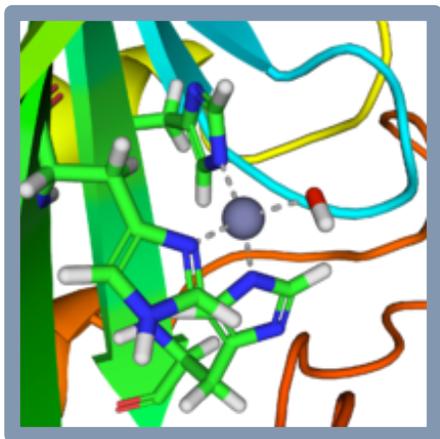


## Biological Coordination-Chemistry: Questions and Answers



Consider [carbonic anhydrase](#), an enzyme which converts  $\text{CO}_2$  to bicarbonate, releasing  $\text{H}^+$  ions in the process. Its active site consists of a  $\text{Zn}^{\text{II}}$  atom coordinated to three histidine ligands and one  $\text{OH}^-$  (hydroxide) ion. The zinc atom functions to polarize one of  $\text{O}=\text{C}$  bonds (of  $\text{CO}_2$ ) producing a large positive dipole on the carbon atom, making it more susceptible to nucleophilic attack by the hydroxide. However, this raises the question: “If the +2-zinc ion is receiving a pair of electrons from each of its ligands ( $8e^-$  in total) how can it possibly bear the positive charge required to directly polarize the  $\text{O}=\text{C}$  bond of  $\text{CO}_2$ ?”

This is certainly a valid question, and a quite perplexing one when first approached. However, the answer is relatively simple, although at first, quite shocking. Even though zinc is not contributing any electrons to its bonds, it bears a positive dipole. How can this be?

A survey of a periodic electronegativity table gives a tremendous value of 3.44 for oxygen, a considerable value of 3.04 for nitrogen, but only a meager value of 1.65 for zinc. Now, this 1.65 value certainly increases when zinc gains its normal +2 charge (i.e., loses 2 electrons). After all, zinc needs a reasonable amount of positive charge to persuade the highly electronegative nitrogen and oxygen atoms to donate electrons to itself in the first place!

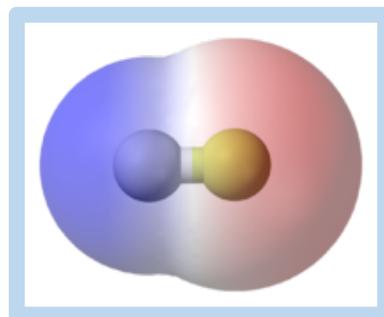
As it turns out, the high electronegativity of oxygen and nitrogen are the key to this conundrum. Let us think of one of the nitrogen atoms as a boy who is eating a candy bar. The zinc ion will represent his little brother who is nagging the boy to give him the candy bar. Of course, the boy doesn't want to, but he can't overcome his little brother's constant nagging. So, the boy gives his little brother part of the candy bar, and the latter is satisfied.

Similarly, the  $\text{Zn}^{2+}$  cation is attracting the lone pair of electrons on the nitrogen atom. However, the highly electronegative nitrogen will not donate its lone pair in a purely covalent fashion. Instead, the N—Zn bond has a certain percentage of covalent and ionic character. In reality, the  $\text{Zn}^{2+}$  cation is not experiencing a full -2 charge donation from the nitrogen.

“Well”, you might say, “here we are only dealing with a single nitrogen atom. Certainly, the partial covalent character of the O—Zn bond and the other two N—Zn bonds should be enough to at least neutralize the zinc cation!”

Well, it's not. Even though the  $\text{Zn}^{2+}$  cation is receiving 4 grudgingly-given electron donations, the electronegativity of the donor atoms is too great when compared with zinc's less-powerful pull. This means that of the 8 electrons present in all the lone pairs of the donor atoms, the  $\text{Zn}^{2+}$  cation may only be experiencing, (for example) 1/7 or 1/8 of the total negative charge available, because the bonds are partially ionic.

But how can covalent bonds be partially ionic, and why do I keep using the word “experience”? Let's step outside of biochemistry for a moment and discuss some general chemistry. A perfectly covalent bond can only be observed in a molecule wherein the atoms are sharing electrons equally



(e.g.,  $\text{N}_2$ ). A perfectly ionic bond can be observed in a molecule wherein one atom completely “steals” an electron from another, forming two oppositely charged ions which attract. The latter of these scenarios is something purely theoretical, because as we now understand, positively charged ions will always demand donations from electron rich atoms.

