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Tetraphosphonated thiopheneligid : mixing the soft and the hard

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Abstract: The synthesis of ligand $L_T H_8$, based on a thiophene framework containing two bis(aminomethyldiphosphonate) functions in *ortho* position to the central sulfur atom, is described, together with the characterization of the intermediate compounds. The physico-chemical properties of the ligand were first studied by means of potentiometry and UV-Vis absorption spectrophotometric titrations to determine its pK values. Six successive equilibrium constants were determined in water solutions. The same means were then used to quantify the interactions of the ligand with Ni(II), Cu(II) and Zn(II). Following the conventional Irving-Williams trend, L_T was shown to have the highest affinity towards Cu(II) ($\log K(CuL_T) = 16.11(3)$), while Zn(II) and Ni(II) showed similar values ($\log K(ML_T) = 10.81(8)$ and $10.9(1)$, respectively), revealing a large selectivity of L_T toward Cu(II). Based on a combination of UV-Vis absorption spectroscopy and EPR measurements as a function of pH, along with DFT calculations, the coordination behavior of the hard phosphonate, medium amino and soft thiophene entities are questioned regarding their coordination to the Cu atom.

Introduction

Based on their luminescent, magnetic or radioactive properties, coordination complexes are continuously arousing a large interest in the various fields of medical applications such as imaging, therapy or diagnosis.¹ Their efficiency is often the result of a subtle equilibrium between the doses and the potential acute toxicity of the complexes, necessitating in most cases a strong coordination to avoid the release of the potentially toxic free cations. The recent examples of the fatal impact of some Gadolinium complexes used in magnetic resonance imaging for patients suffering from renal diseases² is a perfect illustration of the difficulty to achieve this equilibrium. To further improve their properties, there is still the need to design new ligands and to fully understand their binding and physicochemical properties.

Although less studied than their carboxylated counterparts, phosphorylated ligands constitute a family of large medical interest.³ They also present the advantage to form complexes of higher stability with regard to carboxylic acids analogues.⁴ Phosphonate functions may also present unexpected advantages regarding the kinetic aspects, as evidenced recently for the complexation of ⁶⁴Cu with phosphonated cross bridged cyclen ligands.⁵ Finally, the second sphere interactions with solvent molecules and particularly with water provide a strategy to improve their relaxivity properties in the design of metal based MRI contrast agents.⁶

While much efforts have been made to study the coordination of phosphorylated species, especially those related to phosphorylated nucleic acids,⁷ the chemistry of phosphorylated ligands is still largely unexplored and there are large opportunities for the design of new coordinating entities bearing these functions. Within the frame of our search for new complexing agents we have been interested in the design of phosphorylated ligands for the complexation of *d* and *f* transition elements.⁸ Of particular interest, Ligand L_p (Chart 1) was shown to display very promising properties for the complexation of cations such as Cu(II)⁹ and Ln(III)^{6b} with potential applications for ⁶⁴Cu PET and MRI imaging, respectively. Based on a pyridine scaffold functionalized with two bis(aminomethyldiphosphonate) side arms, L_p displayed high stability constants, rapid complexation kinetics of the cations and the possibility to be chemically functionalized to introduce an activated function for biolabelling.

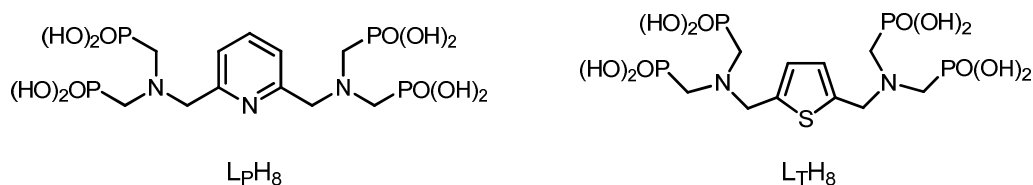


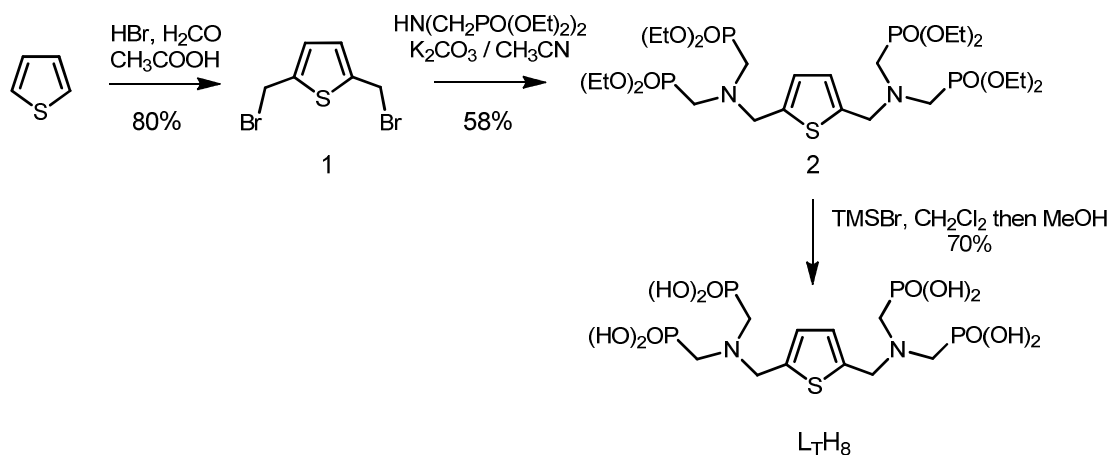
Chart 1

In this contribution, we present the synthesis and the complexation properties of L_T, an analogue of L_p in which the central pyridyl ring has been replaced by a thiophene one. The influence of the replacement of the N atom by the softer S atom,¹⁰ and of the changes of the C-X-C angle (X = N or S) due to the smaller five membered ring of thiophene, on the coordination of different *d* elements such as Cu(II), Ni(II) and Zn(II), will be questioned.

Results and Discussion

Synthesis of $L_T H_8$

The synthetic procedure to obtain ligand $L_T H_8$ is depicted in Scheme 1. Although 2,5-dibromomethylthiophene **1** can be obtained by bromination of dimethylthiophene¹¹ or of the dihydroxymethyl precursor,¹² it was found that the reaction with formaldehyde and bromhydric acid in acetic acid¹³ was a very convenient way to get the target dibromo intermediate in fair yields. Two nucleophilic substitution reactions at the bromo positions using tetra-ethyliminobis (methanephosphonate)¹⁴ afforded the ethyl ester protected precursor of $L_T H_8$, **2**. The final deprotection of **2** was achieved with TMSBr in dichloromethane followed by methanolysis with a decent 70% yield. It has to be noted that an alternative synthetic strategy was developed in which the dibromomethylthiophene was first transformed into its diamino analogue using a Delepine reaction (HMTA/ $CHCl_3$ followed by hydrolysis with HCl) before being transformed to **2** using formaldehyde and diethylphosphite,¹⁴ but the chemical yields of each step were rather low (respectively 27 and 25%) and the final purification of the ethyl protected precursor by column chromatography was tedious.



