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Enforcing hemidirectionality in Pb(II) complexes: The importance of anionic ligands

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ABSTRACT

Using DFT and ELF topological analysis, we study the directionality of the Pb^{2+} lone pair in the presence of neutral and anionic ligands. Archetypal $[PbL_n(HL)_m]^{2-n}$ complexes ($n = 1–3$, $m = 1–7$, $L = Cl^-$ or SH^-) are investigated in the gas phase or using a solvation continuum. We show that the presence of only one anion within the coordination sphere of Pb^{2+} induces hemidirectionality for all complexes. Such a finding is important for future toxicology studies if one wants to stabilize Pb^{2+} valence shell in a hemidirected structure, a key issue in the search for specific chelators of lead.

1. Introduction

Lead is well-known for its toxicity leading to Saturnism [1–9]. The drugs currently used to extract lead from the body are chelators that are unfortunately not specific of Pb^{2+} as they also remove vital dietary minerals such as Zn^{2+} and Ca^{2+}. Such depletion can lead to important side effects. The aim of this theoretical work is to focus on some characteristics that a chelator must have to be selective. Such an achievement requires a better understanding of the Pb^{2+} valence lone pair behavior in various environments since it has been shown in several quantum chemistry studies to be the driving entity governing the chemical physics of lead at a molecular level [10–17]. Indeed, it is well-known that this lone pair can be hemidirected (extending into one hemisphere and being stereochemically active), holodirected (surrounding the Pb^{2+} cation and being stereochemically inactive), or even bisdirected (stereochemically active but split into two opposite lobes) [13], as depicted in Figure 1. A previous works have shown that the coordination number of Pb^{2+} can be as high as 8 or 9, with the formation of hemi- or holodirected structure, if only neutral ligands are involved. However, if only anionic ligands are considered, the coordination does not exceed 3, leading to hemidirected structures only [16]. Since *in vivo* ligands can be either neutral or anionic, it is of interest to investigate the behavior of the Pb^{2+} valence lone pair in the presence of both neutral and anionic ligands.

In this Letter, model complexes such as $[PbL_n(HL)_m]^{2-n}$ with $n = 1–3$, $m = 1–7$ and $L = Cl^-$ or SH^- have been considered. We chose Cl^-/HCl in order to have a representative electronegative ligand and SH^-/SH_2 as a model of a softer ligand. Following our previous studies, we have resorted to the topological analysis of the Electron Localization Function (ELF) [18,19] to characterize the directionality of the valence lone pair [10–17].

2. Results

2.1. Geometrical study

Tables 1 and 2 display the results for the complexes obtained for each ligand L according to the different number of neutral ligands surrounding the cation.

The analysis of the tables shows that, for a given number of anionic and neutral ligands, complexes $[PbCl_n(HCl)_m]^{2-n}$ have the same type of structure as $[Pb(SH)_n(SH_2)_m]^{2-n}$. For example, in the case of 6 LH neutral ligands and 2 L anionic ligands, we obtain the $[Pb(L)_2(LH)_2]$ complex and 4 free LH.

Concerning the geometry of the complex, the analysis of results can be divided into two sections. First, we will consider the case where all the ligands are in the same hemisphere (complexes with small number of neutral ligands). In that configuration, the hemidirected structure is obvious. The second section concerns the remaining complexes where ligands are more or less all centered around Pb^{2+} (*i.e.* complexes with a high number of neutral ligands). In that case, the orientation of the lone pair cannot be known without any further analysis.

First, let us start to focus on the simplest case. In regard to complexes with one anionic ligand only, the maximal number of neutral ligands being able to interact with the Pb^{2+} cation is 4, organized in squared pyramid geometry. The excess of neutral ligands goes in the second shell of coordination and is stabilized

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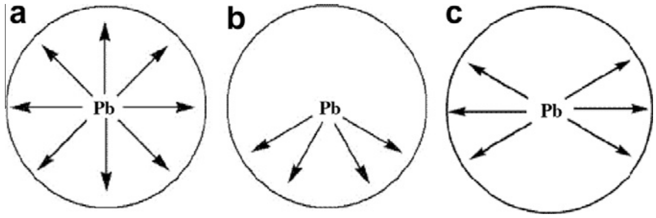


Figure 1. (a) Hemidirectionality vs. (b) holodirectionality vs. (c) bisdirectionality of the Pb^{2+} lone pair. Arrows display the ligand distribution.

by hydrogen interactions with the first shell ligands. The anionic ligand is located about around 2.4 Å from the cation in the case of Cl^-/HCl, about around 2.5 Å in the case of SH^-/SH_2 and the neutral ligands are set around 3.3 Å.

