Inorganic Chemistry of Life
Chemistry 2211a

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Check instruct.uwo.ca/chemistry/211a

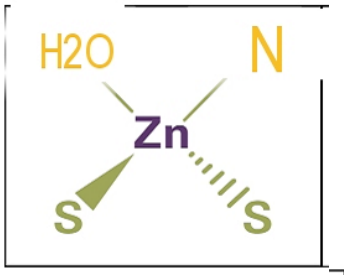
*d^{10} – no colour – zinc proteins are colourless unlike Fe & Cu proteins.

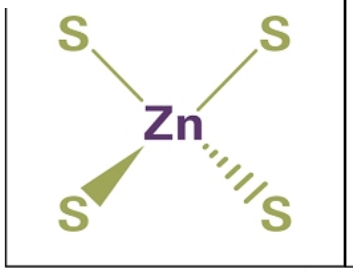
R10-11-3

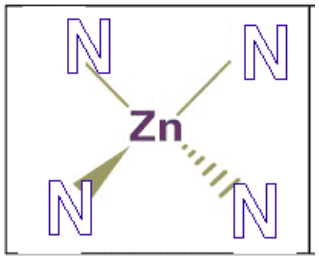
2211a-ZINC-S8-L28-L30-R10-11-03.doc 2010-11-08 12:49:00 PM

The role of zinc (an essential group 12 metal)

1. Zinc is everywhere in our environment
2. Zinc is a constituent of over 300 enzymes involved in numerous body functions, including enzymes involved in gene expression, wound healing, growth.
3. Deficiency impairs cell growth and repair of tissue injury; leads to poor growth, delayed wound healing, impairment of sexual development and decreased taste acuity.
4. Zinc is present in gustin, a salivary polypeptide that is necessary for the development of taste buds.
5. Its binding motifs are: Intermediate-Intermediate or S-I or H-I (ligand-metal order) – such a versatile metal!
6. HIS and CYS are favourite amino acids – plus water and carboxylic acids (GLU, ASP) in the 3rd and 4th position if chemistry takes place there. TETRAHEDRAL geometry – sometimes 5 groups but from 4 different ligands – ie the carboxylic group of GLU or when acting as a protease.



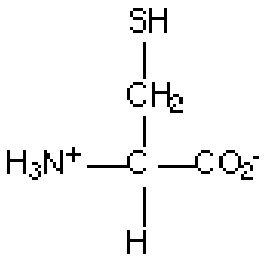




Proteins of interest:

1) Carbonic anhydrase (CA) 3 HIS 1 water; - below

2) Carboxypeptidase A (CPA) 2 HIS; 1 GLU; 1 water; - below

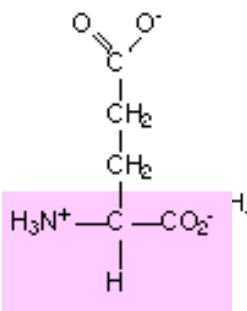


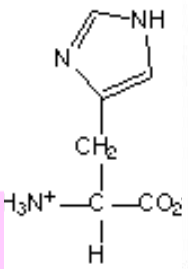
3) Alcohol dehydrogenase (ADH) (2 Zn) 2 CYS; 1 HIS; 1 water; - below

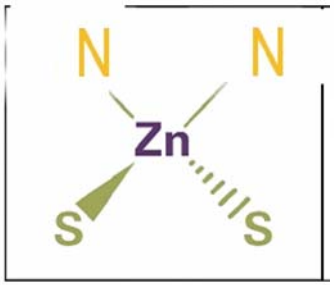
4) Metallothionein (7 Zn) 4 CYS; -below

5) Zn – finger proteins CYS-CYS HIS-HIS - briefly below

(CYS – SH HIS =N- or –NH-; GLU -OH & =O)







L-B	R-M	K-S	Problems to do
P 8-9; 22,23;178184;Ch 10 257-275;	Tables on: p. 4 – 6 –8-	Ch 12 242-266	See Qu 1 – p 279 L&B.

Zinc	A (high intake), calcium, copper, phosphorus	brewer's yeast, liver, seafood, soybeans, spinach, sunflower seeds, mushrooms	burn & wound healing, carbohydrate digestion, prostrate gland function, reproductive organ growth & development, sex organ growth & maturity, vitamin B1, phosphorus & protein metabolism	delayed sexual maturity, fatigue, loss of taste, poor appetite, prolonged wound healing, retarded growth, sterility

NOTE: For any treatment or diagnosis of illness see your physician. The use of certain dietary supplements may result in allergic reactions in some individuals, consult your physician. This Mineral chart is not intended to be diagnostic or prescriptive and therefore Swiss Herbal Remedies Ltd. assumes no responsibility.

KEY
*essential for proper
**equal dosage requi

Let's return to our chart from the first lectures:

2 g in a 70 g human – right up next to Fe.

RDA: for adults - males: 15 mg & females: 12 mg

Zinc Requirement and Effects of Deficiency

Zinc is essential in -

1. Development and functioning of the brain.
2. Zinc dependent enzymes and neurotransmitters play a role in the central nervous system, which may in turn affect cognition.
3. Important for healthy skin, a healthy immune system, and resistance to infection.
4. Wound healing with Zn ointments (from the ancient world).
5. Growth is dependent on Zn.

•Good sources meat, liver, eggs and seafood are good dietary sources, whereas zinc in vegetable sources (green leafy vegetables and legumes), and particularly in cereal grains, is less bioavailable.

Beef is a major source of iron and zinc for American children and adults – actually is the number one source of zinc

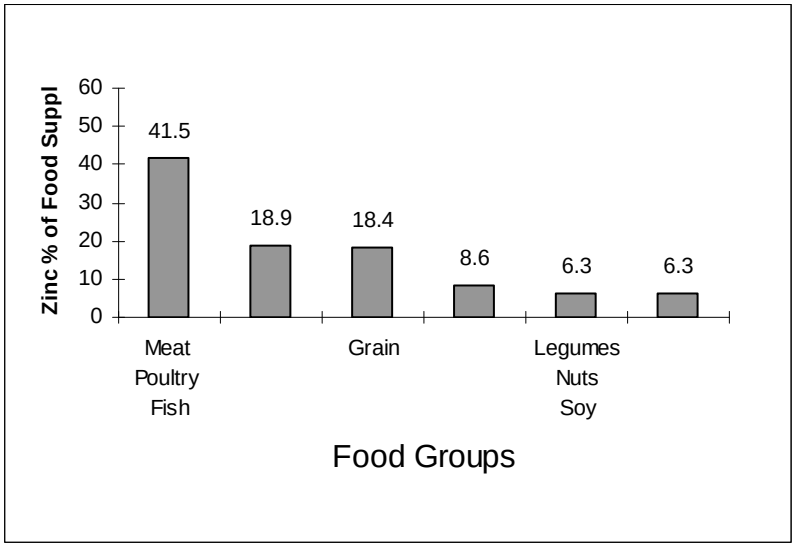
Supplement: no more than 40 mg (above this is considered toxic)

1 veggie hot dog	3.75 mg
1 cup cooked greens	0.8 mg
¼ cup peanuts.....	3.6 mg
¼ cup pumpkin seeds...	2.6 mg
1 cup Cheerios.....	4.5 mg

Emerging research on human models supports a beneficial role for zinc in human cognitive development and functioning

Meat is much better as a source of Zn than cereals. High Zn is found in the fetus – developmental reasons?

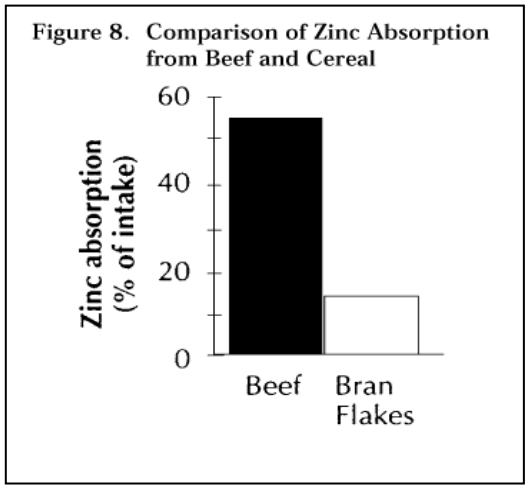
Mainly transported by the protein metallothionein (see below), which controls absorption



Zinc deficiency can lead to:

1. Hair loss,
2. Delayed wound healing
3. Dwarfism when there is major zinc deficiency due to poor diet – was the case in rural Iran in 1960's
4. Structural malformations in the brain
5. Changes in enzymes and proteins important for neurotransmission
6. Behavioural problems - reduced attention
7. Reduced memory - reduced ability to learn
8. Low zinc status during pregnancy may affect the development of the infant's nervous system and later cognitive functioning
9. In older adults (aged 65-90) dietary zinc is positively linked to cognitive function
10. Low levels of zinc in the blood and brain tissues of patients with Alzheimer's

Severe zinc deficiency is seen primarily in alcoholics (especially if they have developed cirrhosis), patients with chronic renal disease or severe malabsorption diseases



Zheng JJ, Mason JB, Rosenberg IH, et al. Measurement of zinc bioavailability from beef and a ready-to-eat breakfast cereal in humans: application of a whole-gut lavage technique. Am J Clin Nutr. 1993; 58: 902-907.

1999

Where are we in the Periodic Table?

Group 12 (recent numbering scheme for groups)

All 2+ cations (well, Hg can be 1+: $[Hg_2]^{2+}$)

As 2+ cations, all are d^{10}

Become 'softer' down the triad

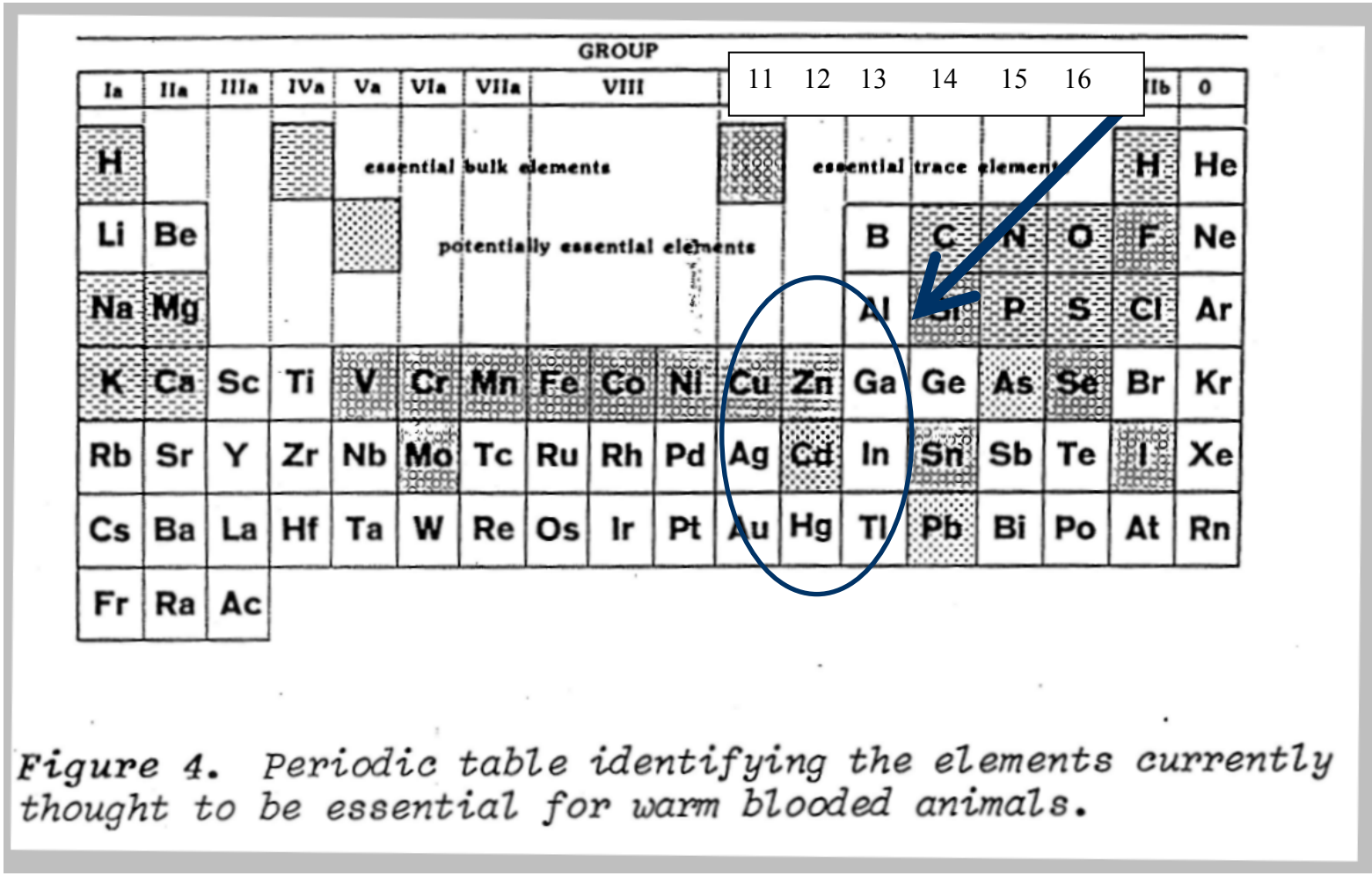


Figure 4. Periodic table identifying the elements currently thought to be essential for warm blooded animals.

Need to memorize this triad

What is special about Zn(II)?

$3d^{10}$ – so no contribution to bonding – bonds form between s and p orbitals – empty now.

No redox chemistry possible – it's Zn(II) all the time. So why Zn(II)? That's the point – it can help make changes in organic molecules without being involved. It acts as a tether. Most important changes the acid-base properties of ligands so that acid-base chemistry takes place that shouldn't at pH 7 – see CA mechanism below.

L-B	R-M	K-S	Problems to do
1-2; 9	2	4	See the questions at the end

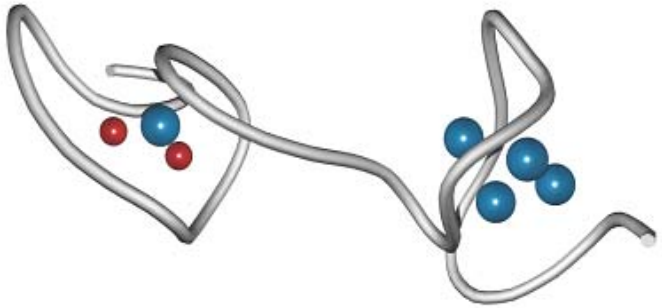
Zinc containing proteins and enzymes:

1) Metallothionein (MT)- 7 Zn (and Cd) 4 CYS ligands each metal – tetrahedral coordination solely by CYS

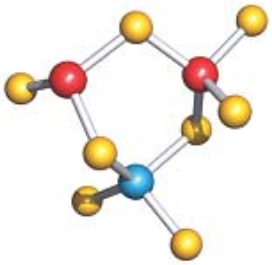
7 METALS – 20 CYS

2 domains some CYS are shared – see (b) and (c) for the structures of the metal binding sites.

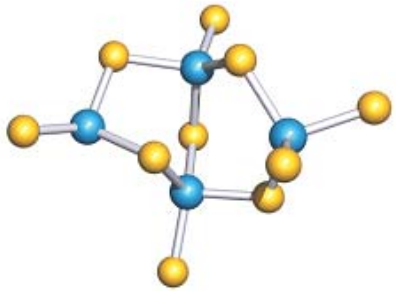
Major zinc binding protein – acts as a storage site. Essentially no free zinc in a cell. $K_F = \beta_7 = 10^{11}$ for 7 Zn(II).



