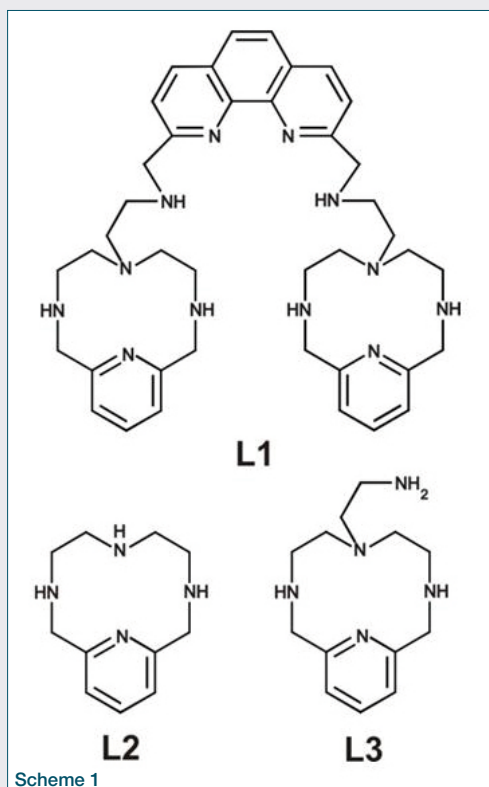


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## MOVEMENT OF $\text{Cu}^{2+}$ METAL IONS WITHIN A POLYTOPIC DOUBLE TAIL-TIED SCORPIAND-TYPE RECEPTOR BY EQUILIBRIUM AND KINETIC STUDIES

Coordinated molecular reorganisations induced by chemical or physical impuls are central to life. Here it is reported one of the first kinetics studies of metal reorganisations between the different sites of a tritopic polyaza ligand that can be described as a double scorpiand-type ligand.

Organized molecular motions are at the heart of crucial biological processes. For instance,  $\text{Ca}^{2+}$  induced conformational changes of the calmoduline family of proteins trigger the activity of different enzymes, ionic pumps and other proteins [1]. The rotational motion of flagella that permits the straight swimming of bacteria constitutes a beautiful example of a pH-driven molecular motion [2]. ADP condensation with the so-called inorganic phosphate to give ATP in  $F_0/F_1$  ATP synthase is associated to a rotary motion activated by the entrance of protons into mitochondria or chloroplasts [1, 3]. In the last times, these motions have inspired the research of a number of groups that have prepared more or less sophisticated systems able to perform movements and/or reorganizations controlled by external stimuli that can be of a chemical (pH gradient, presence of a metal ion, etc.) or a physical nature (light irradiation, flux of electrons, etc.). The preparation of first catenanes and rotaxanes, in which a molecule is either interlocked or threaded with respect to another one, represents a real breakthrough in this field of chemistry [4]. Another strategy for achieving systems able to perform controlled molecular motions and reorganizations consists of making molecules having a rigid and a flexible unit, so that the latter unit can change its position with respect to the former one corresponding to a given chemical or physical impulse. Within this topic, Kaden, Fabbrizzi and

García-España's groups [5] started several years ago to prepare polyamines consisting of a fixed macrocyclic core appended with a flexible arm, coined these compounds with the term "scorpiand" to describe the movement performed by the tail to coordinate a metal center placed in the macrocyclic core. Furthermore, García-España's group has recently designed several ligands consisting of two macrocyclic cores appended with a flexible arm and connected through a coordination unit such as phenanthroline (*phen*) or pyridine named with the term "double tail-tied scorpiands", for its similarity to two scorpiands interconnected by their tails [6]. Here it is reported the kinetics of  $\text{Cu}^{2+}$  reorganisation motions within the polytopic ligands L1 and its thermodynamic properties. L1 can be described as a double tail-tied scorpiand-type ligand in which the tails of two identical scorpiand moieties have been connected through a 2,9-dimethylphenanthroline unit [6]. Therefore, L1 presents three clearly differentiated binding sites: two macrocyclic units, one phenanthroline site and the secondary nitrogen atoms at the bridge (Scheme 1). The relative disposition of the different binding sites of the ligand prevents their simultaneous coordination to a single  $\text{Cu}^{2+}$  ion, allowing a potential motion of the metal ion between them. Furthermore, the spectroscopic properties of the phenanthroline and pyridine units can permit to signal either the binding and releasing of  $\text{Cu}^{2+}$  from these sites.

