Bioinorganic Chemistry Chemistry 3391B

(A) L1-L6: Introduction - Complete overview of the course plus some Inorganic Chemistry

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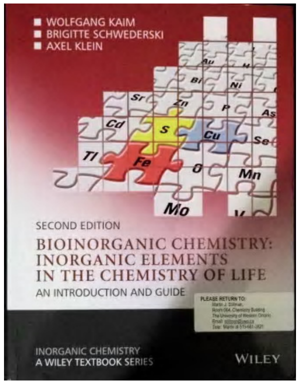
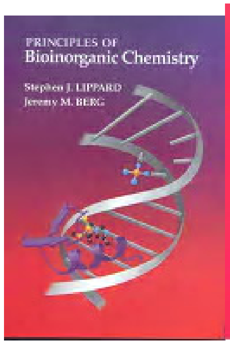
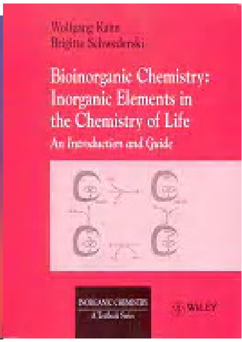
Special Information: Course outline (detailed lecture sequence)

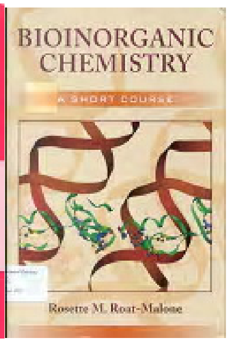
Check instruct.uwo.ca/chemistry/3391b
Dates Lectures Tue 11 :30-12 :30 Thur 10 :30 - 12 :30 ChB 9.
Term test: Thursday Feb 16, 2017 10 :30 – 12;30 (in class time but not in ChB 9)

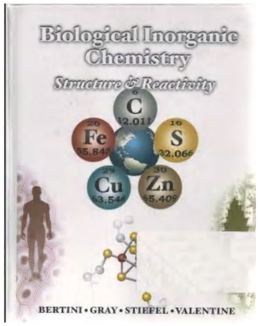
Texts: New-- Kaim, Schwederski, Klein KSK 2013… Wiley →
OTHERS Kaim & Schwederski (K-S) 1st Ed.- just old and suffers from a poor translation in parts. Roat-Malone (R-M) - 2nd Ed.-new but restricted in content- - then Lippard-Berg (very old); then look at Inorganic Texts - Shriver & Atkins (S&A) (5th Ed) - not very good unfortunately; Ch 29 in Housecroft &Sharpe - pretty good - although short. Bertini? Kraatz?

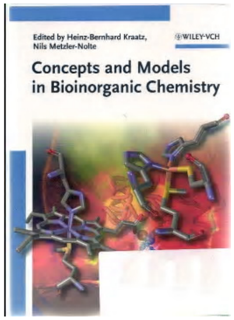












1 Introduction to “Bioinorganic Chemistry” or may be “Metals in Life”

… Why study bioinorganic chemistry?

See KSK Ch 1 FOR ADDITIONAL IDEAS. Especially Fig 1.4 - need to know Fig 1.4

To answer questions about metals and their roles in life’s processes:

(i) Incorporation of metals into Life’s processes – we are what we evolved from? Just C, N, O, H?

(ii) Putting metals in context – what fraction of life are they?

(iii) How do we classify the metals in any organism? Either from what's in the organism (content) or what the organism needs to live healthily (nutrition).

(iv) We –that’s mammals really- contain lots of Ca and must ingest quite a lot each day (about 1,300 mg) but only ingest about 20 mg Fe each day - but for Co - ah, I don't mean Co, I mean cobalamin (Vit B12) - it lasts for 5 years - so pig out on some red meat every so often. So, speciation matters.

(v) Bulk by mass or fraction - mostly oxygen! (ca. 45 kg* or 65% - really mostly water..); -- most prominent metal, yes, Ca - 1.5% or 1 kg - in our *70 kg 'man'.

(vi) The least? Possibly Co <3 mg - but think about this as a fraction - 0.003/70,000.00 - that % ? Consider how to measure that…… hmmm not really a very nice thought. Really needs a super - Chem 3372B experiment.

(vii) Then: Nutrition - what we need to eat to stay healthy -

(viii) Primary Nutrients or Macronutrients are CHNOPS and ….

(ix) Macro- and Micro-minerals (remember - C HOPKiNS Coffee Mug with zany salt) - ok - we'll decode this in a minute - 13 elements with Rec Daily Intake > 1 mg/day-

(x) What processes involve metals directly in Nature?

(xi) We can choose randomly - What about; Mg, Fe, Cd, Pb, As? Only Mg & Fe for sure.

(xii) How many metals do humans need to eat?

(xiii) Where do these elements come from in the Periodic Table? Is there a pattern? A trend?

(xiv) The metals to know - what do we have to memorize?

(xv) Metals in the sea and metals in humans …quite a trend

(xvi) Food with metals – eg Cobalt for Vit B12? Needs to come with the B12.. can't be made in humans, without Vit B12? Calamity.

(xvii) We are what we eat – note Ca, Fe, Mg, Zn – from where? Ideas? See later.

(xviii) Functions of metals - 30% of proteins require metals to work - which proteins? How do they work?

(xix) How metals actually carry out their biological function: coordination by ligands - donor atoms in proteins

(xx) Consider Fe in heme:

(xxi) Why are some metals essential and some not? Toxicity and Essentiality – coexist?

(xxii) Can we define essential vs. toxic for a metal, easily?

(xxiii) Metals in medicine. How can we use metals therapeutically?

a. Treat deficiencies Cu, Fe, Zn…
b. Treat disease - Bi, Pt, Li*, Au, V - insulin , (*specially treats - psychiatric diseases - bipolar/mania.. etc)
c. Diagnostics - radiopharmaceuticals - Mo, NaI,
d. Imaging ^{99m}Tc, Gd,
e. Cause diseases other than toxic metals? Well may be Cu & Zn in Alzheimer's Disease (AD)

(xxiv) Which are the common, absolutely essential metals of life? See the Periodic Table

(xxv) Which are absolutely always toxic? What about Pb? As? Cd? Easy? Cu? Cr? Not so easy?

(xxvi) Back to the Periodic Table

- -

Read Chapters 1 and 2 of Kaim (KSK) to see other descriptions of Bioinorganic Chemistry

Summary from Thursday 5th Jan 2017

- need to know your way round the Periodic Table
  - especially d-block but most of the rest as well – ie As Pb Bi Hg ⋮
- * how to explain O_2 binding to iron in hemoglobin?
  - multiple aspects
    - nutrition – meat vs beans for iron
    - form hemoglobin – bind O_2
    - but O_2 is dangerous? Di-radical?

sickle cell anemia in the news because?

- need to be able to assign oxidation numbers to molecules
  - is NO a problem?

(and count electrons in MOs holding molecules together)

- did I mention that you must remember electronic configurations of all d block metals – $Co^{I}/Co^{II}/Co^{III}$ for example and ligand field splitting diagrams for Tet, O_h & D_{4h} – sq. planar.

Theory –

Questions to answer:

We study Bioinorganic Chemistry to:
Answer questions about metals and their roles in living organisms
And, to determine What physiological processes involve metals directly?
And also to Learn from Nature – how to mimic the processes of life synthetically.
From these studies: We understand the intricate workings of physiological chemistry → nutrition; curing disease (*); recognizing toxic metals (**)

A definition or two - BioInorganic Chemistry is…

"the interface between inorganic chemistry and biology" or

"about how metals function *in vivo* (meaning in living biological systems)" or

"about how metals pass through physiological systems from absorption to transport to use to excretion"

Aspects of current research:

-develop mimics of natural chemistry

-understand how metalloproteins work – how is the coordination chemistry tuning the chemistry?

-probe how metals control protein folding?

-work out how to 'improve' on Nature – curing disease or accidental damage

So, then what is Bioinorganic Chemistry

- Broadly defined, bioinorganic chemistry is the study of inorganic elements, with an emphasis on metals, in living systems.

  1. Which elements are necessary for life?
  2. How about their chemical speciation?
  3. What are their physiological roles?
  4. What are their mechanisms of action?
  5. How did we evolve to use those elements?
  6. Why are some metals toxic?
  7. Can metals be used therapeutically?

Will be on a test

- Chem 3391b will explore those questions and examine the role of selected elements in humans and other organisms. This section introduces the topic of essential elements and the importance of chemical speciation.

Not tested

* James Lind FRSE FRCPE (4 October 1716 in Edinburgh – 13 July 1794 in Gosport) was a Scottish physician.

By conducting the first ever clinical trial, [1] he developed the theory that citrus fruits cured scurvy.

Scurvy is a disease now known to be caused by a deficiency of Vitamin C, but in Lind's day, the concept of vitamins was unknown. Vitamin C is necessary for the maintenance of healthy connective tissue. In 1740 the catastrophic result of Anson's circumnavigation attracted much attention in Europe; out of 1900 men, 1400 had died, most of them allegedly from having contracted scurvy. According to Lind, scurvy caused more deaths in the British fleets than French and Spanish arms.[4]

He divided twelve scorbutic sailors into six groups. They all received the same diet but, in addition, group one was given a quart of cider daily, group two twenty-five drops of elixir of vitriol (sulfuric acid), group three six spoonfuls of vinegar, group four half a pint of seawater, group five received two oranges and one lemon, and the last group a spicy paste plus a drink of barley water. The treatment of group five stopped after six days when they ran out of fruit, but by that time one sailor was fit for duty while the other had almost recovered. Apart from that, only group one also showed some effect of its treatment. AN ARGUMENT FOR BASIC SCIENCE

In 1753 he published A treatise of the scurvy, which was virtually ignored. In 1758 he was appointed chief physician of the Royal Naval Hospital Haslar at Gosport. When James Cook went on his first voyage he carried wort (0.1 mg vitamin C per 100 g), sauerkraut (10–15 mg per 100 g) and a syrup, or "rob", of oranges and lemons (the juice contains 40–60 mg of vitamin C per 100 g) as antiscorbutics, but only the results of the trials on wort were published. In 1762 Lind's Essay on the most effectual means of preserving the health of seamen appeared. In it he recommended growing salad—**i.e. watercress (662 mg vitamin C per 100 g)—**on wet blankets. This was actually put in practice, and in the winter of 1775 the British Army in North America was supplied with mustard and cress seeds. However Lind, like most of the medical profession, believed that scurvy was essentially a result of ill-digested and putrefying food within the body, bad water, excessive work and living in a damp atmosphere which prevented healthful perspiration. Thus, while he recognised the benefits of citrus fruit (although he weakened the effect by switching to a boiled concentrated or "rob", the production of which unfortunately destroyed the vitamin C), he never advocated citrus juice as a single solution. The medical establishment ashore continued to be wedded to the idea that scurvy was a disease of putrefaction, curable by the administration of elixir of vitriol, infusions of wort and other remedies designed to 'ginger up' the system. It could not account for the benefits of citrus fruits and dismissed the evidence in their favour as unproven and anecdotal. In the Navy however, experience had convinced many officers and surgeons that citrus juices provided the answer to scurvy even if the reason was unknown. On the insistence of senior officers, led by Rear Admiral Alan Gardner, in 1794 lemon juice was issued on board the Suffolk on a twenty-three week, non-stop voyage to India. The daily ration of two-thirds of an ounce mixed ingrog contained just about the minimum daily intake of 10 mg vitamin C. There was no serious outbreak of scurvy. This astonishing event resulted in a widespread demand within the Navy for lemon juice, …(http://en.wikipedia.org/wiki/James_Lind)

****Can wearing a copper bracelet cure arthritis?** Arthritis is a condition that results in deterioration and loss of the joint surface cartilage, where the repair process fails to keep up with the breakdown. Copper bracelets have long been sold as a cure for arthritis. Vendors propose that the metal is absorbed through the skin and helps cartilage regeneration. But there are certain facts you should know before you rush out and buy that bracelet. According to the Center for Hand and Upper Extremity Surgery at UAMS, copper deficiency is extremely rare and most regular diets provide enough copper to meet the daily requirements. Research has shown that excessive copper can result in poisoning. This can be seen after ingesting foods boiled in copper vessels or from contamination of water from corroding copper pipes, causing vomiting and, in severe cases, liver damage. In reality no modality of treatment has been shown to cure or reverse the changes of arthritis. …(http://www.uamshealth.com/?id=882&sid=1)
http://www.arthritis.org/living-with-arthritis/treatments/natural/other-therapies/magnetic-copper-bracelets.php
http://www.nhs.uk/news/2009/10October/Pages/Copper-bracelets-and-arthritis.aspx

<u>In the beginning</u> – the hot, dusty, anaerobic atmosphere gave way to the clear, oxygen-rich atmosphere of today – about 2.2 Gyr ago.

Before that life evolved – but how? And, what does this mean?

Life requires elements to form compounds and to provide a means for biological chemistry to take place – this meant synthesizing a vast number of complex organic molecules and finding a way to obtain the energy required to sustain life.

Metals provided some of the tricky chemistry needed, but which metals to choose?

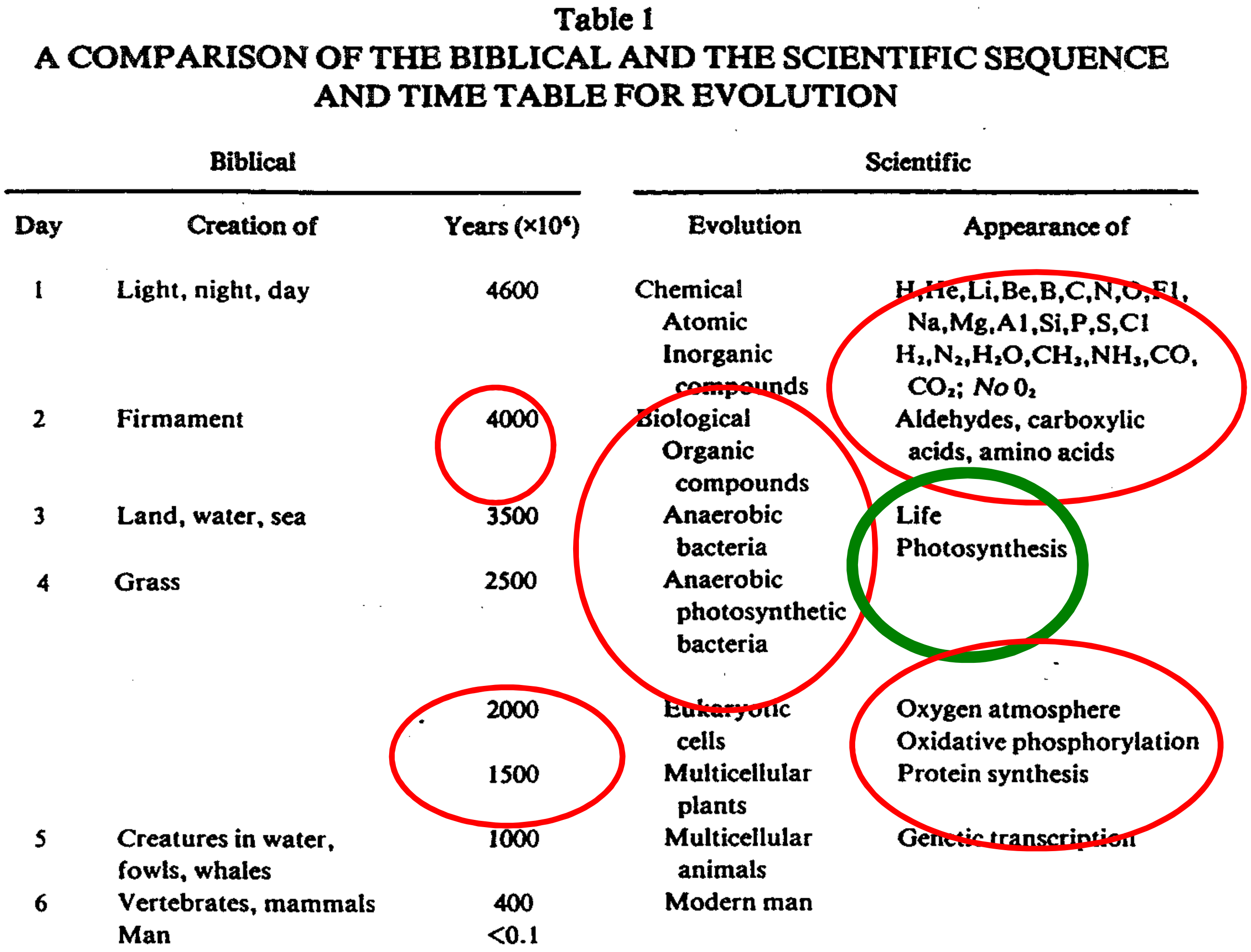


Table 1

A COMPARISON OF THE BIBLICAL AND THE SCIENTIFIC SEQUENCE AND TIME TABLE FOR EVOLUTION

Biblical			**Scientific**	
Day	**Creation of**	**Years (×10⁶)**	**Evolution**	**Appearance of**
1	Light, night, day	4600	Chemical Atomic Inorganic compounds	H,He,Li,Be,B,C,N,O,Fl, Na,Mg,Al,Si,P,S,Cl H_2,N_2,H_2O,CH_3,NH_3,CO, CO_2; *No* 0_2
2	Firmament	4000	Biological Organic compounds	Aldehydes, carboxylic acids, amino acids
3	Land, water, sea	3500	Anaerobic bacteria	Life Photosynthesis
4	Grass	2500	Anaerobic photosynthetic bacteria	
		2000	Eukaryotic cells	Oxygen atmosphere Oxidative phosphorylation
		1500	Multicellular plants	Protein synthesis
5	Creatures in water, fowls, whales	1000	Multicellular animals	Genetic transcription
6	Vertebrates, mammals	400	Modern man	
	Man	<0.1		

Cyanobacteria are micro-organisms that live primarily in seawater. They are believed to have been the first organisms on Earth to perform oxygenic photosynthesis. *Nature* **455**, 1101-1104 (2008)

REFERENCES

1. Genesis 1:1-5.
2. Genesis 1:6-8.
3. Genesis 1:9,10.
4. Genesis 1:11-13.
5. Genesis 1:14-19.
6. Genesis 1:20-23.
7. Genesis 1:24.

