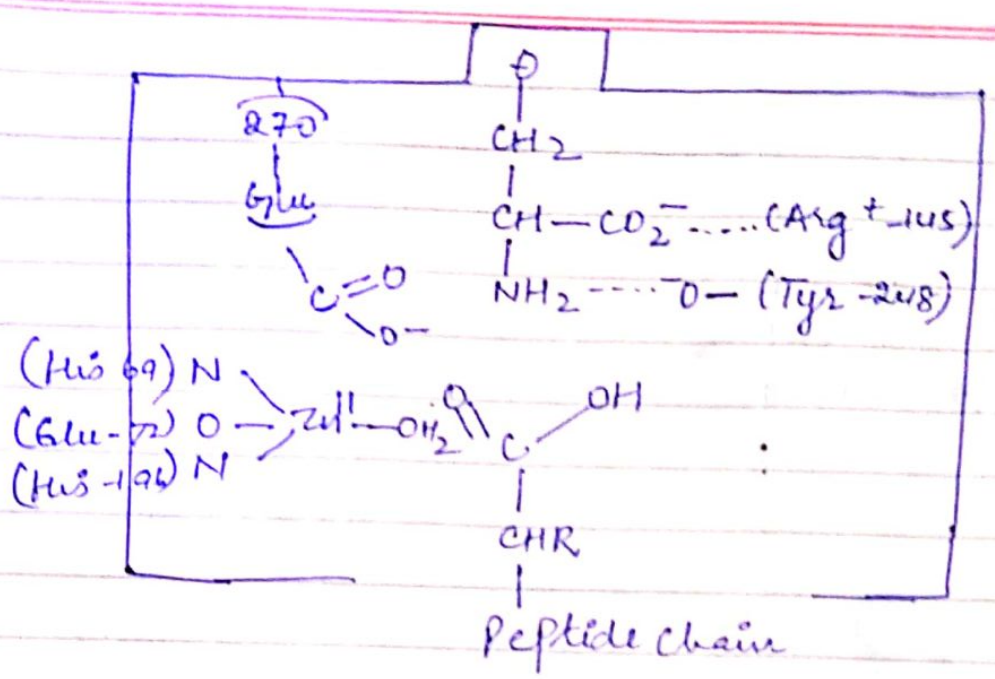


Carbonic-Anhydrase (CA): Structure and Reactivity

→ Zn (II) containing metalloenzyme CA is responsible for reversible hydration of CO_2 in blood.

The hydration of CO_2 and dehydration of H_2CO_3 is imp. in animals, plants and several bacteria.

$$CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+ \quad (K \simeq 10^{-1} s^{-1})$$
(at physiological pH)

$$CO_2 + H_2O \overset{CA}{\rightleftharpoons} HCO_3^- + H^+ \quad (K_{cat} \simeq 10^6 s^{-1})$$
(at physiological pH)

→ The rate constant is high for catalysed by CA at physiological pH.

→ It has a turnover number $10^6 s^{-1}$ (which is one of the highest known biological rates).

→ The rate of spontaneous dehydration of HCO_3^- ion is $\sim 10^4 s^{-1}$ while the CA catalysed rate is $15 s^{-1}$.

⇒ Structural feature :-

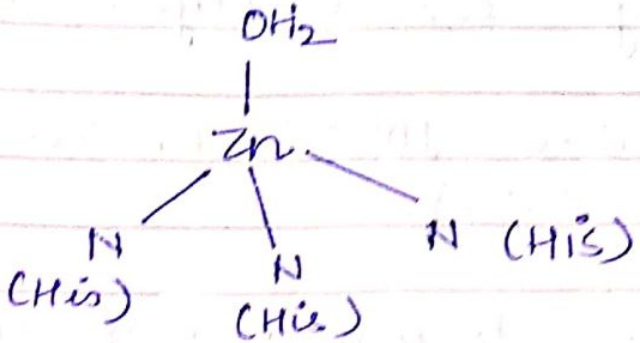
In terms of activity :- CA II high ($K_{cat} \simeq 10^6 s^{-1}$)
CA I low ($K_{cat} \simeq 10^5 s^{-1}$)
CA III very low ($K_{cat} \simeq 10^3 s^{-1}$)

If the source is human they are known as HCA I, HCA II

→ In all these isoenzymes there exists one Zn(II) site per molecule and these are single chains polypeptides (260 A-Acids)

→ Zn(II) is a distorted tetrahedral geometry and it is coordinated with three histidine-N sites (His-94, His 96, His-119) and the fourth coordination by a H_2O or OH^- ion.