## Results and discussions

In order to check the coordination properties of L1, it has been carried out potentiometric studies on the formation of Cu<sup>2+</sup> complexes of L1 (Tab. 1) [7]. The pH-metric titrations show formation of mono-, bi- and trinuclear species. The stoichiometries found for mononuclear species are CuH<sub>x</sub>L<sup>(2+x)</sup> with x varying from 3 to 0, binuclear Cu<sub>2</sub>H<sub>x</sub>L<sup>(4+x)</sup> species with x ranging from 2 to -1 and a trinuclear species of Cu<sub>3</sub>L<sup>6+</sup> stoichiometry. Regarding to mono- and binuclear complexes, the first aspect that deserves to be commented is the close values of the stepwise formation constants of the 1:1 and 2:1 complexes, Cu<sup>2+</sup> + L ⇌ CuL<sup>2+</sup>, log K=20.3(1) and CuL<sup>2+</sup> + Cu<sup>2+</sup> ⇌ Cu<sub>2</sub>L<sup>4+</sup>, log K=19.0(1), suggesting that complexation occurs at independent sites of the molecule. These values are somewhat higher than that corresponding to Cu<sup>2+</sup> coordination to L2 (log K=17.78) and closer to that found for L3 (log K=20.43). Taking account these values and the crystal structures obtained for [CuL2](ClO<sub>4</sub>) and [CuL3](ClO<sub>4</sub>)<sub>2</sub> in which Cu<sup>2+</sup> is coordinated to the four nitrogens of the macrocyclic cavity for L2 [8] and an additionally nitrogen of the side arm for L3 [9], it can be suggested that in the CuL<sup>2+</sup> and Cu<sub>2</sub>L<sup>4+</sup> species each metal ion is coordinated to one macrocyclic cavity and the adjacent aliphatic amine group in the linking unit.

Additional information of the Cu<sup>2+</sup> coordination mode was provided by paramagnetic <sup>1</sup>H NMR experiments on solutions containing the binuclear Cu<sub>2</sub>L<sup>4+</sup> complex. Those experiments provide further evidence of penta-coordination for both metal ions in agreement with the electronic spectra and the results of the potentiometric study.

The constant for coordination of the third metal ion is lower (Cu<sub>2</sub>L<sup>2+</sup> + Cu<sup>2+</sup> ⇌ Cu<sub>3</sub>L<sup>6+</sup>, log K=4.9) than that for the Cu<sup>2+</sup>-phen complex (log K=7.4) [10]. This difference in stability can be understood in terms of the steric effects associated with the bulky substituents in the phen unit and the electrostatic repulsion between the third metal ion and the highly positive binuclear complex. In addition, there is the possibility that coordination of the third Cu<sup>2+</sup> occurs with structural reorganization, so that the two previously coordinated metal centers are coordinated exclusively at the macrocyclic sites allowing for coordination of the entering Cu<sup>2+</sup> at the phen site and the aliphatic nitrogens in the bridges.

Furthermore, the analysis of paramagnetic <sup>1</sup>H NMR experiments on solutions containing the trinuclear Cu<sub>3</sub>L<sup>6+</sup> complex indicates for the trinuclear complex two possible coordination modes, in the first one two copper ions would be pentacoordinated to the four nitrogens of the macrocyclic cavity and the nitrogen of the side arm while the third copper ion would be

298.1 ± 0.1 K.