Scheme 1. Synthesis of $L_T H_8$

Physico-chemical studies

Protonation constants of L_T

Ligand L_T possesses ten protonation sites, two tertiary amines and the two oxygen atoms of each of the four phosphonate groups. Protonation constants, as defined by equations (1) and (2) were determined by a combination of potentiometric (Figure S1, SI) and UV-Vis absorption spectrophotometric titrations vs pH (Figure 1).



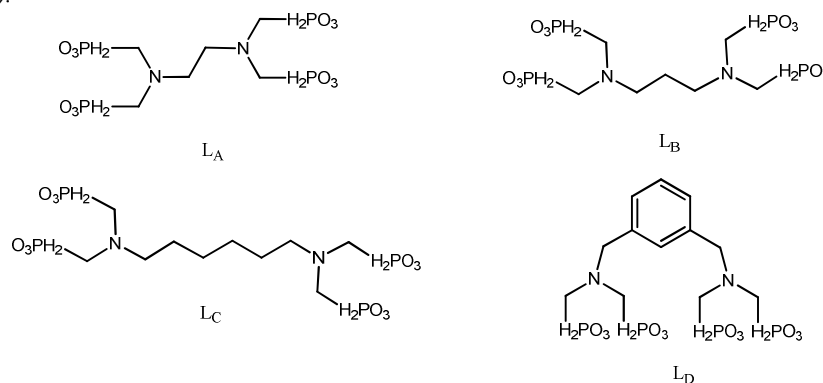
$$K_n^H = \frac{[\text{L}_T\text{H}_n]}{[\text{L}_T\text{H}_{n-1}][\text{H}^+]} \quad n = 1 - 10 \quad (2)$$

The statistical analysis of the potentiometric data versus pH led to the determination of six protonation constants of ligand L_T (Table 1). In accordance with literature on polyaminophosphonated ligands (Table 1 and Scheme 1),^{9,15-17} the first two protonation constants (K_1^H , K_2^H), with $\log K$ higher than 10, were assigned to the tertiary amines, while the four lower protonation constants were attributed to the first protonation of the four phosphonate functions. The second stepwise protonation constants of the phosphonate functions could not be determined under our experimental conditions and were thus assumed to be lower than 2 ($\log K$) as suggested by other phosphonic acid systems.¹⁸

Table 1. Successive protonation constants ($\log K_n^H$) of the free ligand L_T and related polyaminomethanediphosphonate derivatives

	Tertiary amines		Phosphonates			
	$\log K_1^H$	$\log K_2^H$	$\log K_3^H$	$\log K_4^H$	$\log K_5^H$	$\log K_6^H$
L_T^a	12.50(7)	10.65(4)	6.92(4)	6.10(4)	5.15(4)	4.43(4)
$\Delta \log K^H$	1.9		0.8	1.0	0.6	
L_P^9	11.21	10.29	8.04	6.49	5.53	4.19
$\Delta \log K^H$	0.92		1.55	0.96	1.34	
$\text{L}_A^{16,17}$	13.5	10.2	8.08	6.41	5.08	2.71
$\Delta \log K^H$	3.3		1.67	1.33	2.37	
$\text{L}_B^{16,17}$	13	11.15	6.99	6.07	5.18	4.37
$\Delta \log K^H$	1.85		0.92	0.89	0.81	
$\text{L}_C^{16,17}$	13.3	13.0	6.88	6.13	5.29	4.61
$\Delta \log K^H$	0.3		0.75	0.84	0.68	
$\Delta \log K(\text{statistical})^{19}$	0.6		0.43	0.35	0.43	

^a Solvent: H_2O ; $I = 0.1 \text{ M}$ (NaClO_4); $T = 25.0(2) \text{ }^\circ\text{C}$. Values are given with their standard deviation in parenthesis (σ).



Scheme 2. Polyaminophosphonated ligands used for comparison

Figure 1 presents the evolution of the UV-Vis absorption spectra of L_T measured as a function of pH. Between pH 12.82 and 9.29, the spectrophotometric titration showed hyperchromic variations at 240 nm, attributed to the π - π^* transition of the thiophene ring.²⁰ Below pH 9.29, almost no spectral variations were observed, suggesting that lower protonation constants are located at a long distance from the chromophoric thiophene ring. Due to this lack of spectral information below pH 9, only the $L_T H$, $L_T H_2$ and $L_T H_6$ protonation constants, which were in agreement with the potentiometric results, could be determined spectrophotometrically (Table S1, SI). The calculated electronic spectra of the species identified by the spectrophotometric titrations are presented in Figure S2 (SI).

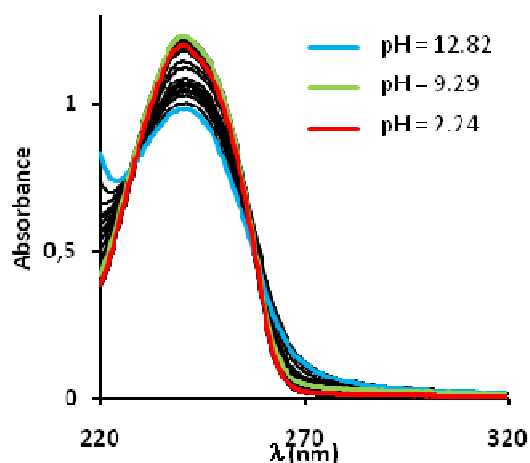


Fig. 1 Spectrophotometric titration of L_T vs pH ($[L_T]_{\text{tot}} = 1.0 \times 10^{-4}$ M, $2.24 < \text{pH} < 12.82$, H_2O , $I = 0.1$ M (NaClO_4), $T = 25.0(2)$ °C).

In addition to the results obtained for L_T , Table 1 presents the protonation constants of L_P and of a series of bis(aminomethyldiphosphonate) ligands L_A - L_C (Scheme 2) having varying spacers between the two aminomethyldiphosphonate groups. In order to compare the protonation constants of L_T with those of the other ligands and to evaluate the level of interaction between the different coordination sites (tertiary amines and phosphonates), the differences between the successive protonation constants ($\Delta \log K^H$) were calculated. For a defined number of identical and independent coordination sites the difference between two successive protonation constants is expected to meet the statistical factor¹⁹ (Table 1).

For L_T the $\Delta \log K^H$ of the tertiary amines is 1.9, about three times the statistical factor for two identical and independent sites, suggesting that at least one N atom of L_T is involved in intramolecular interactions. Moreover, it is noticeable that this value is very close to those observed for ligand L_B , with intermediate spacer length between its two aminomethyldiphosphonate sites compared to L_A (high $\Delta \log K^H$, strong interactions due to short spacer) and L_C ($\Delta \log K^H$ close to statistical factor, low interactions due to long spacer). Surprisingly, the thiophene spacer in L_T seems to induce more inter-unit hydrogen bonds than the pyridine spacer in L_P .