Structure of Carbonic Anhydrase



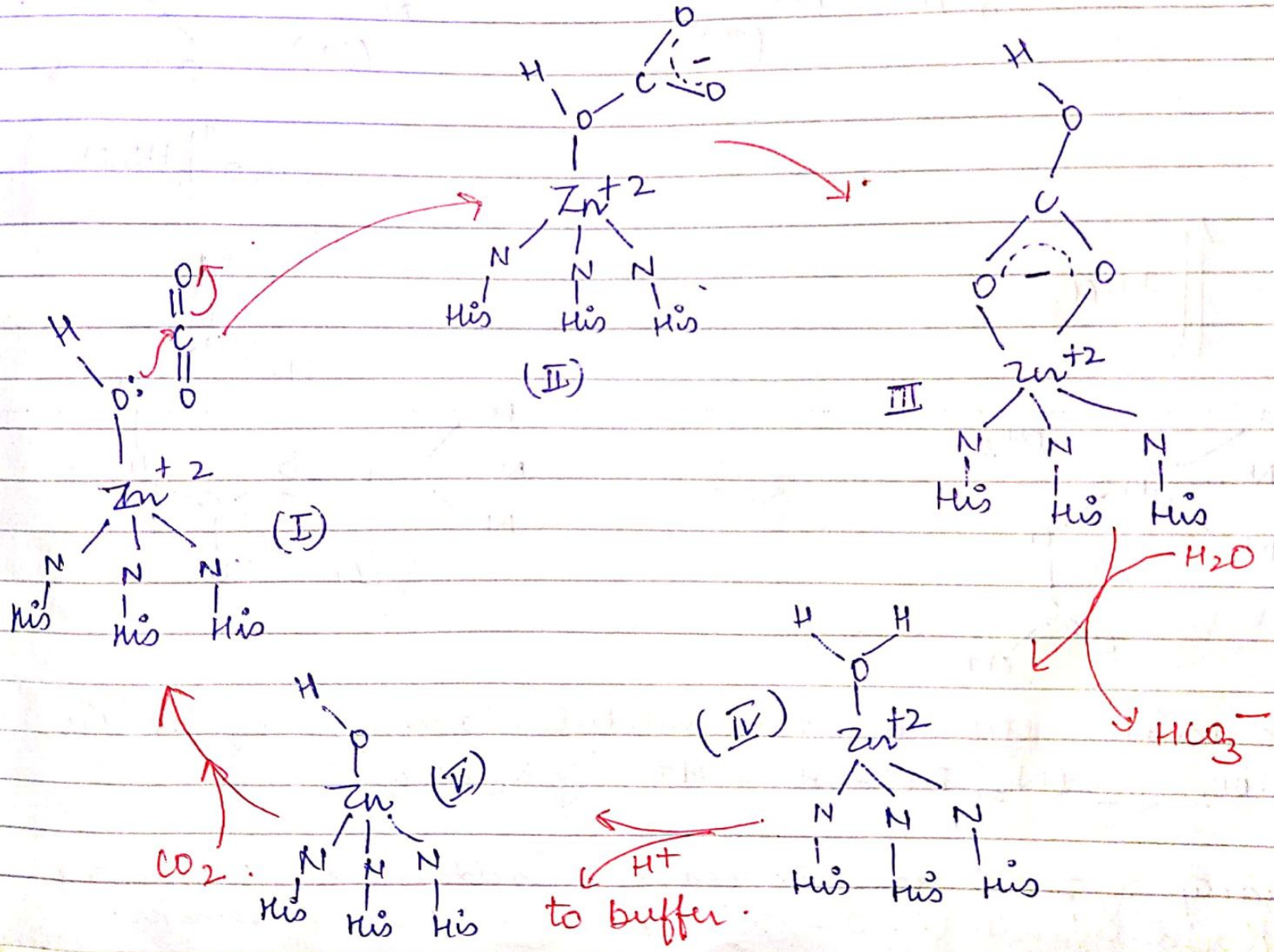
Working / functioning

The Zn^{+2} is more acidic in CA than in CPA. Also the presence of neutral or less basic histidine residue than glutamate residue contribute to the greater acidity of Zn^{+2}

Also the three histidine residues are pulled back ∴ the Zn^{+2} is more electronegative and more acidic toward the fourth position. ∴ the coordinated water becomes more polarized and loses H^+ ion to give $Zn-OH^-$. This Nu OH^- then attacks on the carbon atom of CO_2 captured in the hydrophobic pocket near the Zn^{+2} ion and a transient five coordinate Zn^{+2} ion is formed in which carbonato oxygen from HCO_3^- coordinates to the Zn^{+2} ion.