1046c1

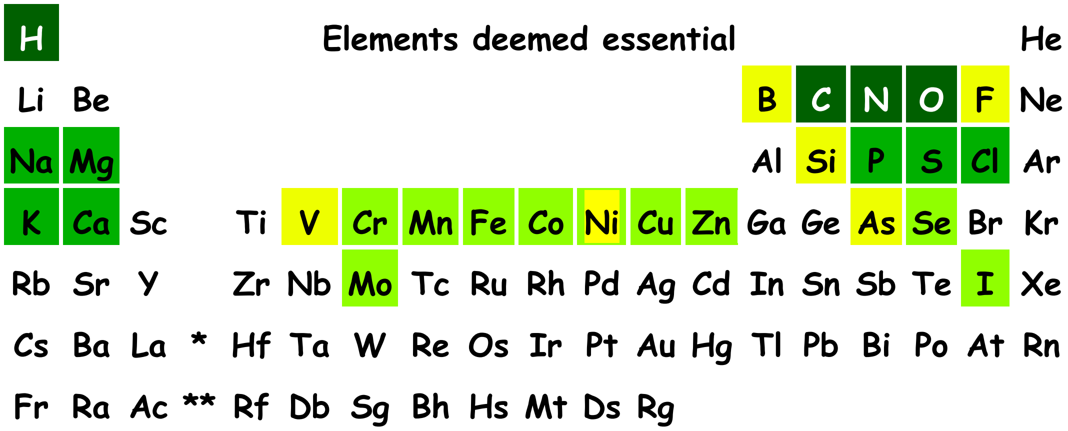
- consider the human body-1…

We separate amounts into

1. Primary Nutrients or Macronutrients are

   CHNOPS,

2. Macro- and Micronutrients
3. C H O P i K N S coffee mug with zany salt or C H O P K N S Ca Fe Mg with Zn Na Cl - groan (trace- (<1000μg/day) Cr-Cu-I-Mo-Se)
   - watch out - Ni?
4. **May be essential in the diet-Si for sure.**
5. What surprises you?
6. Do we know what each of these elements does?
7. Are all of the elements found in the body essential elements? No.
8. There is no connection between the amount of an element and whether it is essential or not. Examples:
   a. A relatively large amount of Rb exists, but it has no biological function.
   b. There is very little V, but it is an essential element.
9. What is their environment? (=coordination of each metal)
10. We need to look at the metal-containing proteins - really the ligands that are part of theose proteins
11. …. How do we handle these concentration units



Elements deemed essential

H																		He
Li	Be													B	C	N	O	F	Ne
Na	Mg													Al	Si	P	S	Cl	Ar
K	Ca	Sc		Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y		Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	*	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	**	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg							

Dk-bulk-H; lighter-macro; light-micro; yellow-probably

Remember $Co^{II/III}$ — μg/day
in the body — mg

Thursday ↓

For 70 kg human we find:

Element	Mass	Ratio
oxygen	43 kg	61%
carbon	16 kg	23%
hydrogen	7 kg	10%
nitrogen	1.8 kg	2.60%
calcium	1 kg	1.40%
phosphorus	780 g	1.10%
potassium	140 g	0.20%
sulfur	140 g	0.20%
sodium	100 g	0.14%
chlorine	95 g	0.14%
magnesium	19 g	271 ppm
iron	4.2 g	60 ppm
fluorine	2.6 g	37 ppm
zinc	2.3 g	33 ppm
silicon	1 g	14 ppm
rubidium	0.68 g	10 ppm
strontium	0.32 g	5 ppm
bromine	0.26 g	4 ppm
lead	0.12 g	2 ppm
copper	72 mg	1 ppm

macro

micro

* enzymes

Element	Mass	Ratio
aluminum	60 mg	857 ppb
cadmium	50 mg	714 ppb
cerium	40 mg	571 ppb
barium	22 mg	314 ppb
iodine	20 mg	286 ppb
tin	20 mg	286 ppb
titanium	20 mg	286 ppb
boron	18 mg	257 ppb
nickel	15 mg	214 ppb
selenium	15 mg	214 ppb
chromium	14 mg	200 ppb
manganese	12 mg	171 ppb
arsenic	7 mg	100 ppb
lithium	7 mg	100 ppb
cesium	6 mg	86 ppb
mercury	6 mg	86 ppb
germanium	5 mg	71 ppb
molybdenum	5 mg	71 ppb
cobalt	3 mg	43 ppb
antimony	2 mg	29 ppb

Element	Mass	Ratio
silver	2 mg	29 ppb
niobium	1.5 mg	21 ppb
zirconium	1 mg	14 ppb
lanthanium	0.8 mg	11 ppb
gallium	0.7 mg	10 ppb
tellurium	0.7 mg	10 ppb
yttrium	0.6 mg	8.6 ppb
bismuth	0.5 mg	7.1 ppb
thallium	0.5 mg	7.1 ppb
indium	0.4 mg	5.7 ppb
gold	0.2 mg	2.9 ppb
scandium	0.2 mg	2.9 ppb
tantalum	0.2 mg	2.9 ppb
vanadium	0.11 mg	1.6 ppb
thorium	0.1 mg	1.4 ppb
uranium	0.1 mg	1.4 ppb
samarium	50 µg	710 ppt
beryllium	36 µg	510 ppt
tungsten	20 µg	290 ppt

speciation toxic vs nontoxic

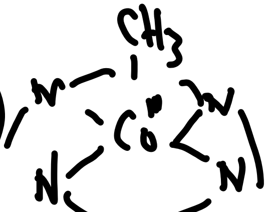
many element

enormous mass range 43kg → 20μg

only a few known to be essential

lipid soluble (crosses BBB)

Vit B_{12} (cobalamin)



3+

$+ HgCl_2 \longrightarrow Hg(CH_3)Cl$

monomethyl mercury

1046c1

- consider the human body-2…

First – how do we calculate concentrations?

Units?

Parts per million (1 in 10^6)
Parts per billion (1 in 10^9)

Also - a recent controversy over As in place of P … see next page for details but what is the implication - lots of As and very small amounts of P.

COMPOSITION OF THE HUMAN BODY

1- Up to 35 elements found – are all essential?

Bulk	Macromineral	Micromineral
Lots: kg & g	>=5 gm = less: 1-100 ppm	not much: <1 ppm**

**It's tricky to determine these amounts – can you think of why that might be?

How to convert mass in grams to ppm? It's all about the right ratios.

Eg

1) If 0.2 mg of NaCl (a small grain of sand) is added to a 44 gal barrel of water (44 Imp gal approx x 4.54 = 200 L) this then has a mass of approx 200 kg.

So: 0.2 mg/200 kg = 0.0002 g/200,000 g = 1 ppb (1 part in 10^9 by mass)

2) – So what is the concentration of arsenic in our 70 kg human? (In ppm). (about 3 mg in 70 kg = ??)

3) And the concentration in ppm of zinc is? (1750 mg)

4) And, selenium? (2 mg)

5) A thought – how can such vastly different concentration be equally important to the health of an organism – say, humans?

"But now researchers have coaxed a microbe to build itself with arsenic in the place of phosphorus, an unprecedented substitution of one of the six essential ingredients of life. The bacterium appears to have incorporated a form of arsenic into its cellular machinery, and even its DNA, scientists report online Dec. 2 in *Science*." Science News

"The bacterium in arsenic-rich Mono Lake was said to redefine the building blocks of life, surviving and growing by swapping phosphorus for arsenic in its DNA and cell membranes. Biologists consider these six elements as necessary for life: carbon, hydrogen, nitrogen, oxygen, phosphorus and sulfur. Arsenic is similar to phosphorus but is typically poisonous to living organisms. " **KERRY SHERIDAN, AGENCE FRANCE-PRESSE** | Jul 9, 2012 9:56 AM ET

Richard A. Lovett for National Geographic News Published July 9, 2012

It was hailed in 2010 as the most "alien" life-form yet: bacteria that reportedly, and unprecedentedly, had rewritten the recipe for DNA. And the secret ingredient was arsenic. But now two new studies seem to have administered a final dose of poison to the already controversial finding.

Researchers led by then NASA astrobiologist Felisa Wolfe-Simon had found the organism, dubbed GFAJ-1, in arsenic-rich sediments of California's Mono Lake. They later reported in the journal *Science* that the bacterium thrived in arsenic-rich, phosphorus-poor lab conditions. The team concluded that GFAJ-1 must be incorporating arsenic into its DNA in place of phosphorous, which is essential for the DNA of all other known organisms. (Get a genetics overview.) The find was exciting to astrobiologists, who'd previously speculated that extraterrestrial life might survive in unexpected places if only such a swap were possible—arsenic and phosphorous being chemically similar. (Related:"Saturn's Largest Moon Has Ingredients for Life?") Soon after the announcement, though, other researchers began saying they were having trouble replicating Wolfe-Simon's results. Those criticisms were finally given formal voice Sunday in the form of two different studies with very similar results.

The new studies, also published in *Science,* found that the bacterium did in fact grow in the conditions described in the 2010 study.

But when the amount of phosphorous was reduced even further than in Wolfe-Simon's experiments, GFAJ-1 stalled. Furthermore, biologist Rosemary Redfield writes in the new study, no signs of arsenic could be found in GFAJ-1's DNA. **The new conclusion: the arsenic-loving life-form does in fact need phosphorous to grow, but shockingly tiny amounts of it.**

Not Backing Down

Wolfe-Simon, now of the Lawrence Berkeley National Laboratory, stands by her results. The new paper, she said, shows only that the arsenic doesn't show up in the DNA, not that the organism never uses it. The fact that the organism has extreme resistance to arsenic and takes it up from the environment means that something unusual is happening with that arsenic, Wolfe-Simon said by email. "We are working to define where the arsenate is [in the organism], rather than where it is not," she said. "How does GFAJ-1 thrive in such high levels of arsenic? Where is the arsenic going? This is our continued focus."

Arsenic Tolerance No Sign of "Second Genesis"

For astrobiologists, the new finding is a disappointment but not a severe setback in the search for alien life. The 2010 study sprang from a quest proposed by astrobiologist Paul Davies, director of the BEYOND Center for Fundamental Concepts in Science at Arizona State University, Tempe. Davies encouraged scientists to look for organisms on Earth so exotic that they must have come not just from a different branch of our own tree of life but from an entirely separate founding ancestor. If we could find such organisms, Davies suggested, they would indicate that life originated more than once here on Earth—a "second genesis." And if life began more than once here, it would seem more likely that life exists on other earthlike planets. The new papers have no impact on this quest, he said, because genetic studies had already indicated that GFAJ-1 is related to other known bacteria.

"It was clear from early on," he said, "that GFAJ-1 did not constitute evidence for a second genesis."

Elias, M. *et al*. *Nature* http://dx.doi.org/10.1038/nature11517 (2012).

The latest paper shows that the “arsenic monster” GFAJ-1 goes to a huge amount of effort, “even more than other life”, to avoid arsenate, says Wolfgang Nitschke from the Mediterranean Institute of Microbiology in Marseilles, France, who co-authored a commentary questioning the conclusion that GFAJ-1 could replace phosphate with arsenate[4]. “This shows clearly that life doesn’t like arsenate in cytoplasm,” he says.

What Is an Essential Element?

In order for an element to be classified as *essential*, it must satisfy all of these criteria for *essentiality*:

1) When the element is removed from the diet, a physiological or structural abnormality appears.
2) The addition of the element to the diet restores or relieves the abnormality.
3) The element has a specific biochemical function even if the function of the element is not fully understood, as in the case of many *ultratrace* elements.
4) The element follows a *dose-response curve*. -- see later….
5) Essential elements can be classified according to either the amount present in the body or the dietary requirement (recommended daily intake/allowance):
6) Bulk elements
7) Major elements / macronutrients / macrominerals
8) Minor elements / micronutrients / microminerals Trace elements Ultratrace elements

From the tables above and Periodic Table below assemble your own table:

4 essential but trace metals..
4 toxic metals..
4 therapeutically important metals ..

So, we need (need?) many different metals – some quite unexpected.

Essential elements in some species or other– about 25 shown here have been identified – another 10 are considered to be essential in some organisms but their roles have not been determined (fully) – eg As

For the course –

Macronutrients: C-H-O-P-K-i-N-S-Ca-Fe-Mg—Zn-Na-Cl (13) mnemonic- C HOPKiNS coffee mug with zany salt

Minerals= metals (plus Si, I, Se)

Dietary point of view - minerals

Macrominerals: Calcium, magnesium, sodium, potassium, phosphorus, sulfur (5) **(require <12 mg/day - FDA)**

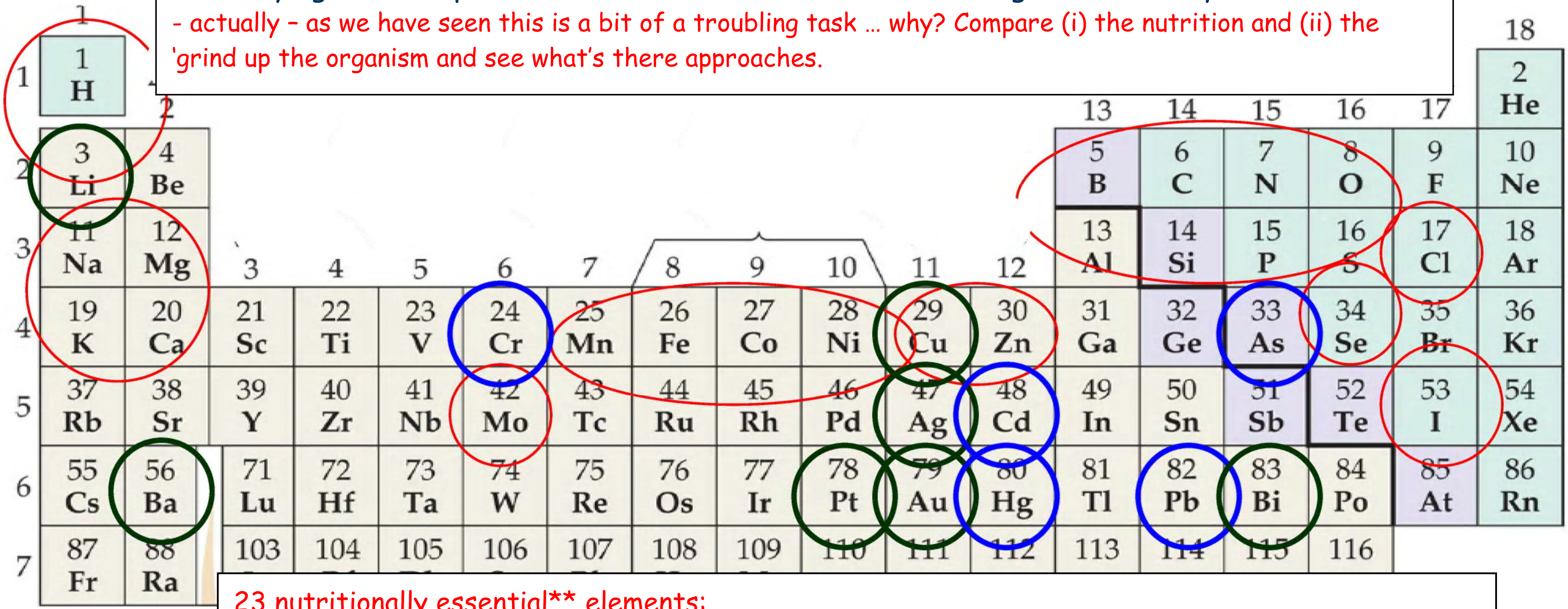
Microminerals (trace-minerals): iron, silicon, vanadium, zinc, iodine, selenium, copper, manganese, fluoride, chromium, cobalt, tungsten, nickel (13)

Ultra Trace Elements (<1 mg): The following elements may be essential but deficiency has been difficult to demonstrate - molybdenum, boron, tin, lead, and arsenic have been found in animals. (5)…. and more each day

The Periodic Table

Identifying the **important** elements in INORGANIC biological chemistry

- actually – as we have seen this is a bit of a troubling task … why? Compare (i) the nutrition and (ii) the 'grind up the organism and see what's there approaches.