The comparison of $\Delta \log k^H$ for the phosphonate functions showed trends similar to L_B and L_C with values much closer to the statistical factors for four identical and independent sites than ligands L_A (short spacer, little flexibility) or L_P . We can thus suggest that, as L_B and L_C , the phosphonate functions of L_T present intramolecular interactions of intermediate strength compared to L_A and L_P , which are able to weave a tighter net of interactions between the phosphonate oxygen atoms. The distribution diagram of the species as a function of the pH of the solution (Figure 2) shows that, under acidic conditions ($\text{pH} < 4$), L_T mainly exists as its $[L_T H_6]^{2-}$ species while under physiological conditions ($\text{pH} 7.4$) the diprotonated form ($[L_T H_2]^{6-}$) with two protonated tertiary amine is predominant ($\sim 80\%$). As a comparison, it can be noted that, for ligand L_P , the $[L_P H_3]^{5-}$ species was predominant under the same conditions.⁹

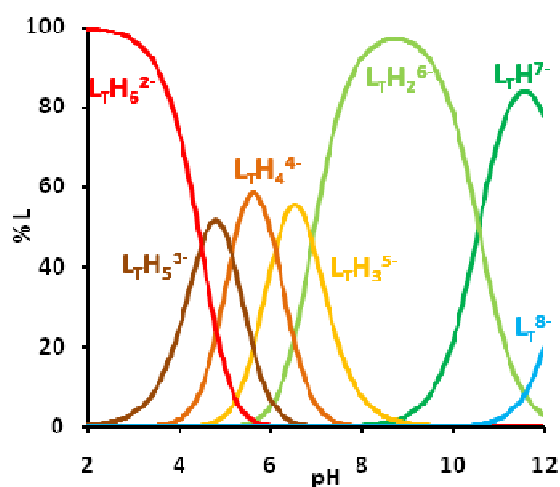


Fig. 2 Distribution diagram of the protonated species of L_T ($[L_T]_{\text{tot}} = 1.0 \times 10^{-4}$ M, H_2O , $I = 0.1$ M NaClO_4 , $T = 25.0(2)$ °C).

Stability constants of ML_T complexes

The Cu(II), Zn(II) and Ni(II) complexes of L_T have been studied and characterized by means of potentiometric (Fig S3) and spectrophotometric titrations vs. pH (Fig S4-S6). Table 2 summarizes the values of the stability constants for these three cations obtained by potentiometry, which are in excellent agreement with those obtained by spectrophotometric titrations (Table S2). These results clearly showed a selectivity of L_T for Cu(II) compared to Zn(II) and Ni(II) with more than five orders of magnitude difference in the $\log K_{ML}$ value.

Table 2. Stability constants ($\log K$) of metallic complexes of L_T ($M = \text{Cu(II)}, \text{Zn(II)}, \text{Ni(II)}$)

	Cu(II)	Zn(II)	Ni(II)
ML_T	16.11(3)	10.81(8)	10.9(1)
$ML_T H$	9.98(4)	10.67(9)	10.66(3)

ML_TH₂	6.56(4)	7.18(9)	6.78(3)
ML_TH₃	5.15(3)	6.56(8)	6.03(3)
ML_TH₄	4.45(3)	4.99(8)	5.05(5)
ML_T(OH)	4.2(2)	/	/

Solvent: H₂O; I = 0.1 M (NaClO₄); T = 25.0(2) °C. standard deviation (σ) are given in brackets on the last significant digit. Charges have been omitted for the sake of clarity. $\log K_{\text{Cu(OH)}} = -6.29$ and $\log K_{\text{Cu(OH)}_2} = -13.1$; $\log K_{\text{Zn(OH)}} = -7.89$ and $\log K_{\text{Zn(OH)}_2} = -14.92$; $\log K_{\text{Ni(OH)}} = -8.1$ and $\log K_{\text{Ni(OH)}_2} = -16.87$.²¹

In order to compare the chelating ability of L_T for Cu(II), Zn(II) and Ni(II) with other ligands their pM values at a physiological pH of 7.4 were calculated (Table 3).²² By definition, $\text{pM} = -\log[\text{M(II)}_{\text{free}}]$ with $[\text{M}] = 10^{-6}$ M and a 10 fold excess of ligand, a pM value of 6 thus means that there is no complexation of the metal by the ligand.

Table 3. Calculated pM values ($[\text{L}_T] = 10^{-5}$ M, $[\text{M}] = 10^{-6}$ M, M = Cu(II), Zn(II), Ni(II), pH = 7.4) for L_T, polyaminomethylphosphonate derivatives and biologically relevant ligands.

	pCu	pZn	pNi
L _T	11.2	6.9	6.8
L _p ⁹	15.46	12.45	11.79
L _A ²²	14.10	11.67	10.45
L _D ²³	8.89	/	/
Histidine ²⁴	8.72	/	/
WT-CAII ²⁵	/	12.35	/

The pCu values show that the affinity of L_T for Cu(II) is three orders of magnitude higher than that of ligand L_D (Scheme 2) at physiological pH, suggesting that a thiophene ring as spacer between the two aminobiphosphonate moieties is more likely to meet the structural requirements of Cu(II) coordination than a benzene ring. This structural advantage is lost by shortening the spacer as in L_A, or by exchanging the thiophene spacer with a pyridine ring, thus adding a new chelation site (L_p). These features suggest that pre-organisation of the complex, through short spacer (L_A) or additional chelation site (N-pyridine in L_p), is a major factor in achieving high Cu(II) affinity.

Under physiological conditions, the affinity of L_T for potential competitor ions like Zn(II) and Ni(II) is very low. From Table 3, it is noticeable that this feature is quite uncommon among acyclic phosphonated chelators, as usually strong Cu(II) chelation seems to imply strong Zn(II) chelation too. Although the affinity of L_T for Cu(II) is lower than those obtained for the previously synthesized acyclic ligand L_p, possessing a pyridine instead of the thiophene moiety, a much higher selectivity of L_T for Cu(II) is observed (Table 3). Moreover, this stability should be sufficient to avoid dissociation of the complex in the presence of histidine, an essential amino-acid for humans and common coordinating ligand in metalloproteins. Additionally, unlike L_p or L_A, pZn of L_T is very low (Table 3), and thus the Cu(II) complex of L_T is not expected to undergo metal-ion exchange reactions with Zn containing proteins such as carbonic anhydrase (WT-CAII), which would otherwise result in a risk of release of radioactive ⁶⁴Cu(II) in PET applications.

The replacement of a pyridine (L_p) by a thiophene ring (L_T) as spacer induced a loss of pre-organisation of the ligand (through the pyridine nitrogen) and a lower affinity of L_T for Cu(II) but ended up with a ligand able to fit the geometrical requirements of Cu(II) better than those of Zn(II) and Ni(II), thereby achieving a greater selectivity. This may be explained by the d^9 electronic structure of Cu(II), which can accommodate strongly distorted octahedral geometry or penta-coordination (square pyramidal or trigonal bipyramidal) through the Jahn-Teller effect, which is less favorable with d^8 Ni(II) or d^{10} Zn(II) metals.

Spectroscopic studies of the Cu(II) complexes of L_T

To better understand this behavior, the coordination of Cu(II) to L_T was investigated in detail using UV-Vis absorption spectrophotometry, on both the UV (240 nm, $\pi \rightarrow \pi^*$ transitions centered on the thiophene unit) and the visible domain (500-800 nm, d-d transitions of Cu(II)), and by EPR spectroscopy. The variations observed during the spectrophotometric titration of Cu(II) were very complex and the full details can be found in Figure S4 (SI). To follow the influence of the pH on the spectroscopic data, Figure 3 represents the distribution of the species formed during the titration (left) and the evolution of the absorbance of the sample at different significant wavelengths (right), while Figure 4 represents the electronic spectra of the complexes calculated from the titration experiments.

