8.6 \pm 0.4) \times 10^2$ M^{-1} and $(7.8 \pm 0.3) \times 10^2$ M^{-1} were obtained in methanol/water solutions (95:5) for LOMe and LOH, respectively. Coordination of bis(3,5-dimethyl-pyrazol-1-yl)methane (bpm) ligand to $ZnCl_2$ is weaker, as evidenced by the lower value of the association constant $(5.3 \pm 0.3) \times 10^2$ M^{-1}. When bpm was added to solutions of **1** or **2**, an equilibrium shifted toward the (bmp)$ZnCl_2$ species was observed. The thermodynamic parameters for this reaction were determined by VT NMR analysis. The optical properties of the ligands (LOMe, LOH) and of the corresponding zinc complexes **1** and **2** were also investigated by means of UV−vis and fluorescence spectroscopy to assess the potential use of these ligands as fluorescent sensors for Zn^{2+} detection.

Introduction

The investigation of the second-sphere bonding interactions of coordination compounds is an emerging area of research in the scientific literature: non-coordinating active-sites can have important role in the molecular recognition and activation processes involving catalysts. These interactions have been exploited to optimize the recognition process between the substrate and the catalyst[1] and to impart or to improve enantioselectivity to the catalyst itself.[2] It has also been proposed that these interactions may be solely responsible for the activation process without the necessity of substrate-metal interactions in analogy with enzymatic and organo catalysis.[3] The presence of functionalities suitable for intermolecular noncovalent interactions in the second coordination sphere may also lead to self-aggregation of transition-metal complexes.[4] Among these weak noncovalent interactions, hydrogen bonding (HB) is probably the most important.[5] Indeed it strongly contributes to determine structure and reactivity of coordination compounds.[6]

We were interested in exploring the coordination behavior of neutral bispyrazolylmethane ligands containing HB donor or acceptor sites toward Zinc ion. Zinc is the second most abundant transition-metal ion in the human body and serves as active site of several metalloproteins found in nature such as carboxypeptidase A, thermolysin, and leucine aminopeptidase.[7] Their active sites exhibit a common structural motif

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composed of a pseudo-tetrahedral Zinc center in combination with nitrogen, oxygen, and/or sulfur donors.[8] To understand how the $[N_xO_yS_z]$ donor array modulates the chemistry around the Zinc center, a large number of small synthetic analogues to these Zinc metalloproteins have been synthesized and characterized in the past years.[9]

In particular we considered the 1-[(3,5-di-*tert*-butyl-2-methoxyphenyl)(3,5-dimethyl-pyrazol-1-yl)methyl]-3,5-dimethyl-pyrazole (LOMe) and the corresponding hydroxyl derivative 2,4-di-*tert*-butyl-6-[bis(3,5-dimethyl-pyrazol-1-yl)-methyl]phenol (LOH) in which the methoxy-phenyl and the hydroxy-phenyl group can act as HB acceptor and donor site, respectively. Because of the spatial arrangement of the donor atoms, these ligands can be considered heteroscorpionate ligands[10] in which the bis(pyrazolyl)methane skeleton exhibits R′ substituent, $HC(pz)_2R'$, such as , for example, phenol,[11] thiophenol,[12] carboxyl,[13] or dithiocarboxyl group.[14] These ligands have been widely utilized for developing metalloprotein models; in fact, they can be considered as synthetic models of the 2-His-1-carboxylate triad.

Herein we describe the synthesis, the solution properties, and the reactivity of new Zinc complexes bearing the LOMe and LOH ligands. The supramolecular structures of both ligands and complexes were investigated in solution by means of NMR experiments focusing the attention on the role of the pendant methoxy/hydroxy-phenyl group. The peculiar behavior of these complexes was compared with that of an analogous Zinc complex bearing a bis-pyrazolyl ligand lacking the pendant methoxy/hydroxy-phenyl group.

Moreover we describe the solution and the optical properties of these two heteroscorpionate ligands (LOH, LOMe) whose overall characteristics (e.g., chemical stability and easy of synthesis) make them potential candidates for the development of fluorescent-based Zn^{2+} sensors.

Experimental Section

General Procedures. All experiments were performed under nitrogen atmosphere using standard Schlenk-type techniques or MBraun glovebox. Toluene, hexane, and tetrahydrofuran (THF) were distilled over sodium/benzophenone; dichloromethane was distilled over CaH_2. 2,4-Di-*tert*-butyl-6-[bis(3,5-dimethyl-pyrazol-1-yl)methyl]phenol (LOH) and bis-(3,5-dimethyl-pyrazol-1-yl)methane (bpm) were prepared as previously reported.[15] C_6D_6 and CD_2Cl_2 were degassed by three successive "freeze-pump-thaw" cycles, dried over molecular sieves (4 Å) and stored in a glovebox prior to use. NMR spectra were recorded on a Bruker AM300 and Bruker AVANCE 400 operating at 300 and 400 MHz for ^1H, respectively. The ^1H and ^{13}C chemical shifts are referred to $SiMe_4$ using the residual protio impurities of the deuterated solvents. Mass spectrometry analyses were carried out using a Micromass Quattro micro API triple quadrupole mass spectrometer equipped with an electrospray ion source (Waters, Milford, MA).