Second, concerning complexes with two anionic ligands, the maximum number of neutral ligands is 2 organized in a *cis*-divacant geometry. The excess of neutral ligands is ejected in the second shell of coordination and is stabilized by hydrogen interactions with the first shell ligands. The anionic ligands are located at 2.5 Å from the cation in the case of Cl^-/HCl, about around 2.6 Å in the case of SH^-/SH_2 and the neutral ligands are set about around 3.3 Å.

At last, complexes with three anionic ligands accept no neutral ligands in the first sphere of coordination. Indeed all the neutral ligands are in the second-shell, around $[PbL_3]^-$. These complexes have a C_{3v} symmetry. The anionic ligands are distant from the metal cation by a 2.7 Å distance.

For complexes containing either less than five neutral ligands and one anionic ligand, or less than four neutral ligands and two anionic ligands, the structures are hemidirected (see Figure 2).

Now we must address the hardest case where the number of neutral ligands is higher: some ligands could be located in the other hemisphere. A representation of the Pb^{2+} lone pair in such complexes could be helpful in order to determine if a transition between hemi- and holodirected structures can occur or not. To do so, we have performed Electron Localization Function (ELF) topological analysis on all complexes.

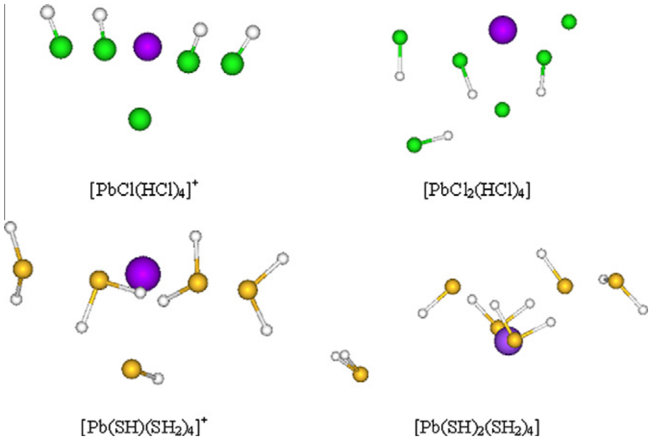


Figure 2. Hemidirected structures of some $[Pb(L)_n(HL)_m]^{2-n}$ complexes (violet: Pb^{2+} atom, yellow: S atom and green: Cl atom). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Figure 3 displays some of them which are representative of the possible repartition of neutral ligands around Pb^{2+}.

The signposted ligands are those belonging to the second sphere of coordination. Each case is discussed below.

In the case of the $[PbCl(HCl)_6]^+$ complex, the second shell HCl molecules are stabilized by hydrogen interactions with ligands from the first coordination sphere. As we can see in Figure 3a all the ligands are located in one hemisphere, so the complex is hemidirected.

In the case of the $[Pb(SH)(SH_2)_6]^+$ complex, one of the two ligands of the second shell (SH_2 1) is located slightly in the hemisphere of the lone pair whereas the other one (SH_2 2) is in the other hemisphere with all the ligands. In spite of this fact, the complex is hemidirected. It can be understood if one knows that this ligand is located at 5.1 Å from the cation: the lone pair has enough free space to extend in this particular case.

In the $[PbL_2(HL)_6]$ complexes, the ligands of the first coordination sphere are all in the same hemisphere (see Figure 3c and d).

Table 1
Various complexes obtained for $L = Cl^-$.

