Toward a ligand specific of Pb^{2+} with respect to the Zn^{2+} and Ca^{2+} cations: A track from quantum chemistry

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ABSTRACT

From computational chemistry simulations, a ligand has emerged that could be selective of Pb^{2+} toward Zn^{2+} and Ca^{2+}, an important point when designing new chelators usable *in vivo* as remediation agents against lead poisoning (saturnism). Some electronic properties of 1,4,7,10,13,16-hexaoxa-cyclooctadeca-2,5,8,11,14,17-hexaene (*hoc-18*) are examined here in details, together with those of some thio-analogs. Several interpretative *ab initio* methodologies that allow clarifying a number of characteristics of *hoc-18* towards Zn^{2+}, Ca^{2+} and Pb^{2+} are considered from the viewpoint of coordination chemistry.

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1. Introduction

Lead intoxication – saturnism – has been known since antiquity, but few theoretical studies have been dedicated to a better understanding of saturnism at a molecular scale, and to the design of new specific chelators usable in remediation processes with reduced risks of side-effects such as the elimination of other metallic elements essential to *in vivo* processes, or redeposition phenomena [1,2]. Such an achievement requires knowing more on the coordination chemistry of the Pb^{2+} cation.

Numerous crystallographic and theoretical studies have made clear that Pb^{2+} complexes belong to two distinct families, the definitions of which we take from the pioneering paper by Shimoni-Livny et al. [3]:

(i) *holodirected, in which the bonds to ligand atoms are distributed throughout the surface of an encompassing globe, and* (ii) *hemidirected, in which the bonds to ligand atoms are directed throughout only part of an encompassing globe, i.e., there is an identifiable void in the distribution of bonds to the ligands.*

In the second case, the valence lone pair of the cation is stereochemically active and expands in the hemispheric void not occupied by the ligands; in the first case, this lone pair remains centered at the cation position and is stereochemically inactive. Despite this dichotomy relies on a purely static viewpoint and neglects dynamic effects [4], it has been able to provide many hints about the molecular toxicity induced by Pb^{2+} in a number of rigid metalloenzymatic sites such as those encountered in proteins or their models [5–19].

From a given stoichiometry, it is however not evident to predict whether a Pb^{2+} complex will be holo- or hemidirected. Most certainly, low-coordination complexes can be expected to be hemidirected whereas those of higher coordination can be expected to be holodirected [3,20,21]; but it has been recently evidenced that things are not that simple and that, among other parameters, the charges of the ligands are of primary importance [22].

A new cause of complexity has emerged from a recent theoretical work firstly revealing a third structural or topological family of Pb^{2+} complexes: *bisdirected* structures in which the external valence lone pair of Pb^{2+} shares the two hemispheres that define a planar structure [23]. Following the description made by Shimoni-Livny et al. [3]: this new situation must be defined as cases in which *the bonds to ligand atoms are directed throughout two parts of an encompassing globe, but leaving <u>TWO</u> identifiable voids in the distribution of bonds to the ligands, one of them in each hemisphere of an encompassing globe*. It was initially thought that such a topology comes from the highly symmetrical character of the complex investigated, but it is now clear that such behavior is intrinsic as it can also be encountered within less symmetrical surroundings such as those relevant to some metalloproteins, the crystallographic leaded-structures of which are known [24].

To the best of our knowledge, the first molecular structure reported to exhibit a bisdirected topology characterized as such is that made of planar ligand 1,4,7,10,13,16-hexaoxa-cyclooctadeca-2,5,8,11,14,17-hexaene (thereafter ligand *hoc-18*, Figure 1) chelating Pb^{2+} [23].