Reaction <sup>a</sup>	L1	L2	L3
3H + Cu + L ⇌ CuH <sub>3</sub> L	46.28(5) <sup>b</sup>		
2H + Cu + L ⇌ CuH <sub>2</sub> L	39.25(6)		
H + Cu + L ⇌ CuHL	30.40(7)		24.28(2)
Cu + L ⇌ CuL	20.27(9)	17.78(2)	20.43(3)
Cu + L + H <sub>2</sub> O ⇌ CuL(OH) + H			9.42(3)
2H + 2Cu + L ⇌ Cu <sub>2</sub> H <sub>2</sub> L	47.74(9)		
H + 2Cu + L ⇌ Cu <sub>2</sub> HL	45.03(7)		
2Cu + L ⇌ Cu <sub>2</sub> L	39.31(9)		
2Cu + L + H <sub>2</sub> O ⇌ Cu <sub>2</sub> L(OH) + H	28.84(9)		
3Cu + L ⇌ Cu <sub>3</sub> L	44.19(1)		
CuH <sub>2</sub> L + H ⇌ CuH <sub>3</sub> L	7.02(6)		
CuHL + H ⇌ CuH <sub>2</sub> L	8.85(3)		
CuL + H ⇌ CuHL	10.1(1)		3.85(3)
CuL + H <sub>2</sub> O ⇌ CuL(OH) + H			-11.01(3)
Cu <sub>2</sub> LH + H ⇌ Cu <sub>2</sub> H <sub>2</sub> L	2.71(5)		
Cu <sub>2</sub> L + H ⇌ Cu <sub>2</sub> HL	5.72(4)		
CuL + Cu ⇌ Cu <sub>2</sub> L	19.0(1)		
Cu <sub>2</sub> L + H <sub>2</sub> O ⇌ Cu <sub>2</sub> L(OH) + H	-10.46(6)		
Cu <sub>2</sub> L + Cu ⇌ Cu <sub>3</sub> L	4.9(1)		

<sup>a</sup> Charged omitted. <sup>b</sup> Values in parenthesis show standard deviation in the last significance figure.

Tab. 1.- Logarithms of the stability constants for the formation complexes of Cu<sup>2+</sup>: L1, L2 and L3 calculated in 0.15 M NaCl at 298.1±0.1 K

only coordinated to the phenanthroline ring completing its coordination sphere with solvent molecules. In the second coordination mode, the three copper ions would be four-coordinated; two of the copper ions would be bound by the nitrogens of the macrocyclic subunits while the third copper ion would be coordinated to the phenanthroline moiety and the two secondary amino groups of the arms (Scheme 2). However, the analysis of the stability constant values seems to fit better with the first proposed coordination mode (Scheme 2B) [11].

The distribution diagrams show that the nuclearity of the species formed depends very much on the Cu<sup>2+</sup>-L molar ratio (Fig. 1). Trinuclear complexes are observed in the whole pH range above pH ca. 3 for 3:1 Cu<sup>2+</sup>:L molar ratio. Although binuclear complexes have been reported in many systems consisting of two macrocycles linked by different alkyl or aryl bridges, the number of systems in which trinuclear species has been evidenced is much more scarce [12].

Kinetic experiments were performed to obtain information about the dynamics of the processes involving the coordination of one, two or three metal ions to a single molecule of the receptor. To this purpose, solutions containing L1 were mixed in a stopped-flow instrument with solutions containing Cu<sup>2+</sup> at the concentrations required to achieve a Cu:L1 molar ratio of 1:1, 2:1 or 3:1. To obtain information about the relative contributions of the different protonated species of L1 to the rate of complex formation the kinetic experiments were carried out at different starting pH values within the 3.0-5.5 range [13].