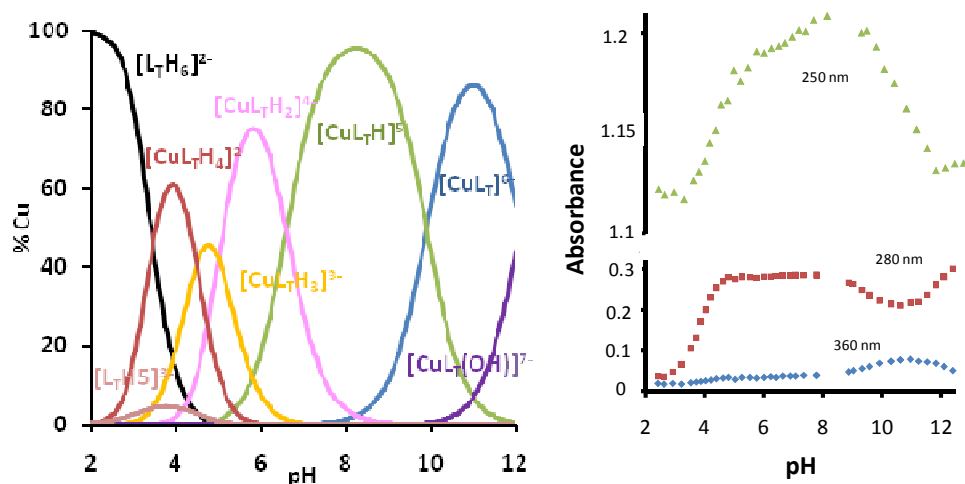


Fig. 3 Distribution diagram of the Cu: L_T (1:1) species as a function of pH ($[L_T]_{tot} = 1.02 \times 10^{-4}$ M, $H_2O, I = 0.1$ M ($NaClO_4$), $T = 25.0(2)$ °C, left) and evolution of the absorbance of an equimolar solution of Cu(II) and L_T (1.0×10^{-4} M) vs pH at 250 (green), 280 (red) and 360 (blue) nm (right).

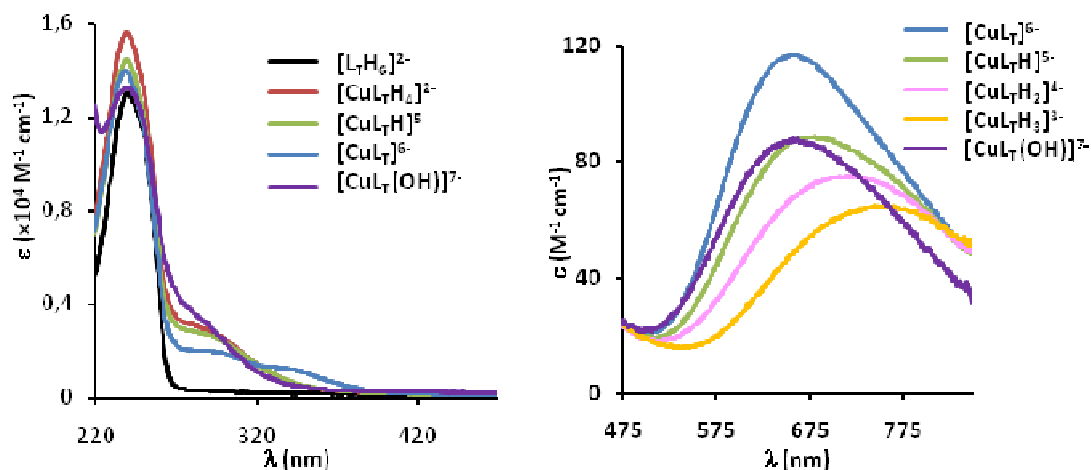


Fig. 4. Calculated electronic spectra of the Cu:L_T (1:1) species. Solvent : H₂O; I = 0.1 M (NaClO₄); T = 25.0(2)°C.

In the UV domain at acidic pH (Fig S4), the spectrum corresponds to that of the free ligand with the main absorption band corresponding to the $\pi \rightarrow \pi^*$ transitions centered on the thiophene moiety pointing at 240 nm. When the pH increased from 2 to ca 7.5, an hyperchromic effect is observed on the $\pi \rightarrow \pi^*$ transitions of the thiophene, together with the appearance of a new absorption band centered at 280 nm, which was ascribed to a N \rightarrow Cu(II) charge transfer (LMCT) band reminiscent of the complexation of the Cu(II) to the nitrogen atoms of L_T.^{9,26} The distribution diagram relates these changes to the formation of the [CuL_TH₄]²⁻ complex followed by the successive deprotonation steps affording the [CuL_TH₃]³⁻, [CuL_TH₂]⁴⁻ and [CuL_TH]⁵⁻ species (Fig 3). These successive deprotonations of the complex only affect smoothly the UV absorption spectra and are expected to occur on phosphonate functions (PO₃H). Moreover, the first two deprotonation constants of the [CuL_TH₄]²⁻ complex are identical to the free ligand protonation constants LH₅ (log K₅^H = 5.15(4)) and LH₆ (log K₆^H = 4.43(4), Table 1), suggesting that they take place on phosphonate oxygen atoms that are not involved in the complexation of Cu(II). From pH 7.8 to 10.3, a drastic change was observed with the decrease of the N \rightarrow Cu(II) LMCT transition (280 nm), and the appearance of a new band at 360 nm (Fig 3 and S4). Considering its intensity and its energy, this transition was attributed to the presence of a second N \rightarrow Cu(II) LMCT transition of lower energy, as if the deprotonation of [CuL_TH]⁵⁻ species to form [CuL_T]⁶⁻ was accompanied by a weakening of one of the two amine-Cu(II) bonds. It can be surmised that this last deprotonation step, affording a fully deprotonated ligand complexed to Cu(II) will drive the coordination towards the phosphonate functions, weakening one of the N-Cu(II) bonds. Finally, above pH 11.0, this second LMCT band disappeared, while the first LMCT transition was slightly hypsochromically shifted. In this pH range, a hydroxy species is formed ([CuL_T(OH)]⁷⁻) and the coordination of the hydroxy anion probably results in the breaking of the weak Cu(II)-N bond.

The variations measured in the visible region from 500 to 800 nm, which correspond to *d-d* transitions of the Cu(II) atom, were also very informative. The progressive deprotonation of the species, starting from [CuL_TH₃]³⁻ up to [CuL_T]⁶⁻, resulted in a gradual hypsochromic shift of the *d-d* transition, that may be indicative of a change in the coordination chemistry of the Cu(II) cation, with a strengthening of the ligand field. The formation of the hydroxy species [CuL_T(OH)]⁷⁻ did not induce

further hypsochromic shift, but a decrease of intensity, which are in agreement with an OH^- group replacing one N in the coordination sphere. This behavior was totally opposite to that observed for L_p for which the deprotonation of the complex resulted in a bathochromic shift of the $d-d$ transitions.^{9b} The high energy position of the $d-d$ transition in basic solutions points to an octahedral, square planar or square pyramidal coordination around the Cu(II) atom.²⁷

To further investigate the stoichiometry of the M:L complexes we carried out an isothermal titration calorimetry (ITC) experiment (Figure 5) and a spectrophotometric titration (Figure S7) of L_T by Cu(II) at a fixed pH of 4.3 in acetate buffer.