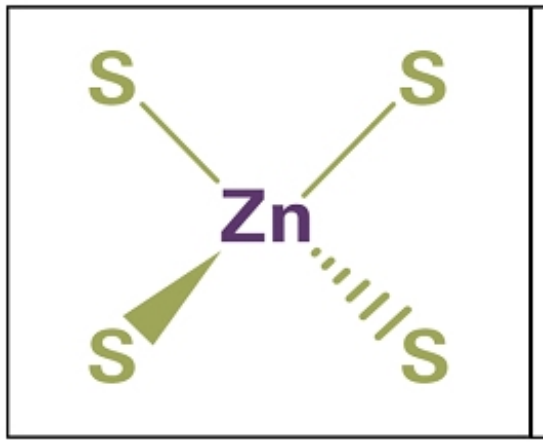
(a)

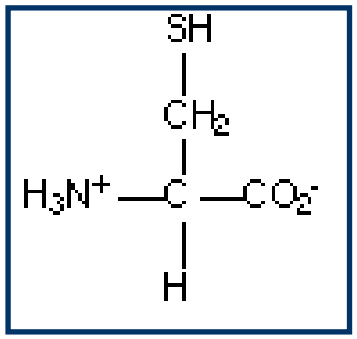


(b)



(c)





In enzymes very many examples, we will select:

2) carbonic anhydrase (CA)

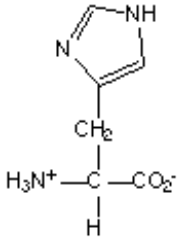
3) matrix metalloproteases (MMPs), secreted by cells – involved in wound healing

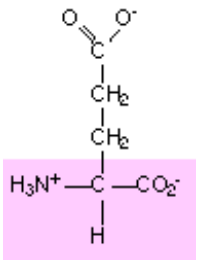
3) carboxypeptidase A (CPA)

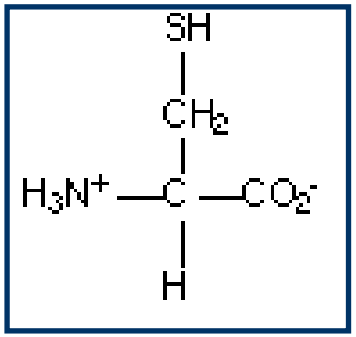
4) alcohol dehydrogenase (ADH) – from liver = LADH

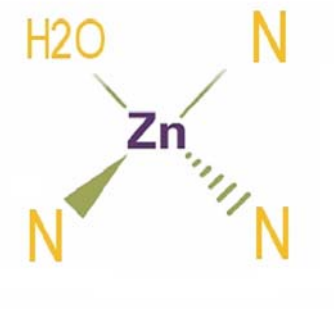
5) zinc finger DNA-binding-proteins (and A1)

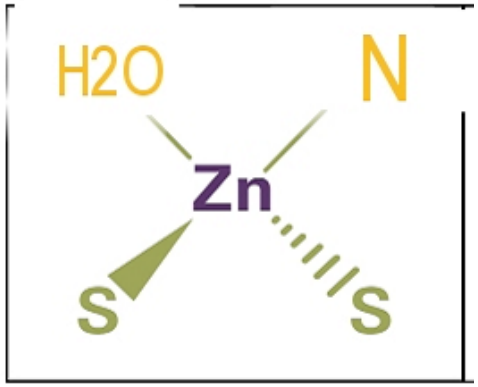
Appendix 4) Superoxide dismutase (ZnCuSOD) – only at the end.











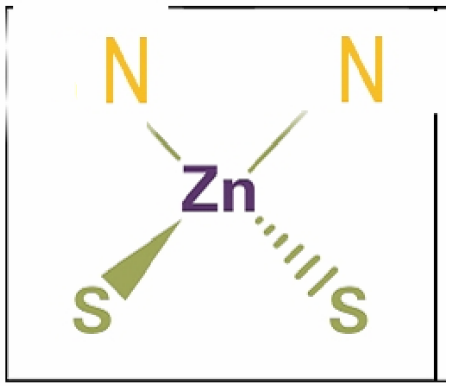
See the end of the file (Appendix) for structural summary of these.

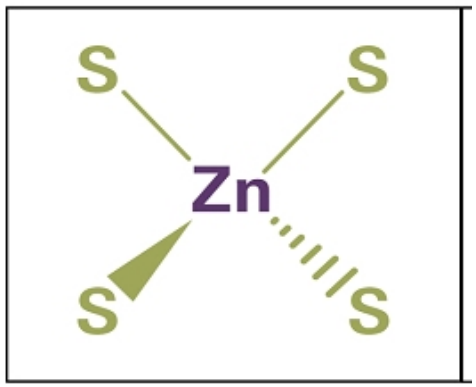
ZINC in catalytic roles binds readily to HIS, CYS, GLU, ASP, and water.

Zn^{2+} acts as a Lewis Acid – so, is an electron acceptor – binds anions – so the ligand usually becomes charged – the effect is a reduction over several orders of magnitude of the pKa of the group (makes the group dramatically more acidic) – **BUT HAS TO HAVE A VACANT SITE.**

As an enzyme – **major role is activating water** (or ROH or $R_2C{=}O$) – making the water (and other groups) far more acidic – that is changing H_2O almost into OH^-.

BUT Binds to 4 cys – or 2 cys & 2 his in structural roles





2) Carbonic anhydrase - CA

Zn^{2+} activation of H_2O in carbonic anhydrase

Carbonic Anhydrase was the first enzyme identified that contained a zinc atom

In CA, Zn^{2+} is bound to the enzyme through 3 Histidines + water – see the next pages for more details about the reaction = NOT a structural role-

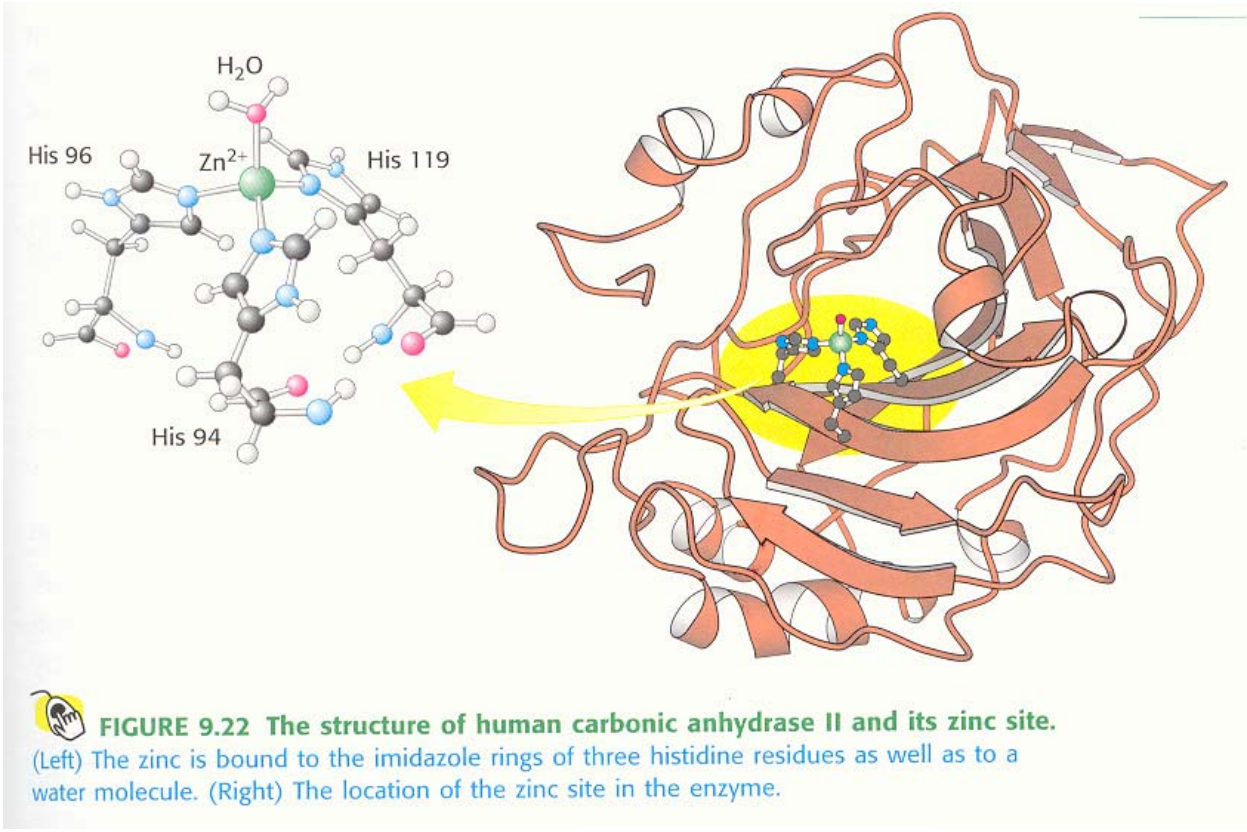
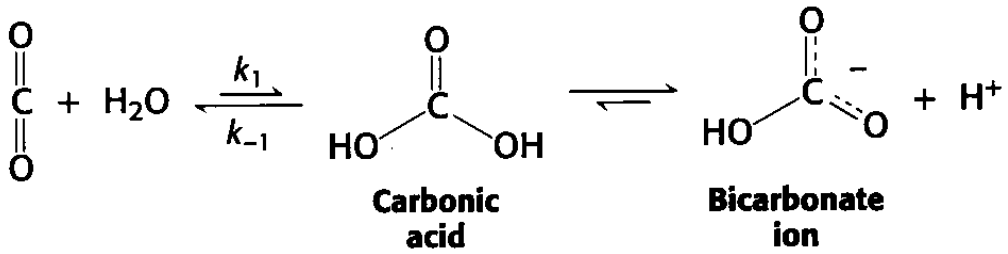
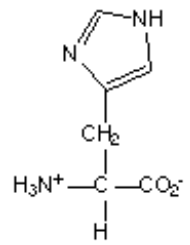


FIGURE 9.22 The structure of human carbonic anhydrase II and its zinc site. (Left) The zinc is bound to the imidazole rings of three histidine residues as well as to a water molecule. (Right) The location of the zinc site in the enzyme.

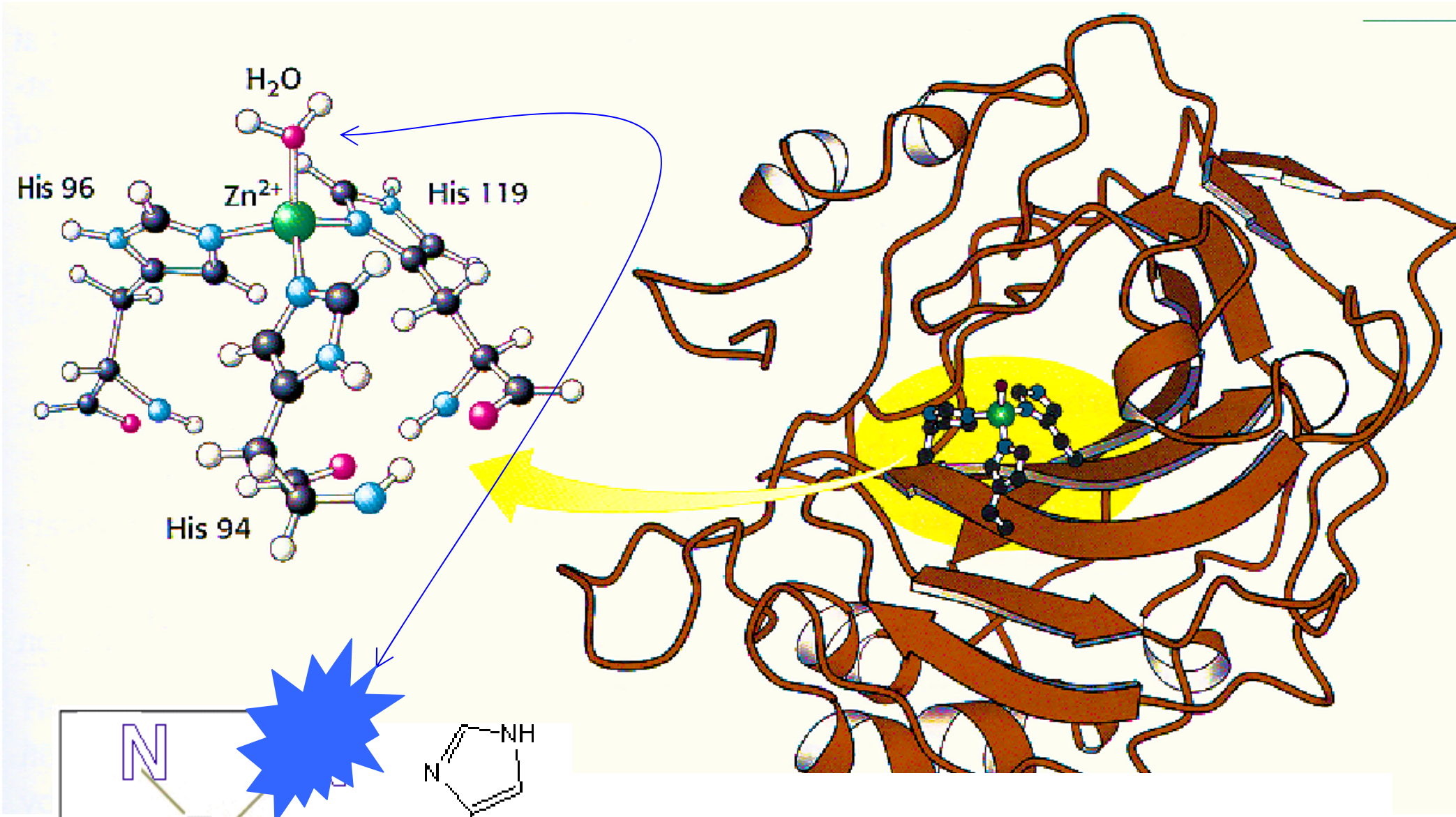
The overall reaction catalysed:





How does it do this? And what is special about the zinc coordination site? It's all to do with the histidine/imidazole nitrogen Intermediate ligand on an Intermediate metal – not a soft ligand like??). See next 3 pages..

L-B	R-M	K-S	Problems to do
	P 3-5	4	See the questions at the end


H_2O
His 96
Zn^{2+}
His 119
His 94
N
Zn
N
N
NH
N
CH_2
H_3N^+
C
CO_2^-
H

Mechanism of Carbonic Anhydrase

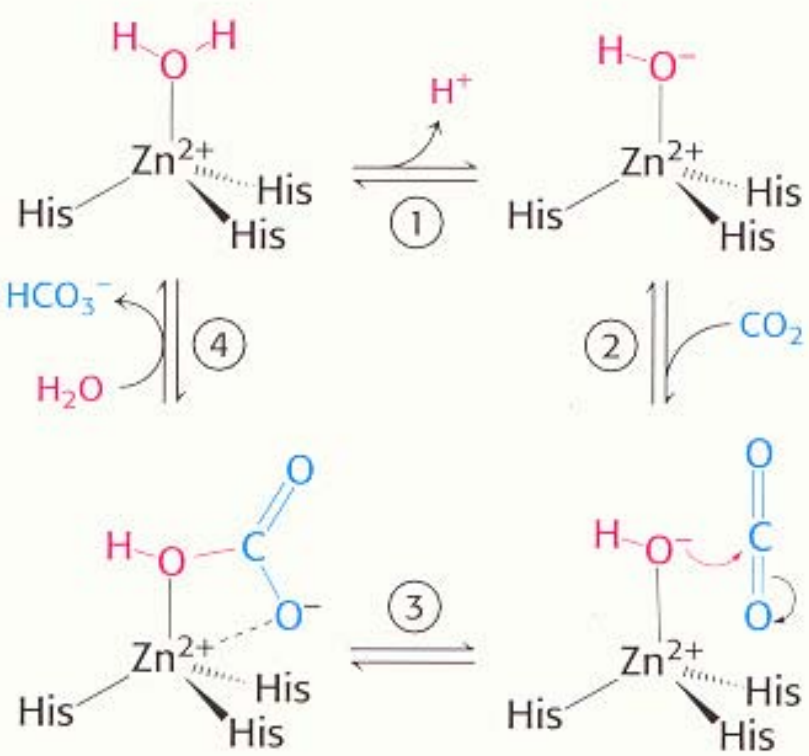


FIGURE 9.25 Mechanism of carbonic anhydrase. The zinc-bound hydroxide mechanism for the hydration of carbon dioxide catalyzed by carbonic anhydrase.