Synthesis of 1-((3,5-Di-*tert*-butyl-2-methoxyphenyl)(3,5-dimethyl-pyrazol-1-yl)methyl)-3,5-dimethyl-pyrazole (LOMe). A solution of LOH (900 mg, 2.2 mmol) in acetone (80 mL) was added to a suspension of K_2CO_3 (910 mg, 6.6 mmol) in acetone (80 mL). The resulting mixture was refluxed under stirring. Iodomethane (2.1 g, 11 mmol) was added dropwise by a siringe, and the resulting mixture refluxed for 3 h. All volatiles were then removed in vacuo, and the product was extracted with water and diethylether. The organic layer was dried over Na_2SO_4, and the solvent removed by distilling in vacuo. Recrystallization of the crude product from acetone afforded LOMe as a colorless bright microcrystalline solid. Yield: 620 mg (67%). Anal. Calcd for $C_{26}H_{38}N_4O$: C, 73.89; H, 9.06; N, 13.26. Found: C, 73.94; H, 9.17; N, 13.19. ^1H NMR (400 MHz, CD_2Cl_2, 25 °C): δ 1.19 (s, 9H, 5-^{t}*Bu*-Ph), 1.38 (s, 9H, 3-^{t}*Bu*-Ph), 2.05 (s, 6H, 5-CH_3-Pz), 2.17 (s, 6H, 3-CH_3-Pz), 3.44 (s, 3H, OCH_3), 5.86 (s, 2H, Pz-*H*), 6.94 (d, 1H, *J* = 2.4 Hz, 6-Ph), 7.36 (d, 1H, *J* = 2.4 Hz, 4-Ph), 7.61 (s, 1H, -C*H*-). $^{13}C\{^1H\}$ NMR data (100 MHz, CD_2Cl_2, 25 °C): 11.5, 14.1, 31.4, 31.5, 34.7, 35.5 61.9, 70.6, 106.9, 125.1, 125.5, 129.7, 140.5, 141.8, 145.7, 148.1, 155.4. MS (ESI acetonitrile): *m*/*z* (%) 445.8 (100) $[M^+ + Na]$, 327.7 (18) $[M^+ - ZnCl_2 - 3,5\text{-}Me_2\text{-}pz]$.

Synthesis of (LOMe)$ZnCl_2$ [LOMe = 1-((3,5-Di-*tert*-butyl-2-methoxyphenyl)(3,5-dimethyl-pyrazol-1-yl)methyl)-3,5-dimethyl-pyrazole] (1). A solution of LOMe (63 mg, 0.150 mmol) in dichloromethane (1.0 mL) was added to a suspension of $ZnCl_2$ (20 mg, 0.150 mmol) in dichloromethane (1.0 mL). The mixture was stirred overnight. All volatiles were then removed in vacuo. Recrystallization of the crude product from dichloromethane-pentane 1:1 (v/v) afforded **1** as a bright microcrystalline solid. Yield: 60 mg (72%). Anal. Calcd for $C_{26}H_{38}N_4OZnCl_2$: C, 56.07; H, 6.88; N, 10.06. Found: C, 56.23; H, 7.01; N, 9.98. ^1H NMR (400 MHz, CD_2Cl_2, 25 °C): δ 1.22 (s, 9H, 5-^{t}*Bu*-Ph), 1.38 (s, 9H, 3-^{t}*Bu*-Ph), 2.48 (s, 6H, 5-CH_3-Pz), 2.50 (s, 6H, 3-CH_3-Pz), 3.33 (s, 3H, OCH_3), 6.18 (s, 2H, Pz-*H*), 6.42 (d, 1H, *J* = 2.4 Hz, 6-Ph), 7.49 (d, 1H, *J* = 2.4 Hz, 4-Ph) 7.50 (s, 1H, -C*H*-). $^{13}C\{^1H\}$ NMR data (100 MHz, CD_2Cl_2, 25 °C): δ 11.9, 14.3, 31.3, 32.2, 35.1, 36.1 63.5, 66.4, 108.5, 123.5, 128.1, 129.6, 142.8, 144.8, 147.7, 154.9, 155.1. MS (ESI acetonitrile): *m*/*z* (%) 521.6 (50) $[M^+ - Cl]$, 445.7 (50) $[M^+ - ZnCl_2 + Na]$, 327.7 (100) $[M^+ - ZnCl_2 - 3,5\text{-}Me_2\text{-}pz]$.

Synthesis of (LOH)$ZnCl_2$ [LOH = 2,4-di-*tert*-butyl-6-(bis-(3,5-dimethyl-pyrazol-1-yl)methyl)phenol] (2). A solution of LOH (61 mg, 0.150 mmol) in dichloromethane (1.0 mL) was added to a suspension of $ZnCl_2$ (20 mg, 0.150 mmol) in dichloromethane (1.0 mL). The mixture was stirred overnight. A bright crystalline solid was isolated after cooling of the filtrate solution at −20 °C. Yield: 55 mg (68%). The crystalline sample spontaneously and slowly releases dichloromethane molecules clathrated in the lattice. Anal. Calcd for $C_{25}H_{36}N_4OZnCl_2$: C, 55.31; H, 6.68; N, 10.32. Found: C, 55.65; H, 6.89; N, 10.15. ^1H NMR (400 MHz, CD_2Cl_2, 25 °C): δ 1.22 (s, 9H, 5-^{t}*Bu*-Ph), 1.40 (s, 9H, 3-^{t}*Bu*-Ph), 2.48 (s, 6H, 5-CH_3-Pz), 2.51 (s, 6H, 3-CH_3-Pz), 5.15 (s, 2H, Pz-*H*), 6.12 (s, 1H, -O*H*), 6.54 (d, 1H, *J* = 2.4 Hz, 6-Ph), 7.34 (d, 1H, *J* = 2.4 Hz, 4-Ph), 7.59 (s, 1H, -C*H*-). $^{13}C\{^1H\}$ NMR data (100 MHz, CD_2Cl_2, 25 °C): δ 11.9, 14.3, 30.8, 31.4, 34.3, 34.9, 66.0, 107.9, 122.5, 123.3, 126.8, 134.5, 144.2, 145.1, 149.6, 154.8. MS (ESI acetonitrile): *m*/*z*

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Table 1. Crystallographic Data

	(LOH)ZnCl$_2$ (**2**)	(LOH)FeI$_2$ (**3**)
formula	$C_{25}H_{36}Cl_2N_4OZn\cdot 2(CH_2Cl_2)$	$C_{25}H_{36}FeI_2N_4O$
M	714.70	718.23
space group	$P2_1/c$	$P2_1/c$
crystal system	monoclinic	monoclinic
a/Å	8.9520(2)	12.0259(2)
b/Å	19.7884(5)	19.3743(4)
c/Å	19.6539(5)	14.5478(3)
β/deg	90.510(1)	112.254(1)
U/Å^3	3481.5(2)	3137.1(1)
Z	4	4
T/K	295	295
D_c/g cm^{-3}	1.364	1.521
F(000)	1480	1416
μ(Mo Kα)/cm^{-1}	11.92	24.70
measured reflections	23888	26090
unique reflections	6737	6780
R$_{int}$	0.0663	0.0362
obs. refl.ns [$I \geq 2\sigma(I)$]	4865	4386
$\theta_{min} - \theta_{max}$/deg	3.26−26.00	2.82−27.00
hkl ranges	−11,11;−24,24;−24,24	−14,15;−22,24;−17,18
$R(F^2)$ (obs.refl.ns)	0.0754	0.0456
$wR(F^2)$ (All Refl.ns)	0.2248	0.1126
no. variables	366	312
goodness of fit	1.042	1.046
$\Delta\rho_{max}$; $\Delta\rho_{min}$ /e Å^{-3}	0.97; −0.90	1.07; −1.25

(%) 529.6 (38) [M$^+$ − HCl + Na], 507.6 (8) [M$^+$ − Cl], 431.7 (84) [M$^+$ − ZnCl$_2$ + Na], 335.7 (100) [M$^+$− HCl −ZnCl − 3,5-Me$_2$-pz + Na].