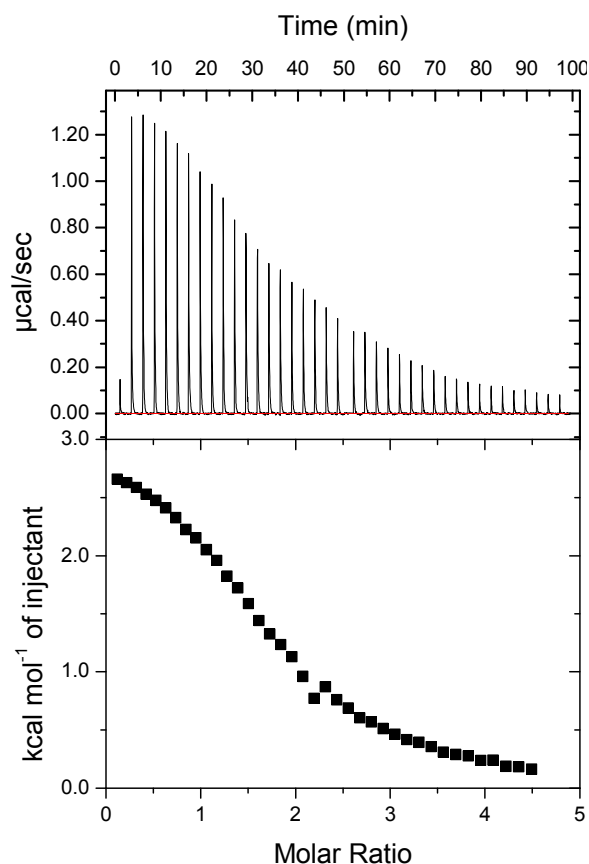


Fig. 5 Heat effect and enthalpogram of the titration of L_T by Cu(II) at pH 4.3. $[L_T]_{\text{tot}} = 2.0 \times 10^{-4}$ M; $0 < [\text{Cu(II)}]/[L_T] < 4$; Solvent: acetate buffer 0.1M; $T = 25.0(2)$ °C.

Processing of the ITC data suggested the formation of two species, $\text{Cu}L_T'$ and Cu_2L_T' with conditional stability constant of $\log K'_{\text{Cu}L_T'} = 5.1(1)$ and $\log K'_{\text{Cu}_2L_T'} = 4.1(1)$ (the prime label designates the apparent conditions of pH). Any other coordination model resulted in poor fit or the refinement of the data failing to converge. The lower stability for the coordination of the second Cu^{2+} together with the small spectral variations caused by its coordination made the fitting of the spectrophotometric data difficult. But fixing $\log K'_{\text{Cu}L_T'}$ to the value obtained from the ITC experiment returned a good fit and allowed us to calculate a $\log K'_{\text{Cu}_2L_T'} = 3.8(1)$, in good agreement with the value obtained from the ITC experiment.

The distribution curves calculated from these constants (Figure S9) showed that at one equivalent of Cu, only 10% of species is formed. The lower stability and little prevalence of Cu_2L_T in these conditions explain that this minor species was not detected in our complexation studies versus pH.

These results are also supported by the DFT calculations that suggested the possible coordination of two Cu^{2+} to one ligand and formation of a $\text{Cu}_2(\text{L}_T)_2$ complex. It was not possible to identify this species under our experimental conditions but its existence remains plausible as the coordination of a second ligand would be the best option to fill the coordination sphere of the two Cu(II) in Cu_2L_T .

To verify the agreement between the CuL_T conditional stability constant and the previous results obtained from our titrations vs pH, the conditional stability constant was recalculated from our data versus pH according to:

$$\beta_{\text{CuL}_T}^{\text{cond}} = \beta_{\text{CuL}_T}^{\text{form}} \times \frac{\alpha_{\text{CuL}_T}}{\alpha_{\text{Cu}}\alpha_{\text{L}_T}}$$

Where $\beta_{\text{CuL}_T}^{\text{form}}$ is the formal stability constant determined from the titrations versus pH and α_{L_T} , α_{CuL_T} and α_{Cu} are the schwarzenbach coefficients associated to the protonated species of L_T , CuL_T and Cu at pH 4.3.²⁸ The calculated conditional constant, $\log K'_{\text{CuL}} = 5.09$ was found to be in excellent agreement with the experimental value and supported our coordination model.

Moreover, the ITC experiment gave us access to the thermodynamic parameters of the complexation (Table 4). The positive sign of the heat exchanged during the titration (Figure 5) highlights that the formation of the complexes is endothermic and that the reaction is entropy driven, suggesting that the limiting process of the complex formation is desolvation.

Table 4. Thermodynamic parameters of the complexation of Cu(II) by L_T at pH 4.3 determined by ITC.

	$\log K'$	ΔH (kJ.mol ⁻¹)	$-T\Delta S$ (kJ.mol ⁻¹)	ΔG (kJ.mol ⁻¹)
CuL	5.1(1)	11.6	-40.6	-29.0
Cu₂L	4.1(1)	9.4	-32.8	-23.4

Solvent = acetate buffer (0.1M), T = 25°C. ΔH and K' were determined experimentally and ΔS was calculated with the Gibbs–Helmholtz equation: $\Delta G = \Delta H - T\Delta S$, with $\Delta G = -2.303 RT \log K'$

To get insights into the coordination behavior of L_T , a study of an equimolar solution of Cu(II) and L_T was monitored as a function of pH by EPR spectroscopy in an EtOH/H₂O glassy matrix at 150K (Figure 6 and S10, Supp. Inf.). The X-Band EPR spectrum of complex frozen solution exhibits a strong absorption at about 3200 G, attributed to the allowed transitions $\Delta MS = 1$. The shape of the spectrum consists of four equidistant absorptions in the parallel region as expected for the coupling of the unpaired copper electron with the copper nucleus ($I = 3/2$). In acidic conditions at pH = 2.2 and up to 3, only uncomplexed Cu(II) could be observed, while above pH 12 the EPR spectrum is similar to

that of copper hydroxide in solution. Above pH =3, a characteristic pattern appears, which is completely different from that obtained with the L_p systems^{9b} (Fig 6), but is similar to those corresponding to the hetero ligand species formed by glycine phosphonic acid (GlyP) with copper(II) in a 2N and 2O coordination mode.²⁹ The obtained EPR parameters are $g_{//} = 2.326$, $g_{\perp} = 2.074$, $A_{//} = 161.2$, and $A_{\perp} = 10.4 \cdot 10^{-4} \text{ cm}^{-1}$, while for the $[\text{Cu}(\text{GlyP})_2]^{2-}$ system the following parameters were reported: $g_{//} = 2.275$, $g_{\perp} = 2.055$, $A_{//} = 164$, and $A_{\perp} = 14 \cdot 10^{-4} \text{ cm}^{-1}$. Furthermore, the $[\text{Cu}(\text{GlyP})_2]^{2-}$ complex presents a maximum due to $d-d$ transitions in the absorption spectrum at 658 nm, in good agreement with the corresponding maximum observed for the complex. These results strongly suggest that the two systems have a similar Cu(II) coordination environments. The observed g values for these two systems ($g_{//} > g_{\perp} > g_e$) suggest that the unpaired electron resides in a $d_{x^2-y^2}$ orbital. The $g_{//}/A_{//}$ ratio, which is a good indicator of the stereochemistry around the copper, as well as an empirical index of the distortion for a tetragonal geometry³⁰ can be calculated. For square planar complexes the $g_{//}/A_{//}$ ratio is normally in the range 105-135 cm, while for distorted tetrahedral complexes falls within 135-258 cm. This ratio is of 144.3 cm for the complex of L_T , and 139 cm for $[\text{Cu}(\text{GlyP})_2]^{2-}$, that is, very close to the limiting values characteristic of the two coordination environments and an unequivocal assignment of the Cu(II) coordination environment to one of these coordination polyhedra was not possible.