23 nutritionally essential** elements:

(red circles) –non-metals - H, C, N, O, P, S, Cl, I, Se (9) and then metals Ca, Mg, Na, K, Fe, Co, Zn, Cu, Mn, Mo, Cr, Ni, Si, B (14) = 23 (let's say about 25 essential elements across a number of organisms).

Dk Green- therapeutic agents in some form – Li, Cu, Ag, Au, Pt, Bi. Imaging agent: Ba/Tc- X-ray. Supplements: Ca/Fe - also note the LIGAND section for removing excess metals

Blue – known to be toxic – includes Cd, Hg, Pb, As, Cr^{6+**}but not Cr^{3+} , which is essential ..

**These elements have been identified as clearly essential in the human diet – but other elements are known/thought-to-be essential but less convincing evidence for nutrition – means we obtain these elements without trying: inc. Br? As? B? and others up to over 30 essential and not-proven-to-be-essential-yet elements. See:

http://www.eatwell.gov.uk/healthydiet/nutritionessentials/

(Note: Na-Ca; and, except for Mo, I, all are in row 4 and above = "light" metals)

Application of the principles of inorganic chemistry to biological molecules - use model as guides (ok?) - use spectroscopic techniques to determine electronic structures and coordination. **Leads to "Structure tells us about Function".**

B.1 Elements in biological systems

Range of elements and their respective content (g) in mammals other than PCHNO & S is surprisingly large.

Some statistics:

- the rough composition in human mammals is -

99.35 % C, N & O; 0.646 % Na, Mg, Ca, P;
0.003 % I, V, Cr, Mn, Fe, Mo, Co, Cu, Zn, Si,Se, Sn
(Sn, Si are unexpected)

In a 70 kg human (rough amounts) -

Main group non-metal

H - 6,580 g C - 12,590 g
N - 1,815 g O - 43,550 g
P - 680 g ~~Cl - 115 g~~ Ca 1,700 g
~~S~~ - 100 g Na 70 g; Mg 42 g; K 250 g;

Then Fe - 5 g; Zn - 1.75 g; Si 1-2 g estimates - suggested involvement in bone formation everything else << 1 g

Nutritional guide (UK)
http://www.nhs.uk/Conditions/vitamins-minerals

B.2 How has nature subdivided its use of metals?

Not surprisingly around the chemical properties already exhibited in the Periodic Table - but often from what was available in sea water - see the graph.

- ionic properties of Groups 1 and 2 -
- ligand binding of the Transition Metals (d Block) - Fe, Zn
- redox chemistry of the Transition Metals - Co, Cu, Fe, but not Zn.

B.3 What goes wrong? With such a palette of metals, substitution of one by an unexpected element can cause chaos - As for P; Cd for Zn; Pb for Ca.

Also binding of an inactive metal in place of the target metal can produce toxic effects - Hg^{2+} readily binds to RSH.

B4. Metabolism of metals? We can, of course, talk about the metabolism of metals - but may be we should reserve this term to describe the complete passage of metals through the biological system - transport in/absorption, trafficking, usage, excretion.

B.5 Essential trace elements across species:

Trace or Microminerals (<100 mg/day): Fe, Si, Zn, I, Se, Cu, Mn, F, Cr, Co, Ni, Mo, B, W (not mammals), V (not mammals)
Macrominerals (nutrition) Na, K, Mg, Ca, P, Cl (humans >100mg/day)
Toxic elements: Cd, Hg, Pb, As,,, Be, Rn, U, ...
Therapeutic metals: Li, Ba, Pt, Ag, Bi, Au, Cu
Macronutrients: - core nutrient elements: (BULK C HOPKINS café Mg Zn NaCl)

[illegible]

Transition elements are present < 1 g quantities - except Fe (4-5 g) & Zn (2 g). The other transition elements are only present in trace amounts. When concentrations are very low it is difficult to determine physiological use. (Sum of V, Mn, Co, Cr, Si, Se, is less than 1 g.) Elements such as Se have only relatively recently entered the 'essential' list - Glutathione Peroxidase (see below).

Metals like Cd (found in the liver &kidneys of mammals) and Hg (in most fish and shellfish - see later) are considered to be always toxic.

But, most elements, eg Cu, are toxic to most life forms if there is exposure above trace levels - these metals are toxic to cells if added to cell cultures, but the metals are essential and must be part of the organism's nutritional supply.

is where?

There are 3 major electrolytes ionic metals

Na, K, Cl^{-} and Ca, P and Mg as structural elements (this is group 1 and 2) → in bones +

Sodium (Na) - principal cation in extracellular fluids - functions include: osmotic equilibrium; acid-base balance; carbon dioxide transport; cell membrane permeability; muscle irritability
(Joseph and Meltzer "The influence of sodium and calcium upon direct and indirect muscle irritability and their mutual antagonistic." Proc Soc Exp Biol Med 1909, 6:104)

Metabolism: readily absorbed & excreted in the urine and sweat

RDA for adults: 1.1 to 3.3 g/day (under the heading of macromineral) energy

ATP requires Mg^{2+}

-sodium deficiency: dehydration; acidosis; tissue atrophy
-sodium excess: edema (hypertonic expansion; hypertension

Sodium supplements: Gatorade and other sports drinks; food sources: table salt, salty foods, baking soda, milk

Potassium (K) - - principal cation in intracellular fluid - all inside cells -almost none in serum
functions: buffer constituent; acid-base balance; water balance membrane transport; neuromuscular irritability

metabolism: readily absorbed (more so than sodium); intracellular; secreted by kidney (also in sweat)
Fresh fruits: bananas, cantaloupe, oranges, strawberries, kiwi, avocados, apricots; Fresh vegetables: greens, mushrooms, peas, beets, tomatoes; Meats: beef, fish, turkey; Juices: Orange, prune, apricot, grapefruit

RDA for adults: 1.5 - 4.5 g/day (under the heading of macromineral)

-deficiency (hypokalemia - low blood K)
symptoms: profound weakness of skeletal muscles (paralysis and impaired respiration; weakness of smooth muscles; cardiac anomalies: AV block, cardiac arrest
-excess (hyperkalemia - high blood K);
symptoms: weakness and paralysis; cardiac anomalies - cardiac arrest

Chloride (Cl) - an essential anion - closely connected with sodium in body tissues and fluids and excretions
Important for osmotic balance, acid-base balance and in the formation of gastric HCl

Hypochloremic alkalosis; pernicious vomiting; psychomotor disturbances

Na^{+} ↑ ↓ K^{+}

pump out Na^{+}
pump in K^{+}

Calcium (Ca) - needed by all cells - found in largest amounts in bones (90%) as hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ - contraction and relaxation of muscles; stabilizes nervous tissue -absorption is enhanced by: acid pH; vitamin D - calcium serum levels controlled by parathyroid hormone (PTH), calcitonin peptide and vitamin D (all work together to control deposition in bone; uptake of Ca from kidneys; Ca serum levels)	RDA adult: 800 mg/day (under the heading of macromineral) Calcium supplements - calcium gluconate ; calcium carbonate, etc. -Hypocalcemia - unusual - seizures; dementia; depression; parkinsonism; -Hypercalcemia - benign to severe
Phosphorus -required in many phases of metabolism -80% is structural – insoluble apatite in bone and teeth) -20% is very active metabolically High energy phosphate compounds- ATP; nucleic acids; phospholipids Regulated by Na-phosphate transporters and PTH	RDA for phosphorus is established on the basis of a 1:1 relationship with calcium : adults: 800 mg/day -hypophosphatemia: Not common -foods rich in calcium are also richest in phosphorus (milk, cheese, eggs, beans, fish)
Magnesium (Mg) - second most plentiful cation in intracellular fluids (after K). 50% of total amount in bone; ~45% in muscle and nervous tissue; ~ 5% in extracellular fluids. Functions: In enzyme systems as a required, transient cofactor of all enzymes involved in phosphate transfer reactions that use ATP and other nucleotide triphosphates	(under the heading of macromineral) Hypomagnesemia: disorientation, psychotic behavior, convulsions; neurological & psychological disorders - Hypermagnesemia - rare - but deadly - heart stops beating.

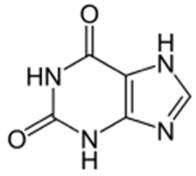
A bit of vocabulary/nomenclature:

'apoenzyme' or 'apoprotein' a protein (or enzyme) missing its essential cofactor (eg myoglobin without the heme = apomyoglobin; carbonic anhydrase without its Zn = apocarbonic anhydrase). Use 'holo' in place of 'apo' when the cofactor is bound.

Native: protein folded using H-bonding, electrostatic forces, and di-sulfide RS-SR bonds (**cystine**) made from 2 **cysteines** (RSH)

Denatured – unfolded – temperature, acid, denaturing agents. Reversible/irreversible.

Systematic names for enzymes - 6 classes (the number is part of the classification of enzymes): (NEED TO KNOW EXAMPLES – in 1,2,3,4 below)

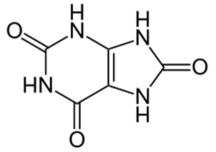


1) Oxidoreductase: Oxidoreductases catalyze oxidation reduction reactions. At least one substrate becomes oxidized and at least one substrate becomes reduced. Also the transfer of H and O atoms.
   alcohol dehydrogenase - Zn (x2); catalases (Fe-heme x4); xanthine oxidase (Mo & FeS) (xanthine to uric acid)

$Fe^{4+} + e^{-} \rightarrow Fe^{3+}$

2) Transferase: Transferases catalyze group transfer reactions- the transfer of a functional group from one molecule to another.
   methyltransferase (uses cobalamin - B12 -Co)

3) Hydrolase: In hydrolysis reactions, C-O, C-N, and C-S bonds are cleaved by addition of H_2O in the form of OH^- and H^+ to the atoms forming the bond.
   carboxypeptidase - Zn



4) Lyase: Lyases cleave C-C, C-O, C-N, and C-S bonds by means other than hydrolysis or oxidation.
   carbonic anhydrase - Zn

5) Isomerase: Isomerases just rearrange the existing atoms of a molecule, that is, create isomers of the starting material. (Often called 'mutases') Starting and finished molecule are isomers.

6) Ligase: Ligases synthesize C-C, C-S, C-O, and C-N bonds in reactions coupled to the cleavage of high energy phosphate bonds in ATP or some other nucleotide.

A note from Thursday – know d orbitals

Then ↓

for notes about enzymes referred to above..

metal/ % of the centre

kinetic role

Metalloenzymes specific binding site metal is firmly bound metal to protein ratio is constant metal to enzyme activity ratio is constant holo metal is unique softer – cys hard tyr no enzyme activity without metal	Examples of metalloenzymes: $Cu^{+/2+}$ superoxide dismutase (Zn and Cu) – O_2^- carboxypeptidase A (Zn) CPA peptide held in place by the Zn^{2+} carbonic anhydrase (Zn) CA cytochrome oxidase (Fe and Cu) CcOx xanthine oxidase (Mo, Co and Fe)
Metal-activated enzymes apo Enz + Metal → holo metal is reversibly bound metal to protein ratio is variable metal to enzyme activity ratio is variable chemistry metal is not necessarily unique enzyme activity may continue without metal metal dumped	Examples of metal-activated enzymes all really different creatine kinase (Mg, Mn, Ca or Co) glycogen phosphorylase kinase (Ca) – Ca^{2+} can use Mn^{2+} salivary and pancreatic alpha-amylases (Ca)

1) Check one of catalase or horseradish peroxidase -- both use which metal and how?
(note xanthoxin dehydrogenase Mo enzymes in plants)

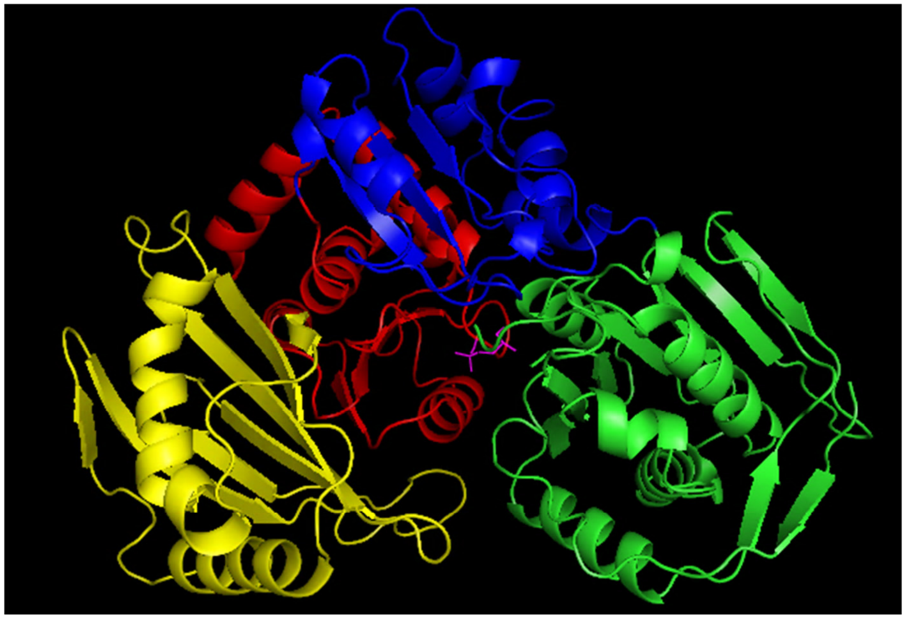
2) Look up cobalamin

3) Carboxypeptidase
-- alkaline phosphatase…why do you think Zn^{2+} is the cofactor for this but not the acid phosphatase? (key)

4) Carbonic anhydrase
(Can you find an example that uses Mg^{2+}, Ca^{2+} or Mn^{2+} ?)

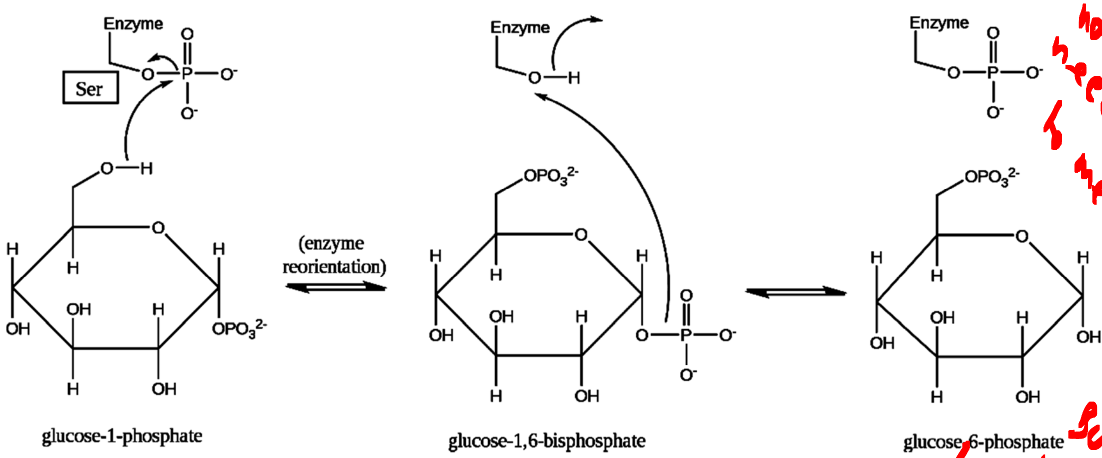
Not required to memorize the enzyme names on this page.

5) Phosphoglucomutase Four Domains EC 5.4.2.2 requires Mg(II) for activity (as usual, other M^{2+} ions work as well - the authors used Cd(II) - Wiki says "Mg & Cd", your view of this extrapolation?



(a mutase is a member of the isomerase enzymes): Mechanism for the phosphoglucomutase-catalyzed interconversion of glucose 1-phosphate and glucose 6-phosphate.