Synthesis of (LOH)FeI$_2$ [LOH = 2,4-Di-*tert*-butyl-6-(bis(3,5-dimethyl-pyrazol-1-yl)methyl)phenol] (3). A solution of LOH (500 mg, 1.2 mmol) in dichloromethane (25 mL) was added to a suspension of FeI$_2$ (380 mg, 1.2 mmol) in dichloromethane (25 mL). The mixture was stirred overnight. Recrystallization of the crude product from diethylether/pentane afforded **3** as a pale brown microcrystalline solid. Yield: 390 mg (38%). Anal. Calcd for $C_{25}H_{36}N_4OFeI_2$: C, 41.81; H, 5.05; N, 7.80. Found: C, 41.99; H, 5.21; N, 7.67. μ_{eff} = 3.7 μ_B (CD_3CN, room temperature (rt)).

NMR Titrations. Dilution ^{1}H NMR titrations for LOH were performed at 25 °C in C_6D_6. A total of 16 spectra were registered using a ligand concentration in the range of 0.200−0.005 M.

Speciation of ZnCl$_2$/LOR (R = H; Me) system was investigated in CD_3OD-D_2O 95:5 (v/v) mixture at 25 °C by collecting ^{1}H NMR spectra of a 0.0050 M ligand solution titrated with aliquots of a 0.10 M ZnCl$_2$ solution. The equilibrium between LOR and (LOR)ZnCl$_2$ occurs in rapid exchange on the NMR time scale. The variation of the chemical shift ($\Delta\delta$) for the resonance of 2-tBu group of the ligand (Scheme 2) was monitored during the titration. The association constant (K_a) was determined by fitting the plot of $\Delta\delta$ versus [ZnCl$_2$]/[LOR].[16] Complexation of ZnCl$_2$ with bpm ligand was studied in the same experimental conditions and with the same procedure.

Absorbance and Fluorescence Measurements. Absorption spectra were recorded on a Perkin-Elmer Lambda EZ201 instrument, using 1 cm quartz cell and PESSW 1.2 Revision E software. Fluorescence spectra were recorded on a Cary Eclipse Spectrophotometer in a 10 × 10 mm airtight quartz fluorescence cuvette (Hellma Benelux bv, Rijswijk, Netherlands). Both absorption and fluorescence measurements were performed at room temperature.

Crystal Structure Determinations. The crystal data of compounds (LOH)ZnCl$_2$ (**2**) and (LOH)FeI$_2$ (**3**) were collected at room temperature using a Nonius Kappa CCD diffractometer with graphite monochromated Mo Kα radiation. The data sets were integrated with the Denzo-SMN package[17] and corrected for Lorentz, polarization and absorption effects (SORTAV).[18] The structure was solved by direct methods (SIR97)[19] and refined using full-matrix least-squares with all non-hydrogen atoms anisotropically and hydrogens included on calculated positions, riding on their carrier atoms. The asymmetric unit of complex (LOH)ZnCl$_2$ (**2**) contains two solvent molecules of CH_2Cl_2 which display some disorder. Furthermore, the 2-tBu group in complex (**2**) was found disordered and the three methyl groups were refined isotropically over two positions with occupation factors of 0.60 and 0.40, respectively.

All calculations were performed using SHELXL-97[20] and PARST[21] implemented in the WINGX[22] system of programs. The crystal data are given in Table 1. Selected bond distances and angles are given in Table 2.

Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 735023−735024. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, Union Road, Cambridge, CB2 1EZ, U.K. [fax: (+44)1223−336033, e-mail: deposit@ccdc.cam.ac.uk].

Results and Discussion

The heteroscorpionate ligand [2,4-di-*tert*-butyl-6-(bis(3,5-dimethyl-pyrazol-1-yl)methyl]phenol (LOH) was prepared according to literature procedures based on the reaction of 1,1′-carbonyldipyrazoles with carbonyl compounds catalyzed by CoCl$_2$.[15] The corresponding methylether derivative 1-[(3,5-di-*tert*-butyl-2-methoxyphenyl)(3,5-dimethyl-pyrazol-1-yl)methyl]-3,5-dimethyl-pyrazole (LOMe) was obtained by

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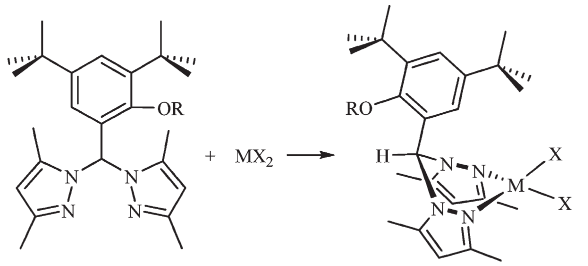
Table 2. Selected Geometrical Parameters (Å and deg)