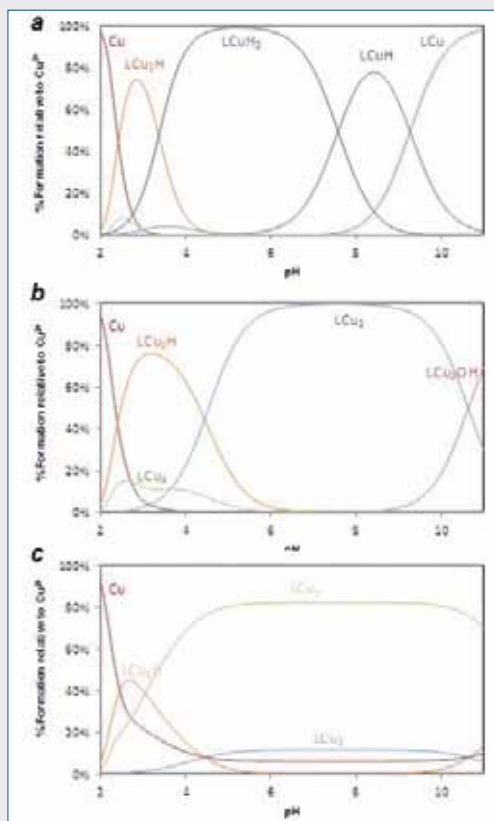
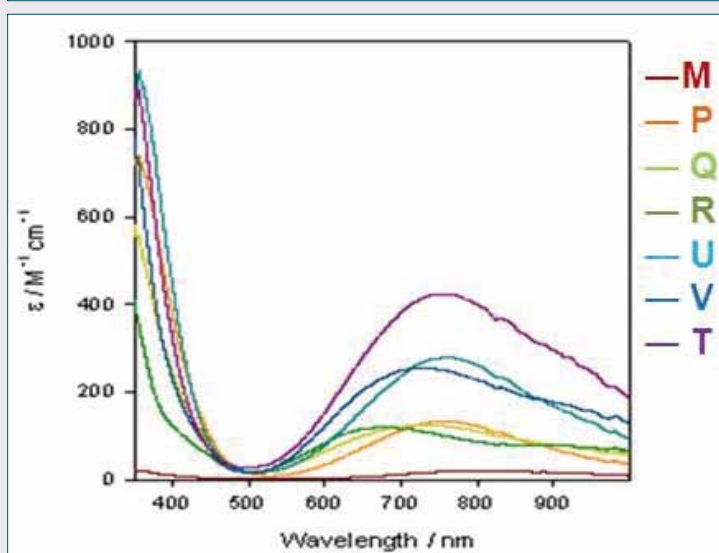
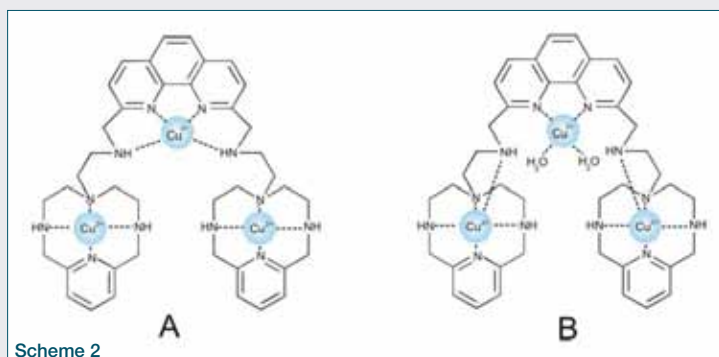


Fig. 1 - Distribution diagrams of the species for the L1/Cu<sup>2+</sup> systems as a function of pH in aqueous solution in 0.15 M NaCl at 298.1 K; [L1]=1×10<sup>-3</sup> M: a) [Cu<sup>2+</sup>]=1×10<sup>-3</sup> M, b) [Cu<sup>2+</sup>]=2×10<sup>-3</sup> M and c) [Cu<sup>2+</sup>]=3×10<sup>-3</sup> M



**Fig. 2** - Spectra of the intermediates and products observed in the formation of mono-, di- and trinuclear complexes

The analysis of the data indicates that the formation of mono, bi and trinuclear  $\text{Cu}^{2+}$  complexes under the experimental conditions used occurs from the  $\text{H}_6\text{L}^{5+}$  species. Although  $\text{H}_6\text{L}^{6+}$  is the prevalent species under those conditions, it appears that its higher charge and the hydrogen-bonding network make this species inefficient for complex formation [6].

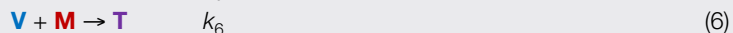
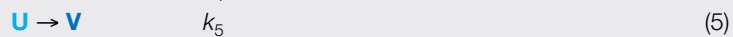
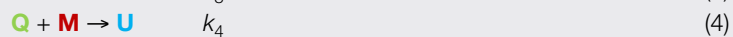
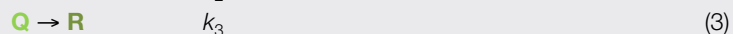
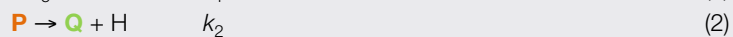
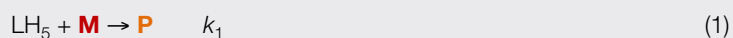
Experiments in 1:1 molar ratio provide information about the kinetics of coordination of the first metal ion and they reveal that it occurs with the initial formation of a species (**P**,  $k_1$ , Scheme 3, see spectra in Fig. 2) with a UV-vis spectrum typical of  $\text{Cu}^{2+}$  coordinated to the phenanthroline centre [14]. However, this species evolves more slowly to a species (**R**,  $k_2$ , Scheme 3, Fig. 2) with a maximum at 680 nm which coincides with that observed for complexes with the metal ion coordinated to the macrocyclic cavity, although some interaction with the NH group in the side arm cannot be ruled out as evidenced by the equilibrium results [8, 9]. In between, there is another intermediate with a band centered at 730 nm (**Q**,  $k_3$ , Scheme