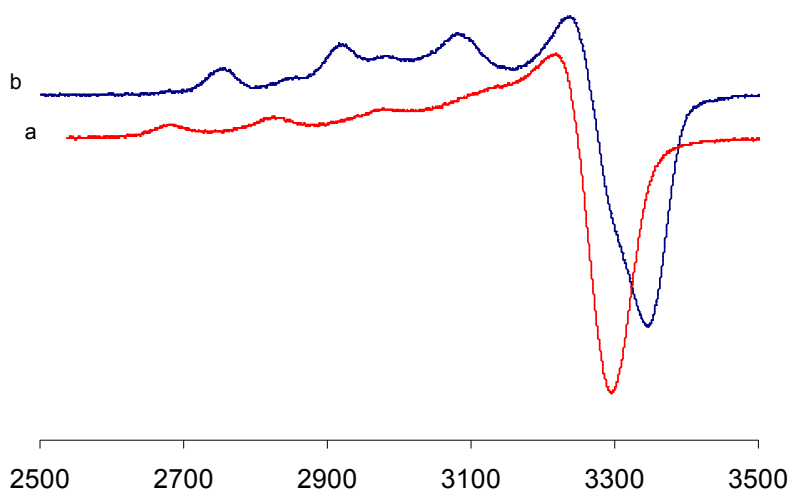


Fig. 6 EPR spectra of an equimolar solution of (a) L_T and (b) L_p Ligand and Cu(II) in EtOH/ H_2O glassy matrix at 150K at pH 7.

DFT studies

Aiming to gain information on the binding mode of the L_T ligand to Cu(II) we performed density functional theory (DFT) calculations (see experimental section for details). A initial set of calculations were performed on the model systems 1,1'-(pyridine-2,6-diyl)bis(N,N -dimethylmethanamine) and 1,1'-(thiophene-2,5-diyl)bis(N,N -dimethylmethanamine), which contain the N_3 and N_2S donor set of L_p and L_T , respectively. The conformations of the starting geometries used for geometry optimization

were such that could allow the simultaneous coordination of the three donor atoms to Cu(II). The optimized geometries (Fig. 7) of these model systems provided distances between the two amine nitrogen atoms of 5.34 and 6.09 Å for the model systems containing a pyridyl and a thiophene head unit, respectively. The longer N...N distance observed for the thiophene derivative is associated to the small C-S-C angle of the thiophene moiety (91.9°) compared with the C-N-C angle of the pyridyl unit (118.8°). As a result, the N₃ donor set of L_p is well suited for a simultaneous coordination of its three donor atoms to a relatively small metal ion such as Cu(II). On the contrary, the N₂S donor set of L_T is likely to be more appropriate for the coordination to larger metal ions.

Different geometry optimizations of the [CuL_T]⁶⁻ system performed using different starting geometries lead to structures where the amine donor atoms of the ligand were not simultaneously coordinated to the metal ion. Since the EPR studies clearly evidenced the coordination of both amine donor atoms to Cu(II), we conclude that the complex species formed in solution must involve the coordination of L_T to more than one Cu(II) center. Presumably, each Cu(II) ion is simultaneously coordinated by two N atoms arising from different L_T units and several O atoms of phosphonate groups. Since the spectroscopic and potentiometric studies described above indicate the formation of complexes with a 1:1 (Cu:L_T) stoichiometry, such coordination must be accompanied by the formation of dimeric or polymeric structures. Calculations performed on the [Cu₂(L_T)₂]¹²⁻ show that the formation of such di- or oligomeric structures is indeed feasible. The optimized geometry of [Cu₂(L_T)₂]¹²⁻ shows the two Cu(II) ions separated by 6.6 Å, each being directly coordinated to two nitrogen atoms of two different ligand moieties and two oxygen atoms of phosphonate groups. The mean Cu-N and Cu-O distances are 2.19 and 1.93 Å, respectively. The Cu-O distances are in excellent agreement with those observed in the solid state for Cu(II) complexes with amino acids, which typically adopt distorted square planar or square pyramidal geometries, the presence of bulky substituents favoring the former. Our calculations provide Cu-N distances somewhat longer than those observed for these complexes in the solid state (~0.14 Å). The coordination environment provided by our DFT calculations for [Cu₂(L_T)₂]¹²⁻ is very similar to that observed for such complexes with amino acids,^{31,32} which also provide EPR parameters close to those determined for the Cu(II) complex of L_T.³³

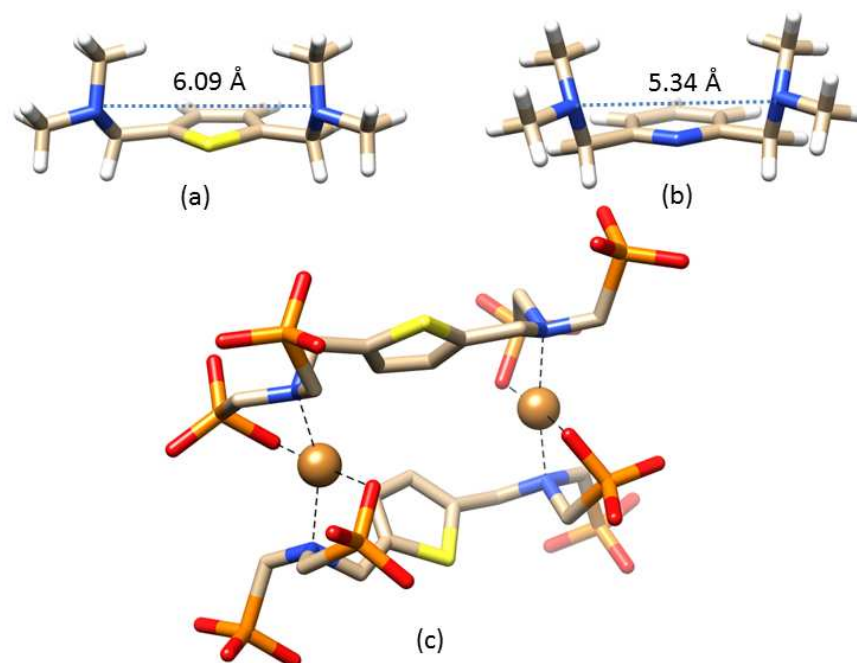


Fig. 7 Structures of 1,1'-(thiophene-2,5-diyl)bis(*N,N*-dimethylmethanamine) (a), 1,1'-(pyridine-2,6-diyl)bis(*N,N*-dimethylmethanamine) (b) and $[\text{Cu}_2(\text{L}_\text{T})_2]^{12-}$ obtained from DFT calculations in aqueous solution.