Rhyu; Ray; Markley (1984). "Enzyme-bound intermediates in the conversion of glucose 1-phosphate to glucose 6-phosphate by phosphoglucomutase. Phosphorus NMR studies". *Biochemistry* **23** (2): 252



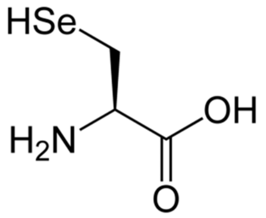
not necessary to memorize the structure of glc-1- & g6P

6) Ligases forming C-O (& C-metal bonds) bonds pyruvate carboxylase - ATP + pyruvate +HCO_3^- → ADP + phosphate + oxaloacetate - a Mn (animals) or Zn (yeast) enzyme -

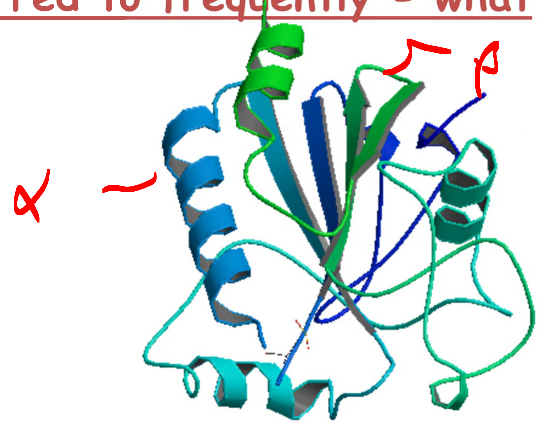
!! magnesium chelatase -- ATP + PPIX + Mg^{2+} → ADP +phosphate + Mg-PPIX + $2H^+$ check for Co-chelatase - where is the end product for this?

$R-\overset{2-}{Se}-\overset{2-}{S}G \rightarrow H_2O_2$ $GS^{\cdot\,1-} \times 2 \rightarrow GSSG$

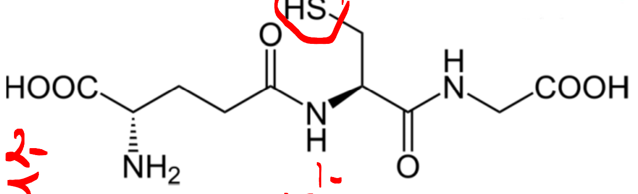
Example - Se referred to frequently - what do we know?



selenocysteine



GSH



no metal !

Glutathione peroxidase catalyzes:

$2GSH + H_2O_2 \rightarrow GS\text{-}SG + 2H_2O$, where GSH represents reduced glutathione, and GS-SG represents glutathione disulfide.

anti oxidant - a strong reducing agent

In the 2nd step, Glutathione reductase then reduces the oxidized glutathione to complete the cycle:

$GS\text{-}SG + NADPH + H^+ \rightarrow 2\ GSH + NADP^+$.

The Se is contained in the form of L-Selenocysteine; the three-letter symbol Sec and the one-letter symbol U. More than 20 human proteins that contain selenocysteine.

How to find out something more detailed - can find the X-ray or NMR coordinates → 3D structure.
http://www.ncbi.nlm.nih.gov/protein/
..here are details from the file for GSHPx

```
TITLE Sequence of a cDNA coding for human
glutathione peroxidase confirms TGA encodes
active site selenocysteine
  JOURNAL   Nucleic Acids Res. 15 (13),
5484 (1987)

/product="glutathione peroxidase 1 isoform 1"
/note="cellular glutathione peroxidase; GPx-1; GSHPx-1"
/calculated_mol_wt=21957
/note="Glutathione (GSH) peroxidase family; tetrameric
selenoenzymes that catalyze the reduction of a variety of
hydroperoxides including lipid peroxidases, using GSH as a
specific electron donor substrate. GSH peroxidase contains
one selenocysteine residue per...; cd00340"

ORIGIN

1 MCAARLAAAA AAAQSVYAFS ARPLAGGEPV
LGSLRGKVL LIENVASLUG TTVRDYTQMN
61 ELQRRLGPRG LVVLGFPCNQ FGHQENAKNE
EILNSLKYVR PGGGFEPNFM LFEKCEVNGA
121 GAHPLFAFLR EALPAPSDDA TALMTDPKLI
TWSPVCRNDV AWNFEKFLVG PDGVPLRRYS
181 RRFQTIDIEP DIEALLSQGP SCA
```

one-letter symbol U

Some examples ….(see next pages for more details)

OK – the good, the bad and the ugly (metals that is)..

The Good (well two examples)

Magnesium in chlorophyll
Iron in red blood cells

The bad

Cadmium in fertilizer..

The Ugly

As in pressure treated woods

Do a search – for magnesium – other examples in humans?
for cadmium – other sources for humans?
for arsenic – other human exposure? **

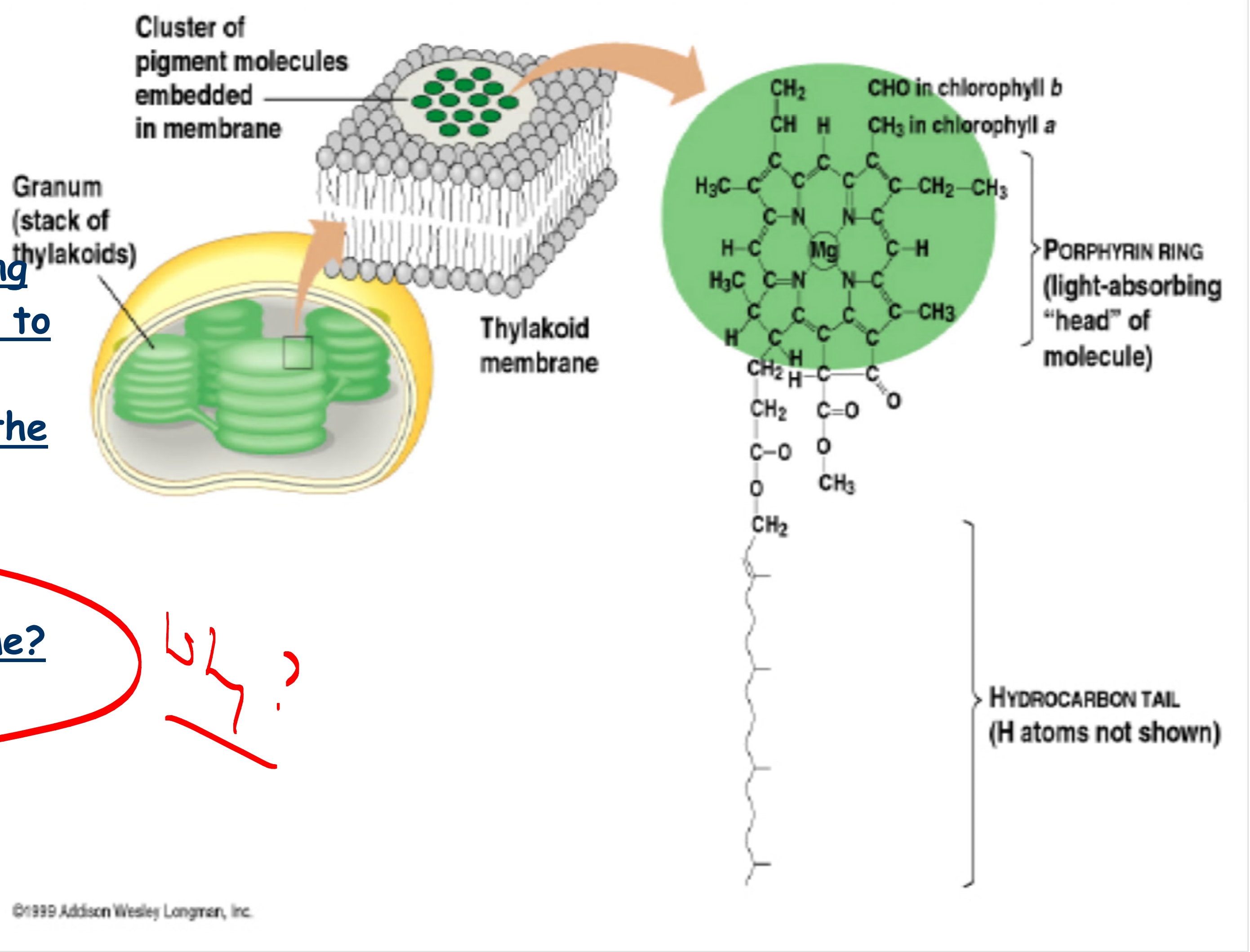
**Some answers to all these questions will be provided on the term test review package – can also ask at the tutorials.

The Good (first example)

Magnesium in chlorophyll

What to know from this?

The structure in the leaf; the structure of the chlorophyll ring (yes? Yes!). Not to draw but to assemble from the bits – to recognize – to identify where the Mg(II) is located.



©1999 Addison Wesley Longman, Inc.

(Why Mg(II) not Fe(II) in heme?
Ans: … .)

Why?

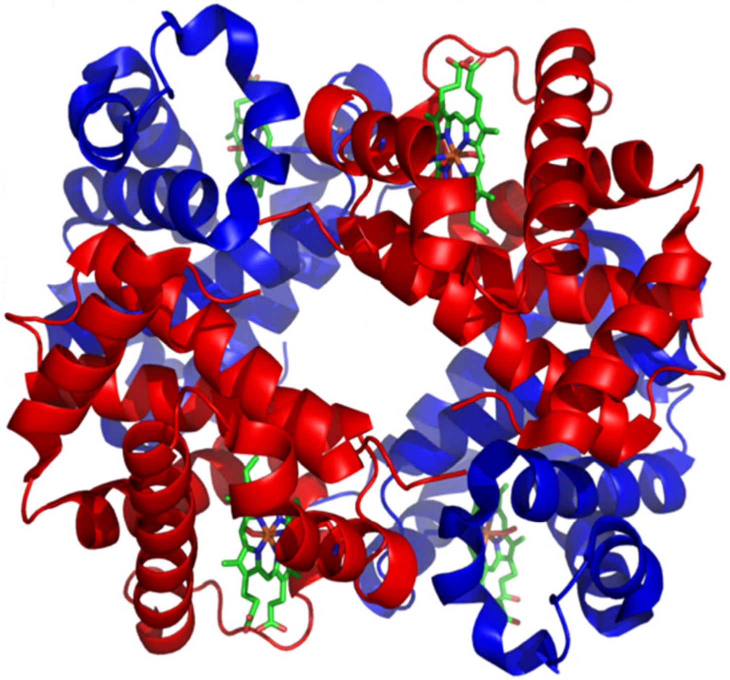
See unit on Mg coming later.

The Good (second example)

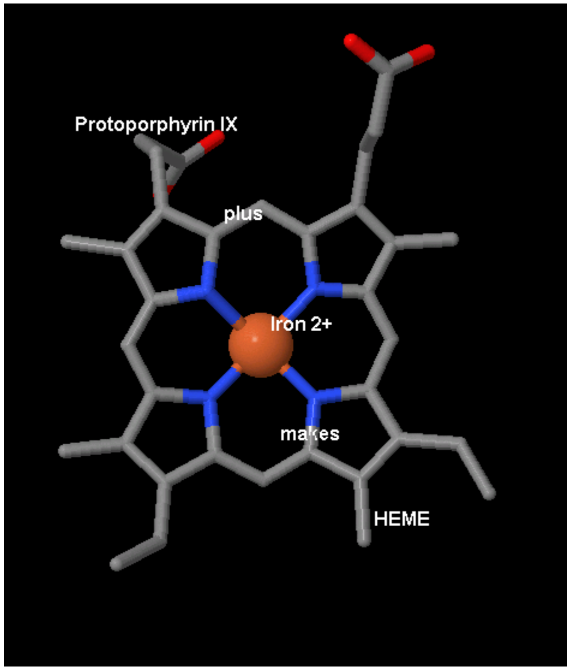
Iron in heme proteins – hemoglobin

RED BLOOD CELLS

HEMOGLOBIN 4 PARTS 4 HEMES



HEME
FE PROTOPORPHYRIN IX



Need to know

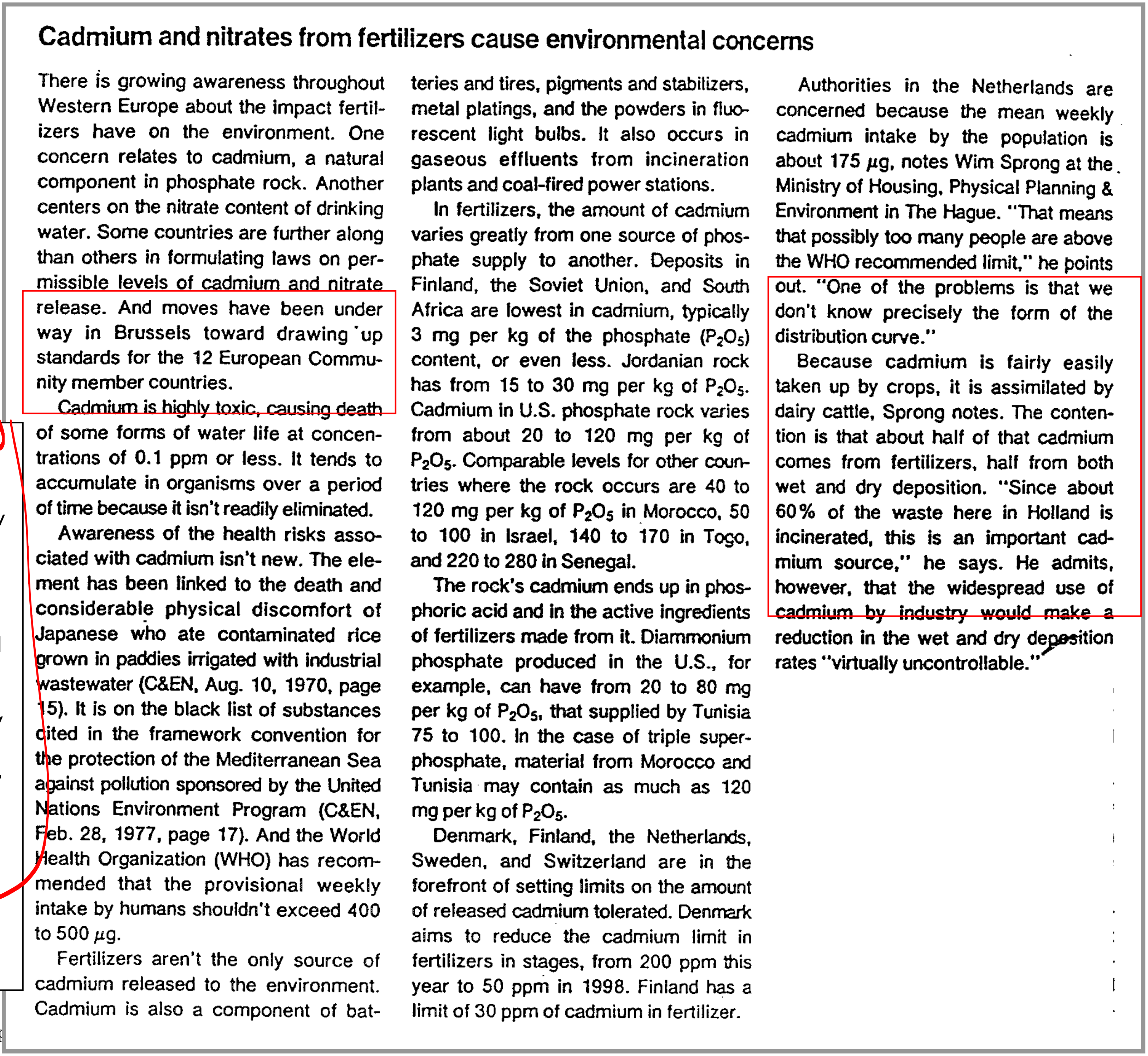
The Bad (two examples)

Cadmium applied to soils in sewage sludge
-this means we get Cd in our veggies
=not good
but also smoking….

Human uptake of cadmium takes place mainly through food. Foodstuffs that are rich in cadmium can greatly increase the cadmium concentration in human bodies. Examples are liver, mushrooms, shellfish, mussels, cocoa powder and dried seaweed.

An exposure to significantly higher cadmium levels occurs when people smoke. Tobacco smoke transports cadmium into the lungs. Blood will transport it through the rest of the body.

http://www.lenntech.com/periodic/elements/cd.htm



Cadmium and nitrates from fertilizers cause environmental concerns

There is growing awareness throughout Western Europe about the impact fertilizers have on the environment. One concern relates to cadmium, a natural component in phosphate rock. Another centers on the nitrate content of drinking water. Some countries are further along than others in formulating laws on permissible levels of cadmium and nitrate release. And moves have been under way in Brussels toward drawing up standards for the 12 European Community member countries.