In this contribution, we will report more deeply on the coordination properties of *hoc-18*, together with those of some thio-derivatives, in order to better understand why this ligand appears

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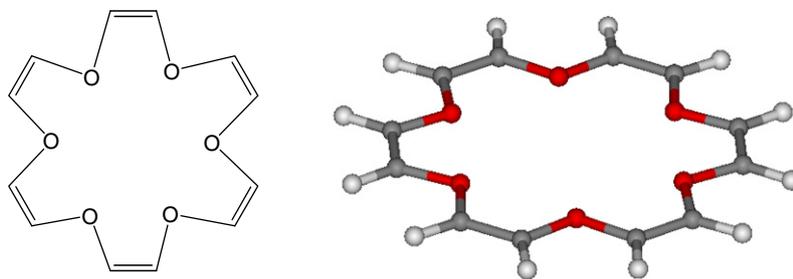[1] Current address: Theoretical Chemistry Department, Lund University, P.O. Box 124, 22100 Lund, Sweden.
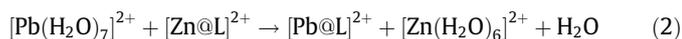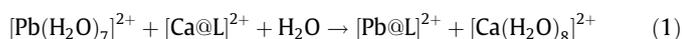
Figure 1. Ligand 1,4,7,10,13,16-hexaoxa-cyclooctadeca-2,5,8,11,14,17-hexaene (L = *hoc-18*).

to be specific of Pb^{2+} with respect to the Ca^{2+} and Zn^{2+} cation, an essential property if aiming at _in vivo_ chelation or remediation. To achieve that point, quantum chemistry computations have been performed and several interpretative tools have been applied.

2. The investigation protocol

2.1. The model

In order to check the specificity of *hoc-18* (ligand L) for Pb^{2+} with respect to Zn^{2+} and Ca^{2+}, we have determined the $\Delta_r E$ and $\Delta_r G$ (Gibbs free energy) values of the following *substitution reactions*:

$$[Pb(H_2O)_7]^{2+} + [Ca@L]^{2+} + H_2O \rightarrow [Pb@L]^{2+} + [Ca(H_2O)_8]^{2+} \quad (1)$$

$$[Pb(H_2O)_7]^{2+} + [Zn@L]^{2+} \rightarrow [Pb@L]^{2+} + [Zn(H_2O)_6]^{2+} + H_2O \quad (2)$$

For both cases, negative $\Delta_r E$ or $\Delta_r G$ values indicate that the chelation of Pb^{2+} by ligand L is favoured. The reason why considering substitution reactions and not simply complexation reactions is that, if living or outliving a day *in vivo*, ligand L very certainly will be coordinated to some cation. The reason why considering hydrated cations and not naked entities is that *in vivo* medium is not gas phase: all cations are mostly coordinated to either a protein, or a set of ligands, or, in our model, water molecules. In the present study, the hydration numbers of the cations have been taken from previous dynamic studies dedicated to their solvation [25–27].

2.2. Computational procedures

All energies and geometries were obtained using the GAUSSIAN-09 code [28]. Within the Density Functional Theory framework, the B3LYP functional was used [29–31]; a few MP2 computations were also performed. Following our previous studies, the 6-31+G** basis set was considered for all atoms, except for Pb^{2+}, Ca^{2+} and Zn^{2+} which have been described by the SDD pseudopotentials, either in their large core (LC, 78 core electrons for Pb^{2+}) or small-core (SC, 60 core electrons for Pb^{2+}) formulations [32,33]. All structures were fully optimized, and a vibrational analysis was performed within the harmonic approximation in order to check the nature (minimum or saddle point) of the species obtained. The vibrational frequencies were used as such (i.e. no scaling procedure was applied) to estimate Gibbs free energies at $T = 298$ K and $P = 1$ bar.

The interpretative methodologies considered involve the well-established Natural Population Analysis (NPA) which allows recovering reasonable partial atomic charges, and the topologic study of the Electronic Localization Function (ELF) which allows visualizing domains of space (*basins*) where electronic pairing is high and thus recovering covalent bonds and lone pairs [34–37]. Beyond, we have also considered the newly-introduced Non Covalent Interaction

(NCI) approach to reveal 3D regions of molecular spaces within which weak interactions expand [38,39].