3, Fig. 2), which seems to indicate that the metal ion is coordinated simultaneously to the phenanthroline subunit and some of the aliphatic nitrogen atoms [13]. The initial coordination to the phen site appears to be a consequence of the protonation pattern of the ligand that reduces the number of free donor atoms available for complex formation.

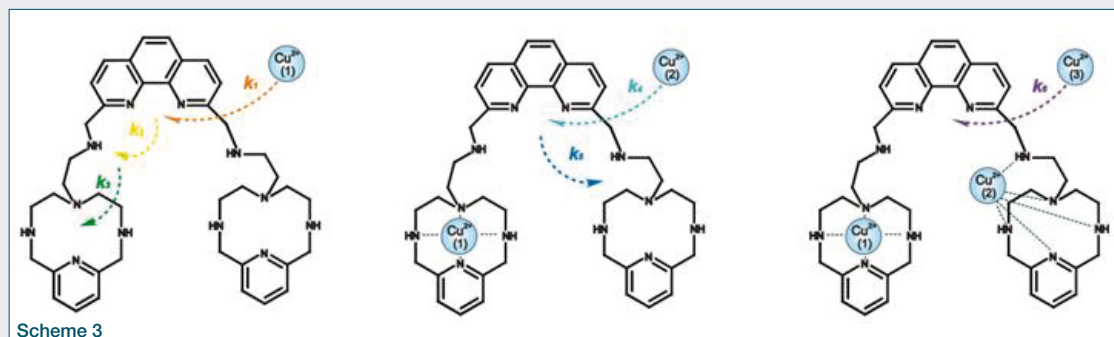
The rate constant for the first formation step is  $k_1=(1.27\pm 0.01)\times 10^4 \text{ M}^{-1}\text{s}^{-1}$  which is much slower than that observed for the formation of  $\text{Cu}^{2+}$  complexes with *phen* ( $6.4\times 10^7 \text{ M}^{-1}\text{s}^{-1}$ ) [15]. However, this difference can be easily rationalized by considering the electrostatic repulsion between the metal ion and the highly protonated ligand species. The subsequent reorganization processes in the mononuclear complex take place with first order rate constants of  $k_2=0.200\pm 0.006 \text{ s}^{-1}$  and  $k_3=(5.67\pm 0.08)\times 10^{-2}\text{s}^{-1}$ .

The analysis of kinetic experiments with 2:1 (Cu:L) molar ratio reveals that the second metal ion reacts with intermediate **Q** to form initially a binuclear species with a maximum at 760 nm (**U**,  $k_4$ , Scheme 3, Fig. 2). As this intermediate evolves to a species with a band centred at 730 nm (**V**,  $k_5$ , Scheme 3, Fig. 2), it appears that the second metal ion is also moving from its initial position in the *phen* site to a phenanthroline-aliphatic coordination. The kinetic data do not provide any evidence of subsequent rearrangement to accommodate this second ion exclusively at the macrocyclic site.

The second order rate constant for coordination of the second metal ion is  $k_4=(3.80\pm 0.05)\times 10^2 \text{ M}^{-1}\text{s}^{-1}$ , whereas the rate constant for the subsequent reorganization process is  $k_5=0.302\pm 0.002 \text{ s}^{-1}$ . The smaller value of  $k_4$  with respect to  $k_1$  can be again rationalized in terms of electrostatic considerations, whereas the similarity of  $k_2$  and  $k_5$  adds further support to the interpretation that they correspond to the same type of molecular reorganization:



Kinetic experiments leading to the formation of the trinuclear species indicated that the third  $\text{Cu}^{2+}$  is placed in the only available site, coordinated to the phenanthroline unit (**T**,  $k_6$ , Scheme 3, Fig. 2).