Cadmium is highly toxic, causing death of some forms of water life at concentrations of 0.1 ppm or less. It tends to accumulate in organisms over a period of time because it isn't readily eliminated.

Awareness of the health risks associated with cadmium isn't new. The element has been linked to the death and considerable physical discomfort of Japanese who ate contaminated rice grown in paddies irrigated with industrial wastewater (C&EN, Aug. 10, 1970, page 15). It is on the black list of substances cited in the framework convention for the protection of the Mediterranean Sea against pollution sponsored by the United Nations Environment Program (C&EN, Feb. 28, 1977, page 17). And the World Health Organization (WHO) has recommended that the provisional weekly intake by humans shouldn't exceed 400 to 500 µg.

Fertilizers aren't the only source of cadmium released to the environment. Cadmium is also a component of batteries and tires, pigments and stabilizers, metal platings, and the powders in fluorescent light bulbs. It also occurs in gaseous effluents from incineration plants and coal-fired power stations.

In fertilizers, the amount of cadmium varies greatly from one source of phosphate supply to another. Deposits in Finland, the Soviet Union, and South Africa are lowest in cadmium, typically 3 mg per kg of the phosphate (P_2O_5) content, or even less. Jordanian rock has from 15 to 30 mg per kg of P_2O_5. Cadmium in U.S. phosphate rock varies from about 20 to 120 mg per kg of P_2O_5. Comparable levels for other countries where the rock occurs are 40 to 120 mg per kg of P_2O_5 in Morocco, 50 to 100 in Israel, 140 to 170 in Togo, and 220 to 280 in Senegal.

The rock's cadmium ends up in phosphoric acid and in the active ingredients of fertilizers made from it. Diammonium phosphate produced in the U.S., for example, can have from 20 to 80 mg per kg of P_2O_5, that supplied by Tunisia 75 to 100. In the case of triple superphosphate, material from Morocco and Tunisia may contain as much as 120 mg per kg of P_2O_5.

Denmark, Finland, the Netherlands, Sweden, and Switzerland are in the forefront of setting limits on the amount of released cadmium tolerated. Denmark aims to reduce the cadmium limit in fertilizers in stages, from 200 ppm this year to 50 ppm in 1998. Finland has a limit of 30 ppm of cadmium in fertilizer.

Authorities in the Netherlands are concerned because the mean weekly cadmium intake by the population is about 175 µg, notes Wim Sprong at the Ministry of Housing, Physical Planning & Environment in The Hague. "That means that possibly too many people are above the WHO recommended limit," he points out. "One of the problems is that we don't know precisely the form of the distribution curve."

Because cadmium is fairly easily taken up by crops, it is assimilated by dairy cattle, Sprong notes. The contention is that about half of that cadmium comes from fertilizers, half from both wet and dry deposition. "Since about 60% of the waste here in Holland is incinerated, this is an important cadmium source," he says. He admits, however, that the widespread use of cadmium by industry would make a reduction in the wet and dry deposition rates "virtually uncontrollable."

and
Lead in paint -
Trivial examples, unless
you are a kid of 3 who
sucks the Barbie…

The Canadian Press

or much more serious -
paint in homes

Most dangerous toys 2013 include lead-laced product, small items

By The Associated Press, Suzanne Kennedy November 26, 2013 - 01:28 pm

Read more: http://www.wjla.com/articles/2013/11/trouble-in-toyland-report-released-by-u-s-public-interest-research-group-97391.html#ixzz2penrMgWI

http://www.cdc.gov/nceh/lead/

Thousands of Barbie accessory toys recalled after lead violation

Last Updated: Wednesday, September 5, 2007 | 11:40 AM ET

The Associated Press

The U.S. Consumer Product Safety Commission, in co-operation with Mattel Inc., announced late Tuesday that it is recalling about 675,000 Chinese-made toys that have excessive amounts of lead paint.

A display of Barbie dolls at a department store in Beijing in August.
(Greg Baker/Associated Press)

The voluntary recall covers units of various Barbie accessory toys that were manufactured between Sept. 30, 2006, and Aug. 20, 2007.

"Consumers should stop using recalled products immediately unless otherwise instructed," said the agency's website.

As well, 8,900 different toys involving Big Big World 6-in-I Bongo Band toys from the company's Fisher-Price brand were recalled. Those products were sold nationwide from July 2007 through August 2007.

New Requirements to Protect Children from Lead-Based Paint Hazards

Release date: 03/31/2008
Contact Information: Timothy Lyons, (202) 564-4355 / lyons.timothy@epa.gov; En español: Lina Younes, (202) 564-4355 / younes.lina@epa.gov Washington, D.C. - March 31, 2008)

To further protect children from exposure to lead-based paint, EPA is issuing new rules for contractors who renovate or repair housing, child-care facilities or schools built before 1978. Under the new rules, workers must follow lead-safe work practice standards to reduce potential exposure to dangerous levels of lead during renovation and repair activities

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Cranium Cadoo Board Games Recalled Due to Violation of Lead Paint Standard

WASHINGTON, D.C. - The U.S. Consumer Product Safety Commission, in cooperation with the firm named below, today announced a voluntary recall of the following consumer product. Consumers should stop using recalled products immediately unless otherwise instructed.

Name of Product: Cranium Cadoo Board Games
Units: About 38,000
Importer: Cranium Inc., of Seattle, Wash.
Hazard: The surface paint on the die contains excessive levels of lead, violating the federal lead paint standard.

Lead-Based Paint Violations; Includes $6,760 Penalty and Major Window Replacement Project

Font Scale: AAA
Posted 04 September 2008 @ 11:45 am EST

CHICAGO, Sept. 4 /PRNewswire-USNewswire/ -- U.S. Environmental Protection Agency Region 5 has settled a complaint against Wesley Realty Group in Evanston, Ill., for allegedly failing to warn tenants of 11 apartment buildings that their homes may contain lead-based paint hazards. A $6,760 penalty must be paid and a window replacement project undertaken.

Lead paint still a 'hazard' at playground after 15 years

Getting the Lead out

Meghan Foley, Senior Reporter
Issue date: 5/8/08 **Section:** Getting the lead out

The really Ugly (one example)

Arsenic in wood preservative
- think cottage decks and docks

What to know from this?

Cd is toxic (and essential)
Pb is toxic and no known requirements – always toxic – especially to children!
As is also toxic but very small amounts in the diet appear to be essential

… next how did "we" evolve using so many metals?

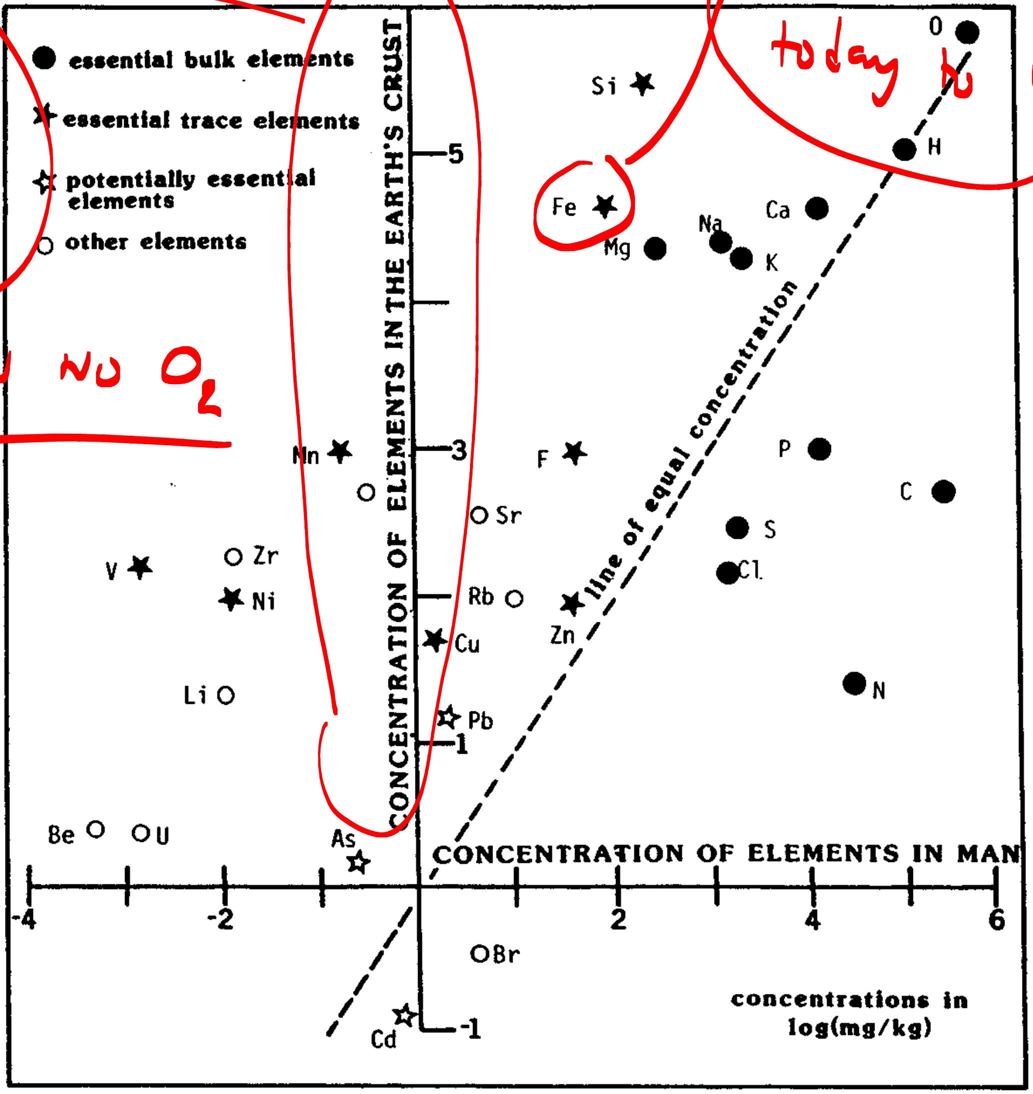
.3081

How did we evolve to use as many metals as this?

1. This graph suggests a possible reason.
2. Why so many different metals?
3. Why is Fe used so often?
4. Which are the key metals?
5. And how did the atmosphere influence evolution?
6. We'll come back in some more detail later in section 5.

oceans dissolved the crust

WHEN NO O_2



zero [ ] today to H_2O

Figure 3. *A comparison of the concentrations of elements in man and the environment showing accumulation and exclusion of certain elements by man. Data from ref. 9.*

Thursday !

3081

How did we evolve to use as many metals as this?

Although we find a large number of elements – they are not all in the same environment

1. Typically as free ions: group 1 and 2 – never (well never is a bit strong) for other metals (see the clause **..) Na^+, K^+, Mg^{2+}, Ca^{2+}, These ions are involved in 'pumps' – gradients across membranes – osmotic pressure – electrical potentials – pH gradients
2. Coordinated metals – we find 'ligands' coordinated atoms for these metals – for all the other metals. Actually, Nature doesn't want 'free' metal ions floating around, because..?
3. Why is Fe so common?
    a. 3 common oxidation states in biology: 2+, 3+ and 4+ (rarer)
    b. Can be coordinated by 4, 5 or 6 ligands
    c. Binds to S from Cys to N from His
4. Atmosphere – was oxygen poor and iron-rich to begin with, then? Oxygen from photosynthesis.

**

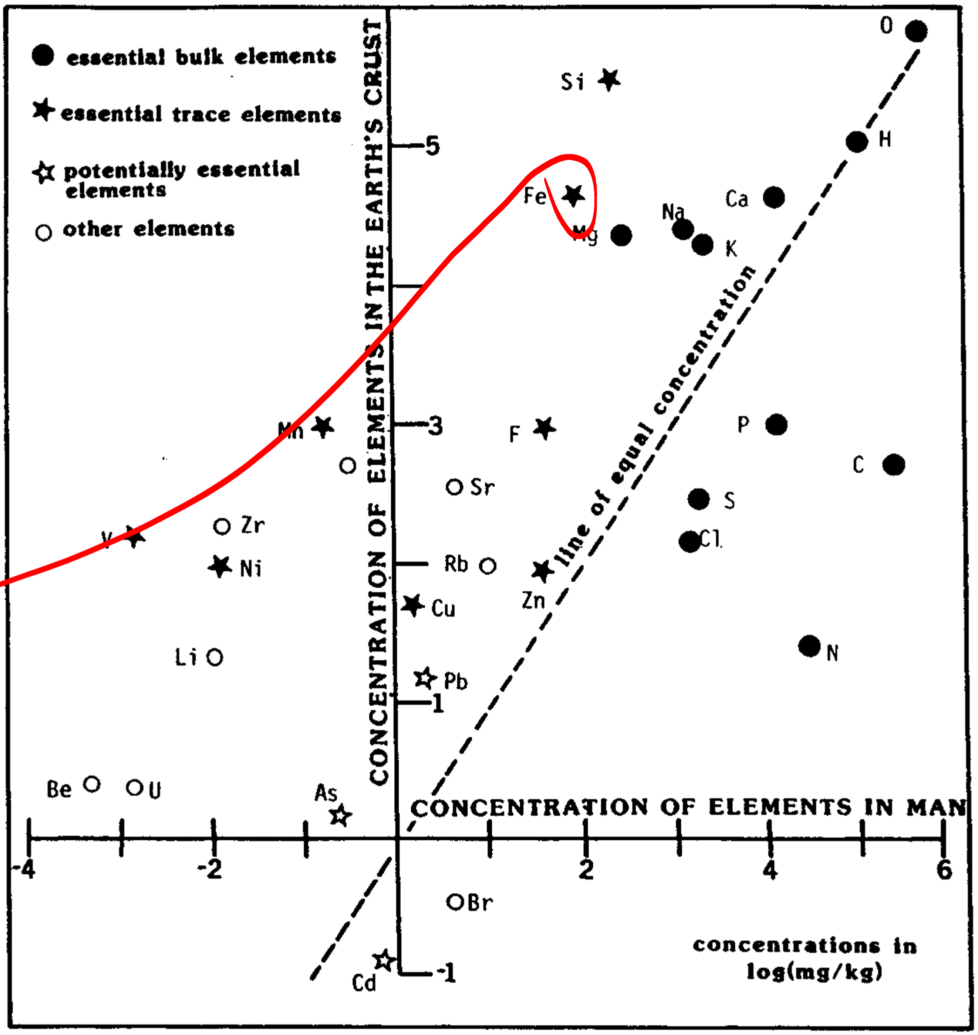


Figure 3. A comparison of the concentrations of elements i man and the environment showing accumulation and exclusio of certain elements by man. Data from ref. 9.

We now know that metals are vital to health

How many foods do we eat contain metals?

1. Simple examples? Salt? Iron in?

Vitamin B12 – what is vitamin B12? – it's a vitamin so where's the … metal? Is this molecule common in biology?

2. Do we have to learn this?

Porphyrins -- p 22 KSK

Cobalamins - ch 3 KSK

Problems to do

Identify 5 foods containing different metals using the text book or the internet or the next table

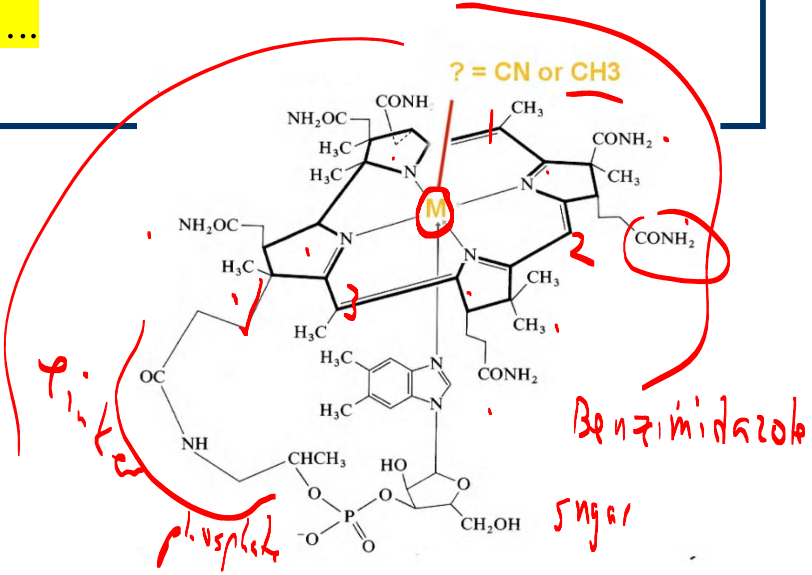
Foods with metals: Where do we obtain vit B12 from if not pills?