(LOH)ZnCl$_2$ (**2**)		(LOH)FeI$_2$ (**3**)	
	Distances		
Zn1−Cl1	2.230(2)	Fe1−I1	2.5843(8)
Zn1−Cl2	2.219(2)	Fe1−I2	2.5763(7)
Zn1−N1	2.038(4)	Fe1−N1	2.063(3)
Zn1−N3	2.040(4)	Fe1−N3	2.087(3)
	Angles		
Cl1−Zn1−Cl2	112.74(6)	I1−Fe1−I2	117.71(3)
Cl1−Zn1−N1	114.6(1)	I1−Fe1−N1	114.6(1)
Cl1−Zn1−N3	114.6(1)	I1−Fe1−N3	114.4(1)
Cl2−Zn1−N1	110.7(1)	I2−Fe1−N1	107.6(1)
Cl2−Zn1−N3	109.7(1)	I2−Fe1−N3	108.4(1)
N1−Zn1−N3	92.9(2)	N1−Fe1−N3	90.8(1)
	Torsion Angles		
C1−C6−C7−N2	76.6(5)	C1−C6−C7−N2	158.1(3)
C1−C6−C7−N4	−157.0(4)	C1−C6−C7−N4	−74.8(4)
	Dihedral Angle		
N1−N2−C8−C9−C10$\hat{}$			
N3−N4−C13−C14−C15	138.0(2)	N1−N2−C8−C9−C10$\hat{}$	
N3−N4−C13−C14−C15	134.3(2)		
	O−H···X−M H-bond*		
O1···Cl1(x−1, y, z)	3.246(4)	O1···I1(1−x, y−1/2, 3/2−z)	3.528(3)
H1···Cl1(x−1, y, z)	2.61	H1···I1(1−x, y−1/2, 3/2−z)	3.01
O1−H1···Cl1	125	O1−H1···I1	118
H1···Cl1−Zn1	114	H1···I1−Fe1	122

* The O−H distances were normalized.

Scheme 1



M = Zn, R=Me, X = Cl (**1**)
M = Zn, R=H, X = Cl (**2**)
M = Fe, R=H, X = I (**3**)

reaction of LOH with iodomethane in the presence of potassium carbonate.

The complexes (LOR)ZnCl$_2$ [R = Me (**1**), H (**2**)] were prepared in high yield by reacting ZnCl$_2$ with the neutral ligand in 1:1 molar ratio in dichloromethane (Scheme 1). The two complexes are soluble in halogenated or oxygenated solvent and slightly soluble in aromatic solvents.

As far as the coordination capabilities of the ligands are concerned, the two pyrazolyl ring and the phenol group could provide the N$_2$O donor set required for a hypothetical pentacoordinate complex. Nevertheless, the reaction of these heteroscorpionate ligands with ZnCl$_2$ led to mononuclear tetrahedral complexes in which the heteroscorpionate ligand resulted κ^2-coordinated to the metal center through the imino nitrogen atoms of the two pyrazolyl rings. Iron(II) and Zinc(II) have similar atomic radii; therefore, one can expect that the reaction of Zinc and Iron salts with a given ligand can result in the same structural motif. For comparative purpose we investigated the reaction of LOH with FeI$_2$: the same coordination mode was observed for the corresponding (LOH)FeI$_2$ (**3**) complex.

Solid-State Structures. The Oak Ridge Thermal Ellipsoid Plot (ORTEP)[23] views of the complexes **2** and **3** are shown in Figures 1 and 2. The Zn(II) in **2** is tetrahedrally κ^2-*N*,*N* coordinated to two pyrazolyl rings of LOH and to two chloride ligands. The distortion of the Zn(II) from the ideal tetrahedral coordination is mainly determined by the N−Zn−N angle of 92.9(2)° constrained by the bite of the *bis*-chelating LOH ligand. The Zn−Cl distances of 2.230(2) and 2.219(2) Å and Zn−N (pyrazole) ones of 2.038(4) and 2.040(4) Å are in agreement with the values found in similar complexes.[24]

The Fe(II) tetrahedral coordination in **3** is similar to that exhibited by Zn(II) of the previous complex, with Fe(II) κ^2-*N*,*N* bound to two pyrazolyl rings of LOH ligand and to two iodide ligands. The distortion of the tetrahedral Fe(II) is mainly determined by the N−Fe−N angle of 90.8(1)° constrained by the bite of the bis-chelating LOH ligand.

In both complexes (**2**) and (**3**) the metal bonded halogen atoms Cl and I are strongly polar and good acceptors of HB.[25,6] Accordingly, the uncoordinated hydroxy phenyl

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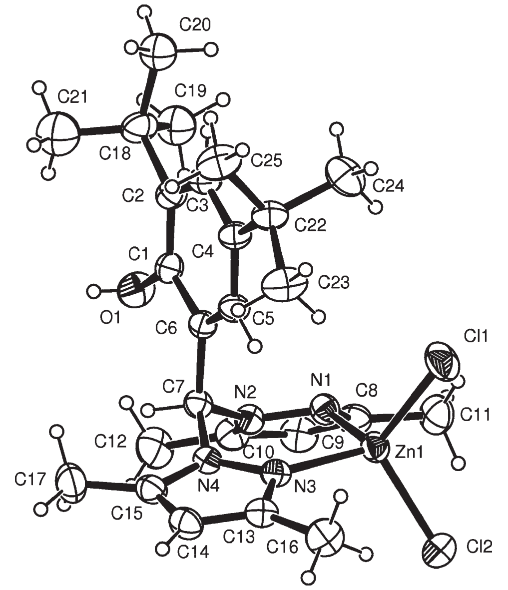

Figure 1. ORTEP view of the complex (LOH)ZnCl$_2$ (**2**) showing the thermal ellipsoids at 30% probability level.

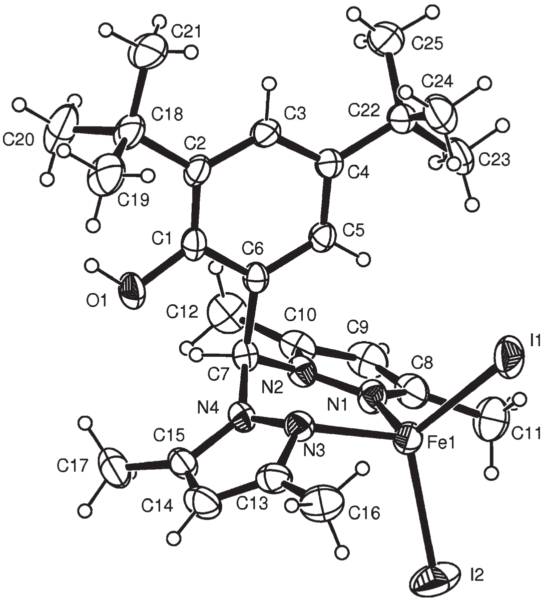

Figure 2. ORTEP view of the complex (LOH)FeI$_2$ (**3**) showing the thermal ellipsoids at 30% probability level.