3. Results

3.1. Structures and energies

Table 1 reports the $\Delta_r E$ and $\Delta_r G$ values obtained from different levels of computation for Eqs. (1) and (2).

The B3LYP/SDD(LC) energies and Gibbs free energies are negative, which means that the substitutions are favoured toward the complexation of Pb^{2+} by *hoc-18*. The same conclusion holds for the B3LYP/SDD(SC) computations, and is corroborated by the MP2/SDD(LC) approach. In view of the magnitude of the $\Delta_r G$ and $\Delta_r E$ values reported in Table 1, *hoc-18* thus appears as a ligand specific of Pb^{2+} with respect to Ca^{2+} and Zn^{2+}.

From a geometrical viewpoint, the structural variations observed using one or another theoretical approach are negligible. From the structures reported on Figure 2, it appears that *hoc-18* chelates Ca^{2+} at the cost of significant distortions within the ligand, and that Zn^{2+} is stabilized 3 Å above the mean plane of the ligand. At the opposite, Pb^{2+} inserts the center of *hoc-18* and maintains the initial and the final planarity of *hoc-18*.

The distortions induced upon the complexation of Ca^{2+} increases the energy of the left-hand part of Eq. (1) as there is an energy cost to pay for breaking planarity of *hoc-18*.

The large distance (3 Å) appearing between the ligand and the cation in the $[Zn@L]^{2+}$ complex does not seem to induce any strong stabilization neither for the cation nor for the planar ligand: at such a distance, only electrostatic interactions can be involved, especially with the oxygen atoms, but there is no way for covalence: this increases the energy of left-hand part of Eq. (2).

$[Pb@L]^{2+}$ appears energetically favoured. Indeed, *hoc-18* is in its planar preferred conformation, no distortion is observed, and Pb^{2+}, located at the center of the complex, is expected to interact with both the in-plane and the out-of-plane orbitals of the ligand, as detailed in a forthcoming section. Such behavior is reflected within

Table 1
Energies and Gibbs free energies of substitutions for *hoc-18* (kcal/mol).

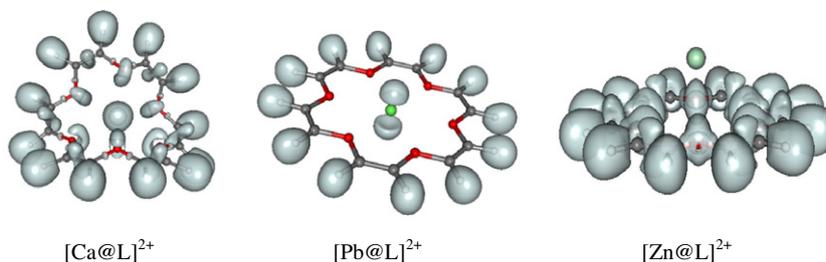| $[M@L]^{2+}$	$\Delta_r E$	$\Delta_r G$
B3LYP/SDD(LC)		
$[Ca@L]^{2+}$	−29	−15
$[Zn@L]^{2+}$	−15	−20
B3LYP/SDD(SC)		
$[Ca@L]^{2+}$	−18	−22
$[Zn@L]^{2+}$	−31	−17
MP2/SDD(LC)		
$[Ca@L]^{2+}$	−50	
$[Zn@L]^{2+}$	−35	

Figure 2. Structural and ELF representations of the [M@L]$^{2+}$ systems. The B3LYP/SDD(LC) electronic densities have been used for the ELF analysis.

Table 2
Energies and Gibbs free energies of substitutions (kcal/mol, B3LYP/SDD(LC)) for ligand 1,4,10,13-tetraoxa-7,16-dithia-cyclooctadeca-2,5,8,11,14,17-hexaene (L').

[M@L']$^{2+}$	$\Delta_r E$	$\Delta_r G$
[Ca@L']$^{2+}$	−27	−16
[Zn@L']$^{2+}$	12	7

Table 3
NPA electronic populations (B3LYP/SDD(LC)) of the 6s and 6p orbitals of Pb^{2+} when complexed to *hoc-18* (L) or to its per-hydrogenated counterpart (L$^{\neq}$).