Practice drawing the porphyrin molecule – 4 parts – the metal and its ligand; the ring; the adenine; the sugar phosphate linker – we'll come back to these porphyrin-like molecules later

1. Salt – NaCl – controls fluid levels in mammals.
2. Iron in – hemoglobin – dioxygen transport (O_2).
3. Vitamin B12 is a cofactor – the key element in an enzyme – a cofactor makes the enzyme (catalyst) active. B12 has many roles, one is the methylation of Hg(II) to make CH_3HgCl – monomethyl mercury chloride – a neural toxin.
4. B12 is everywhere – other use is in extending alkyl chains – adding CH_3 connected with Folic Acid metabolism – very serious problems - but see the unit on B12 coming up.
5. For now note Co(III) is the metal that isn't toxic but Cr(VI) was worth a movie - the name was? staring?
6. Zinc, now zinc, such a wonderful metal….
7. Your choice…..

Co I/II/III

4N
4 rings
3 linkages



So, what do we eat? And why?

1. Ca …muscles - nerves - skelton dev /cramps
2. Mg…bones - metabolism- energy - /confusion   high + low Mg^{2+}
3. Cr… isn't that in steel?-glucose metabolism - /diabetes
4. Cu – that's in wire? – bone formation – respiration – sorts out the chemistry …–/ impaired respiration - weakness

What will we study?

1. Co – vit B12 - /pernicious anemia – (anemia will not end and death ensues)
2. Fe – lots of roles - hemoglobin - /anemia
3. Zn – like reinforcing rods – has a structural role in many enzymes - but also enzymatic active site role - wound healing – protein metabolism – gene chemistry - deficiency → retarded growth – steriltiy – lots of problems
4. And, the use of metals for therapeutic reasons – eg Pt – see KSK ch. 18/19
5. And, which metals are toxic – Hg, Cd, Pb, As - KSK ch 17

See more details next and later…

METAL	Sources (note the necessity of augmenting nutrients)	ESSENTIAL FUNCTIONS	SOME REPORTED Deficiency Symptoms
Calcium	milk, cheese, molasses, yogurt, dolomite Dairy, broccoli, figs, sardines	bone/tooth formation, blood clotting, heart rhythm, nerve transmission, muscle growth & contraction Muscle and nerve signaling, bone growth	heart palpitations, insomnia, muscle cramps, nervousness, arm & leg numbness, tooth decay
Chromium	brewer's yeast, clams, corn oil, whole grain cereals	blood sugar level, glucose metabolism	atherosclerosis, glucose intolerance in diabetics
Copper	legumes, nuts, organ meats, seafood, raisins, molasses, bone meal Lobster, crab, beans, nuts	bone formation, hemoglobin & red blood cell formation. "Mops up" of free radicals	general weakness, impaired respiration, skin sores
Iodine	seafood, kelp tablets, salt (iodized)	energy production, metabolism (excess fat), thyroid gland	cold hands & feet, dry hair, irritability, nervousness, obesity
Cobalt	Leafy green vegetables; meat and dairy products	Red blood cell formation	Folic acid deficiency – pernicious anemia
Iron	molasses, eggs, fish, organ meats, poultry, wheat germ, beans, spinach	Hemoglobin production, stress & disease resistance - Red blood cell function	breathing difficulties, brittle nails, iron deficiency anemia (pale skin, fatigue), constipation
Magnesium	Dark leafy vegetables;	Strong bones and teeth, muscle contraction	confusion, disorientation, easily aroused anger, nervousness, rapid pulse, tremors
Manganese	bananas, bran celery, cereals, egg yolks, green leafy vegetables, legumes, liver, nuts, pineapples, whole grains	enzyme activation, reproduction & growth, sex hormone production, tissue respiration	ataxia (muscle coordination failure), dizziness, ear noises, loss of hearing
Phosphorus	eggs, fish grains, glandular meats, meat, poultry, yellow cheese	bone/tooth formation, cell growth & repair, energy production, heart muscle contraction, kidney function, metabolism (calcium, sugar), nerve & muscle activity	appetite loss, fatigue, irregular breathing, nervous disorders, overweight, weight loss
Potassium	dates, figs, peaches, tomato juice, blackstrap, molasses, peanuts, raisins, seafood	heartbeat, rapid growth, muscle contraction	acne, continuous thirst, dry skin, constipation, general weakness, insomnia, muscle damage, nervousness, slow irregular heartbeat, weak reflexes
Sodium	salt, milk, cheese, seafood	normal cellular fluid level, muscle contraction	appetite loss, intestinal gas, muscle shrinkage, vomiting, weight loss
Sulphur	bran, cheese, calms, eggs, nuts, fish, wheat germ	collagen synthesis, tissue formation	not known
Zinc	brewer's yeast, liver, seafood, soybeans, spinach, sunflower seeds, mushrooms oysters, chick peas, whole grains	burn & wound healing, carbohydrate digestion, reproductive organ growth & development	delayed sexual maturity, fatigue, loss of taste, poor appetite, prolonged wound healing, retarded growth, sterility

Metals work with the enzymes to speed up essential chemical reactions.

- "Good metals" (*e.g.*, calcium, zinc, cobalt) are important dietary staples – but, are "bad metals" always "bad"? What about the case of Se? Does more mean better?

A quick summary of metals so far:

Regulatory action: The metal ion gradients set up between Na^+ and K^+ and Mg^{2+} and Ca^{2+} using cell membranes

pumps Na^+ K^+

Roles in structural biology – particularly the skeleton and teeth: Mg^{2+} and Ca^{2+}

Fe^{4+}

Roles in electron transfer: biological systems we need electrons to function and use Fe^{2+} / Fe^{3+} in the cytochromes and ferredoxins, and Cu^{2+} in azurin, plastocyanin and stellacyanin.

The enzymes carboxypeptidase and alcohol dehydrogenase use Zn^{2+}; superoxide dismutase (SOD) uses both Cu^{2+} and Zn^{2+}

non heme iron

FeS cmpds.

Examples:

The enzymes horseradish peroxidase, cytochrome c peroxidase, and most important for mammals, catalase and cytochrome P450 **all use Fe in oxidation states of 2+/3+ and 4+ bound to a porphyrin ring, the heme group**

Oxygen (except in special circumstances) is at the key to oxidative phosphorylation - - the energy source – see LB ch 11, p 284.

In mammals – hemoglobins do this using the Fe in protoporphyrin IX - heme (p 285)

In molluscs and anthropods – crabs – hemocyanin uses 2 copper atoms – LB p 297.

In marine invertebrates – hemerythrin uses 2 non-heme Fe atoms - LB 291.

1046c2

Functions inspired by .. metals:

1. Microminerals and Ultratrace – so Na / K / Ca/ Mg not included!

BUT Vital.

2. DiOxygen transport and storage

3. $\overset{O_2}{Fe}$, $\overset{O_2}{Cu}$, $\overset{O}{Fe}$

(Twice? Yes – hemoglobin and hemerythrin – see LB p 4)

4. Electron transport and electron transfer

5. Structural control – Zn

6. All ESSENTIAL

repeats the information from 2 pages back

Table 1.3 *Functions of essential macrominerals and trace elements*

no need to memorize

Element	*Chief functions in the body*
Calcium	Principal constituent of bones and teeth: involved in muscle contraction and relaxation, nerve function, blood clotting, blood pressure.
Phosphorous	Part of every cell: involved in pH buffering
Magnesium	Involved in bone mineralization, protein synthesis, enzyme action, normal muscular contraction, nerve transmission.
Sodium	Helps maintain ionic strength of body fluids
Chloride	Part of stomach acid, necessary for proper digestion
Potassium	Facilitates many reactions, including protein synthesis, nerve transmission and contraction of muscles.
Sulfur	Component of certain aminoacids, part of biotin, thiamin and insulin.
Iodine	Part of thyroxin, which regulates metabolism
Iron	Haemoglobin formation, part of myoglobin, energy utilization.
Zinc	Part of many enzymes, present in insulin, involved in making genetic material and proteins, immunity, vitamin A transport, taste, wound healing, making sperm, normal fetal development
Copper	Absorption of iron, part of several enzymes
Fluoride	Formation of bones and teeth, helps make teeth resistant to decay and bones resistant to mineral loss
Selenium	Helps protect body compounds from oxidation
Chromium	Associated with insulin and required for the release of energy from glucose
Molybdenum	Facilities enzyme functions and many cell processes
Manganese	Facilities enzyme functions and many cell processes
Cobalt	Part of vitamin B_{12}, which involves in nerve function and blood formation
Vanadium	Control of sodium pump: inhibition of ATPase, *p*-transferases
Nickel	Constituent of urease, reduced haemopoiesis
Cadmium	Stimulates elongation Betois in ribosomes
Tin	Interactions with riboflavin
Lead	Many enzyme effects
Lithium	Control of sodium pump
Silicon	Structural role in connective tissue and osteogenic cells
Arsenic	Increased arginine urea + ornithine, Meto, metabolism of methyl compounds
Boron	Control of membrane function, nucleic acid biosynthesis and lignin biosynthesis

Structural form of the metal changes

1. How the metal is bound to other atoms directly and completely controls its activity = function

2. We call this coordination by ligands

3. We will discuss this later but here are some examples

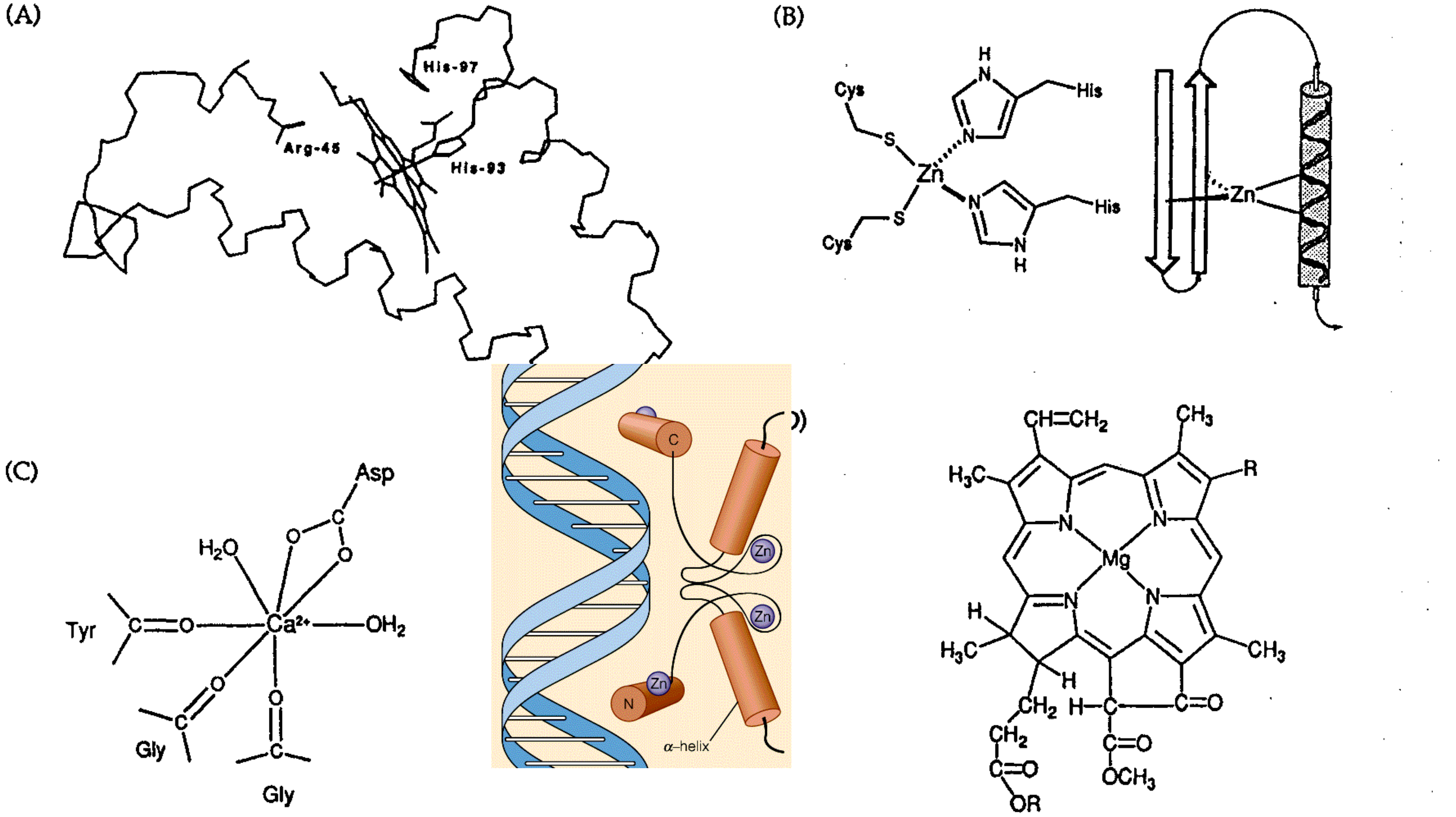


Figure 1.15 Coordination modes for metal binding to metalloproteins and peptides. (A) The heme prosthetic center and a portion of the backbone in myoglobin. (B) Bound Zn^{2+} in a zinc finger. On the right the portion of the protein backbone that forms the "finger" is traced. Figure 1.19 gives more details on such schematic diagrams. (C) The metal-binding domain of a Ca^{2+}-activated enzyme (phospholipase A_2) showing coordination of a chelating carboxylate, two water molecules, and three backbone carbonyls. (D) Chlorophyll from the light-harvesting complex of the photosynthetic reaction center.

What are the ligands? Identify the atoms next to the metals in these examples and the molecules they are part of. See KSK ch. 7 for examples with Fe – Fe4S4 – ferredoxin - see Mg section

3105

Structural form of the metal changes

4. How the metal is bound to other atoms directly and completely controls its activity = function

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6. We will discuss this later but here are some examples

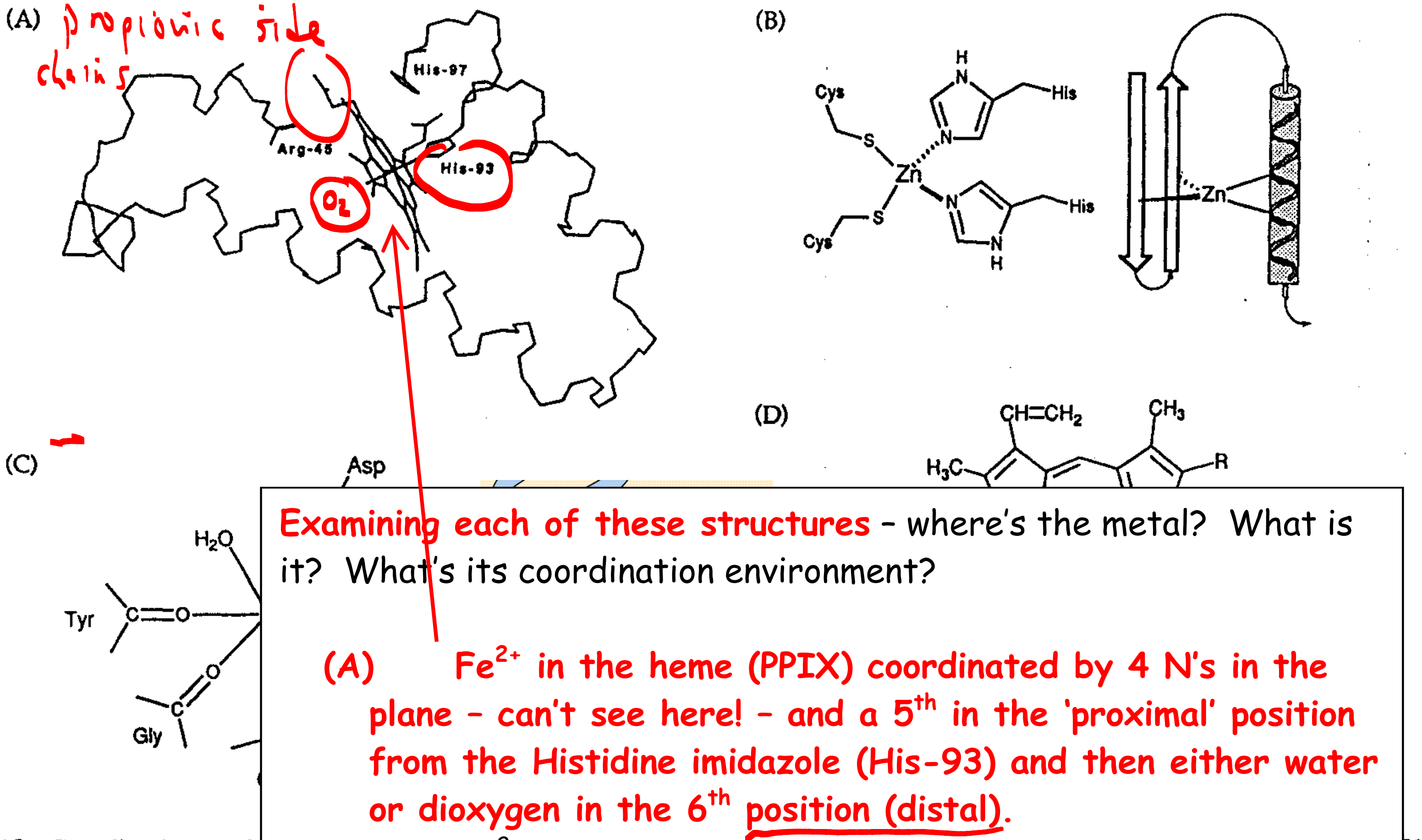

Figure 1.15 Coordination mode
backbone in myoglobin. (B) Bou
Figure 1.19 gives more details o
showing coordination of a chela
vesting complex of the photosynt

Examining each of these structures – where's the metal? What is it? What's its coordination environment?