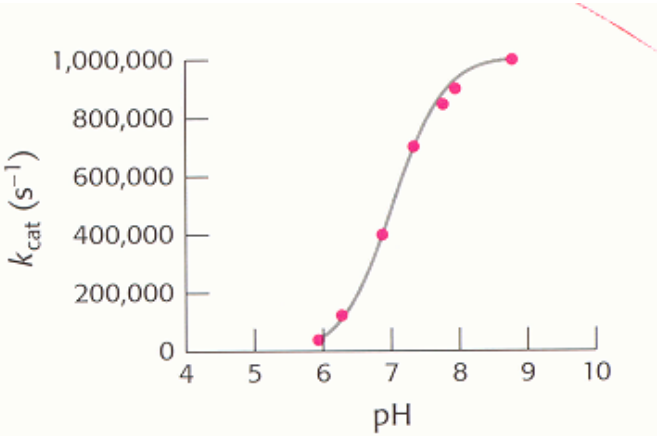


FIGURE 9.23 Effect of pH on carbonic anhydrase activity. Changes in pH alter the rate of carbon dioxide hydration catalyzed by carbonic anhydrase II. The enzyme is maximally active at high pH.

The H_2O is activated by the Zn(II) – makes it more acidic – so the H^+ is lost at neutral pH rather than at the much higher pH normally needed. The reaction usually takes place at pH 7 – 8 – acidosis of the blood would dramatically slow down the chemistry (above) because there would be H^+ present driving the reaction to the LEFT. See next page.

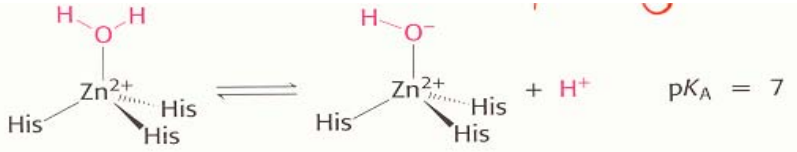
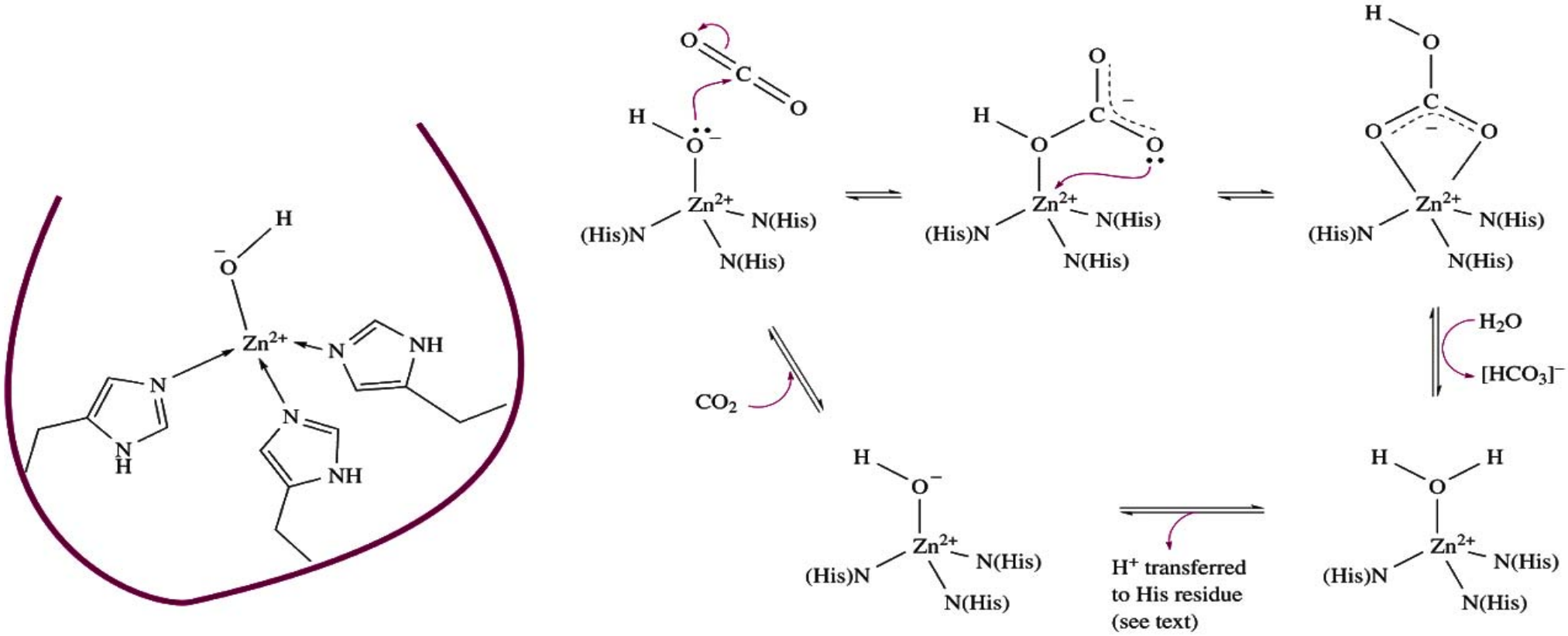
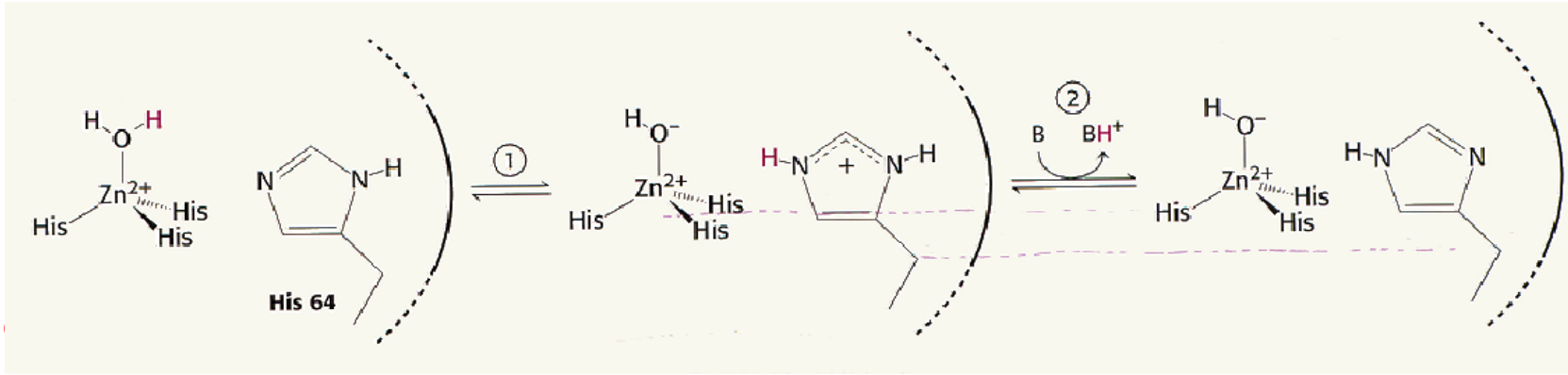


FIGURE 9.24 The pK_a of water-bound zinc. Binding to zinc lowers the pK_a of water from 15.7 to 7.

We can see the mechanism in more detail here:

Key – activation of the CO_2 by the negatively charged OH on the zinc. Then the now negatively charged O on the CO_2 (the new Lewis base) binds to the zinc(II) – it's the Lewis acid. Now we have a Glu-like binding pattern. Incoming water displaces the HCO_3^- product.





3) Zinc proteases (metalloproteases) include:

digestive enzymes – eg carboxypeptidases CPA

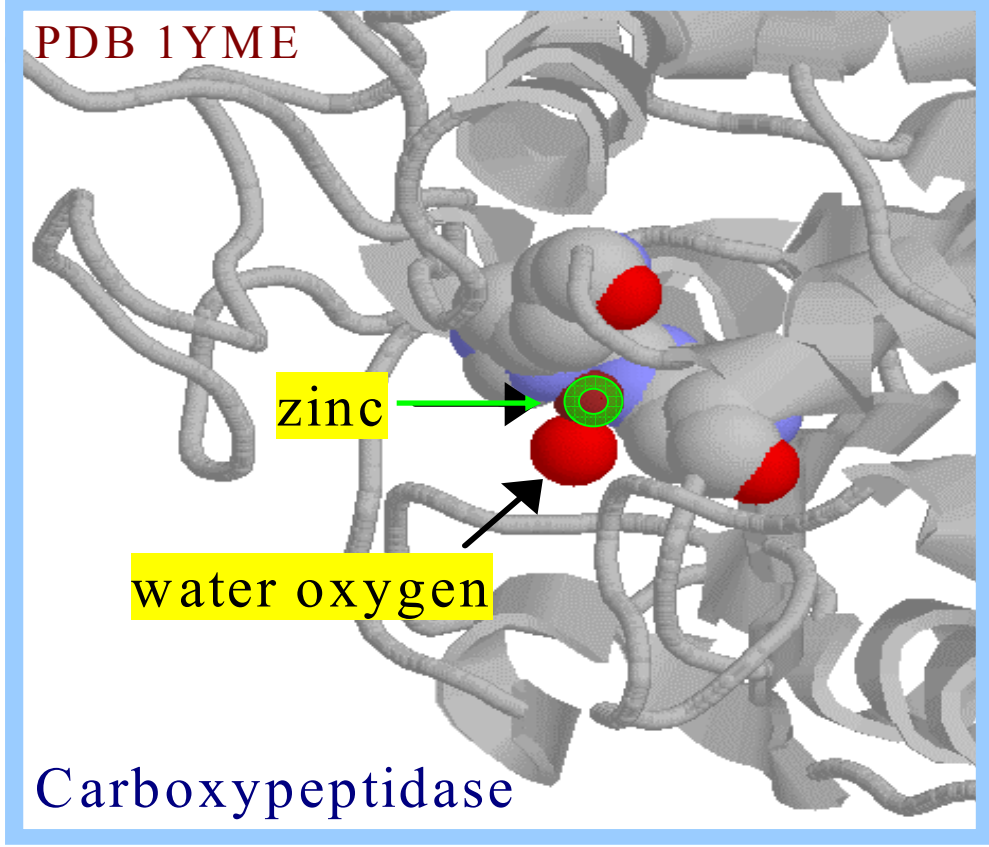
matrix metalloproteases (MMPs), secreted by cells

Some MMPs (e.g., collagenase) are involved in degradation of extracellular matrix during tissue remodelling.

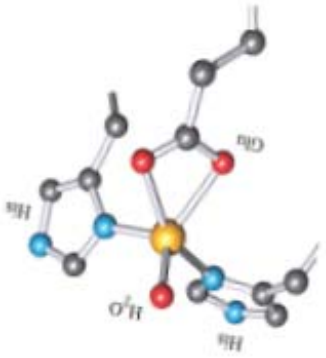
Some MMPs have roles in cell signalling relating to their ability to release cytokines or growth factors from the cell surface by cleavage of membrane-bound pre-proteins.

The zinc-binding motif at the active site of a metalloprotease includes: 2 His residues whose imidazole side-chains are ligands & 1 Glu with 2 oxygens = catalysis NOT a structural role

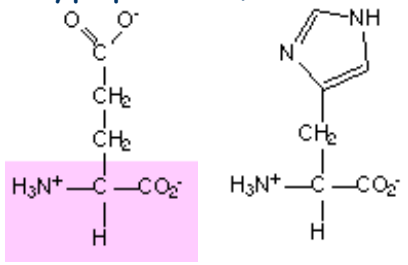
During catalysis, the Zn^{2+} promotes nucleophilic attack on the carbonyl carbon by the oxygen atom of a water molecule at the active site. The active site base (Glu in facilitates this reaction by extracting H^+ from the attacking H_2O.



3) Carboxypeptidase – a pancreatic digestive enzyme that cleaves the carboxyl terminal amino acid from a peptide chain by hydrolysing the amide link:



Carboxypeptidase)

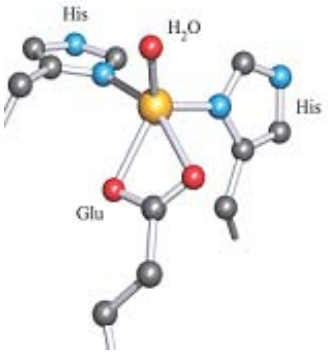


Example: LEU-GLU-PHE ➔ LEU-GLU + PHE

This is the reverse of the peptide chain expansion reaction

Mass: 34,500, 1 Zn, the Zn is bound in a crevice with almost 5 coordination –

HIS HIS GLU (both O's) and water - details coming .. catalysis NOT a structural role



So what's the reaction?

To cleave, break up, digest the peptide chain, hence a peptidase.

The organic chemistry says: nucleophilic attack of the C=O should work, but what with?

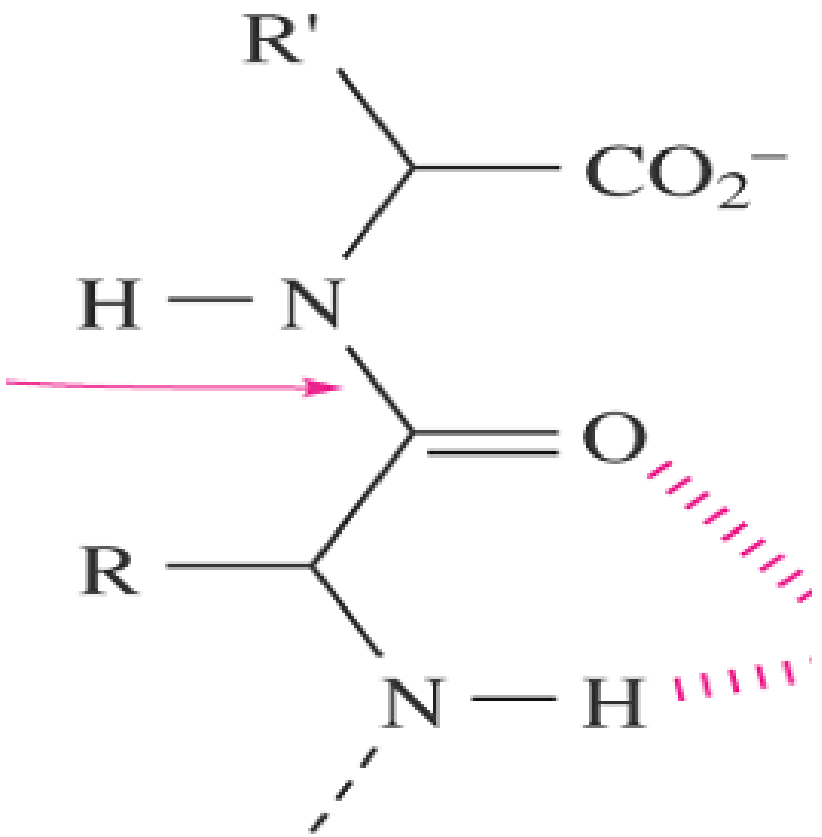
Needs an OH^- - where do we get that from?