groups are weakly hydrogen bonded to adjacent molecules with Cl···H and I···H distances of 2.61 and 3.01 Å shorter than the sums of van der Waals radii of 2.95 and 3.18 Å[26] (Table 2, Figures 3). Furthermore, the H···X−M angles of 114 and 122° are in agreement with the hypothesis that the O−H···X−M hydrogen bonds in crystals are almost exclusively donated roughly perpendicular to the M−X bond.[27]

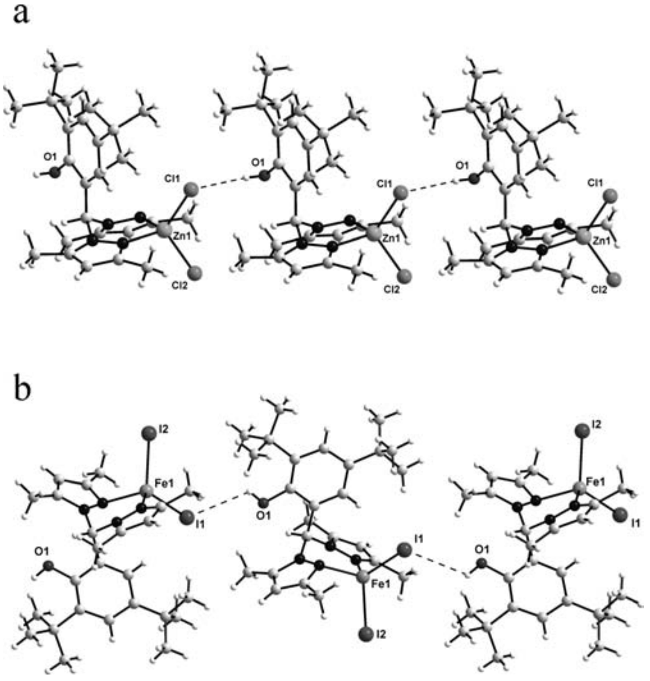

Figure 3. Diagram of molecules of complexes (LOH)ZnCl$_2$ (**2**) and (LOH)FeI$_2$ (**3**) to illustrate the O−H···Cl (a) and O−H···I (b) H-bond interactions.

These heteroscorpionate ligands were mainly found as tri- or bidentate anionic ligands which coordinate metal centers through one or two pyrazolyl nitrogens and the oxygen of the phenolate group.[24,28] Conversely, the complexes reported in the present study represent a class of compounds where the phenolic group of the heteroscorpionate ligand is not involved in the coordination mode with the central metallic core.[11,29]

Solution Properties. The solution structures of LOR (R = Me, H) ligands and complexes **1**−**2** were investigated by means of NMR spectroscopy. The assignments of the proton resonances were based on previously reported data[28] and corroborated by means of mono- and bidimensional NMR experiments.

Dilution and ^{1}H−^{1}H Nuclear Overhauser Effect Spectroscopy (NOESY) experiments were carried out to discriminate the presence of intra- or intermolecular HB interactions. The chemical shift of the proton resonances did not change in dilution experiments of LOMe in C_6D_6 from 200 to 5 mM ($\Delta\delta_{CH} < 0.01$) indicating that no intermolecular interaction occurs. NOESY of LOMe (in C_6D_6 solution) showed, in addition to the interactions of the neighboring protons, a strong contact between the aliphatic methine proton (CH, Scheme 2) and the methoxy group (Figure 4). This suggested that the phenyl ring has a preferred orientation in which the MeO group is roughly opposite to the pyrazol rings. This conformation is probably stabilized by a labile intramolecular HB between the acidic CH proton and the Lewis basic methoxy group. However, the reorientation of the phenyl ring is not hampered, and other conformations for the molecule are possible as indicated by the presence of a

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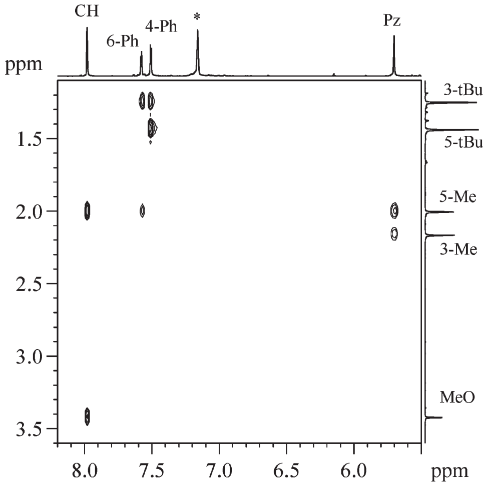
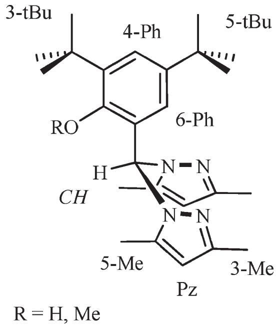


Figure 4. Section of $^1H-^1H$ NOESY spectrum of LOMe (C_6D_6, rt, 400 MHz). The proton resonances are labeled according to the Scheme 2.

Scheme 2



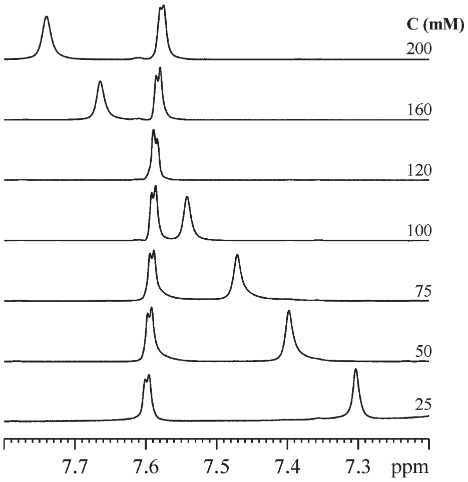
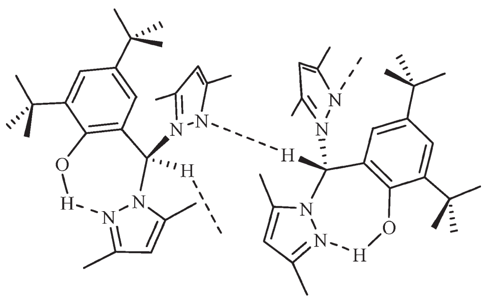


Figure 5. Stacking plot of partial ^1H NMR spectra of LOH in C_6D_6 at different concentrations. The drift of the aliphatic methine proton (CH) resonance is shown.