(A) Fe^{2+} in the heme (PPIX) coordinated by 4 N's in the plane – can't see here! – and a 5^{th} in the 'proximal' position from the Histidine imidazole (His-93) and then either water or dioxygen in the 6^{th} position (distal).

(B) Zn^{2+} in a zinc finger protein – and the colour picture – 2 sulfurs from cysteines (Cys) and 2 nitrogens from histidine (His)

(C) Ca^{2+} - coordinated to 7 ligands (usually just 6) all oxygen, 4 amino acids and 2 waters – Tyr, Asp, Gly, Gly

(D) Chlorophyll –Mg^{2+} coordinated through the same 4 nitrogens as the Fe^{2+} in the heme, plus 5^{th} and 6^{th} positions will have waters.

3105

Structural form of the metal changes

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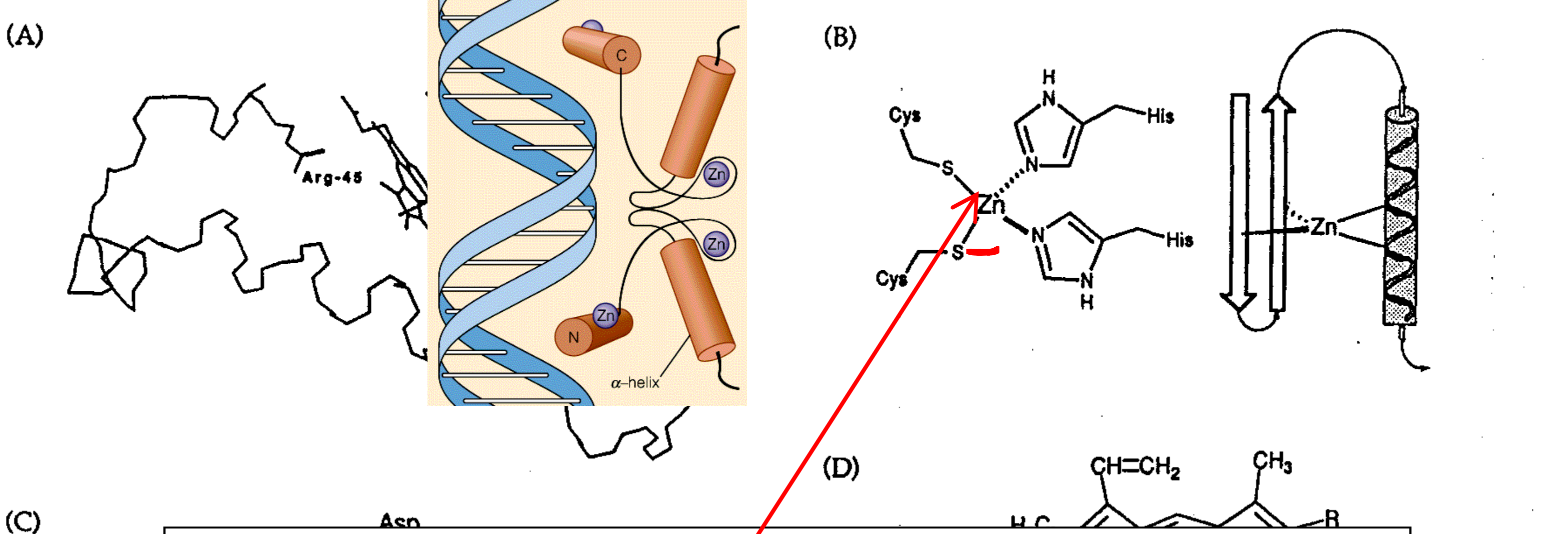

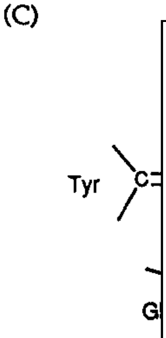

Figure 1.15 Coordina
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3105

Structural form of the metal changes

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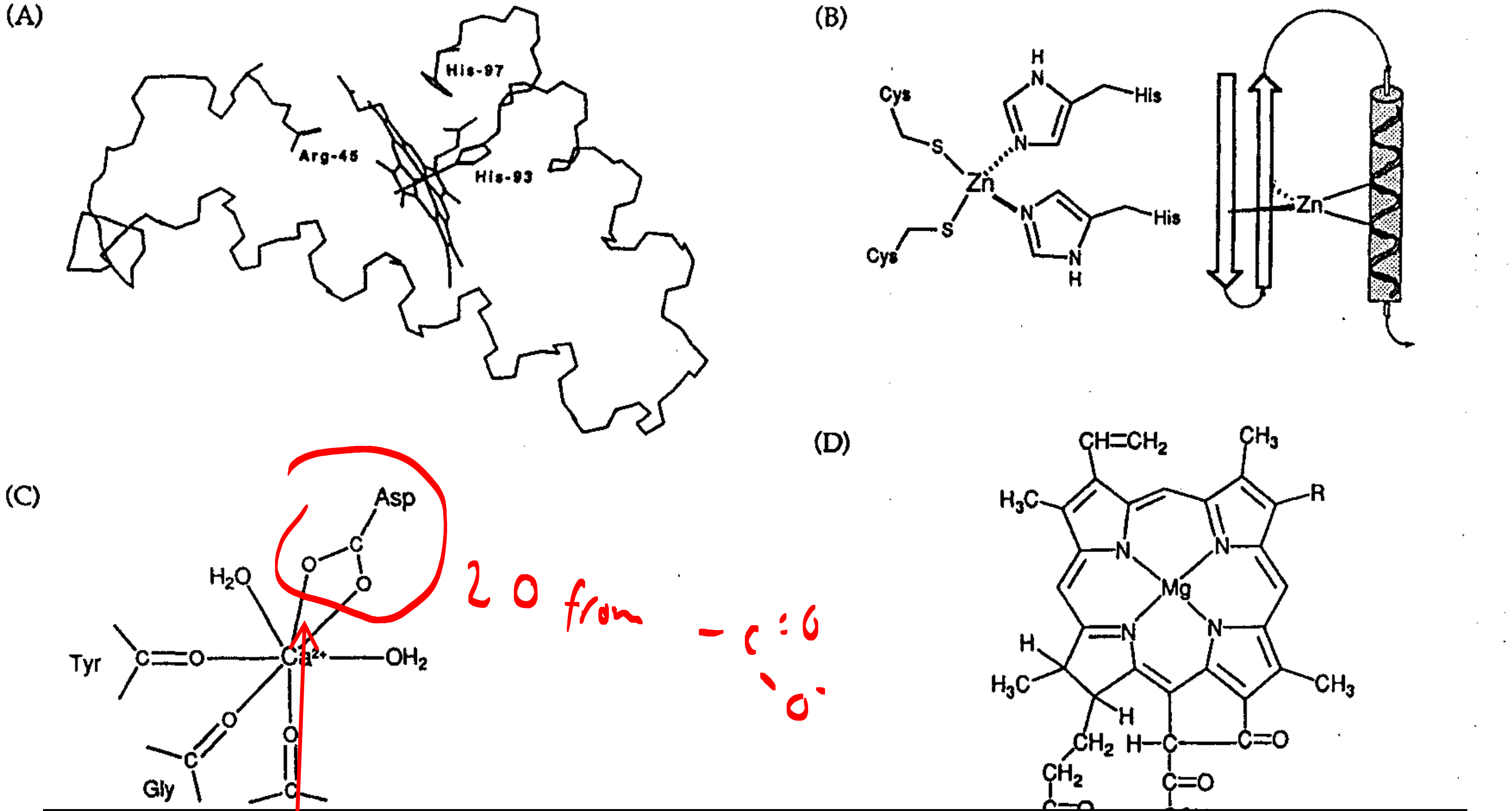
11. We call this coordination by ligands

12. We will discuss this later but here are some examples



2 O from -C:O
O

Figure 1.15
backbone in
Figure 1.19
showing coo
vesting comp

of the
raced.
se A_2)
t-har-

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Structural form of the metal changes

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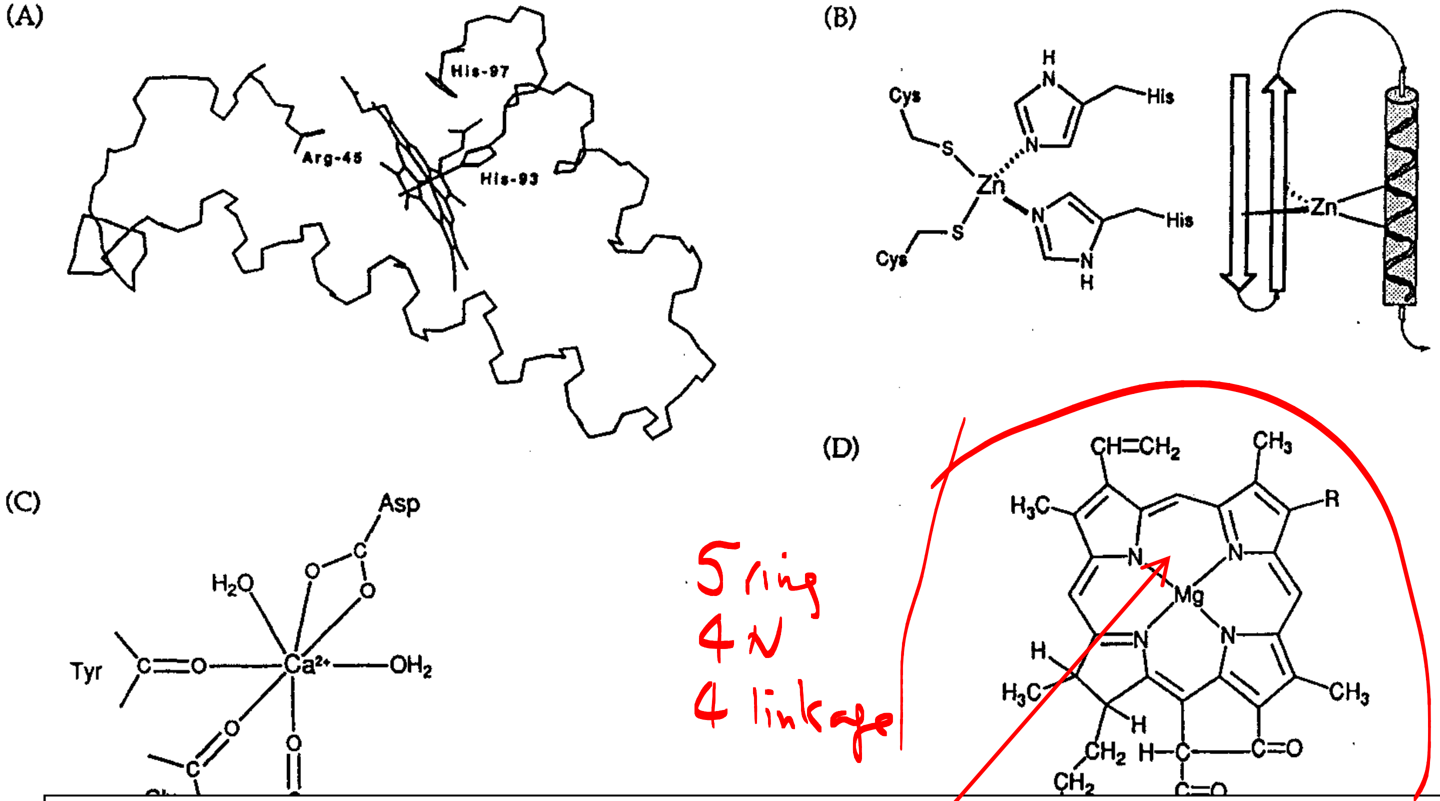

5 ring
4 N
4 linkage

Figure 1.15
backbone in
Figure 1.19
showing coo
vesting comp

of the
raced.
se A_2
t-har-

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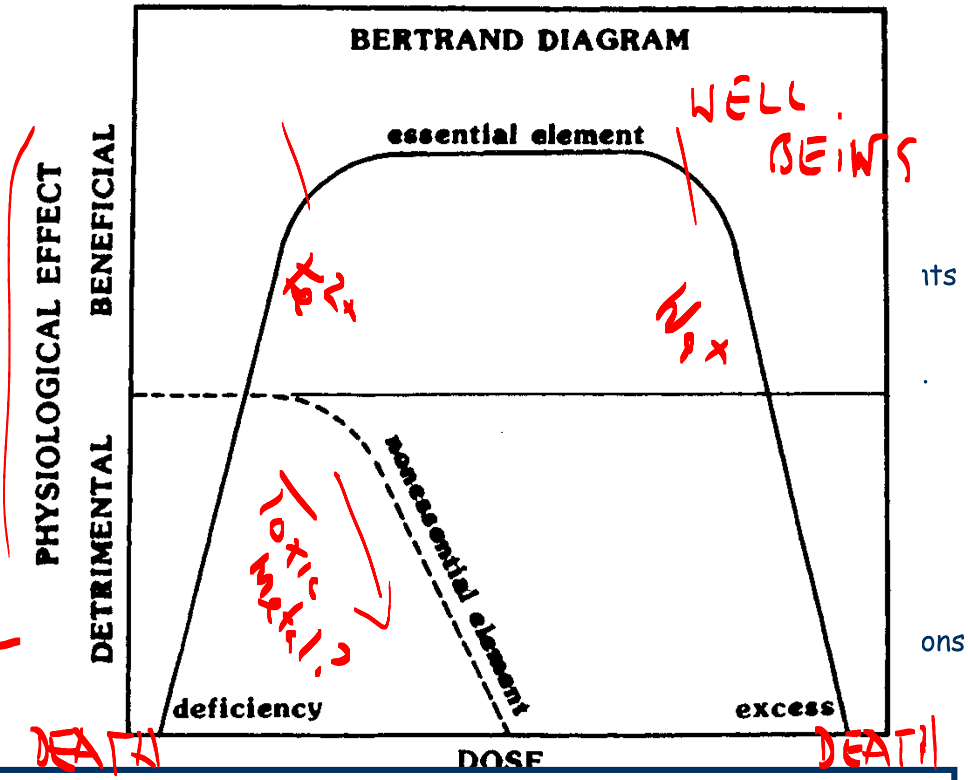
Which are toxic and why?

A powerful conceptual model

1. Toxic: Usually large and below the 4th row in the period table – its when in 'excess'.
2. Key toxic metals: – Cd, Hg, Pb, As, but also Cr(VI) – 6+ not 3+? What coordinates it? Where does it end up? What does it block?
3. The chemical form is key to toxicity: eg Hg^{2+} vs. $(CH_3)Hg^+$.
4. Deficiency – Fe – for many –
5. Excess – Na for many …
6. Disease – Sometimes genetic effects – Wilson's due to copper ons such as the effect of clearing cisplatin for cancer.