The majority of molecules lie between these two extremes. Any difference of electronegativity between two atoms results in a polar covalent bond. A bond of this type can be observed in a molecule of hydrogen fluoride, where the fluorine atom has a considerably larger electronegativity value than hydrogen (3.98 vs. 2.20, respectively). Both atoms are

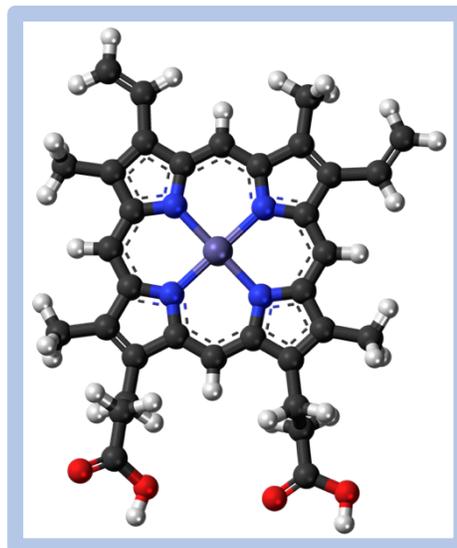
contributing one electron to the bond, but there is clearly a greater electron density around the fluorine nucleus than the hydrogen nucleus, as shown in the diagram above. Why? Because the fluorine atom is causing hydrogen's electron to spend more time closer to the fluorine nucleus! There is still an amount of "sharing" in this bond, but there is also an amount of "stealing" present. And that's how a bond can be covalent and ionic at the same time.

Returning to our original example with zinc, the situation is slightly different because one atom is contributing both of the electrons in the bond. However, the basic principles are still the same. All that the  $\text{Zn}^{2+}$  cation is doing is disrupting the electron density on the donor atoms by forming coordinate-covalent bonds with them. In doing so, it pulls the lone pairs toward its nucleus, but the high electronegativity of the donor atoms ensures that they still possess a higher negative charge density than the zinc atom. The  $\text{Zn}^{2+}$  cation is receiving a pair of electrons from each of its 4 donor atoms, but the bonds are so polarized in the direction of the donors that the actual negative charge it experiences is relatively small.

So, the summarized answer to the original question is that the zinc atom's partial positive charge is caused by the fact that the N—Zn and O—Zn bonds are highly **polarized**—to such a degree that they exhibit considerable ionic (i.e., salt-like) character—with a large amount of electron density on the donor and a large positive dipole on the acceptor.

And we're done! Hoor—hold on just a minute. The zinc atom has a partial positive charge, but where did the rest of the charge go? We started with a +2 charge! To answer this question, let us analyze the cofactor of another important metallo-protein: hemoglobin. Pictured below is the oxygen-carrying molecule, **deoxy-heme**. In its center, there is a  $\text{Fe}^{\text{II}}$  atom coordinated to 4 porphyrin nitrogen atoms. As with the zinc atom in carbonic anhydrase, the metal-ligand bonds are sufficiently polarized so that the iron atom bears a partial positive charge. (This enables heme to carry oxygen, because passing  $\text{O}_2$  molecules are attracted to the iron atom and bind to it.) But where is the rest of the +2 charge?

Besides the carboxyl oxygen atoms, the 4 coordinating nitrogen atoms are the most electronegative particles in the molecule. Because they are forced to give some amount of negative charge density to the  $\text{Fe}^{2+}$  ion, they will “tug” a bit harder on the less-electronegative carbons to which they are bonded. These carbons, in turn, will then tug harder on the carbon atoms to which they are bonded, and so on down to the hydrogens at the tips of the molecule. A similar chain reaction should also be observed in carbonic anhydrase, in order to maintain the mathematical integrity of the original charge (of  $\text{Zn}^{2+}$ ).



Thus, the conclusion at which we arrive is: The charge of a metal cation is associated with the entire molecule to which the cation is coordinated. As observed in the deoxy-heme part of the original charge was spread throughout the whole ring. However, as observed in carbonic anhydrase, part of the positive charge remains localized on the metal ion itself.

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- Carbonic anhydrase active site: [https://en.wikipedia.org/wiki/Carbonic\\_anhydrase](https://en.wikipedia.org/wiki/Carbonic_anhydrase)
- Hydrogen fluoride molecule: <https://commons.wikimedia.org/wiki/File:Hydrogen-fluoride-elpot-transparent-3D-balls.png>
- Deoxy-heme molecule: [Unknown artist?](#)