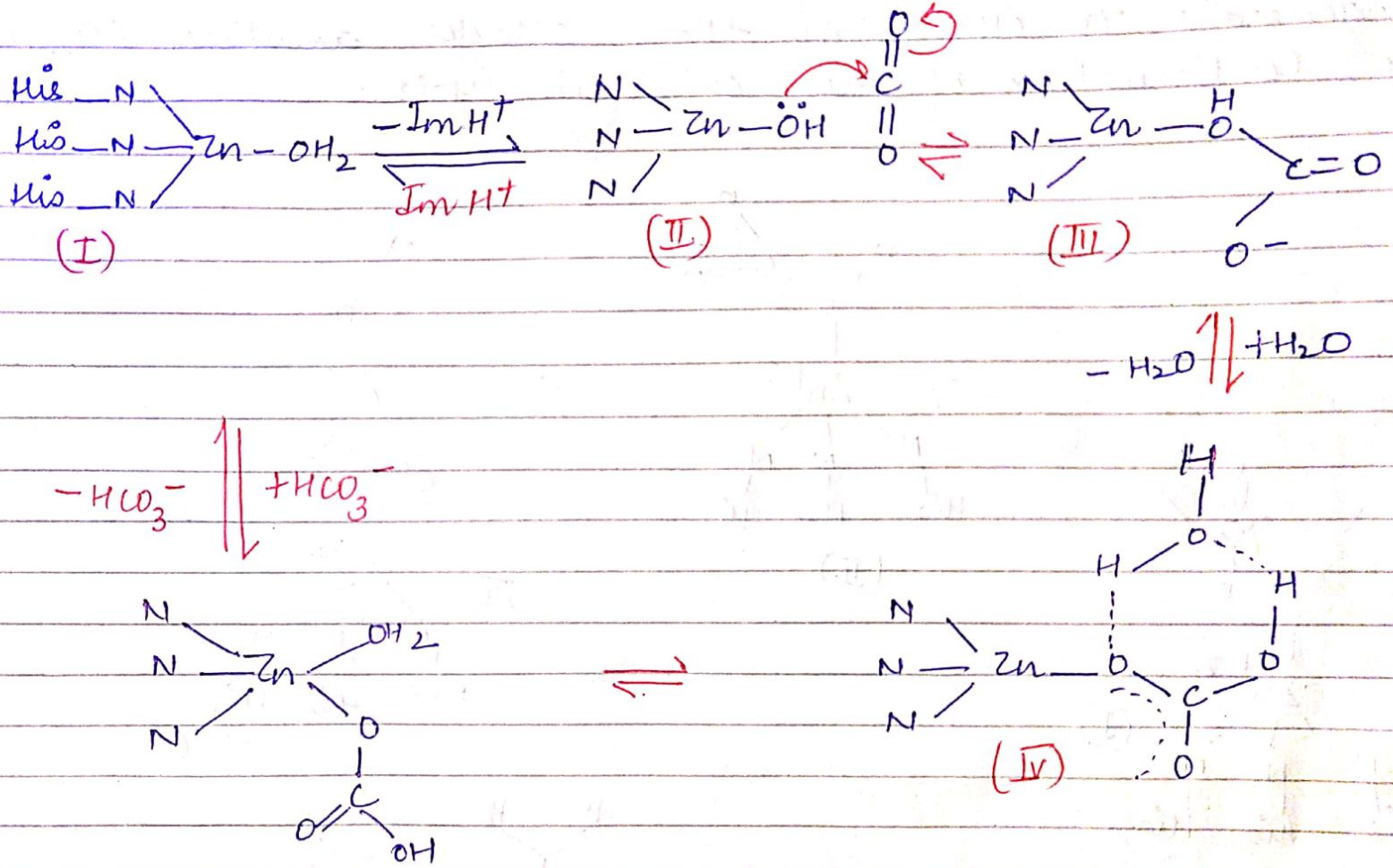
After rearrangement, the HCO_3^- ligand is replaced by H_2O.

The protonation of H_2O ligand coordinated to Zn^{+2} ion - then regenerate $Zn-OH^-$ which then attacks another CO_2 with the continuation of the catalytic cycle.



An Alternate cycle

Im = Imidazole.



The most crucial step in the catalytic activity of CA is:-

$$(N_3)\,Zn^{II}-OH_2 \rightleftharpoons (N_3)\,Zn^{II}-OH + H^+ \quad (pK_a \approx 7.0)$$

The Lewis acidity of Zn(II) is enhanced by imidazole rings (moieties). They act as π acid ligands ($\because d \rightarrow \pi^*$). Also it enhances H^+ transfer.

⇒ The formation of Zn (II) $-OH$ to offer a better nucleophile. ∴ hydration of CO_2 by OH^- is much faster than hydration by H_2O. But at physiological pH, availability of OH^- is unlikely. The CA enzyme $(N_3)Zn-OH_2$ generates metal bound-OH group through deprotonation.