Scheme 3



weaker contact between the 6-Ph and the 5-Me-Pz protons (see Scheme 2).

In the X-ray structures of neutral heteroscorpionate ligands featuring a hydroxyl phenyl group an intramolecular HB between the hydroxyl and pyrazolyl groups can be observed.[30] In dilution experiments carried out in C_6D_6 the invariance of the ^1H NMR chemical shift for the proton of the hydroxyl phenyl (OH) group suggested that the same intramolecular interaction occurs in solution. Interestingly, an upfield drift in the chemical shift of the aliphatic methine proton (CH) was observed when the analytical concentration of LOH was decreased from 200 mM to 5 mM (Figure 5), revealing the presence of an intermolecular HB between the CH and the imine nitrogen of one pyrazolyl ring (the only HB acceptor site of LOH) of another LOH molecule. Over the course of dilution, the concentration of the hydrogen bonded species decreases and the population of the shielded proton of the aliphatic methine (CH) increases determining an upfield shift of this ^1H signal. The NOESY experiment showed a strong contact between the latter proton and the 6-Ph proton confirming that the orientation of the phenyl ring in LOH is so that the hydroxyl group and the pyrazol rings are on the same side. As each molecule can be bound to two adjacent molecules, long chains of molecules, assembled via HB, are formed in concentrated C_6D_6 solutions (Scheme 3). In polar solvents bearing HB acceptor sites these intermolecular interactions are missing, and no chemical shift difference was actually observed in dilution experiments carried out for LOH in CD_2Cl_2 solution.

The ^1H and ^{13}C NMR spectra of complexes **1** and **2** are consistent with a tetrahedral C_S symmetric structure resulting from the κ^2-N,N coordination of the ligands to the metal center. The resonances are slightly shifted when compared to the corresponding free ligand. The only exception is the resonance of the hydroxyl group that moved from 10.15 ppm in LOH to 5.15 ppm in **2** (CD_2Cl_2, rt). In the complexes **1**−**2** the nitrogen HB acceptor sites are replaced by chlorine atoms. In this way the behavior expected for the complexes is the same observed for the heteroscorpionate ligands. Unfortunately the search for the intermolecular bond in solution was hampered by the low solubility of these complexes in C_6D_6. Dilution experiments in the narrow concentration range 0.001−0.005 M showed no significant changes in the chemical shifts.

Owing to the paramagnetism of the metal center (μ_{eff} = 3.7 μ_B in CD_3CN at room temperature), the ^1H NMR of **3** displayed broad and featureless resonances.

Coordination Studies. Speciation of LOR/$ZnCl_2$ system was evaluated in anhydrous acetonitrile by adding aliquots of a 0.10 M $ZnCl_2$ solution to a 0.0050 M LOR solution. The equilibrium between the free ligand and (LOR)$ZnCl_2$ occurs in the slow exchange regime on the

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NMR time scale. The integration of diagnostic resonances revealed that the amount of the formed complex is equivalent to the amount of added $ZnCl_2$ suggesting that the association constant (K_a) in anhydrous acetonitrile is over the detectable limit by NMR titration methods ($> 10^5\ M^{-1}$).[16] In a methanol/water (95:5) solution the equilibrium between LOR and (LOR)$ZnCl_2$ occurs in rapid exchange. The association constant (K_a) was determined by fitting the plot of $\Delta\delta$ of the 2-tBu ^1H-resonance versus $[ZnCl_2]/[LOR]$.[16] K_a values of $(8.6 \pm 0.4) \times 10^2\ M^{-1}$ for the association of LOMe to $ZnCl_2$ and of $(7.8 \pm 0.3) \times 10^2\ M^{-1}$ in the case of LOH were determined. When these values were compared to data reported in the literature for similar ligands,[31] they appeared to be lower. This finding can be traced back to the presence of water in the sample solution that probably competes with the ligand in coordinating the acidic Zn center.

As the coordination mode of the heteroscorpionate ligands LOR to acidic Zn^{2+} center is very similar to that found for the bis(3,5-dimethyl-pyrazol-1-yl)methane (bpm) ligand,[32] we were interested in comparing their coordination capabilities. The average Zn−N bond length found in the X-ray structure for **2** (2.039 Å, Zn1−N1 = 2.038(4) Å, Zn1−N3 = 2.040(4) Å, Table 2) is significantly shorter than that for (bpm)$ZnCl_2$ (2.060 Å, Zn1−N1 = 2.057(1) Å, Zn1−N3 = 2.062(1) Å).[32] Moreover, the association constant for the bpm/$ZnCl_2$ system, determined in the same experimental conditions, is lower, $(5.3 \pm 0.3) \times 10^2\ M^{-1}$.

The stronger coordination to $ZnCl_2$ of the LOR ligands compared to the bpm ligand can be ascribed to the presence of the methoxy/hydroxy-phenyl group on the methylene bridge that produces an increase in the basicity of the pyrazolyl nitrogen as a result of the electron-donating properties of these groups.

When a CD_2Cl_2 solution of **1** or **2** reacted with equimolar amount of bpm ligand, an exchange process occurred according to the equilibrium (1):

$$(LOR)ZnCl_2 + bpm \leftrightarrows LOR + (bpm)ZnCl_2 \qquad (1)$$

The area ratio of the ^1H resonances diagnostic for the free and coordinated LOR ligand permitted the conversion grade (α) to be determined as follows:

$$\alpha = A_{LOR}/(A_{LOR} + A_{LORZnCl2})$$

where A_{LOR} and $A_{LORZnCl2}$ are the areas of the aliphatic methine proton (CH) signals in the free and coordinated ligand, respectively. Surprisingly the conversion grades were 0.83 and 0.88 at 20 °C for **1** and **2**, respectively, suggesting that the equilibrium is strongly shifted toward the (bpm)$ZnCl_2$ species in both cases. It is worth noting that the proton resonances of (bpm)$ZnCl_2$ are broad, indicating a rapid exchange equilibrium between the free and the coordinated bpm ligand as shown in the NMR spectra of Figure 6. VT NMR analysis was carried out to evaluate the thermodynamic parameters for these equilibria. When the starting concentration of the two reagents is equal, the equilibrium constants K_{eq} were determined at different temperatures according to the following eq 2:

$$K_{eq} = [LOR][(bpm)ZnCl_2]/[(LOR)ZnCl_2][bpm] = \alpha^2/(1-\alpha)^2 \qquad (2)$$