	6s	6p$_x$	6p$_y$	6p$_z$
[Pb@L]$^{2+}$	1.98	0.12	0.12	0.26
[Pb@L$^{\neq}$]$^{2+}$	1.98	0.15	0.15	0.15

the right-hand parts of Eqs. (1) and (2) leading to a very stable conformation.

3.2. Thio-variations

Pb^{2+} is known to exhibit strong thiophilicity [5–11,14,40,41]. In order to examine whether this property could help in reinforcing the selectivity of *hoc-18* for this cation, a number of ligands derived from *hoc-18* by replacing one or several oxygen atoms by sulfur atoms have been investigated, e.g.: 1,4,10,13-tetraoxa-7,16-dithia-cyclooctadeca-2,5,8,11,14,17-hexaene (ligand L'), 1,7,13-tri-oxa-4,10,16-trithia-cyclooctadeca-2,5,8,11,14,17-hexaene, or 1,4,7,10,13,16-hexathia-cyclooctadeca-2,5,8,11,14,17-hexaene. In any case, it is found that these ligands lose planarity upon complexation; as reported previously for such constrained cyclic structures [23], such behavior might be attributed to the properties of the lone pairs of divalent sulfur when compared to those of divalent oxygen. They also lose selectivity for Pb^{2+}, especially with respect to Zn^{2+}. Table 2 reports, for an illustration, what is obtained with ligand L': according to the $\Delta_r E$ and $\Delta_r G$ values, selectivity for Pb^{2+} is lost with respect to Zn^{2+} despite its pronounced thiophilic character, but is retained with respect to Ca^{2+}, an oxophilic and rather thiophobic cation.

4. Discussion on the origin of the selectivity of *hoc-18*

In order to understand which factor(s) could be implied in the especial selectivity of *hoc-18* for Pb^{2+}, several interpretative methodologies have been employed, relying on the electronic densities obtained at the B3LYP/SDD(LC) level.

4.1. NPA population analysis

Table 3 reports the NPA populations of the 6s and 6p orbitals of Pb^{2+} when chelated by *hoc-18*: a population of 0.26 electron appears in the 6p$_z$ orbital of the Pb^{2+} cation, the formally vacant orbital formally engaged in the conjugation of the cycle. Altogether, populations of 0.12 electron appears in each of the (6p$_x$, 6p$_y$) in-plane orbitals of Pb^{2+}. These points reveal a significant charge transfer from ligand L to the central cation (thereafter LMCT: Ligand to Metal Charge transfer), the origin of which can be understood deeper by considering fictitious ligand L$^{\neq}$, the formal per-hydrogenated form of *hoc-18*: L$^{\neq}$ (namely 1,4,7,10,13,16-hexa-

oxa-cyclooctadecane) derives from *hoc-18* by hydrogenation of all its carbon–carbon double bonds, with no geometrical re-optimization. Table 3 reveals that L$^{\neq}$ transfers only 0.15 electron in each of the (6p$_x$, 6p$_y$, 6p$_z$) vacant orbitals of Pb^{2+}.

Comparing the NPA charges in the Pb^{2+} complexes obtained from complexation with either *hoc-18* or L$^{\neq}$, thus allows concluding that about 0.45 electron are transferred from the oxygen atoms of *hoc-18* towards Pb^{2+}, and that supplementary 0.11 electron are transferred from *hoc-18* toward the 6p$_z$ orbital of Pb^{2+}. All together, this formally vacant orbital finally reaches a rather high population of 0.26 electron, which can be the signature of a supplementary conjugation that may be part of the explanation to selectivity: we here seem to face an example of metallo-aromaticity, a rather well-known behavior when involving transition metals [42,43] but less-frequently reported when a non-transition cation is involved. Having an external electronic configuration 6s^2 6p^0, Pb^{2+} can accept π charge transfer from ligand L. None of Ca^{2+} or Zn^{2+}, which share the external electronic configuration 4s^0, can accept such a transfer as symmetry forbids. Consequently, planarity of *hoc-18* collapses upon complexation by Ca^{2+}, or it expels Zn^{2+} 3 Å away from its center as described above, to find a way still ensuring metal–ligand coordination.