The process occurs with a second order rate constant  $k_g=(1.2\pm 0.1)\times 10^2 \text{ M}^{-1}\text{s}^{-1}$ , and leads to a species with an absorption maximum at 750 nm, which is probably the result of the overlap between a  $\text{Cu}^{2+}$ -phen chromophore (ca. 770 nm) [12b, 13], and two  $\text{Cu}^{2+}$  ions coordinated to the macrocyclic cavities (ca. 690 nm).

To complete the information about the dynamics of the reorganization processes in Cu:L complexes, kinetic studies on complex decomposition were also carried out. For that purpose, solutions containing  $\text{Cu}^{2+}$  and L1 in different molar ratio (1:1, 2:1 and 3:1) were prepared and the pH was adjusted according to the species distribution curves to get solutions containing the desired mono-, bi- and tri-nuclear complexes. When these solutions were mixed in the stopped-flow instrument with an excess of acid, the spectra recorded immediately upon mixing do not correspond to those recorded before mixing but it shows in all cases a band centered at 750 nm. For experiments starting with di- and tri-nuclear species, the initial rapid step corresponds to their conversion to a mononuclear species with the  $\text{Cu}^{2+}$  ion coordinated at the phen subunit, probably because the electrostatic repulsion between the metal centers favors the rapid release of all the metal ions except one. More interesting is the observation of a rapid conversion also during the decomposition of the mononuclear species, the development of a band at 750 nm providing strong evidence in the sense that the way out of the metal ion during complex decomposition is essentially the inverse of that depicted in Scheme 3 for complex formation.

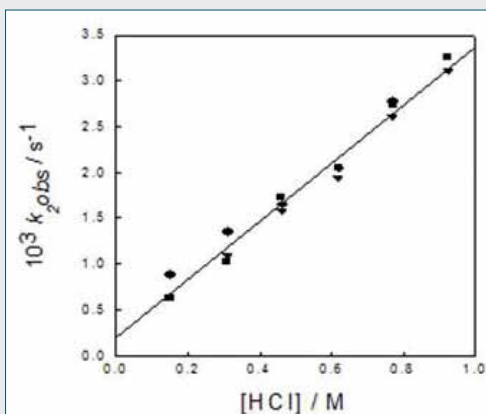


Fig. 3 - Plot of dependence on the acid concentration of the observed rate constant for the second kinetic step in the acid-promoted decomposition of the mono- (circles), di- (triangles) and trinuclear (squares) complexes.

Following the initial rapid spectral changes, the intensity of the band at 750 nm decreases so slowly that the kinetics of the process had to be studied using conventional UV-Vis spectrophotometry and high concentrations of acid. The kinetic results were independent of the species in the starting solution (Fig. 3), thus confirming that the intermediate formed during the decomposition process is the same in all cases. The  $k_{2,obs}$  values show a linear dependence with the acid concentration, and the fit by eq. 7 leads to  $a=(1.8\pm 0.7)\times 10^{-4} \text{ s}^{-1}$  and  $b=(3.2\pm 0.1)\times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ .

$$k_{2,obs} = a + b [\text{HCl}] \quad (7)$$

## Conclusions

The whole set of kinetic results in this extended abstract provide a full picture of the molecular reorganizations in metal complexes with polytopic receptors, and they indicate that this kind of ligands can show well defined routes for the movement of the metal ions. Learning about the factors that define these reorganizations and their kinetics represent a convenient starting point for the development of systems undergoing controlled movements that occur with a given time scale. The equilibrium studies were performed in the supramolecular group in the Universidad de Valencia under the supervision and mentoring of E. García-España and the kinetics analysis were performed in the Universidad de Cadiz by the group for study of stability and mechanisms of inorganic reactions under the supervision of M.G. Basallote.

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# RIASSUNTO

## Studi termodinamici e cinetici hanno rivelato il movimento di ioni di Cu(II) all'interno di un recettore politopico con struttura di doppio scorpiando a code unite

Riorganizzazioni molecolari coordinate indotte da impulsi chimici o fisici sono centrali per la vita. Viene qui riportato uno dei primi studi cinetici di riorganizzazioni di metallo tra i differenti siti di un legante poliaza tritopico che può essere descritto come un legante del tipo a doppio scorpiando.