Conclusions

The replacement of the central pyridine ring of L_P by a thiophene one in L_T did not bring much change to the acido-basic properties of the ligand, the pK values of the amino or phosphonate functions being very similar. In contrast, the impact on the coordination chemistry of transition elements of the first series is very significant. The thiophene ring was responsible for a large decrease of the overall stability of the complexes formed with all the cations studied (Cu(II), Zn(II) and Ni(II)). DFT calculations indicated that the mononuclear CuL_T complex can hardly accommodate the coordination of both N atoms of a L_T ligand, in contrast to EPR and UV-Vis spectrophotometry, which both indicated the coordination of both N atoms. Although these theoretical results have to be handled with great care due to the complexity of the system, a possible explanation would be the formation of $\text{Cu}_2\text{L}_\text{T}_2$ species in which the Cu(II) ions will be coordinated by two N atoms of two distinct ligands. The formation of a $\text{Cu}_2\text{L}_\text{T}$ complex was also evidenced by UV-Vis spectrophotometric titrations. Efforts to evidence monomeric or dimeric species by electrospray mass spectrometry were unfortunately unsuccessful.

If the stability was markedly affected, the selectivity towards Cu(II) with respect to Ni(II) and Zn(II) remained unchanged, following the conventional Irving-Williams trends, but with an improved selectivity for Cu(II) ($\Delta\log K > 5$) compared to L_P . Such ligand combining soft and hard coordination

sites³⁴ combined to marked selectivity, may find interesting applications in the directed coordination of heteropolynuclear species.

Experimental

Materials. Distilled water was purified by passing through a mixed bed of ion-exchanger (Bioblock Scientific R3-83002, M3-83006) and activated carbon (Bioblock Scientific ORC-83005). All the stock solutions were prepared by weighing solid products using an AG 245 Mettler Toledo analytical balance (precision 0.01 mg). Metal cation solutions were prepared from their perchlorate salts ($\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, 98%, Fluka, ($\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, 98.9%, Alfa Aesar and $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, 98%, Aldrich) and their concentrations were determined by colorimetric titrations with EDTA (10^{-2} M, Merck, Titriplex III) according to standard procedures.³⁵ Sodium Hydroxyde (NaOH) and perchloric acid (HClO_4) were used to adjust pH during titrations. The ionic strength of all the solutions was fixed to 0.1 M with sodium perchlorate (NaClO_4 , Fluka, 99.0%). *CAUTION! Perchlorate salts combined with organic ligands are potentially explosive and should be handled in small quantities and with the adequate precautions.*³⁶

Potentiometry. The protonated species of L_T and the stability constants of its Cu(II), Zn(II) and Ni(II) complexes were characterized and quantified by potentiometric titrations in water. Titrations were performed using an automatic titrator system (DMS 716 Titrino, Metrohm) with a combined glass electrode (Metrohm, 6.0234.100, Long Life) filled with NaCl 0.1 M. The electrode was calibrated as a hydrogen concentration probe by titrating known amounts of perchloric acid with CO_2^- free sodium hydroxide solutions.^{37,38} The GLEE program³⁹ was applied for the glass electrode calibration, and allowed to check the carbonate percentage in the NaOH solution used.

In a typical experiment, an aliquot of 10 mL of L_T (10^{-3} M) or M:L (M = Cu(II), Zn(II), or Ni(II), $[\text{M}]/[\text{L}] \approx 1$) was introduced into a thermostated jacketed cell (25.0(2) °C, Metrohm). The solution was continuously de-oxygenated by bubbling with oxygen-free argon. The titrations were then carried out by addition of known volumes of sodium hydroxide solution over the pH range 2-12. The potentiometric data of L_T and its metal complexes were refined with the Hyperquad 2008³⁹ program which uses non-linear least-squares methods, taking into account the formation of metal hydroxide species. The titration of each system was repeated at least in triplicate and the sets of data for each system were treated independently, then merged together and treated simultaneously to give the final stability constants. The distribution curves of the protonated species of L_T and its metal complexes as a function of pH were calculated using the Hyss2009 program.⁴⁰

Spectrophotometry. The protonation constants of L_T and the stability constants of M: L_T (M = Cu(II), Zn(II) and Ni(II), $[\text{M}]/[\text{L}_T] = 1$, $[\text{L}_T] \sim 10^{-4}$ M) were also determined by UV-Visible spectrophotometric titration versus pH by recording simultaneously pH and UV-visible spectra. The free hydrogen ion concentrations were measured with a Mettler Toledo U402-S7/120 (pH 0-14) combined glass electrode. Potential differences were given by a Tacussel LPH430T millivoltmeter. Standardization of the millivoltmeter and verification of the linearity of the electrode were performed with three commercial buffer solutions (pH 4.01, 7.01 and 10.01, 25°C). An aliquot of 20 mL of L_T solution was introduced into a thermostated jacketed cell (25.0(2) °C, Metrohm) with 1 equivalent of metal (M) in the case of M: L_T titrations. A known volume of perchloric acid solution was

added and the titrations were carried out by addition of known volumes of sodium hydroxide solution ($2 \leq \text{pH} \leq 12.5$). Absorption spectra versus pH were recorded using a Varian (Cary 3) spectrophotometer or a Shimadzu 2101-PC equipped with an adjustable cell holder and thermoregulated cell compartment ($25.0(2)^\circ\text{C}$). The software SPECFIT Global Analysis System V3.0 32 bit for Windows⁴¹ was used to calculate the stability constants ($\log \beta$) of the complexes formed.

Isothermal Titration Calorimetry (ITC). The Cu(II) complex was investigated at $\text{pH} = 4.3$ by an ITC titration of a solution of L_T ($2.01 \times 10^{-4} \text{ M}$) with a solution of Cu(II) in acetate buffer (0.1M). The heats of formation were measured on a Microcal ITC200 titration microcalorimeter. The sample cell (0.202 mL) was filled with the L_T solution and the Cu^{2+} solution was placed in a 40 μL continuously stirred (1000 rpm) syringe. The injection sequence consisted in a first injection of 0.4 μL that was discarded in the data analysis, to remove the effect of diffusion across the syringe tip during the equilibration period, followed by 19 injections of 2 μL aliquots. The injections were separated by 150s and the experiment was repeated twice in a row for a total of 38 injections of 2 μL to reach saturation of the system, corresponding to $[\text{Cu}]_{\text{tot}}/[\text{L}_T]_{\text{tot}} = 4.5$. The 2 sets of data were combined and fitted together using the Hyp ΔH program.⁴²

EPR Spectroscopy. EPR spectra were recorded with a Bruker ESP300e spectrometer (X-band) equipped with a Bruker E035M gaussmeter and an HP 5350B microwave frequency counter according to previously published procedures.^{9b} Samples were prepared at a concentration of $5 \times 10^{-3} \text{ M}$ in ethanol/water (50/50) frozen solutions (150K, Bruker ER4111VY variable-temperature unit). The best resolution was obtained at $T = 150 \text{ K}$ by using the modulation amplitude 8.414 G, time constant 81.92 ms, conventional time 81.92 ms and sweep time 167.7 s. The simulation of the EPR spectra was performed using X-sophe software version 1.1.4 for Mandriva 2006 x86-64 developed by the centre for Magnetic Resonance and the Department of Mathematics of the University of Queensland, Brisbane, Australia, for Bruker Biospin GmbH.⁴³ The software uses a line width model with an angular dependence of g and a Simplex optimisation method with the copper element in a natural abundance.