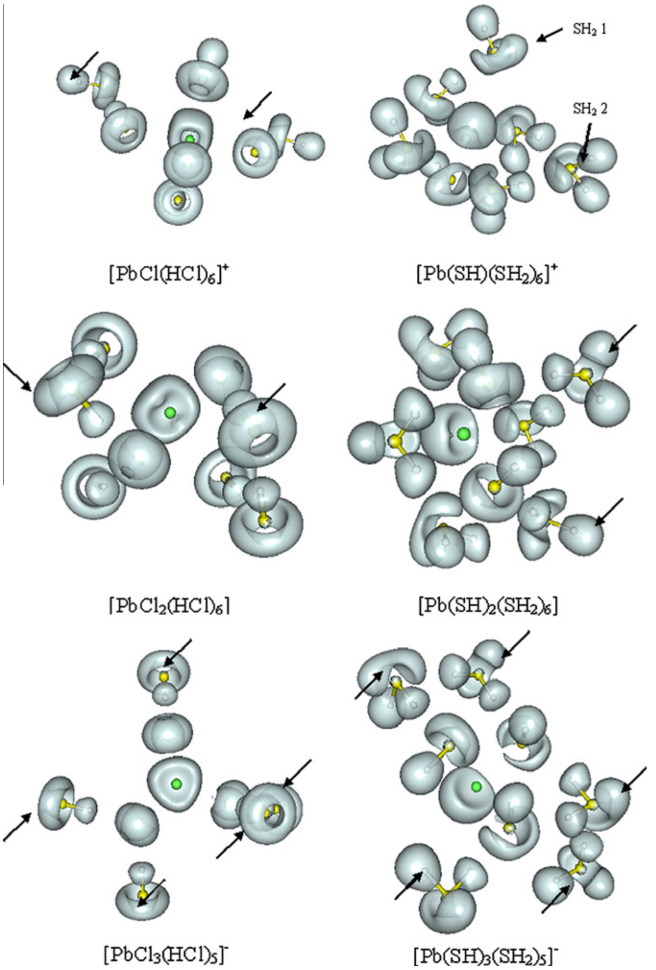
Ligands	HCl	2HCl	3HCl	4HCl
Cl^-	$[Pb(Cl)(HCl)]^+$ C_{2v}	$[Pb(Cl)(HCl)_2]^+$ C_{3v}	$[Pb(Cl)(HCl)_3]^+$ C_{4v}	$[Pb(Cl)(HCl)_4]^+$ Squared pyramid
$2Cl^-$	$[Pb(Cl)_2(HCl)]$ C_{3v}	$[Pb(Cl)_2(HCl)_2]$ C_{4v}	$[Pb(Cl)_2(HI)_2]$ + HCl C_{4v}	$[Pb(Cl)_2(HCl)_2]$ + 2HCl C_{4v}
$3Cl^-$	$[Pb(Cl)_3]^-$ C_{3v}	$[Pb(Cl)_3]^-$ + 2HCl C_{3v}	$[Pb(Cl)_3]^-$ + 3HCl C_{3v}	$[Pb(Cl)_3]^-$ + 4HCl C_{3v}

Ligands	5HCl	6HCl	7HCl
Cl^-	$[Pb(Cl)(HCl)_4]^+$ + HCl Squared pyramid	$[Pb(Cl)(HCl)_4]^+$ + 2HCl Squared pyramid	$[Pb(Cl)(HCl)_4]^+$ + 3HCl Squared pyramid
$2Cl^-$	$[Pb(Cl)_2(HCl)_2]$ + 3HCl C_{4v}	$[Pb(Cl)_2(HCl)_2]$ + 4HCl C_{4v}	$[Pb(Cl)_2(HCl)_2]$ + 5HCl C_{4v}
$3Cl^-$	$[Pb(Cl)_3]^-$ + 5HCl C_{3v}	$[Pb(Cl)_3]^-$ + 6HCl C_{3v}	$[Pb(Cl)_3]^-$ + 7HCl C_{3v}

Table 2
Various complexes obtained for $L = SH^-$.

