

Bioinorganic Chemistry of Lead Toxicity

Homer Chou

Literature Seminar

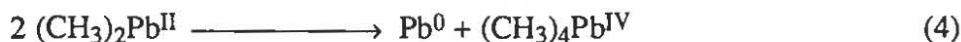
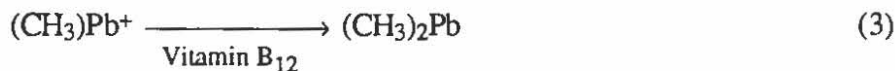
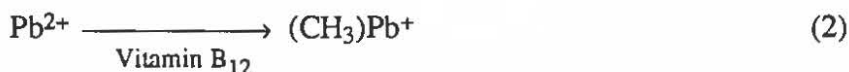
April 9, 1991

Lead poisoning has been a concern since antiquity. The ancient Greeks and Romans documented accounts describing the toxic effects of lead [1]. Although these effects are fairly well characterized, the exact mechanism of how lead disrupts the normal functions of the body remains elusive [2-4]. In order to elucidate this question, the sources of organolead compounds and important physical properties of these molecules will be discussed.

There are two major sources of lead to the human body: inorganic and organic lead. From a number of biological studies of the toxic effects of lead, it has been shown in a variety of organisms that the toxicity of organolead complexes far exceeds that of inorganic lead [5] (Pb^{2+}). Because of this fact, the toxic effects of organolead compounds will be emphasized. The major sources of organolead compounds are gasoline additives and biomethylation of inorganic lead. Tetraethyllead, a proven anti-knock agent, is made by the free radical addition of four equivalents of ethyl chloride to a lead/sodium alloy [6,7].



Biomethylation can proceed via one of three possible mechanisms: the transfer of a carbocation (CH_3^+), a carboanion (CH_3^-), or a free radical methyl group ($\cdot\text{CH}_3$) to the metal. The first mechanism has been used to explain methylation via *S*-adenosylmethionine [8]. The latter two utilize Vitamin B₁₂ as the active agent. While the biomethylation via Vitamin B₁₂ is well understood for tin and mercury [9], the mechanism for lead biomethylation is still in dispute. The present-day consensus is that two equivalents of Vitamin B₁₂ are used to form a $(\text{CH}_3)_2\text{Pb}^{\text{II}}$ intermediate that immediately disproportionates to $(\text{CH}_3)_4\text{Pb}^{\text{IV}}$ [10-12].



One way in which organolead complexes disrupt the normal function of the body is by destroying Cl^-/OH^- gradients across membranes. Trialkyllead halide complexes are surprisingly soluble in both aqueous and organic medium. Both the unusual solubility and the weak lead-halide bond play a key role in anion transport through membranes. As seen in Figure 1, trialkyllead cations will tend to stay on the surface of the membrane. Once a mono-anion is coordinated to the metal, the complex's solubility in the membrane increases dramatically, and thus it cannot pass through the membrane. However, since the bond strength of the lead-halide bond is relatively weak, once the complex reaches the other side the halide can be displaced, thus reforming the cation. This cycle can now be repeated going in the other direction. If there is a concentration gradient between two anions across the membrane, invoking the law of mass

action, the anion which was transported across the membrane in one direction will not be the anion transported in the reverse direction. Because the extracellular fluid in the body contains a higher concentration of Cl^- than the intracellular fluid, these lead complexes will cause Cl^- to enter the cell while OH^- pumps out [13-16].

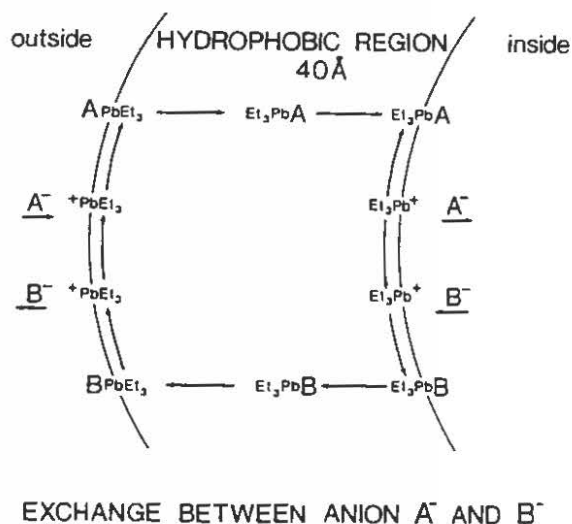


Figure 1

The effects of destroying pH gradients across membranes are devastating. One major consequence of a decrease in pH is that in order for a cell to maintain the necessary intracellular pH, it must actively transport H^+ out via a proton pump. This uses ATP as the energy source. If the pump cannot keep up with the rapid influx caused by the lead compounds, the cell will quickly atrophy due to lack of energy [15,17].

Because of the unique solubility properties of organolead compounds, they are readily incorporated in the membrane of cells and thus create a pathway for rapid anion exchange across the membrane. In turn, this can lead to a rapid depletion of a cell's energy. While this may not be the only route available for Pb toxicity, this mechanism may provide an explanation for the weakness and fatigue observed in many acute lead poisoning cases.

References

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