We need one bound to a Zn(II), but at pH 7 – not many OH^- around, we have plenty of water though.

LEU-GLU-PHE ➔ LEU-GLU + PHE

R groups appropriate for these amino acids

So, let's look at that structure again a bit closer …

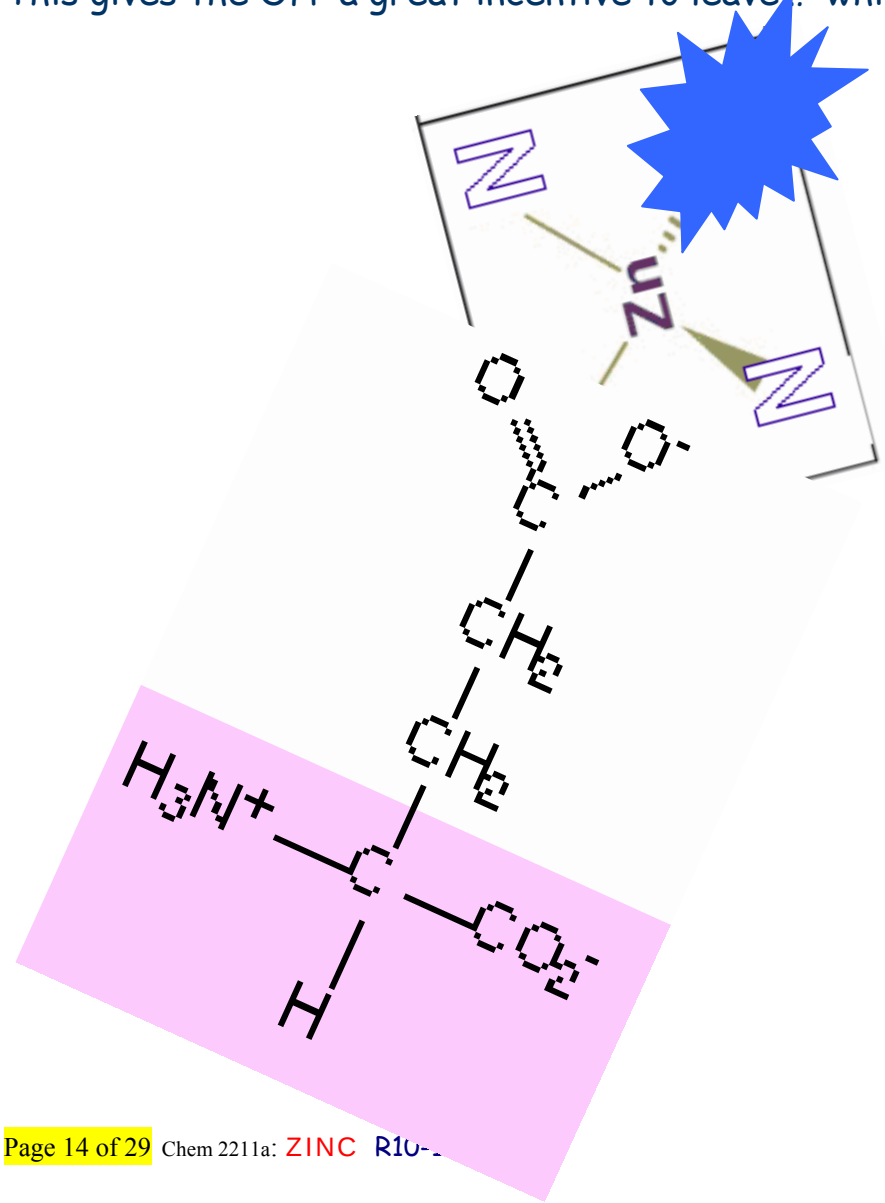


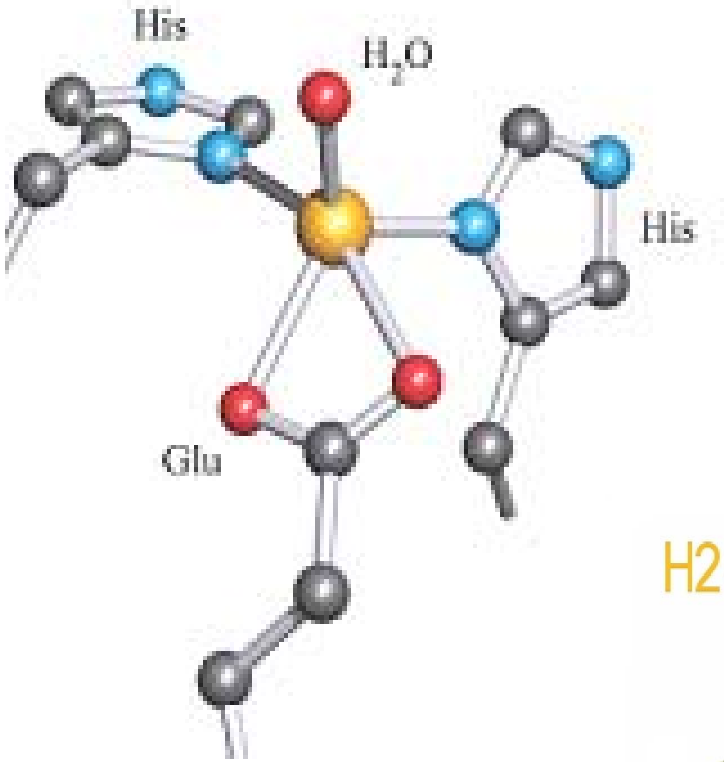
So what's going on here? Why is this changed from CA?

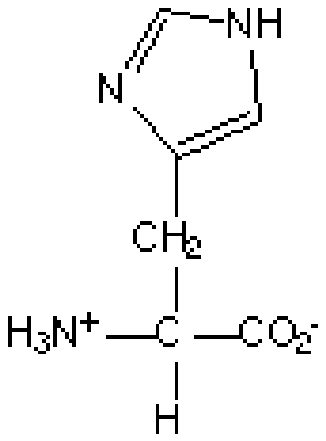
The chemistry of the bound OH^- is even more aggressive and has to be stabilized more. So,

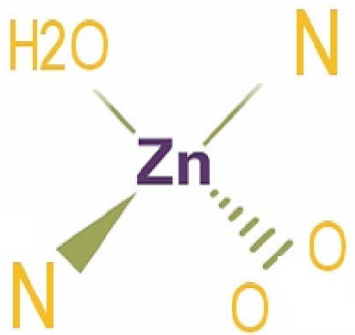
a 5-coordinate Zn(II) – really illegal – but possible with db metals because they can access the 4s, 4p **and 4d** (the 3d are filled) – sp^3d

This gives the OH^- a great incentive to leave. which it does, see next page….









More structural details and the mechanism are on the next slides – the overview – but let's move on step by step on the next pages:

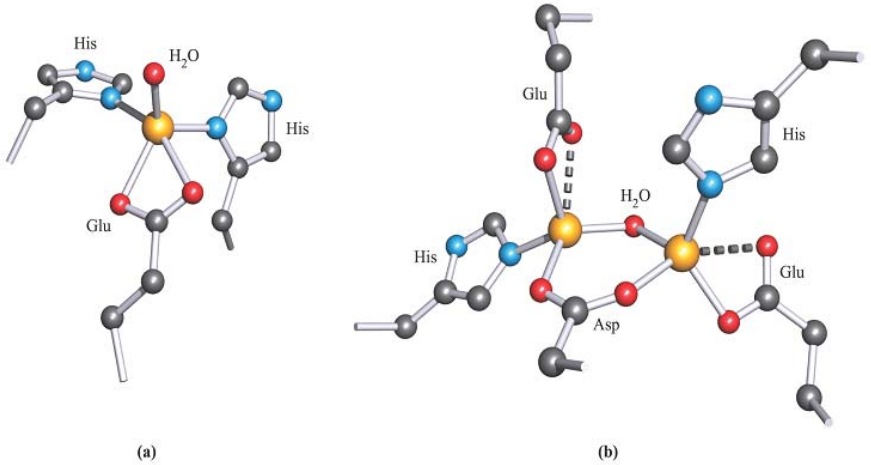
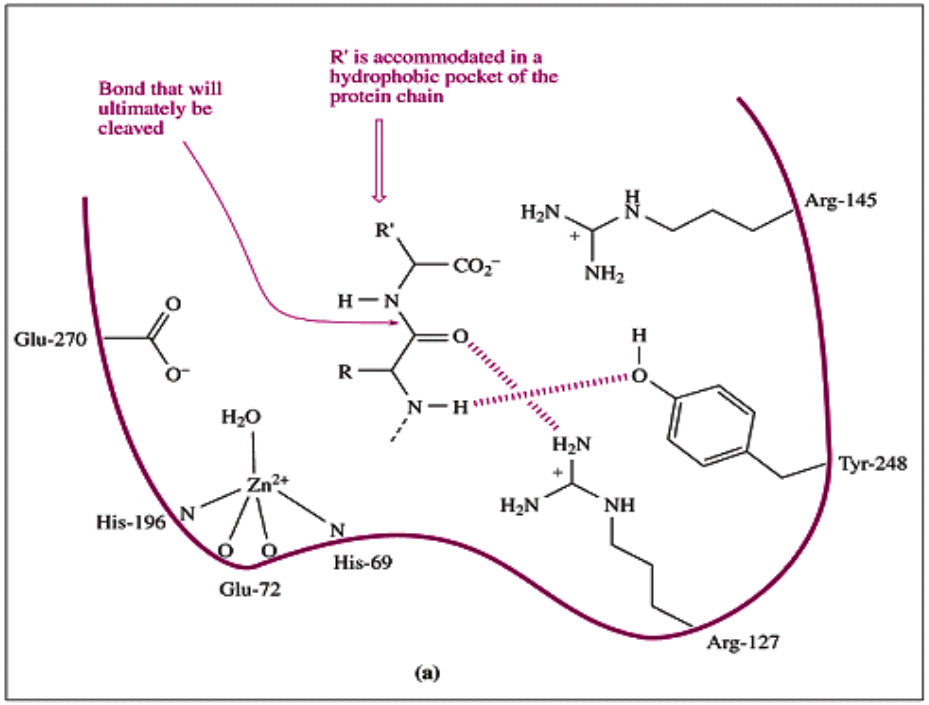


Fig. 28.24 The structures of the active sites in (a) α-carboxypeptidase A (CPA) isolated from bovine (*Bos taurus*) pancreas, and (b) carboxypeptidase G2 (CPG2) isolated from *Pseudomonas* sp.; see *Table 28.2* for amino acid abbreviations. Colour code: Zn, yellow; C, grey, O, red, N, blue.



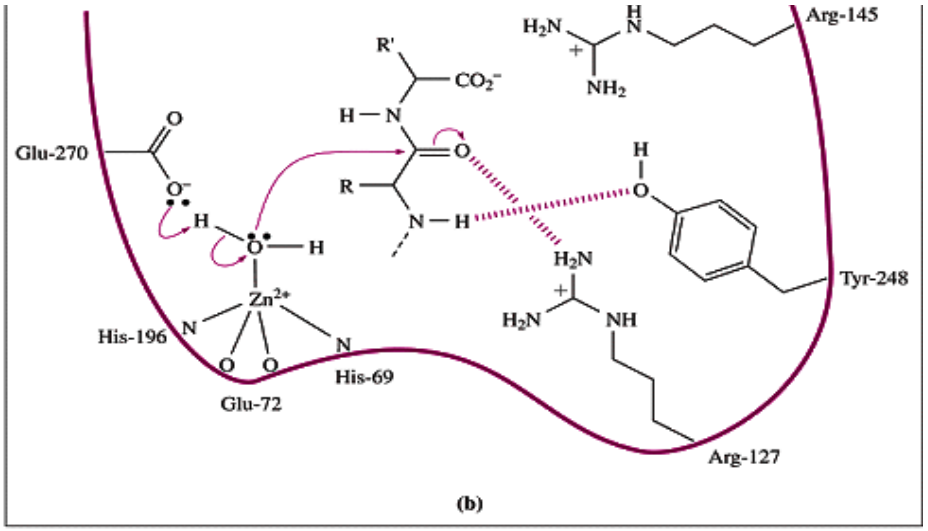
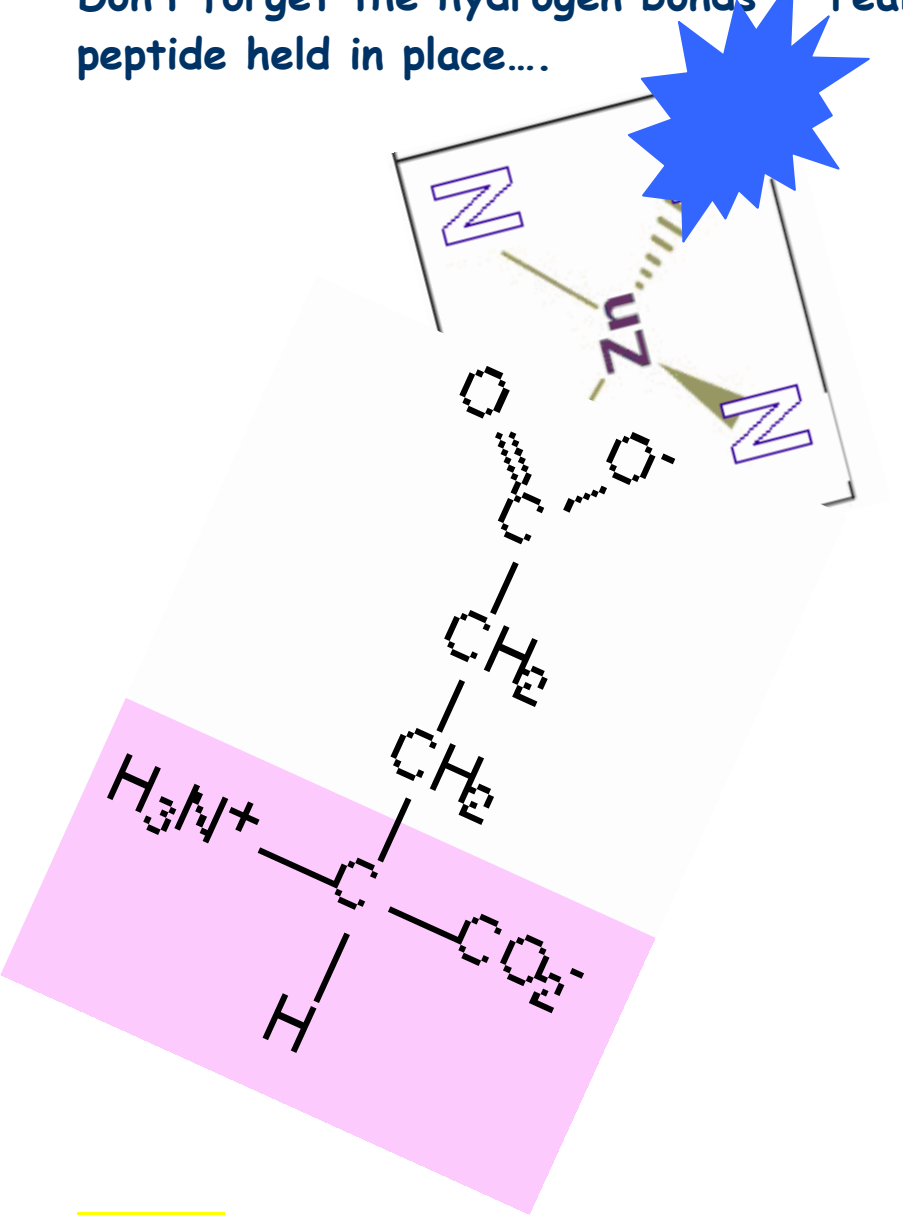


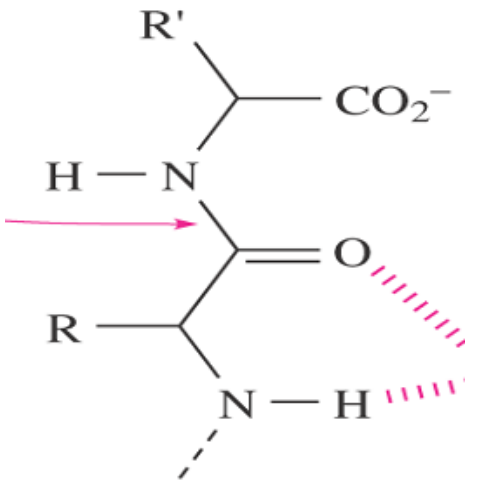
Fig. 28.23a Schematic representation of the generally accepted mechanism for the CPA-catalysed cleavage of a *C*-ter peptide link; see *Figure 28.24a* for a more detailed diagram of the coordination sphere of the Zn^{2+} ion. T line represents the protein chain; only residues mentioned in the discussion are shown. The diagrams do n imply whether a mechanism is concerted or not.