Ligands	SH_2	$2SH_2$	$3SH_2$	$4SH_2$
SH^-	$[Pb(SH)(SH_2)]^+$ C_{2v}	$[Pb(SH)(SH_2)_2]^+$ C_{3v}	$[Pb(SH)(SH_2)_3]^+$ C_{4v}	$[Pb(SH)(SH_2)_4]^+$ Squared pyramid
$2SH^-$	$[Pb(SH)_2(SH_2)]$ C_{3v}	$[Pb(SH)_2(SH_2)_2]$ C_{4v}	$[Pb(SH)_2(SH_2)_2]$ + SH_2 C_{4v}	$[Pb(SH)_2(SH_2)_2]$ + $2SH_2$ C_{4v}
$3SH^-$	$[Pb(SH)_3]^-$ + SH_2 C_{3v}	$[Pb(SH)_3]^-$ + $2SH_2$ C_{3v}	$[Pb(SH)_3]^-$ + $3SH_2$ C_{3v}	$[Pb(SH)_3]^-$ + $4SH_2$ C_{3v}

Ligands	$5SH_2$	$6SH_2$	$7SH_2$
SH^-	$[Pb(SH)(SH_2)_4]^+$ + SH_2 Squared pyramid	$[Pb(SH)(SH_2)_4]^+$ + $2SH_2$ Squared pyramid	$[Pb(SH)(SH_2)_4]^+$ + $3SH_2$ Squared pyramid
$2SH^-$	$[Pb(SH)_2(SH_2)_2]$ + $3SH_2$ C_{4v}	$[Pb(SH)_2(SH_2)_2]$ + $4SH_2$ C_{4v}	$[Pb(SH)_2(SH_2)_2]$ + $3SH_2$ C_{4v}
$3SH^-$	$[Pb(SH)_3]^-$ + $5SH_2$ C_{3v}	$[Pb(SH)_3]^-$ + $6SH_2$ C_{3v}	$[Pb(SH)_3]^-$ + $7SH_2$ C_{3v}



$[PbCl(HCl)_6]^+$ $[Pb(SH)(SH_2)_6]^+$

$[PbCl_2(HCl)_6]$ $[Pb(SH)_2(SH_2)_6]$

$[PbCl_3(HCl)_5]^-$ $[Pb(SH)_3(SH_2)_5]^-$

Figure 3. ELF representations of highly coordinated complexes (in green: Pb^{2+} and in yellow: ligand, signposted ligands belong to the second sphere of coordination). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In addition, the two ligands belonging to the second shell are stabilized by hydrogen interactions with the first shell. All ligands being located in the same hemisphere implies a hemidirected structure.

Finally in the $[PbL_3(HL)_5]^-$ complexes, ligands of the first shell are in the same hemisphere but some H*L* ligands are located in the lone pair side while others are stabilized by hydrogen interactions with first shell ligands. As we can see in Figure 3e and f, the lone pair remains hemidirected. Ligands in the hemisphere of the lone pair $[Pb(SH)_3(SH_2)_5]^-$ have a distance from the cation of about 6 Å and those of $[PbCl_3(HCl)_5]^-$ have a distance of about 5 Å.

At this point, we have only discussed some representative cases among all the performed calculations, but the same behavior has been found for all the tested molecules: all complexes with ligands expanding on both hemispheres are hemidirected.

To conclude, for all the complexes tested, ligands on the side of the lone pair of Pb^{2+} are located far enough from the lone pair to let it extend itself in space and all structures are hemidirected.

To be closer to biological conditions, computations on these complexes have been attempted using a solvation continuum (water, see Section 4 for details). Unfortunately reaching global minima within such calculations has not been possible. Indeed, the complexes rearrange themselves in order to let the lone pair of Pb^{2+} extend as some ligands are trying to find their place in the second shell making difficult to locate any stationary point. Figure 4 shows results obtained for $[Pb(SH)_2(SH_2)_5]$, $[Pb(SH)_2(SH_2)_6]$ and $[Pb(SH)_3(SH_2)_5]^-$. We can see that despite taking into account solvation or not, all complexes are hemidirected whatever the number and the nature of the ligands. After these geometric features, energetic informations are presented below.