4.2. Joint ELF/NCI analysis

To complete the previous NPA analysis, ELF and NCI investigations have been performed.

Let us first consider the NCI analysis of single *hoc-18* depicted in Figure 3a. Six non-covalent and repulsive interaction regions are evidenced as red domains: they can be attributed to both the repulsion of pseudo-adjacent facing oxygen atoms and to the cycle tensions occurring in the formal OCCO sub-cycles that *hoc-18* is made of. Interestingly, there is a small attractive NCI region located at the center of the cycle. It anticipates that cations should easily coordinate at such a site, provided – of course – that the structure of the ligand is preserved upon the complexation. This notion of pre-organization evidenced by the NCI approach has already been observed in several systems of various complexity [38].

Upon Pb^{2+} coordination (Figure 3b), these six repulsive interaction regions are preserved and even reinforced. They are also slightly shifted toward the central cation: the cycle tensions now involve formal PbOCCO cycles. But six new NCI attractive regions (blue domains) appear. This is the clear signature of *hoc-18* interacting with the central cation. Each of these six 3D-domains is
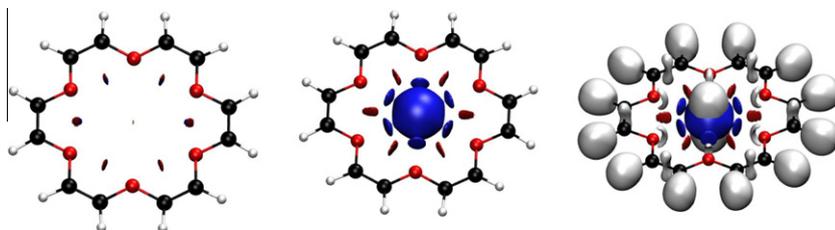
Figure 3. (a) NCI view of ligand L; (b) NCI view of [Pb@L]$^{2+}$; (c) joint NCI/ELF view of [Pb@L]$^{2+}$. For the NCI analysis, red domains correspond to repulsive regions, and blue ones to attractive regions. The B3LYP/SDD(LC) electronic densities have been used for the ELF and NCI analysis.

symmetrical with respect to the molecular plane: they have to be interpreted as the oxygen atoms of *hoc-18* chelating Pb^{2+}, both in the molecular plane – LMCT from the in-plane lone pairs of the oxygen atoms to the vacant (6p$_x$, 6p$_y$) orbitals of Pb^{2+} – and in the conjugation direction – LMCT from the out-of-plane π system towards the 6p$_z$ vacant orbital of Pb^{2+}.

From Figure 3c which superimposes the NCI and ELF domains, it clearly appears that the lone pairs of the oxygen atoms interact with both the in-plane (6p$_x$, 6p$_y$) vacant orbitals of Pb^{2+} and its orthogonal out-of-plane 6p$_z$ orbital.

5. Conclusion

Ligand *hoc-18* – namely 1,4,7,10,13,16-hexaoxa-cyclooctadeca-2,5,8,11,14,17-hexaene – thus exhibits a number of the properties required to selectively chelate Pb^{2+} with respect to Zn^{2+} or Ca^{2+}. Unfortunately, *hoc-18* is an anti-aromatic entity from Hückel's viewpoint. Its synthesis remains however certainly feasible [44,45]; its stability can certainly be improved toward dismutation, or any media-supported redox processes. Replacing oxygen atoms by sulfur atoms seems however not to be the appropriate way of improvement if selectivity for Pb^{2+} with respect to Zn^{2+} is searched. Tuning the anti-aromatic properties of this ligand through playing with extra-cyclic substituents appears more promising.

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