Metal Ions in Enzymes Catalyze

Introduction

More than a quarter of all known enzymes require the presence of metal atoms for full catalytic activity.

It usually exists as cations and often has more than one oxidation state, as with ferrous (Fe^{2+}) and ferric (Fe^{3+}). This positive change can stabilize transition states by electrostatic interactions, giving one mechanism for metal catalysis.

Therefore,

Metal ions can be involved in enzyme catalysis in a variety of ways:

1- Metal ions may accept or donate electrons to activate electrophiles or nucleophiles.
2- Metal ions may mask nucleophiles to prevent unwanted side reactions.
3- Metal ions may hold reacting groups in the required three-dimensional orientation.

Many enzymes contain one or more metal ions, usually held by coordinate covalent bonds from amino acid side chains but sometimes bound by a prosthetic group like heme. Such enzymes are called **metalloenzymes.**

Metal with **metalloenzymes is** tightly bound and retained by the enzyme through purification, while **metal with metal-activated enzymes,** the binding is less tight and purified. Ternary complexes formed between an enzyme (E), metal ion (M), and substrate (S) may be as follows:

1- enzyme bridge complexes **(M-E-S)**,
2- substrate bridge complexes **(E-S-M)**, or
3- metal bridge complexes. $(E-M-S \text{ or } E\begin{smallmatrix}M\\|\\S\end{smallmatrix})$

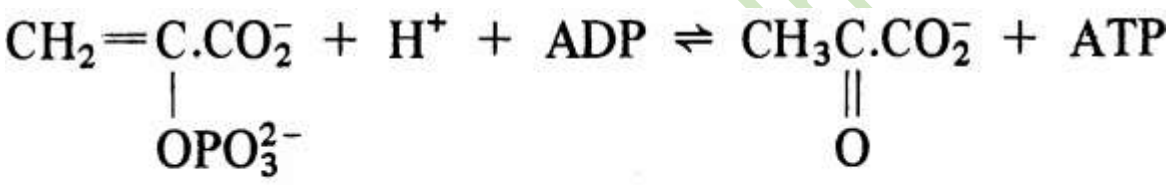
4- Metalloenzymes cannot form substrate bridge complexes because the purified enzyme exists as E-M.

1-Activation of enzymes by alkali metal cations (sodium(Na^+)and potassium(K^+).

Alkali metal cations **bind weakly** to form complexes with enzymes (sodium (Na^+) and potassium (K^+).

Potassium ion (K^+) is the most abundant intracellular cation. It is known to activate many enzymes, particularly those catalyzing phosphoryl transfer or elimination reactions. K^+ appears to **bind to negatively charged groups** on an inactive form of the enzyme and thus causes a change in conformation to a more active form. However, in some cases, **K^+** may also aid substrate binding.

For example, muscle **pyruvate kinase,** a tetrameric enzyme that catalyzes the reaction:



phosphoenolpyruvate (PEP) pyruvate

Pyruvate kinase needs alkali metal cations (K^+), and Mn 2 $^+$ (or $Mg2^+$), alkali metal cations, and **Mn^{2+} bind in the active site region**. The carboxyl group of PEP binds to the enzyme-bound **K^+**. Thus, a conformational change takes place, facilitating the progress of the reaction via an **E-Mn^{2+}- PEP** complex.

2-Activation of enzymes by alkaline earth metal cations (Ca^{2+} and Mg^{2+})

Oxygen atoms are often involved in the bonds of alkali metal and alkaline earth. The cations bonds of alkaline earth metal oxides are stronger than alkali metal oxides. Cations, Ca^{2+} and Mg^{2+} can form six coordinate bonds to produce octahedral complexes.

Mg^{2+} is accumulated by cells in exchange for transport of Ca^{2+} in the opposite direction. As might be expected, therefore, the enzymes requiring Ca^{2+} for activation are mainly be extracellula example., the **salivary and pancreatic *α*-amylases**: the Ca^{2+} appears to play a role in maintaining the structure required for catalytic activity.

In contrast, a variety of intracellular enzymes require Mg^{2+} for activity, and in most cases, this requirement can be replaced in vitro by one for Mn^{2+}. Mn^{2+} is paramagnetic, which helps the system to be more easily investigated. It has been shown that all possible types of ternary bridge complexes involving divalent cations can exist. Most kinases form **E-S-M** complexes, where S (substrate) is the reacting nucleotide.

Example: muscle creatine kinase, the reaction catalyzed:

$$\text{creatine} + \text{MgATP} \rightleftharpoons \text{MgADP} + \text{phosphocreatine} + H^+$$

The true substrate is **Mg-ATP, and the reaction proceeds via the formation of the complex**.

$$E \begin{cases} \text{ATP}-Mg^{2+} \\ \text{creatine} \end{cases}$$

The divalent cation binds to the α- and β-phosphates of the nucleotide but not to the terminal (γ) phosphate transferred to creatine. Therefore, the cation helps in the orientation of the complex and may also assist in breaking the pyrophosphate bond by withdrawing electrons from the β-phosphate.

3- Activation of enzymes by transition metal cations (Cu, Zn, Mo, Fe and Co cations).

Transition metal ions such as **Cu, Zn, Mo, Fe and Co** bind to enzymes much more strongly than metals of alkali and alkaline earth cations and usually form **metalloenzymes.**

Transition metal cations are found in only trace amounts in living organisms, for more significant amounts can be cause toxic. The trace metals Mo and Fe are found in **nitric-oxide reductase,** also, Fe is a component of hemoglobin,

Another trace metal, Co, is found in vitamin B_{12}.