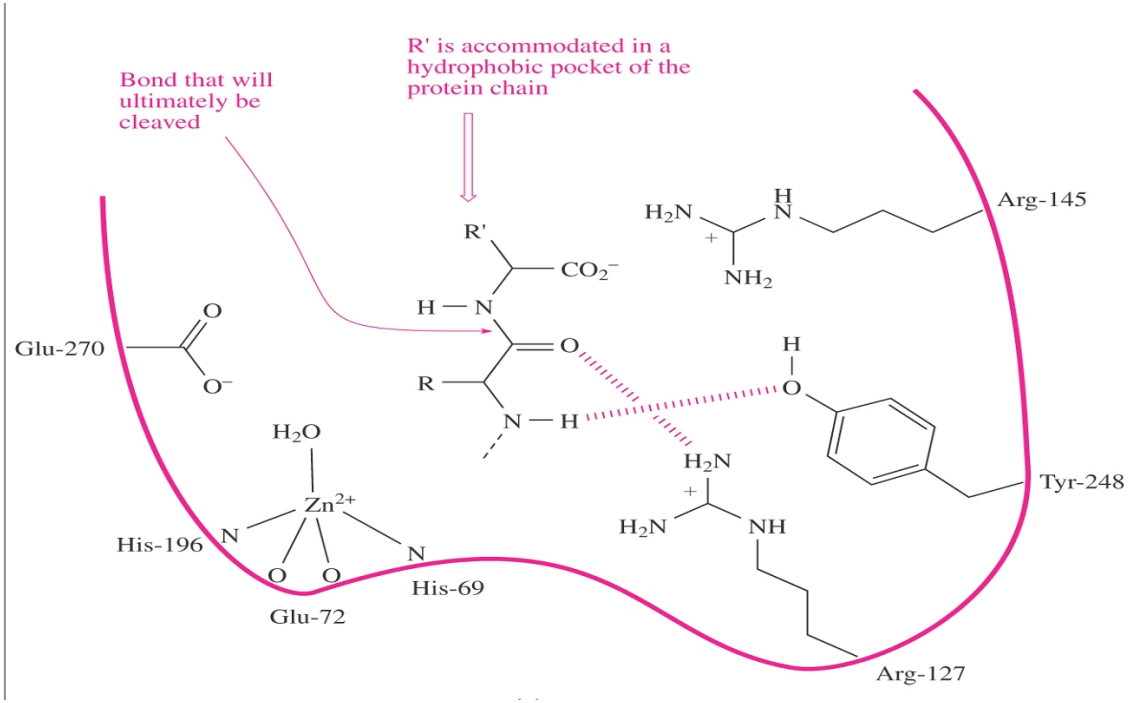
Important to remember the following:

Activate the water, make a stronger base (OH^-) it attacks the C=O.

Don't forget the hydrogen bonds - really essential they keep the peptide held in place….

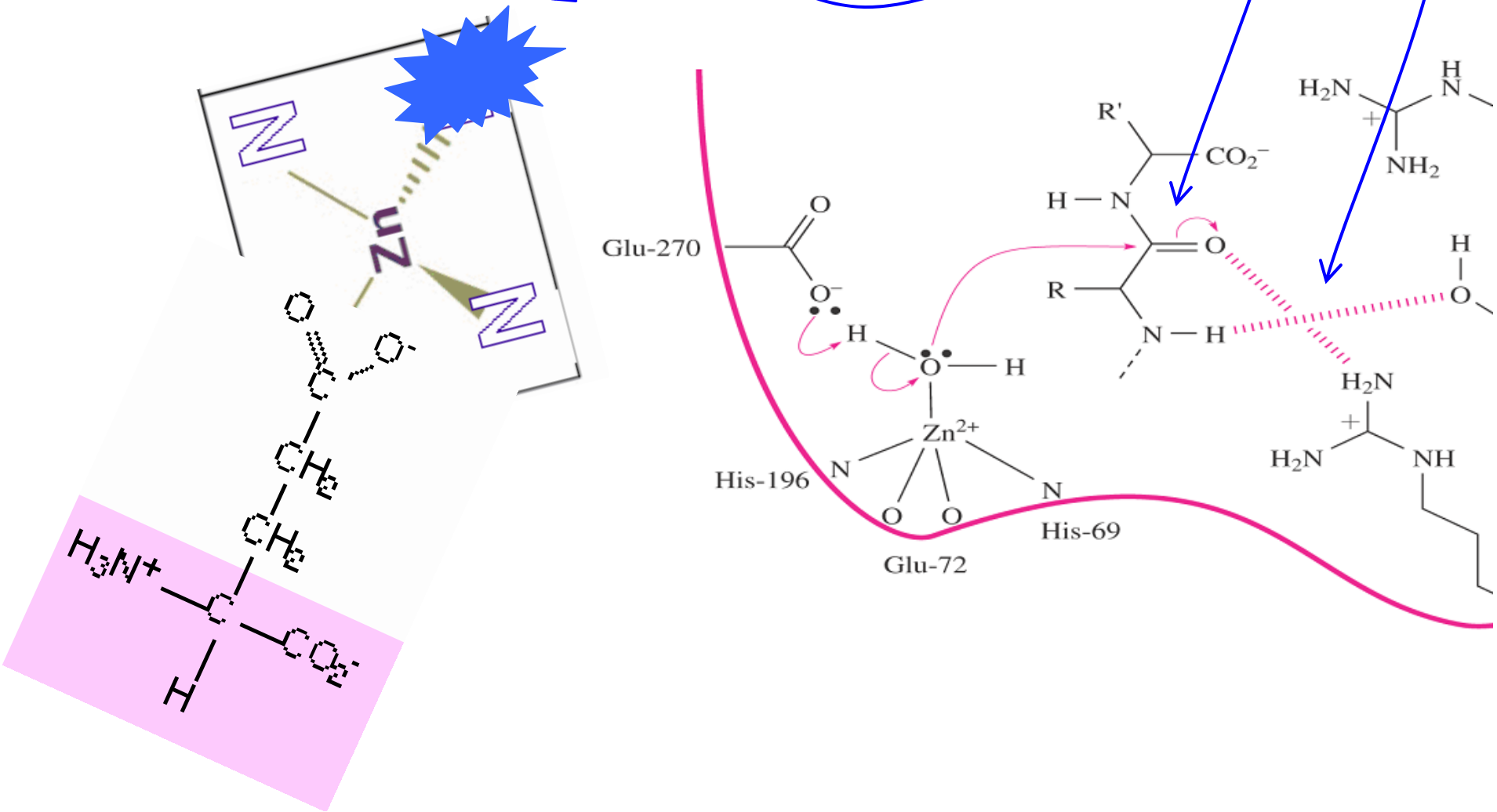






Key points –

The OH^- on the Zn(II) aggressively attacks the C=O – it's a very strong Lewis base – at the same time, to assist, the O in the C=O is hydrogen bonded to the H in NH_2 which also weakens the bond. The next slide shows the breaking of the peptide bond we've added H_2O across the bond – the opposite to the peptide forming reaction.



Key to this reaction is the Lewis acid character of the zinc and the formation of 2 hydrogen bonds to hold the peptide chain in place.

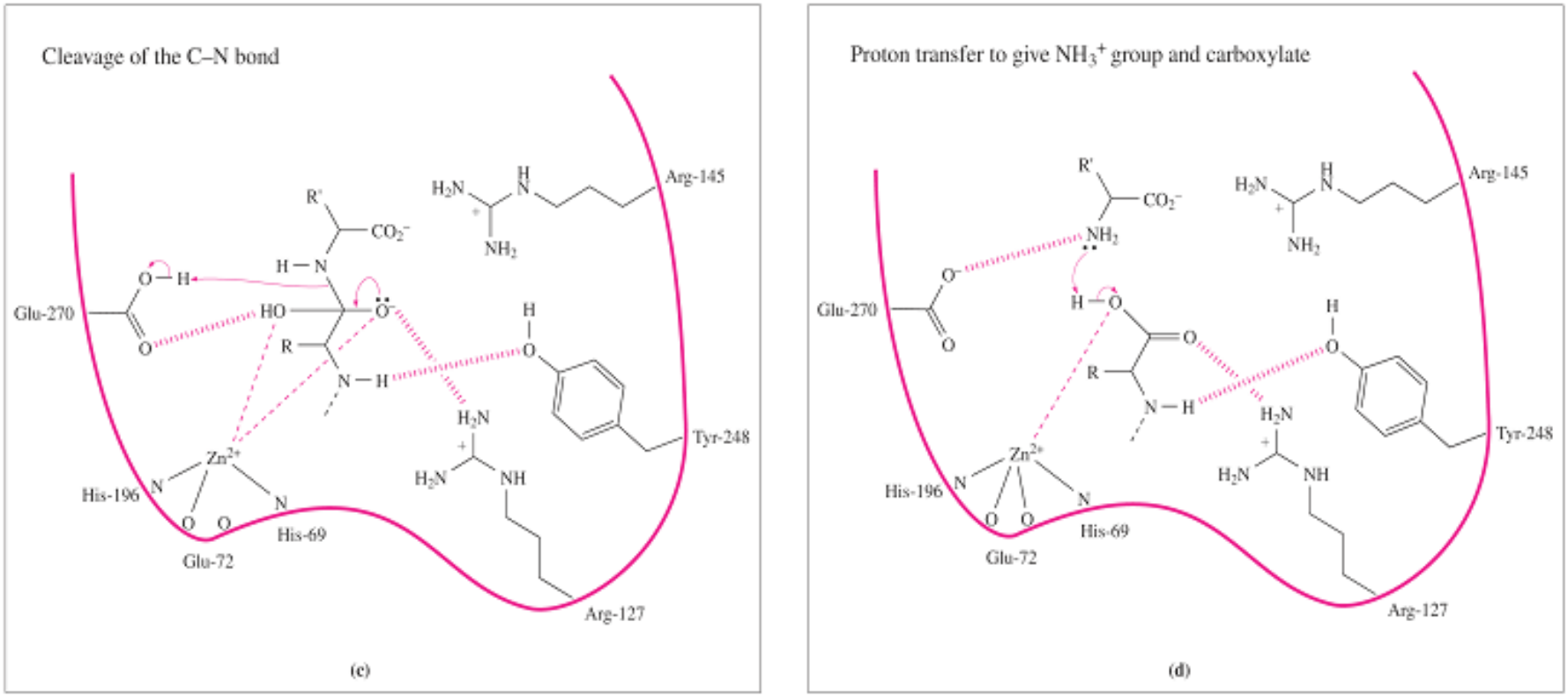
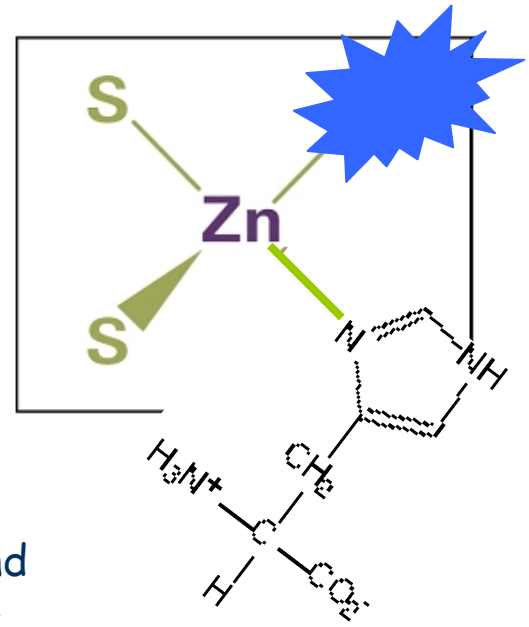


Fig. 28.23b Schematic representation of the generally accepted mechanism for the CPA-catalysed cleavage of a *C*-terminal peptide link; see *Figure 28.24a* for a more detailed diagram of the coordination sphere of the Zn^{2+} ion. The red line represents the protein chain; only residues mentioned in the discussion are shown. The diagrams do not imply whether a mechanism is concerted or not.

4) LIVER ALCOHOL DEHYDROGENASE LADH

A 2-zinc-containing dimeric enzyme (=4 Zn), uses a coenzyme (NAD^+)and ethanol.

A zinc metalloenzyme that oxidizes alcohols to aldehydes or ketones – a member of the oxidoreductase family of enzymes – a redox enzyme – shuttles electrons.



The catalytic zinc is bound to two CYS, 1 HIS and water; the 2nd zinc is bound to four CYS = a structural role..

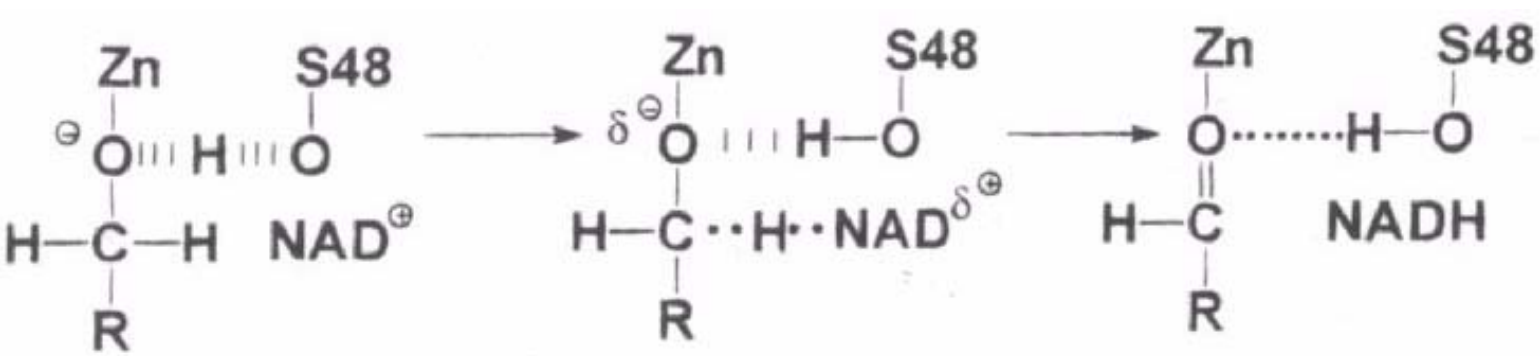
In humans, the enzyme is contained in the lining of the stomach and in the liver. It catalyzes the oxidation of ethanol to acetaldehyde:

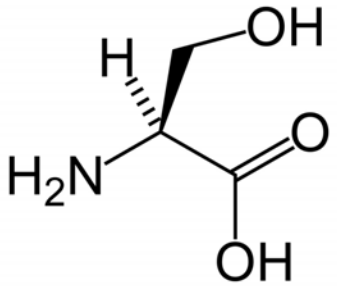
$CH_3CH_2OH + NAD^+ \rightarrow CH_3CHO + NADH + H^+$

It is important to note that the aldehyde is more toxic than the alcohol and water is being used - so dehydration occurs – hence the hang-over – luckily aldehyde is broken down more rapidly… hmmmm

This allows the consumption of alcoholic beverages, but its evolutionary purpose is probably the breakdown of alcohols naturally contained in foods or produced by bacteria in the digestive tract.