2.2. Energetical study

Finally, in order to estimate how neutral ligands stabilize or not the complexes, the complexation energy and free energy, ΔE and ΔG, are computed as follows and are gathered in Table 3:

$$Pb + n\ L + m\ HL \rightarrow [PbL_n(HL)_m]^{2-n}$$

$$\Delta E = E_{complex} - (E_{Pb} + nE_L + mE_{HL})$$

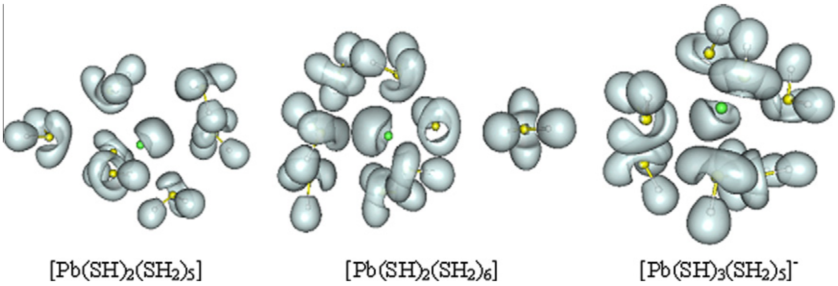
$$\Delta G = G_{complex} - (G_{Pb} + nG_L + mG_{HL})$$

As one can see from Table 3, taking into account entropy is important as it strongly influences the energetic. We will then only consider the ΔG values for the discussion.

In the $[PbL(HL)_m]^+$ series, in which only one anionic ligand is involved, the most stable complex in view of the ΔG value remains $[PbL(HL)_3]^+$. Indeed, whatever the nature of the ligand *L*, Pb^{2+} needs three neutral ligands in addition to the anionic ligand to stabilize its positive charge in the optimal way.

In the case of $[PbL_2(HL)_m]$ complexes in which two anionic ligands appear, the complexes are more stable without any neutral ligands. So with two anionic ligands, the charge of Pb^{2+} is stabilized enough to stay only with the anionic ligands even if the complexation of two neutral ligands in addition is possible, which does not lead to the most stable complex.

The last case is more chaotic: the $[PbCl_3(HCl)_2]^-$ complex appears to be the most stable complex among the $[PbCl_3(HCl)_m]^-$ series whereas $[Pb(SH)_3]^-$ is the most stable among the $[Pb(SH)_3(SH_2)_m]^-$ series. This difference comes from the size and the electronegativity of *L*H. Indeed, from ELF molecular volume computations, SH^- appears larger than Cl^- (366.31 au^3 vs.



$[Pb(SH)_2(SH_2)_5]$ $[Pb(SH)_2(SH_2)_6]$ $[Pb(SH)_3(SH_2)_5]^-$

Figure 4. ELF representation of $[Pb(HS)_n(SH_2)_m]$ complexes in aqueous phase (in green: Pb^{2+} and in yellow: ligand). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Formation ΔE and ΔG values (kcal/mol) for complexes $[PbL_n(HL)_m]^{2-n}$, values in bold are the most stable complexes (ΔG). N.C. = not computed.

	ΔE	ΔG		ΔE	ΔG
$[PbCl]^+$	−319	−314	$[Pb(SH)]^+$	−335	−329
$[PbCl(HCl)]^+$	−330	−318	$[Pb(SH)(SH_2)]^+$	−358	−341
$[PbCl(HCl)_2]^+$	−339	−319	$[Pb(SH)(SH_2)_2]^+$	−371	−345
$\mathbf{[PbCl(HCl)_3]^+}$	−348	**−320**	$\mathbf{[Pb(SH)(SH_2)_3]^+}$	−380	**−345**
$[PbCl(HCl)_4]^+$	−351	−316	$[Pb(SH)(SH_2)_4]^+$	−388	−344
$[PbCl(HCl)_5]^+$	−356	−314	$[Pb(SH)(SH_2)_5]^+$	−393	−341
$[PbCl(HCl)_6]^+$	−361	N.C	$[Pb(SH)(SH_2)_6]^+$	−399	−337
$\mathbf{[PbCl_2]}$	−479	**−468**	$\mathbf{[Pb(SH)_2]}$	**−505**	**−488**
$[PbCl_2(HCl)]$	−484	−464	$[Pb(SH)_2(SH_2)]$	−510	−484
$[PbCl_2(HCl)_2]$	−490	−461	$[Pb(SH)_2(SH_2)_2]$	−514	−478
$[PbCl_2(HCl)_3]$	−489	−453	$[Pb(SH)_2(SH_2)_3]$	−516	−474
$[PbCl_2(HCl)_4]$	−496	−452	$[Pb(SH)_2(SH_2)_4]$	−520	−468
$[PbCl_2(HCl)_5]$	−502	−447	$[Pb(SH)_2(SH_2)_5]$	−521	−462
$[PbCl_2(HCl)_6]$	−507	−444	$[Pb(SH)_2(SH_2)_6]$	−526	−457
$[PbCl_3]^-$	−529	−511	$\mathbf{[Pb(SH)_3]^-}$	−551	**−525**
$[PbCl_3(HCl)]^-$	−540	−514	$[Pb(SH)_3(SH_2)]^-$	−557	−524
$\mathbf{[PbCl_3(HCl)_2]^-}$	−548	**−514**	$[Pb(SH)_3(SH_2)_2]^-$	−564	−521
$[PbCl_3(HCl)_3]^-$	−551	−511	$[Pb(SH)_3(SH_2)_3]^-$	−572	−517
$[PbCl_3(HCl)_4]^-$	−560	N.C.	$[Pb(SH)_3(SH_2)_4]^-$	−576	−513
$[PbCl_3(HCl)_5]^-$	−572	−516	$[Pb(SH)_3(SH_2)_5]^-$	−581	−511