Example: In a little more detail, we will now consider an example of a Cu- and a Zn-metalloenzyme.

1- Superoxide dismutase:

Superoxide dismutase is a copper-metalloenzyme which catalyzes the removal of the highly reactive O_2 produced. The superoxide dismutase reaction is as follows:

$$2O_2^- + 2H^+ \rightleftharpoons H_2O_2 + O_2$$

Bovine erythrocyte **superoxide dismutase is a dimeric protein** containing two. Cu^{2+} ions and two Zn^{2+} ions.

The Zn^{2+} ions appear to have a structural rather than a catalytic role, while the Cu^{2+} ions are involved in the reaction sequence:

$$E - Cu^{2+} + O_2^- \rightarrow E - Cu^+ + O_2$$

$$E - Cu^+ + O_2^- \xrightarrow{+2H^+} E - Cu^{2+} + H_2O_2$$

$$2O_2^- + 2H^+ \rightleftharpoons H_2O_2 + O_2$$

2-Carboxypeptidase-A:

Carboxypeptidase-A zinc metalloenzyme In contrast to the **Superoxide dismutase, the zinc ion** in **carboxypeptidase-A** has a catalytic role in the reaction catalyzed by **Carboxypeptidase A**. Carboxypeptidase-A from the bovine pancreas is a monomeric enzyme containing one zinc atom.

carboxypeptidase-A show that: The carboxypeptidase-A active site contains the zn^{2+} ion attached to histidine-69, glutamate-72, histidine-196, and H2O, as well as a channel for the polypeptide substrate and a hydrophobic region for binding the side chain of the C-terminal amino acid. The terminal carboxyl group of the substrate forms an electrostatic interaction with arginine-145; (Fig. 11.39).

The mechanism of the **carboxypeptidase A** included:

1- The zinc ion (orange circle) binds a water molecule (blue).

2- zinc ion serves as **an electrostatic catalyst** to promote the hydrolysis of **the C-terminal amino acid** from **a peptide substrate (green).**

3- zinc ion **stabilizes the negative charge on oxygen** in the tetrahedral transition state.

Enzyme **active site residues** are indicated by **black coloring,** and the dashed red arrow indicates the bond cleaved**;** Figure 11.39

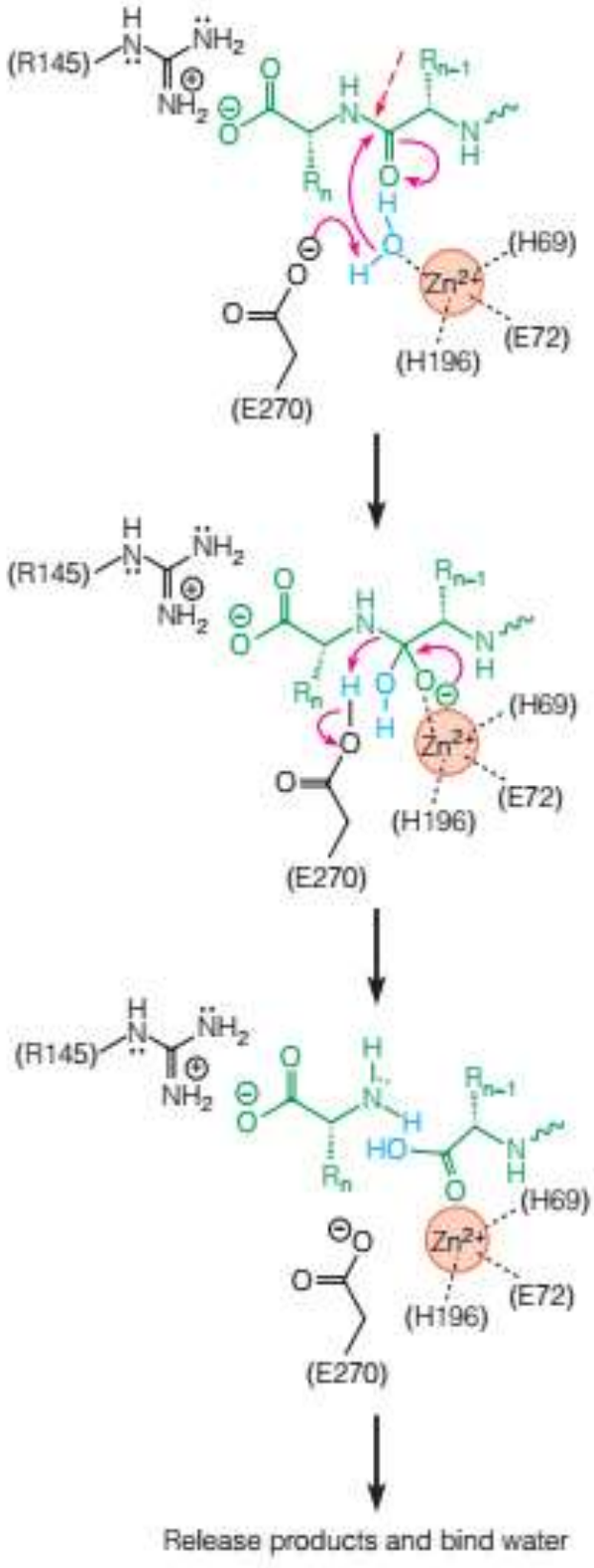


FIGURE 11.39 The mechanism of the **protease carboxypeptidase A**.