Humans have at least six slightly different alcohol dehydrogenases. Serine (S48) provides the route for the proton, above.

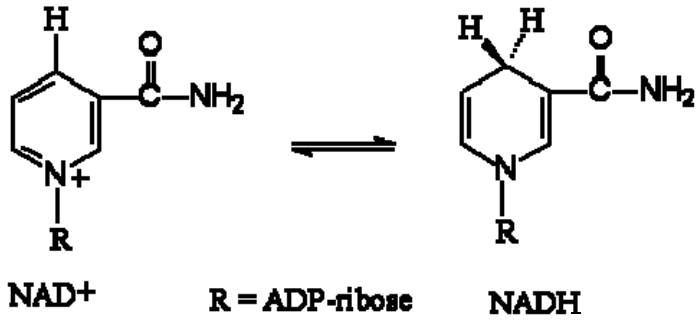




Up to 30% of alcohol is oxidized in the stomach – class IV rxn.

The rate-limiting step is the availability of the coenzyme, NAD^+.

We only have enough enzyme so that, for an average size person, it will take about 90 minutes to metabolize 1 drink (typical oxidation rate is 100 mg ethanol/kg/hr = 11 ml/hr/70 kg).



The liver is the major site of this oxidation, as well as the site of major destruction (cirrhosis) due to excessive amounts of alcohol.

The overall reaction catalyzed (Class I) is the oxidation of alcohol to aldehyde with the concomitant reduction of the coenzyme NAD+ to NADH:

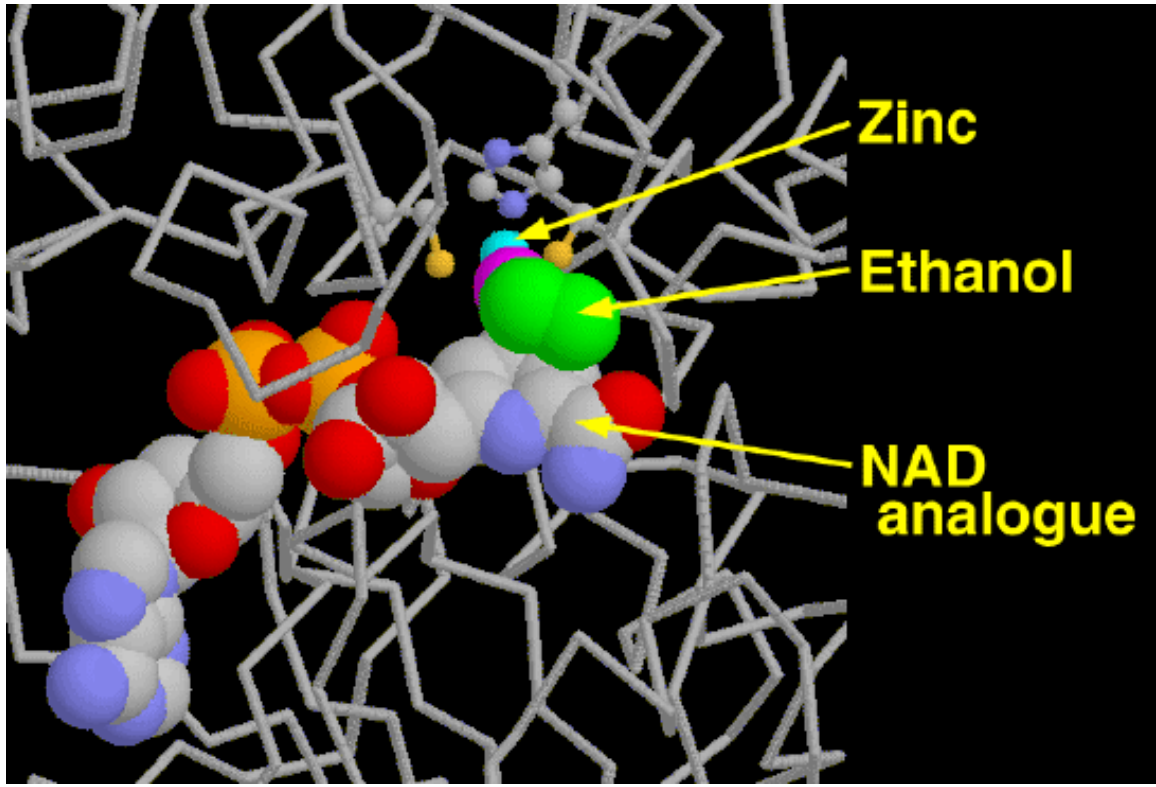
$RCH_2OH + NAD^+ \rightarrow RCHO + NADH + H^+$

We can see how the enzyme works as follows:

- Enz + NAD^+ ➔ Enz-NAD^+
- Enz-NAD^+ + ETOH ➔ Enz-NAD^+-ETOH
- Enz-NAD^+-ETOH ➔ Enz-NADH + aldehyde (RCHO)

AND then ·Enz-NADH ➔ Enz + NADH

--LADH in summary…



1) Two identical subunits in LADH

2) The enzyme contains two Zn^{2+} per subunit; one is in the active-site and involved in catalysis, the other serves a structural role. For the active-site Zn the ligands are 2 Cys, 1 His and a water molecule. The structural Zn has 4 CYS ligands.

3) LADH is a major enzyme in alcohol metabolism, and is most concentrated in the liver. Since vitamin A is an excellent substrate it has been suggested that the "real" substrate is vitamin A – ie NOT alcohol - (the aldehyde of which is critically important in vision and epithelial tissue).

4) Ethanol metabolism in humans follows zero-order kinetics; unfortunately, not inducible (which means the more alcohol you drink …)

5) The rate-limiting step is the availability of the coenzyme, NAD^+.

6) Step 4 – the release of NADH to cycle round to the 1st step.

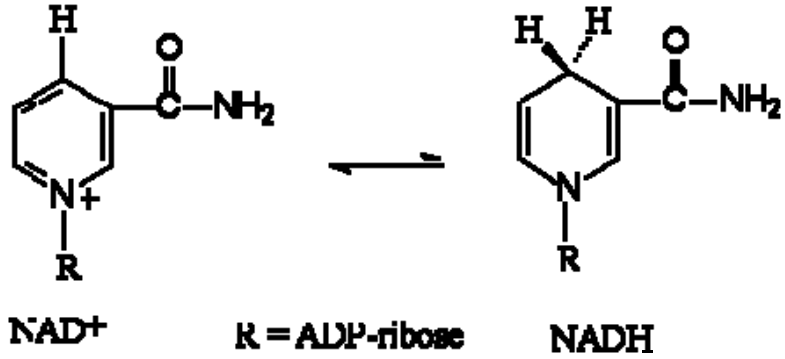
7) We only have enough enzyme such that, for an average size person, it will take about 90 minutes to metabolize 1 drink (typical oxidation rate is 100 mg ethanol/kg/hr = 11 ml/hr/70 kg individual).

8) The liver is the major site of this oxidation, as well as the site of major destruction (cirrhosis) due to excessive amounts of alcohol.

We are interested only in Classes I and IV.

Class I: in the cytosol of the liver of humans – carries out oxidation to the aldehyde

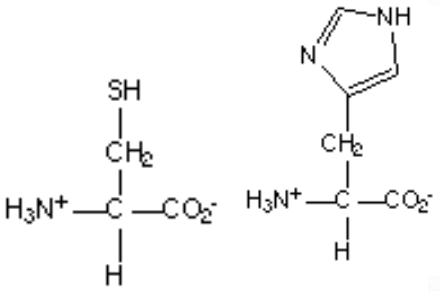
Class IV: in the stomach of humans - carries out the first stage of oxidation of alcohol

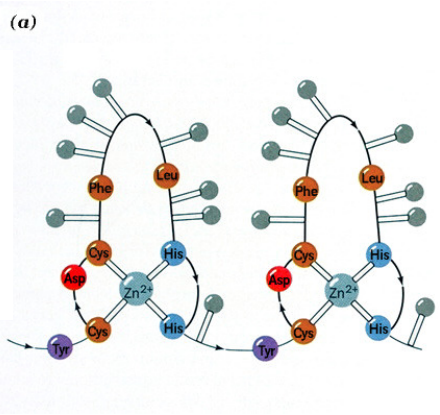


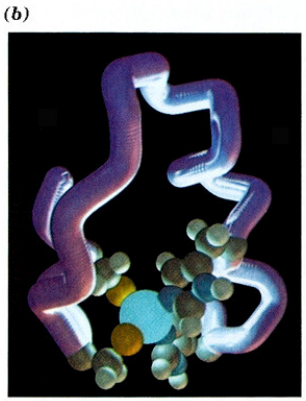
NAD+ R = ADP-ribose NADH

5) …but what about the zinc fingers? CYS CYS HIS HIS – generally –

Zn^{2+} uses 4 CYS or 2CYS and 2HIS for structural jobs – no empty or reactive sites left.







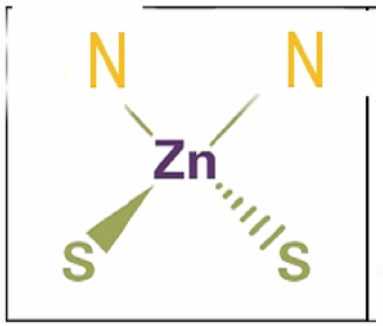
Zinc-finger DNA binding protein family

The DNA-binding motif is found as part of transcription regulatory proteins.

Zinc finger proteins were first discovered as transcription factors.

Zinc finger proteins are among the most abundant proteins in eukaryotic genomes.

Their functions are extraordinarily diverse include DNA recognition,

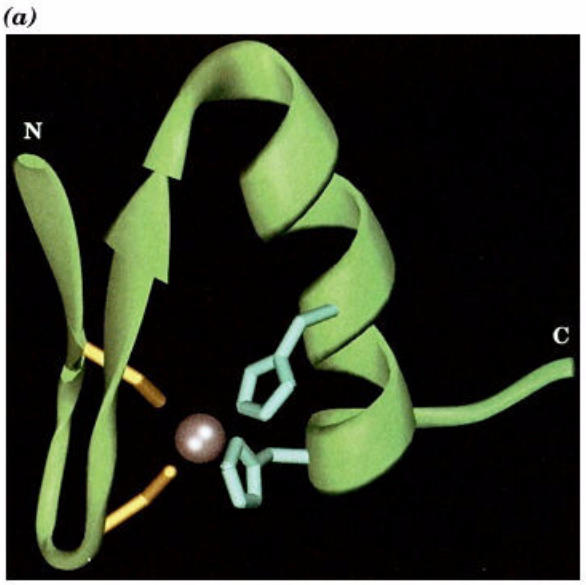


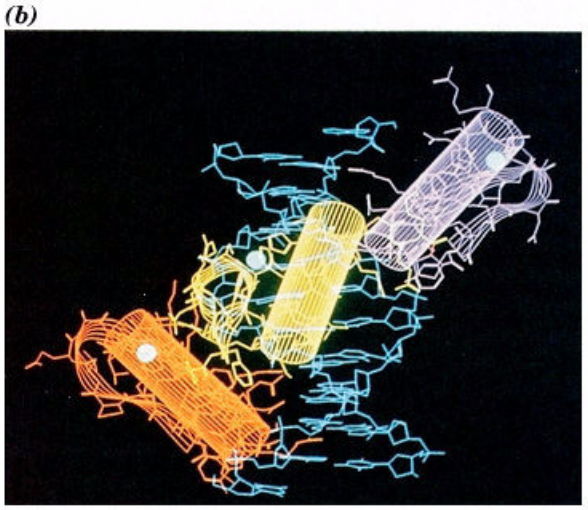
RNA packaging, transcriptional activation, regulation of apoptosis, protein folding and assembly, and lipid binding.

Zinc finger structures are as diverse as their functions.

One of the most abundant DNA-binding motifs.

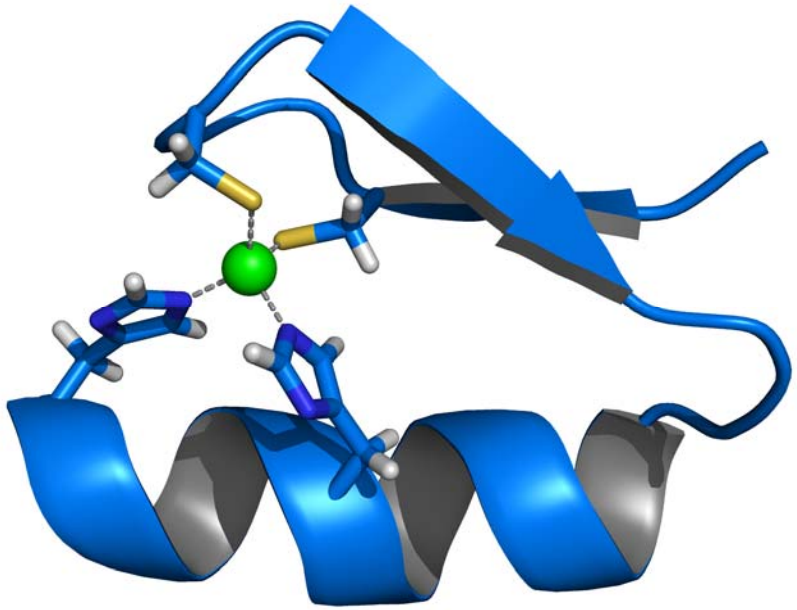
Proteins may contain more than one finger in a single chain.





STRUCTURAL APPENDIX -

The following images are provided to allow us to examine how Nature uses the rules of inorganic chemistry to construct binding sites. Included to allow you to understand more completely the reactions and structures described above.



A1) Zinc finger proteins

Zinc binds to 2 CYS and 2 HIS (2S and 2N).