DFT calculations. All calculations presented in this work were performed employing the Gaussian 09 package (Revision B.01).⁴⁴ Full geometry optimizations were performed in aqueous solution employing DFT within the hybrid meta-GGA approximation with the TPSSh exchange-correlation functional.⁴⁵ For the model systems 1,1'-(pyridine-2,6-diyl)bis(N,N -dimethylmethanamine) and 1,1'-(thiophene-2,5-diyl)bis(N,N -dimethylmethanamine) we used the standard Ahlrich's valence triple- ξ basis set with polarization functions (TZVP),⁴⁶ while for Cu(II) complexes we employed the standard Ahlrichs' valence double- ξ basis set including polarization functions (SVP).⁴⁷ No symmetry constraints have been imposed during the optimizations. In the case of copper complexes calculations were performed by using an unrestricted model, and therefore spin contamination⁴⁸ was assessed by a comparison of the expected difference between $S(S+1)$ for the assigned spin state [$S(S+1) = 0.75$ for the mononuclear copper(II) complexes investigated here] and the actual value of $\langle S^2 \rangle$. Spin contamination was found to be negligible [$\langle S^2 \rangle - S(S+1) < 0.0055$]. The stationary points found on the potential energy surfaces as a result of geometry optimizations were tested to represent energy minima rather than saddle points via frequency analysis. The default values for the integration grid (75 radial shells and 302 angular points) and the SCF energy convergence criteria (10^{-8}) were used in all calculations. Solvent effects were included by using the polarizable continuum model (PCM), in which the solute cavity is built as an envelope of spheres centered on atoms or atomic groups with

appropriate radii. In particular, the integral equation formalism (IEFPCM) variant as implemented in Gaussian 09 was used.⁴⁹

Synthesis

General Methods. Column chromatography and flash column chromatography were performed respectively on silica (0.063-0.200 mm, Merck), and silica gel (40-63 μm , Merck). Solvent mixtures used for TLC and flash column chromatography are reported in v/v ratios. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer at 200 MHz for proton frequency and 50 MHz for carbon frequency. ^{31}P NMR spectra (161.9 MHz) were recorded on Avance 400 apparatus. Chemical shifts are given in parts per million, relative to residual protic solvent peak.⁵⁰ IR spectra were recorded on a Nicolet 380 FT-IR spectrometer (Thermo Scientific). Mass spectra (MS) of synthesized compounds and elemental analysis were obtained by the Service Commun d'Analyse de l'Université de Strasbourg. Solvents were used as purchased. 2,5-dibromomethylthiophene¹³ and tetraethyliminobis(methanephosphonate)¹⁴ were prepared according to literature procedures.

octaethyl (((thiophene-2,5-diylbis(methylene))bis(azanetriyl))tetrakis(methylene))tetrakis(phosphonate), 2. In a Schlenck tube under nitrogen atmosphere, 1 (1.20 g, 4.4 mmol), tetraethyliminobis(methanephosphonate) (2.90 g, 9.14 mmol) and flame dried K_2CO_3 (2.5 g, 18.1 mmol) were dissolved in 20 mL distilled CH_3CN and heated at 60°C for 60 h. The solution was cooled to r.t., evaporated to dryness, and the residue was purified by column chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$; 100/0 to 85/15) to afford 2 (1.92 g, 2.58 mmol, 58%) as a viscous solid. ^1H -NMR (CDCl_3 , 200 MHz): δ 6.70 (s, 2H); 3.92-4.07 (m, 20H), 3.01 (d, 8H, $^2J_{\text{PH}} = 9.9\text{ Hz}$); 1.18 (t, 24H, $^3J = 6.9\text{ Hz}$). ^{13}C -NMR (CDCl_3 , 50 MHz): δ 140.2, 126.8, 61.8 (d, $^2J_{\text{PC}} = 2\text{ Hz}$), 55.1 (t, $^3J_{\text{PC}} = 5.5\text{ Hz}$), 49.2 (dd, $^2J_{\text{PC}} = 104\text{ Hz}$, $^3J_{\text{PC}} = 5.5\text{ Hz}$), 16.4 (d, $^3J_{\text{PC}} = 2.0\text{ Hz}$). ^{31}P -NMR (CDCl_3 , 161.9 MHz): δ 24.21. EI⁺/MS: m/z 742.3 (52 %, M^+), 605.4 (85 %, $[\text{M-P(O)(OEt)}_2]^+$).

(((thiophene-2,5-diylbis(methylene))bis(azanetriyl))tetrakis(methylene))tetrakisphosphonic acid, L_7H_8 . To a solution of 2 (1.20 g, 1.61 mmol) in 20 mL CH_2Cl_2 , was added TMSBr (8.5 mL, 64.4 mmol). The solution was agitated at r.t. for 24 h. A second addition of TMSBr (8.5 mL, 64.4 mmol) was made and the solution agitated again for 24 h. The solvent was evaporated to dryness and the residue was recovered in MeOH (25 mL) stirred for 3 h and evaporated to dryness. The solid was dissolved in MeOH and agitated for 24 h, evaporated to dryness, redissolved in a minimum amount of MeOH and precipitated by the addition of CH_2Cl_2 to afford L_7H_8 (0.59 g, 1.13 mmol) in 70% yield. ^1H -NMR (D_2O , 200 MHz): δ 7.44 (s, 2H), 4.95 (s, 4H), 3.51 (d, 8H, $^2J_{\text{PH}} = 12.8\text{ Hz}$). ^{13}C -NMR (D_2O , 75 MHz): δ 134.16, 53.32, 50.2 (d, $^1J_{\text{PC}} = 144\text{ Hz}$). ^{31}P -NMR (D_2O , 161.9 MHz): δ 7.87. Found: C, 21.33; H, 4.41; N, 4.85. Calc. for $\text{C}_{10}\text{H}_{22}\text{N}_2\text{O}_{12}\text{P}_4\text{S}_2\text{H}_2\text{O}$: C, 21.67; H, 4.73; N, 5.05. IR (cm^{-1} , ATR): ν 715 (w), 933 (s), 1011 (m), 1130 (s), 1420 (w), 1436 (w), 1454 (w), 2991 (w). ESI/MS: m/z 516.97 (100%, 516.976 calc for L_7H_7).

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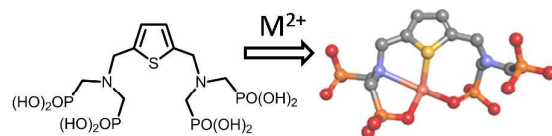
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Table of content :

Graphical abstract:



$\Delta\text{Log}K > 5$ for Cu(II) vs Ni(II), Zn(II)

A tetraphosphonated thiophene based ligand was synthesized and showed decreased stability but increased selectivity relative to similar (hetero)aromatic analogues.