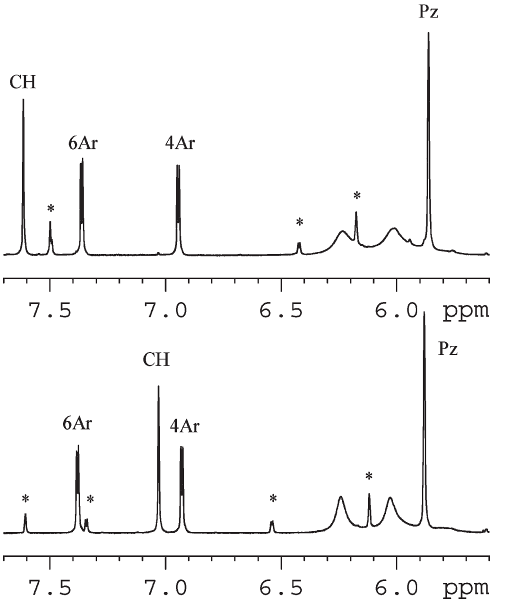

Figure 6. Section of ^1H NMR spectra (CD_2Cl_2, rt, 400 MHz) of **1**/bpm (top) and **2**/bpm (bottom). The resonances are labeled according to the Scheme 2; the signals marked with an asterisk are due to the zinc complexes **1** (top) and **2** (bottom). The broad resonances between 5.9 and 6.3 ppm are due to (bpm)$ZnCl_2$.

The thermodynamic parameters were thus extrapolated from the inverse temperature plot of ln(K_{eq}). The standard enthalpy ($\Delta H°$) and entropy ($\Delta S°$) values of -2.7 ± 0.2 kcal mol^{-1} and -3.0 ± 0.7 cal mol^{-1} K^{-1} were determined for the substitution of LOMe in **1** by bpm; analogously the $\Delta H°$ and $\Delta S°$ values of -3.2 ± 0.3 kcal. mol^{-1} and -3.0 ± 0.9 cal mol^{-1} K^{-1} were determined for the substitution of LOH.

The negative values of $\Delta H°$ indicate that the substitution of the heteroscorpionate ligands for bpm is thermodynamically favored. As (bpm)$ZnCl_2$ is less stable than **1** and **2**, this enthalpic gain originates from the intra- and intermolecular HB interactions previously described for the heteroscorpionate ligands LOR which stabilize the free ligand and promote its substitution. This is confirmed by the negative values found for $\Delta S°$ in the same reaction.

The higher value of α obtained for the substitution of LOH compared to that of LOMe is probably due to the higher capability of the hydroxy-phenyl group to establish HB interactions. To verify this hypothesis we investigated the exchange reactions of Zinc complexes **1**−**2** promoted by the heteroscorpionate ligands. When **1** was treated with 1 equiv of LOH (eq 3) in CD_2Cl_2 solution, a mixture of **1**, **2**, LOH, and LOMe was obtained where **1** and LOH were in slight excess.

$$(LOMe)ZnCl_2 + LOH \leftrightarrows LOMe + (LOH)ZnCl_2 \qquad (3)$$

The conversion grade lower than 0.50, namely, 0.46, confirmed the previous hypothesis. The ^1H−^1H EXSY

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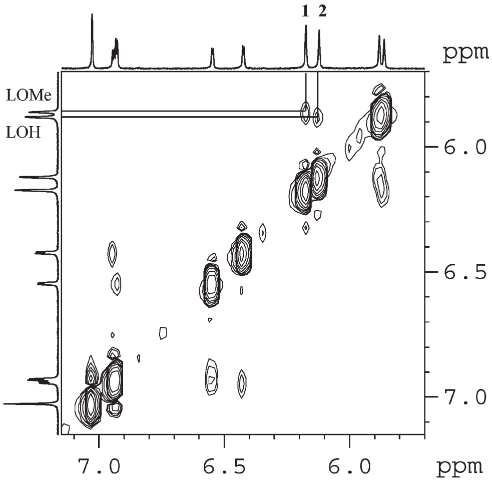

Figure 7. $^1H-^1H$ EXSY spectrum of **1**, **2**, LOH, and LOMe mixture (rt, mixing time = 0.8 s). The exchange of the Pz protons for **1**/LOMe and **2**/LOH is evidenced.

spectrum of this mixture (CD_2Cl_2, $\tau_m = 0.8$ s), along with the negative cross-peaks deriving from cross-relaxation (NOE), showed a set of positive cross-peaks (same diagonal sign) revealing a chemical exchange between **1** and LOMe and between **2** and LOH (Figure 7). The intensity of the correlation peaks found for the two couples **1**/LOMe and **2**/LOH permitted the rate constant (k) to be determined. The values of 0.12 and 0.07 s^{-1} were obtained for the exchange of **1**-LOMe and **2**-LOH respectively. These values suggest a slow exchange of the ligands at room temperature in halogenated solvents.

Optical Properties. Zinc is active in a variety of biological processes such as gene transcription, regulation of metalloenzymes, neural signal transmission.[33] Determination of Zn^{2+} in biological samples, within the range of 1 fM in bacterial cells to 0.1 mM in some vesicles,[34] is of great significance. Currently, direct detection of Zn^{2+} is particularly challenging because of the spectroscopically silent d^{10} electronic configuration. The first used technologies to monitor Zn^{2+} levels were mainly based on histochemical procedures (e.g., use of the colorimetric indicator dithizone and autometallography). Because of their invasiveness, these systems are not ideally suited for studying Zn^{2+}-related biochemistry. To avoid some of the limitations of the existing methodologies[35] recently fluorescence-based methods have been proposed as one of the most effective way for Zn^{2+} detection. To assess the potential use of ligands LOR as fluorescent sensors for Zn^{2+} detection, we investigated their optical properties and the ones of the corresponding Zn complexes by means of UV–vis and fluorescence spectroscopies.