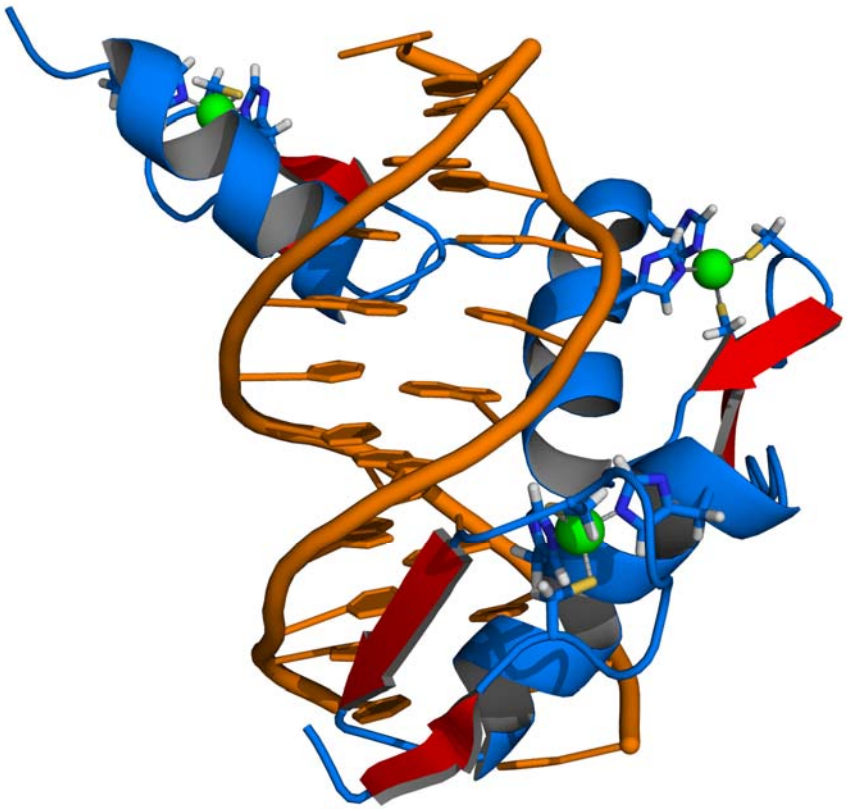
Fingers bind to 3 base-pair subsites and specific contacts are mediated by amino acids in positions -1, 2, 3 and 6 relative to the start of the alpha-helix.

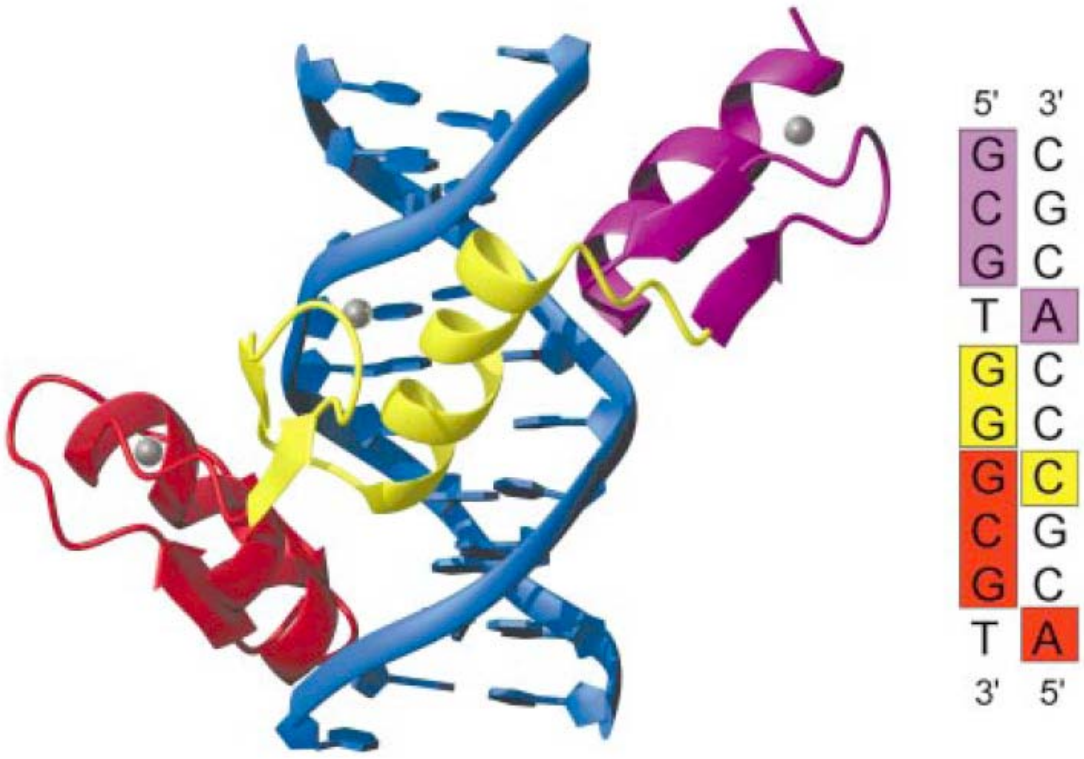
Contacts mainly involve one strand of the DNA.

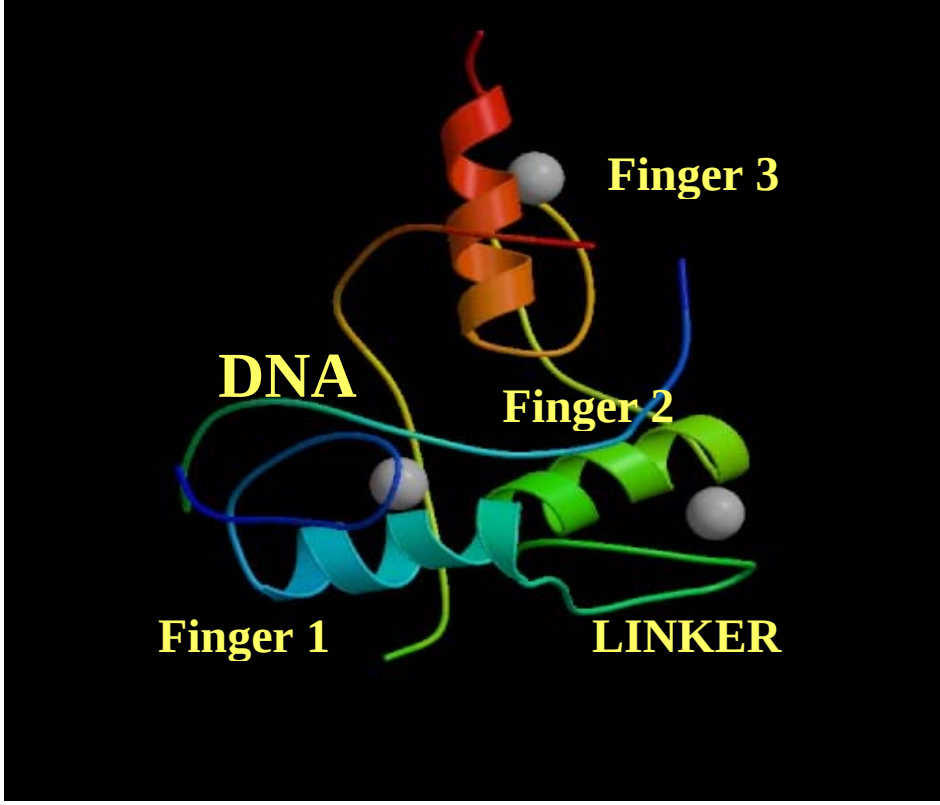
Where proteins contain multiple fingers, each finger binds to adjacent subsites within a larger DNA recognition site thus allowing a relatively simple motif to specifically bind to a wide range of DNA sequences.

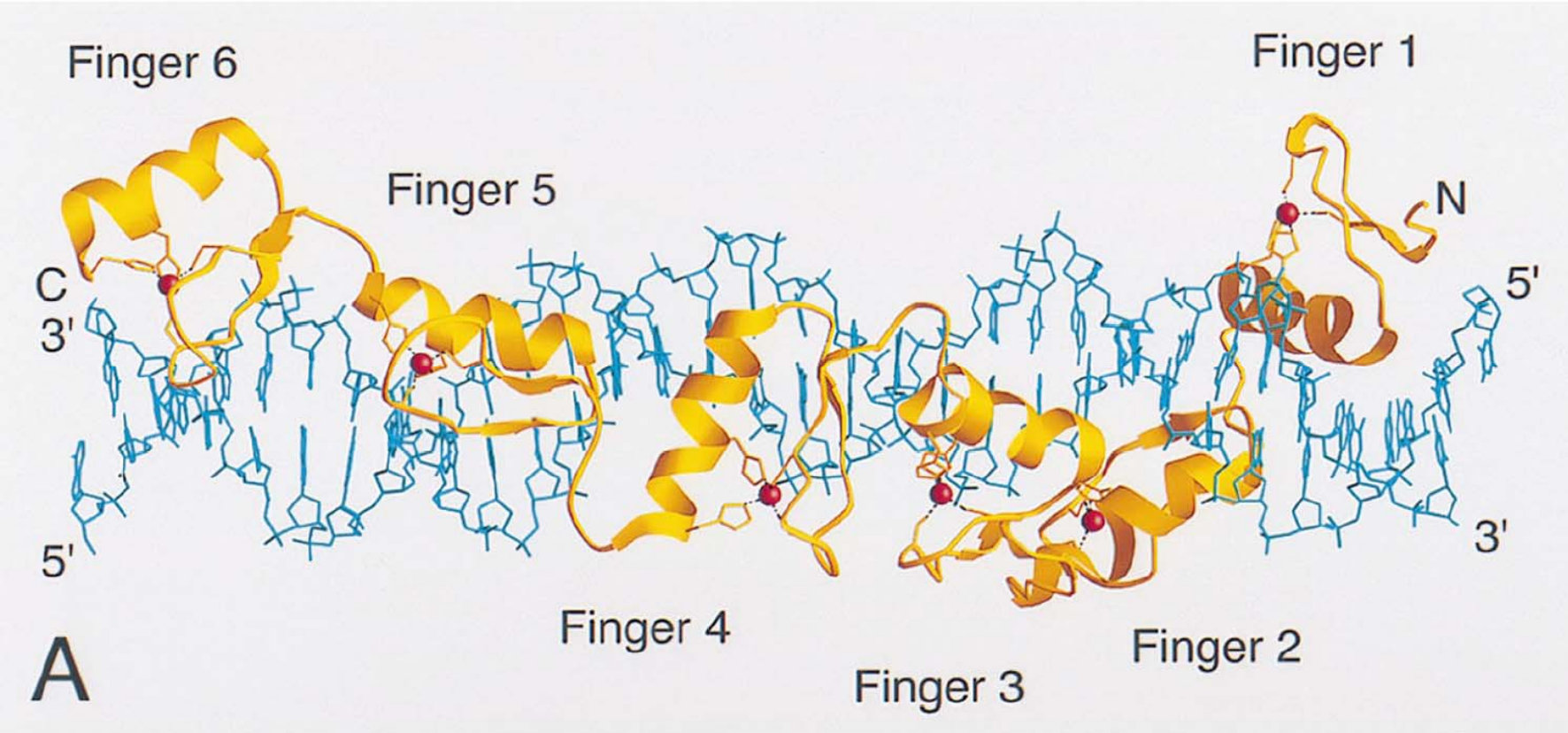
This means that the number and the type of zinc fingers dictate the specificity of binding to DNA

-




5' 3'
G C
C G
G C
T A
G C
G C
G C
C G
G C
T A
3' 5'


Finger 3
DNA
Finger 2
Finger 1
LINKER


Finger 6
Finger 1
Finger 5
N
C
3'
5'
5'
3'
Finger 4
Finger 2
Finger 3
A

L-B	R-M	K-S
1-2		4

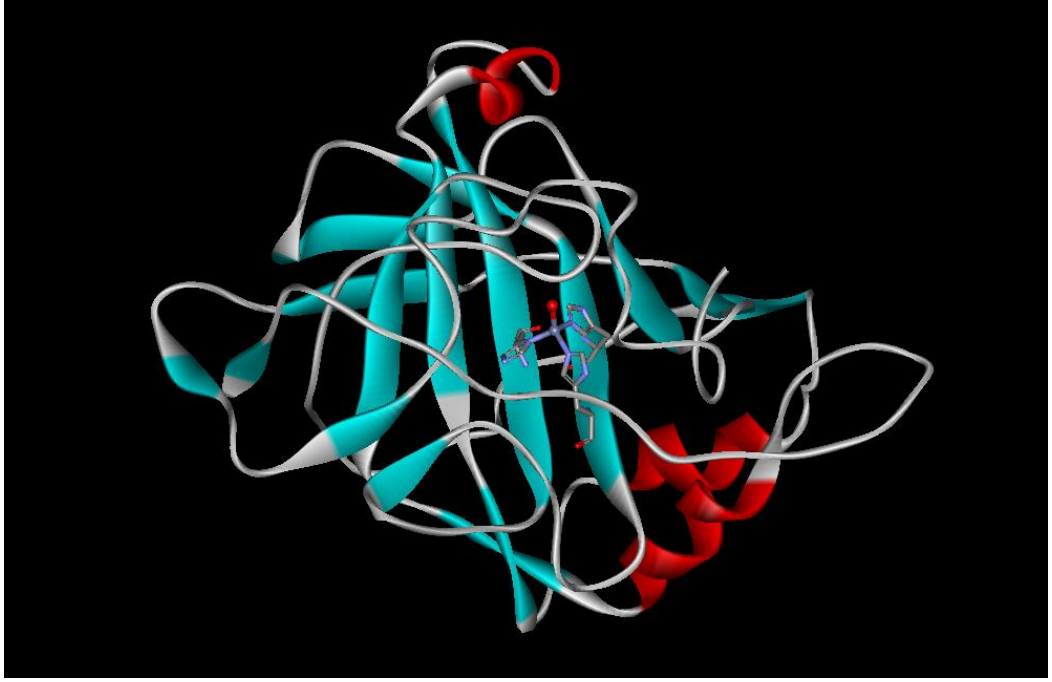
A2) X-ray structures of carbonic anhydrase

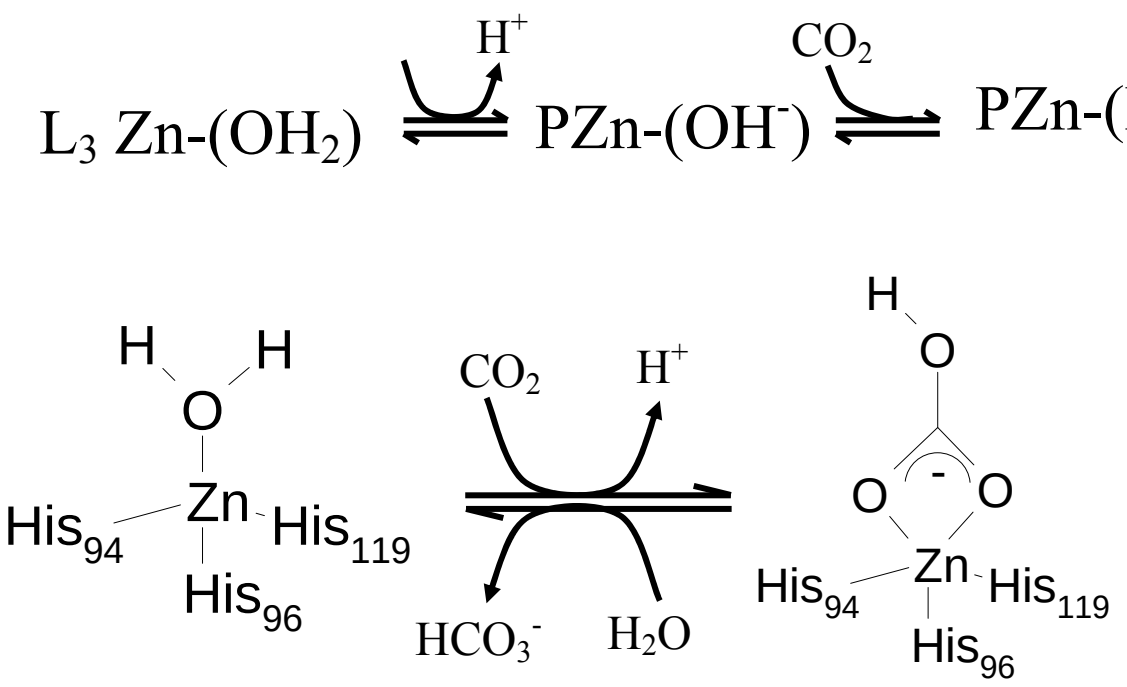
CA – primarily a β pleated structure

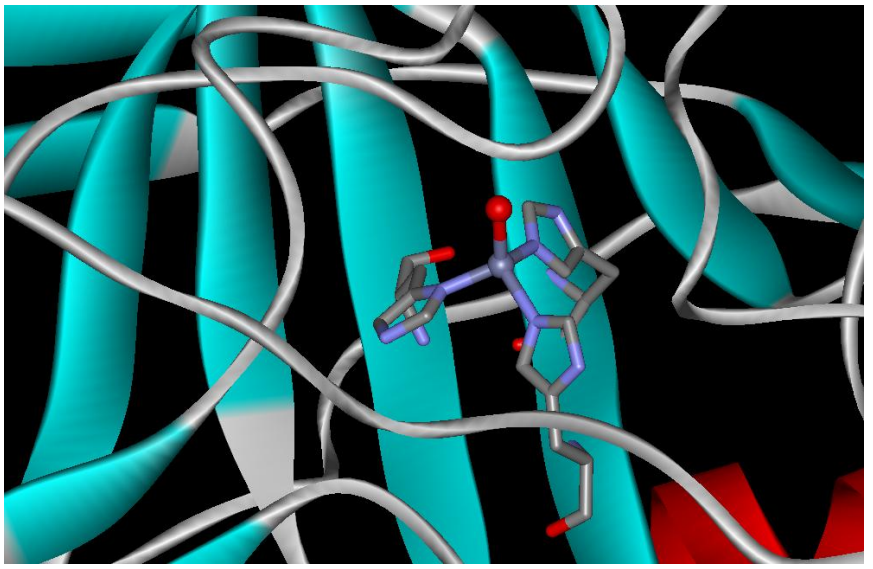
The bicarbonate reaction ---

Note the three HIS and 1 water in the binding site

L_3 represents the 3 HIS amino acids – referred to as P afterwards.