271.14 au^3) and is known to have a lower electronegativity. So $[PbCl_3]^-$ can be stabilized by HCl which is able to perform hydrogen bonds with Cl^-. In other words, the electronic density felt by Pb^{2+} must be comparable to the one with two Cl^-. One can think that one HCl could be not enough to decrease the charge around Cl^- and that, on the opposite, three HCl would decrease too much the charge of Cl^- which would imply that the complex $[PbCl_3]^-$ is less stable than that with two HCl. However, one must recall that no neutral ligand is present in the first sphere of coordination when three anionic ligands are present. For this reason, we observe the stabilization of the $[PbCl_3]^-$ complex and not necessarily of all the $[PbCl_3(HCl)_m]^-$ series. SH^- being softer than Cl^-, there is no real need to stabilize it, explaining why the $[Pb(SH)_2]^-$ and $[Pb(SH)_3]^-$ complexes are more stable without neutral ligands.

3. Conclusion

Our computations show that the interaction between anionic ligands and Pb^{2+} is stronger than between neutral ligands and Pb^{2+} since no anionic ligand is ejected in the second sphere of coordination. The addition of more neutral ligands decreases the interaction between anionic ligands and Pb^{2+} through hydrogen-bond formation. This destabilization is higher than the stabilization brought by the interaction between neutral ligands and Pb^{2+}. One can retain that in spite of the great number of ligands in the hemisphere of the lone pair, the investigated structures are always hemidirected in the presence of at least one anion. This is the key information of this study. Overall, one can conclude that the presence of an anion around the Pb^{2+} generates a loss of holodirectionality. The dominant physics within such complexes requires a good balance of the interactions between the charges provided by the ligands and the Pb^{2+} cation. Such findings are important if one wants to stabilize a hemidirected lone pair, an important issue in the search for chelators. They also appear consistent with the charged nature of the surrounding residues in enzymes such as ALAD which was shown to have a hemidirected organization of its three anionic ligands [11]. Finally, as entropy seems to significantly affect the presented results, our findings could be useful for larger scale molecular dynamics (MD) studies using QM/MM/MD or new polarizable force fields for lead [20,21].

4. Technical appendix

All the calculations were done with GAUSSIAN03 [22] with the B3LYP functional [23,24]. We used the 'SDD' pseudopotential [25] for Pb^{2+} and 6-31+G** [26] for all the other atoms. Such combination of functional and basis sets was shown to be reliable in recent studies [10,17,20]. All ΔG computations have been performed at 298 K within the harmonic approximation. ELF results have been computed using a modified TOP-MOD package [27,28]. Details about the application of the ELF topological analysis to biological systems can be found in a recent review article [12]. Solvation continuum computations were performed the Polarizable Continuum Model (PCM) as implemented in GAUSSIAN (integral equation formalism variant (IEFPCM) [29]).

Acknowledgements

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