The absorption spectra of the heteroscorpionate ligands, LOMe and LOH, are very similar and features two bands centered at 241 and 280 nm. The first band was ascribed to a $\pi-\pi^*$ transition of the pyrazolyl rings, the same observed in the absorption spectrum of the bpm ligand at 223 nm;[36] the second one was attributed to a $\pi-\pi^*$ transition of the phenyl rings. The coordination of the ligands to the metal ion induces no significant variations in the absorption spectra.

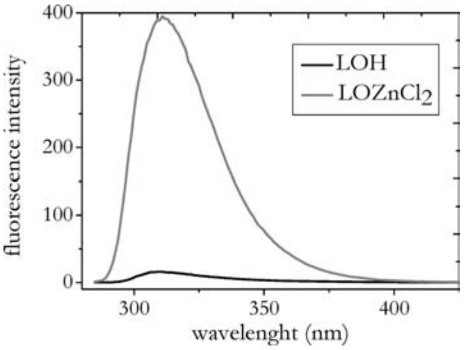

Figure 8. Emission spectrum of LOH (black trace) and LOHZnCl$_2$ (gray trace). (rt, 70 μM in CH_2Cl_2).

Both LOMe and LOH ligands are fluorescent and exhibit an emission band in the near UV region, around 310 nm. The fluorescence intensity is affected by the solvent: in methanol solution the fluorescence intensity displayed by LOH resulted 95% higher than that found in dichloromethane. In the same experimental conditions, the fluorescence intensity of LOMe did not show any solvent dependent effect. In THF solutions the fluorescence intensity displayed by LOH resulted 30% higher than that registered in dichloromethane, whereas that one displayed by LOMe resulted unchanged under the same conditions.

Interestingly, coordination of Zn^{2+} induces a fast enhancement of LOH fluorescence while it quenches that one of LOMe. In other words, Zn^{2+} "turns-on" the fluorescence of LOH and "turns-off" the one of LOMe. In dichloromethane solutions a fluorescence switching of 90% was found in the case of LOH (Figure 8), and of 65% for LOMe (Figure 9). The observed differences in the fluorescent behavior of LOMe and LOH are most likely due to the different tendency to establish intra- or intermolecular HB interactions. In the case of LOH, the hydroxyl phenyl group is HB bound to the imine nitrogen of one pyrazolyl group. When this interaction is absent, such as in MeOH or THF solution or by coordination of Zn^{2+}, an enhancement of LOH fluorescence is observed. A possible explanation for this finding is the interruption of photoinduced electron transfer (PET) of electronic density from the lone pairs on the oxygen atom to the π-system of the fluorophore.[37]

The fluorescence intensities of LOMe and LOH were measured in the presence of a large excess of the most biologically relevant, potentially competing, mobile metal ions. Different results were found for the two heteroscorpionate ligands investigated. Ca^{2+}, Na^+, and Ni^{2+} did not perturb LOH fluorescence while they quenched

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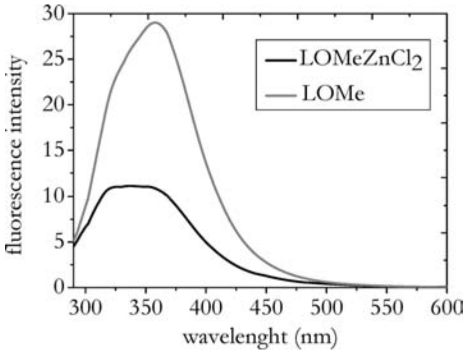

Figure 9. Emission spectrum of LOMe (gray trace) of LOMeZnCl$_2$ (black trace). (rt, 70 μM in CH$_2$Cl$_2$).

the one displayed by LOMe. Co^{2+}, as commonly reported in the case of divalent first-row transition metal ions,[32] turned off the fluorescence emission of both LOH and LOMe. Unfortunately, measurements under simulated physiological conditions could not be performed because of the scarce solubility of both LOH and LOMe in aqueous solutions.

Conclusions

New Zinc and Iron complexes **1**−**3** of two heteroscorpionate ligands have been synthesized and characterized by X-ray diffraction analysis and NMR spectroscopy. The complexes exhibit a tetrahedral geometry in which the ligand is κ^2-coordinated to the metal. The hydroxyl phenyl group of LOH is not coordinated but bound to an adjacent molecule giving long hydrogen bound chains. The solution structures of both ligands and complexes were also investigated by means of NMR spectroscopy to assess the presence of noncovalent interactions in solution.

In comparison with the bis-pyrazolyl-methane ligand, the electron-donor methoxy/hydroxy-phenyl group on the methylene bridge of the heteroscorpionate ligands strengthens the coordination of the pyrazolyl rings. Notwithstanding this, the bis-pyrazolyl-methane replaces the heteroscorpionate ligands from the coordination sphere of Zinc. As matter of fact an exchange process strongly shifted toward (bmp)ZnCl$_2$ species was observed when bpm was added to a solution of **1** or **2**. The analysis of the thermodynamic parameters suggests that the driving force of the reaction is the possibility for the free heteroscorpionate ligands to establish noncovalent interactions in solution.

The higher value of $\Delta H°$ observed for the substitution of LOH compared to LOMe is probably due to the higher capability of the hydroxy-phenyl group (hydrogen-bond donor) to establish HB interactions compared with that of the methoxy-phenyl group (hydrogen-bond acceptor). This feature was also evident in the substitution reactions of Zinc complexes **1**−**2** promoted by the heteroscorpionate ligands.

Finally, the present data provide preliminary results on a proof-of-principle method for monitoring Zn^{2+} by using easily synthesized and robust organic ligands. Within this contribution we are providing guiding principles for designing fluorescence-based zinc sensors. A theoretical understanding of their mechanisms will be undertaken at a later stage in our investigations. Such an achievement, in fact, would be helpful for further rational design of zinc sensors. A fine tailoring of the ligand skeleton aiming at enhancing the scarce solubility in aqueous solution at neutral pH of both LOH and LOMe is currently under way in our laboratory.

Acknowledgment. The authors thank Patrizia Oliva and Dr. Patrizia Iannece of the Department of Chemistry of the University of Salerno for their technical assistance.

Supporting Information Available: Crystallographic data in CIF file format. This material is available free of charge via the Internet at http://pubs.acs.org.