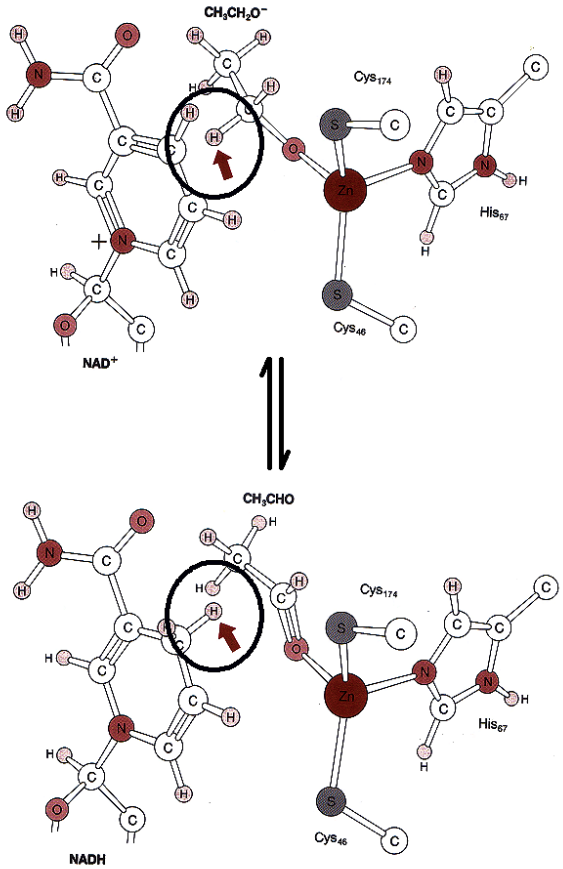


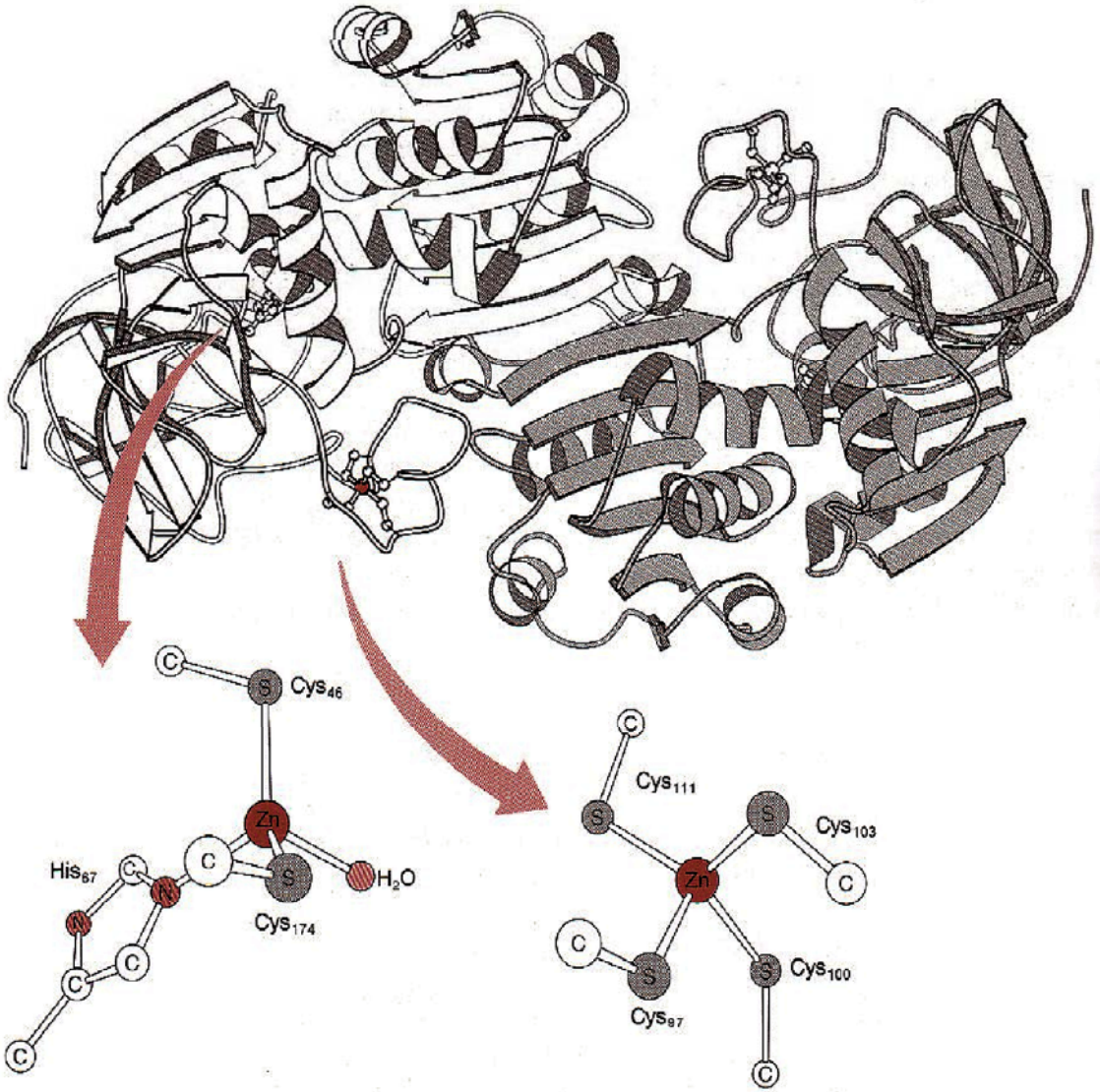
A3) Liver alcohol dehydrogenase (LADH)

$$CH_3CH_2OH + NAD^+ \rightleftharpoons CH_3CHO + NADH + H^{+-}$$

2 Zn atoms – 1 structural, the other catalytic.
Different coordination geometries.
Structural – all four sites occupied – the 4 CYS
Catalytic – 2 CYS & 1 HIS, one active site
This is a dimmer note the location of the other 2 Zn's in the other ½ of the dimmer on the RHS.

The catalytic chemistry involves protonation of the NAD^+ to NADH – this is the rate limiting step.

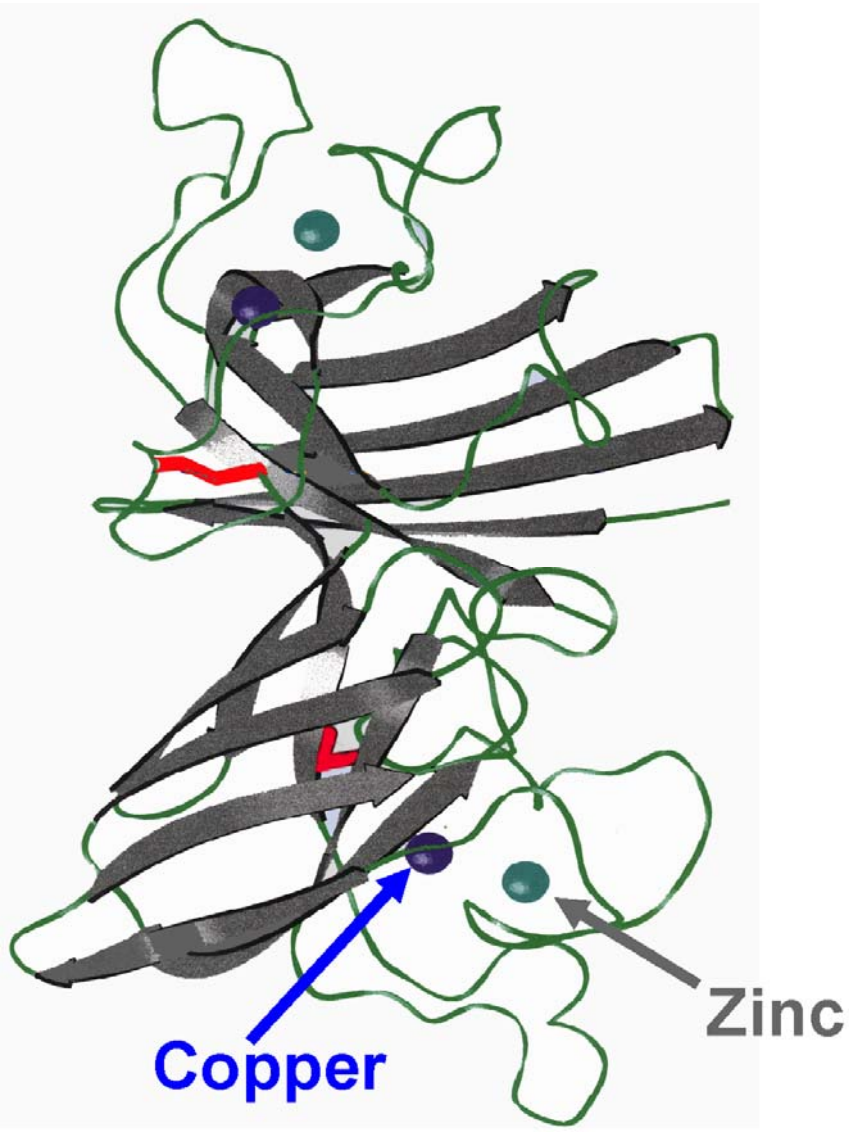


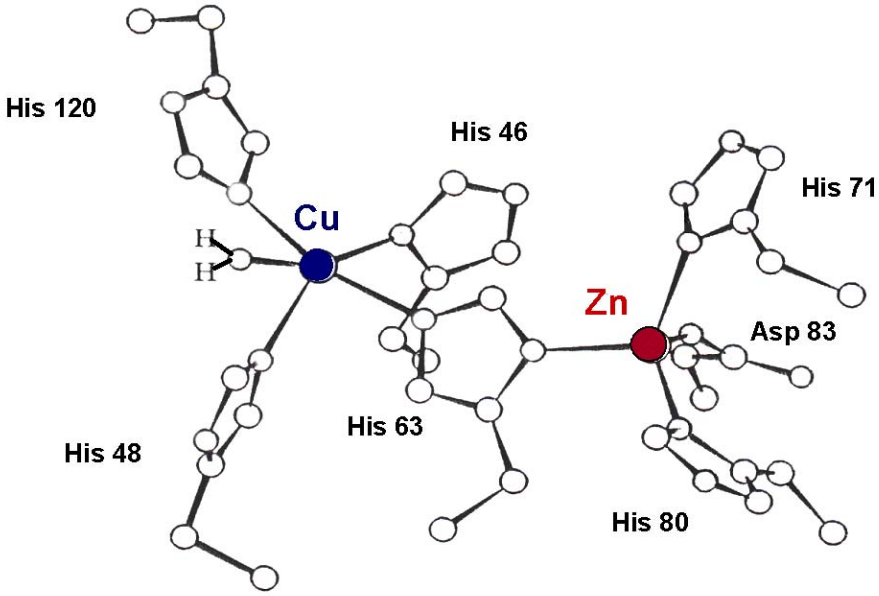


A4) Superoxide dismutase (the binding of the Cu(I) and Zn(II) can be rationalised in terms of our models in the

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

inorganic unit and here) – SOD – implicated in ALS disease due to muscle and nerve degeneration. Note – the O_2^- reaction was described in the inorganic unit. Here, one of a great many, CuZnSOD. Note – needs catalase (Fe(III-IV)-heme enzyme) to decompose the H_2O_2 product.





The chemistry requires both metals. SOD activity first described in a series of famous papers by Fridovich & McCord in 1969 The link to Amyotrophic Lateral Sclerosis (als) was reported in 1993

$$Cu^{2+} + O_2^- \longrightarrow Cu^+ + O_2$$

$$Cu^+ + O_2^- + 2\,H^+ \longrightarrow Cu^{2+} + H_2O_2$$

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

Key points from this unit	
1	Relationship of Zn to other metals – what is its role? Why was the change from anaerobic to aerobic atmosphere not significant for zinc? Common binding site combinations for Zn – check out p 2 – what are the amino acids involved? What are the binding sites of Zn as a catalyst and zinc as a structural metal? Why the difference? What makes Zn such a good catalyst? Why so much Zn do you think? Zn deficiency is hard to achieve (is that a real sentence or thought?) but with not enough Zn – problems like Pb excess (is Pb excess possible?) So, Zn deficiency – cognitive problems – where is Zn deficiency really found? Liver disease – from? List, name , 3 Zn-containing enzymes – and 1 Zn structural-required protein
2	Metal distribution comes from natural and man-made sources – know the cycle- but is Zn toxic? No!! A major played in the transport of Zn is metallothionein – 7 Zn(II) per molecule, bound only to CYS – we see this protein later as a major played for Cd metabolism and toxicity.
3	So, how does Zn act in enzymes? It is its Lewis acid properties – which are what? Carbonic anhydrase – key is CO_2 is polarised – OH^- from water attacks CO_2 – the key is that H_2O is made much wore acidic by the Zn. What are the other ligands in CA? Know the cycle shown on p 16.

	Carboxypeptidase – works the same way – know the key step of attack of C=O by O attached to Zn. – see p. 17 Alcohol dehydrogenase – see p 24 – here the alcohol binds to the Zn –and the aldehyde is formed – how does NAD^+ enter the reaction? What is it called? Recognise it's structure.
4	Zinc finger proteins bind to DNA – how? What does the Zn do?
Study questions from the lectures: What is a Lewis acid? How does it differ from a protonic acid? Why is Zn called a Lewis acid? Name a Lewis base. What is the key property of Zn that is exploited in the zinc- enzymes? How?	
Lectures	
Study questions from the books (S-L; R-M; K-S) and study questions for exams	
L-B Housecroft & Sharpe	Read several pages on Zn enzymes. K&S see ch. 12. Metallothionein binds zinc and cadmium in what sort of way? What is the only ligand known to date? See p 854 for a discussion of Zn as a Lewis acid