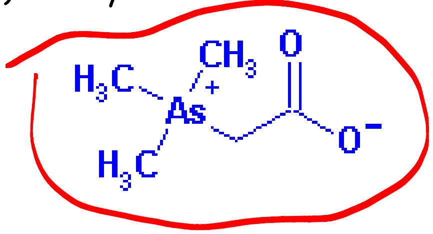
kidney effect



Bertrand diagram helps define: (see KSK p 9)

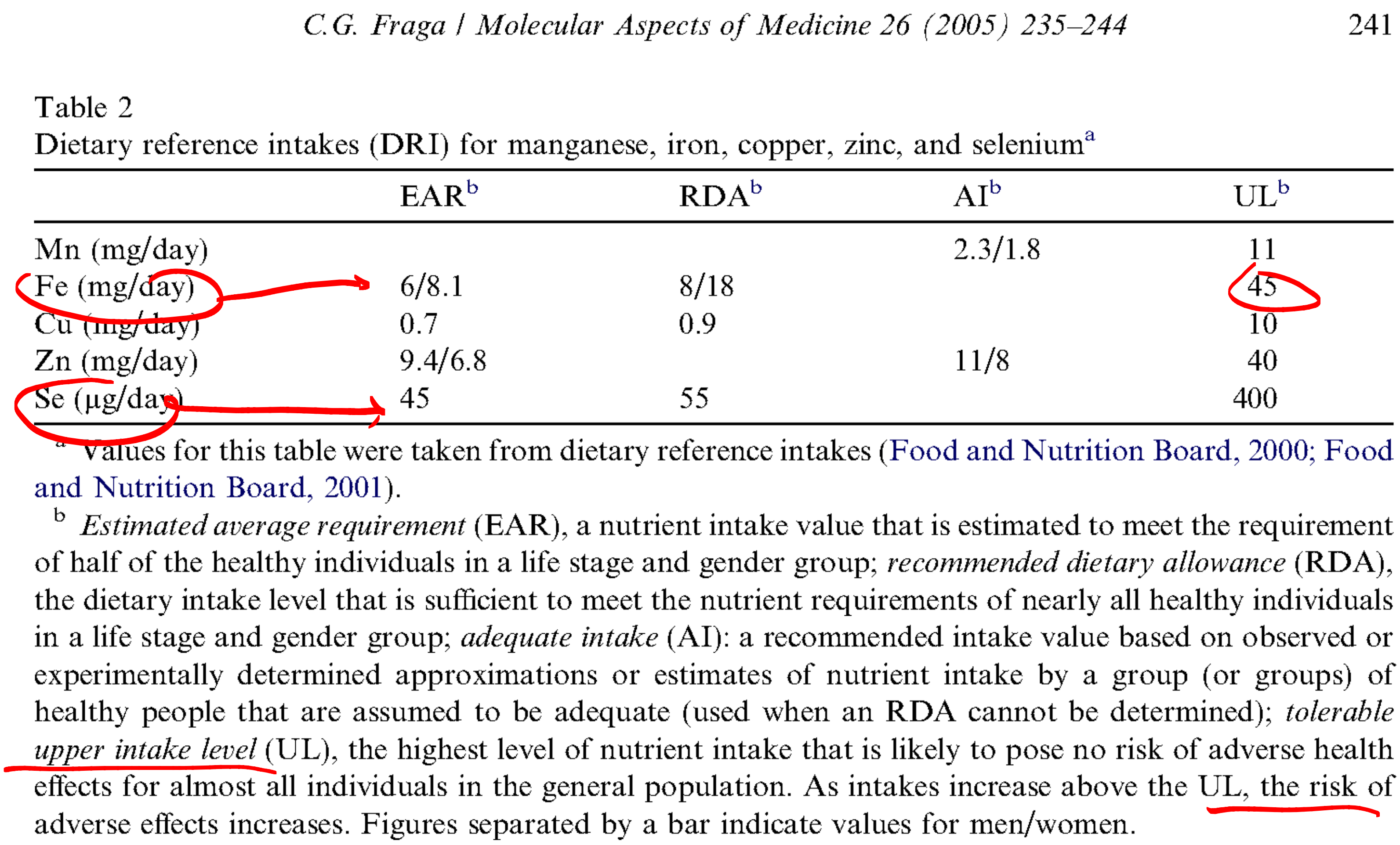
Essential – Normal levels
Deficient levels
Toxic levels

Need to realize that the correct form of a metal is also important, so Cr(III) is essential (diabetes) but Cr(VI) is toxic at all levels. Must define the form-speciation – the oxidation state and in many cases the actual complex. EG As(V) and As(III) are toxic; but if the As(V) exists as arsenobetaine, which it does in many species, eg in sea food– then it is completely harmless to humans!). But chromated copper arsenate (CCA) is very toxic.



Deficiency – Fe → anemia due to a lack of red blood cells – oxygen starvation
Zn → dwarfism – due to poor bone formation
Excess Na →hypertension – an imbalance in fluid ion content
Toxic Any metals (or other agent) that reduces metabolic activity
Of course, Cd^{2+}, Hg^{2+}, As^{3+}, and As^{5+}, but Na^+?

We need essential elements, but more is not always better. All essential elements become toxic when consumed in quantities above a certain threshold.



C.G. Fraga / Molecular Aspects of Medicine 26 (2005) 235–244 241

Table 2

Dietary reference intakes (DRI) for manganese, iron, copper, zinc, and selenium[a]

	EAR[b]	RDA[b]	AI[b]	UL[b]
Mn (mg/day)			2.3/1.8	11
Fe (mg/day)	6/8.1	8/18		45
Cu (mg/day)	0.7	0.9		10
Zn (mg/day)	9.4/6.8		11/8	40
Se (μg/day)	45	55		400

[a] Values for this table were taken from dietary reference intakes (Food and Nutrition Board, 2000; Food and Nutrition Board, 2001).

[b] *Estimated average requirement* (EAR), a nutrient intake value that is estimated to meet the requirement of half of the healthy individuals in a life stage and gender group; *recommended dietary allowance* (RDA), the dietary intake level that is sufficient to meet the nutrient requirements of nearly all healthy individuals in a life stage and gender group; *adequate intake* (AI): a recommended intake value based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of healthy people that are assumed to be adequate (used when an RDA cannot be determined); *tolerable upper intake level* (UL), the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intakes increase above the UL, the risk of adverse effects increases. Figures separated by a bar indicate values for men/women.

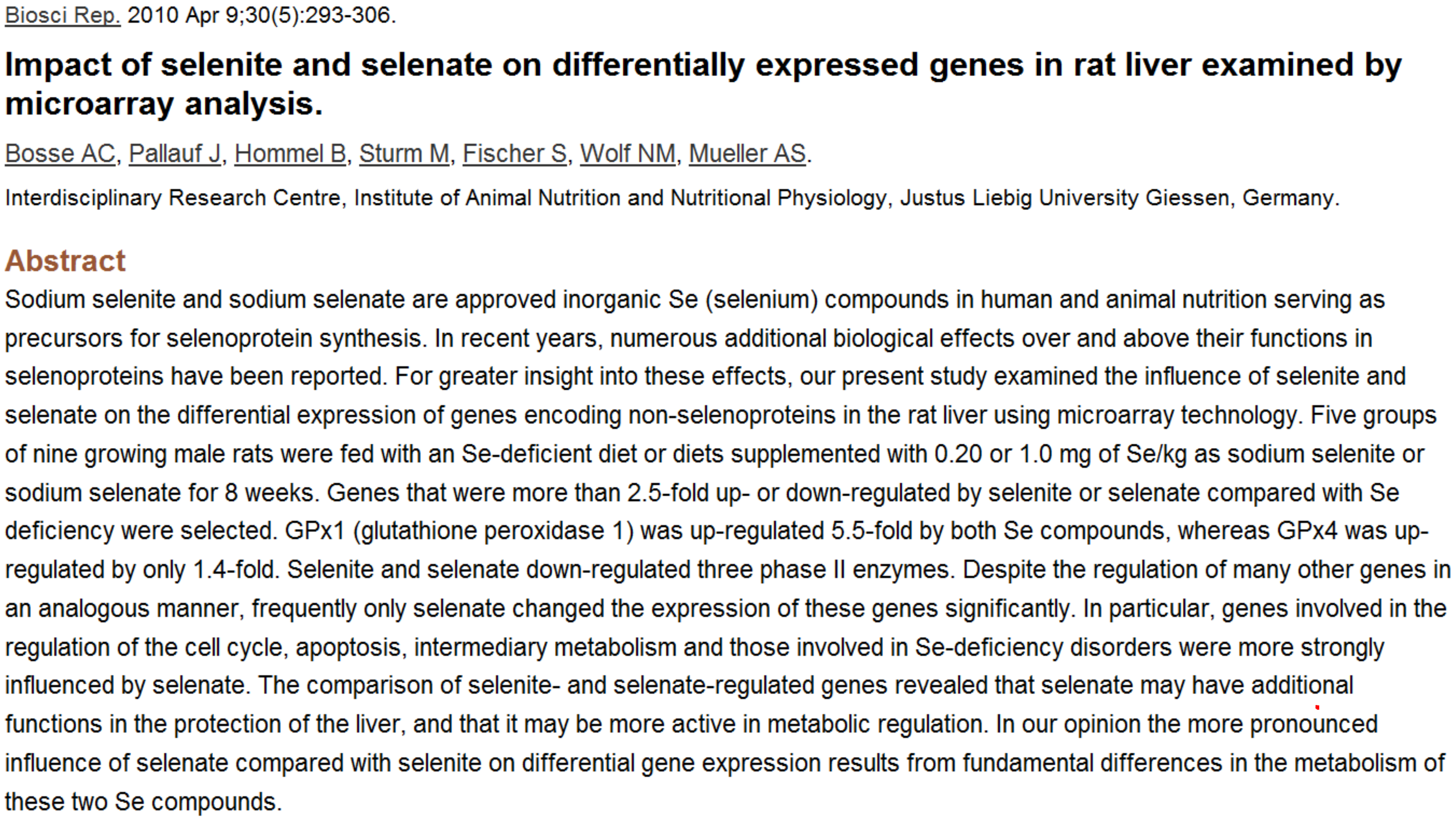
inhibit other functions

Chemical Speciation

example

Speciation refers to the chemical form in which the element is found. What is the oxidation state of the element? Is it “free” or solvated? Is it “organic”?

Different oxidation states can induce different physiological responses.



Biosci Rep. 2010 Apr 9;30(5):293-306.

Impact of selenite and selenate on differentially expressed genes in rat liver examined by microarray analysis.

Bosse AC, Pallauf J, Hommel B, Sturm M, Fischer S, Wolf NM, Mueller AS.

Interdisciplinary Research Centre, Institute of Animal Nutrition and Nutritional Physiology, Justus Liebig University Giessen, Germany.

Abstract

Sodium selenite and sodium selenate are approved inorganic Se (selenium) compounds in human and animal nutrition serving as precursors for selenoprotein synthesis. In recent years, numerous additional biological effects over and above their functions in selenoproteins have been reported. For greater insight into these effects, our present study examined the influence of selenite and selenate on the differential expression of genes encoding non-selenoproteins in the rat liver using microarray technology. Five groups of nine growing male rats were fed with an Se-deficient diet or diets supplemented with 0.20 or 1.0 mg of Se/kg as sodium selenite or sodium selenate for 8 weeks. Genes that were more than 2.5-fold up- or down-regulated by selenite or selenate compared with Se deficiency were selected. GPx1 (glutathione peroxidase 1) was up-regulated 5.5-fold by both Se compounds, whereas GPx4 was up-regulated by only 1.4-fold. Selenite and selenate down-regulated three phase II enzymes. Despite the regulation of many other genes in an analogous manner, frequently only selenate changed the expression of these genes significantly. In particular, genes involved in the regulation of the cell cycle, apoptosis, intermediary metabolism and those involved in Se-deficiency disorders were more strongly influenced by selenate. The comparison of selenite- and selenate-regulated genes revealed that selenate may have additional functions in the protection of the liver, and that it may be more active in metabolic regulation. In our opinion the more pronounced influence of selenate compared with selenite on differential gene expression results from fundamental differences in the metabolism of these two Se compounds.

Some oxidation states are much more toxic than others. Cr(III) is an essential element, but Cr(VI) is highly toxic and carcinogenic.

Toxic chromium found in Chicago drinking water

Detected levels are more than 11 times higher than California's new standard

By Michael Hawthorne, Tribune reporter

August 6, 2011

Chicago's first round of testing for a toxic metal called hexavalent chromium found that levels in local drinking water are more than 11 times higher than a health standard California adopted last month.

But it could take years before anything is done about chromium contamination in Chicago and scores of other cities, in part because industrial polluters and municipal water utilities are lobbying to block or delay the Obama administration's move toward national regulations.

The discovery of hexavalent chromium in drinking water is renewing a debate about dozens of unregulated substances that are showing up in water supplies nationwide. Potential health threats from many of the industrial chemicals, pharmaceutical drugs and herbicides still are being studied, but researchers say there is strong evidence that years of exposure to chromium-contaminated water can cause stomach cancer.

Many metals form organometallic compounds. Mercury that is *biomagnified* in the food chain is usually a lipid-soluble organomercury such as CH_3HgCl. Mercury is a non-essential element and is toxic. KSK ch 17

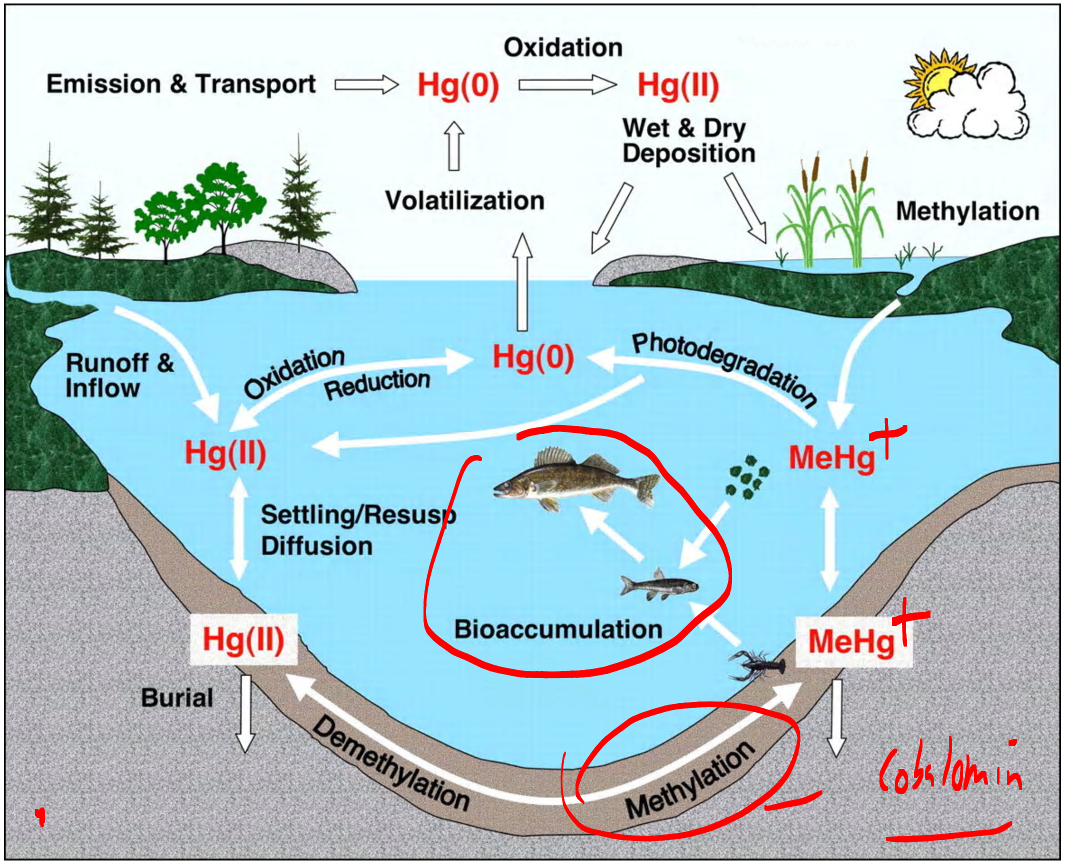


Fig 1. Mercury cycling in a lake and its watershed. Mercury emissions are transported long distances, primarily as gaseous elemental mercury [Hg (0)], oxidized in the atmosphere to reactive gaseous mercury [Hg(II)], and deposited in precipitation and by surface contact (dry deposition). Anaerobic bacteria convert a small portion of the incoming Hg(II) to methylmercury (MeHg), which is then bioconcentrated in the aquatic food chain (by a factor of $\geq 10^6$). Various biotic and abiotic reactions interconvert the different forms of Hg, affecting uptake, burial, and evasion back to the atmosphere.

PNAS 2007, 104, 16394-16395

How can we use metals therapeutically?

KSK ch 19

To:

(A) Treat deficiencies

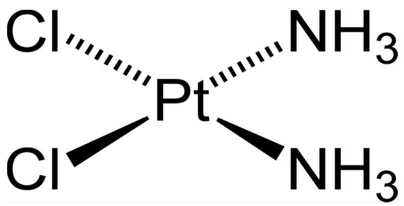
(B) Treat disease

(C) **What other therapeutic uses of metals do you know?**

Think Bi, Li, etc. Your list?

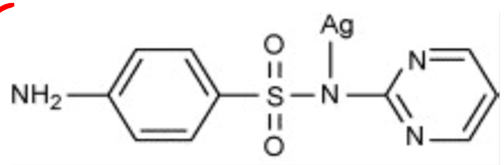
cis- Diamminedichloroplatin(II) (cisplatin)

treatment of testicular cancer



silver sulfadiazine cream

treatment of burns



Returning to our theme…

In the beginning – the hot, dusty, atmosphere gave way to the clear, rich atmosphere of today.

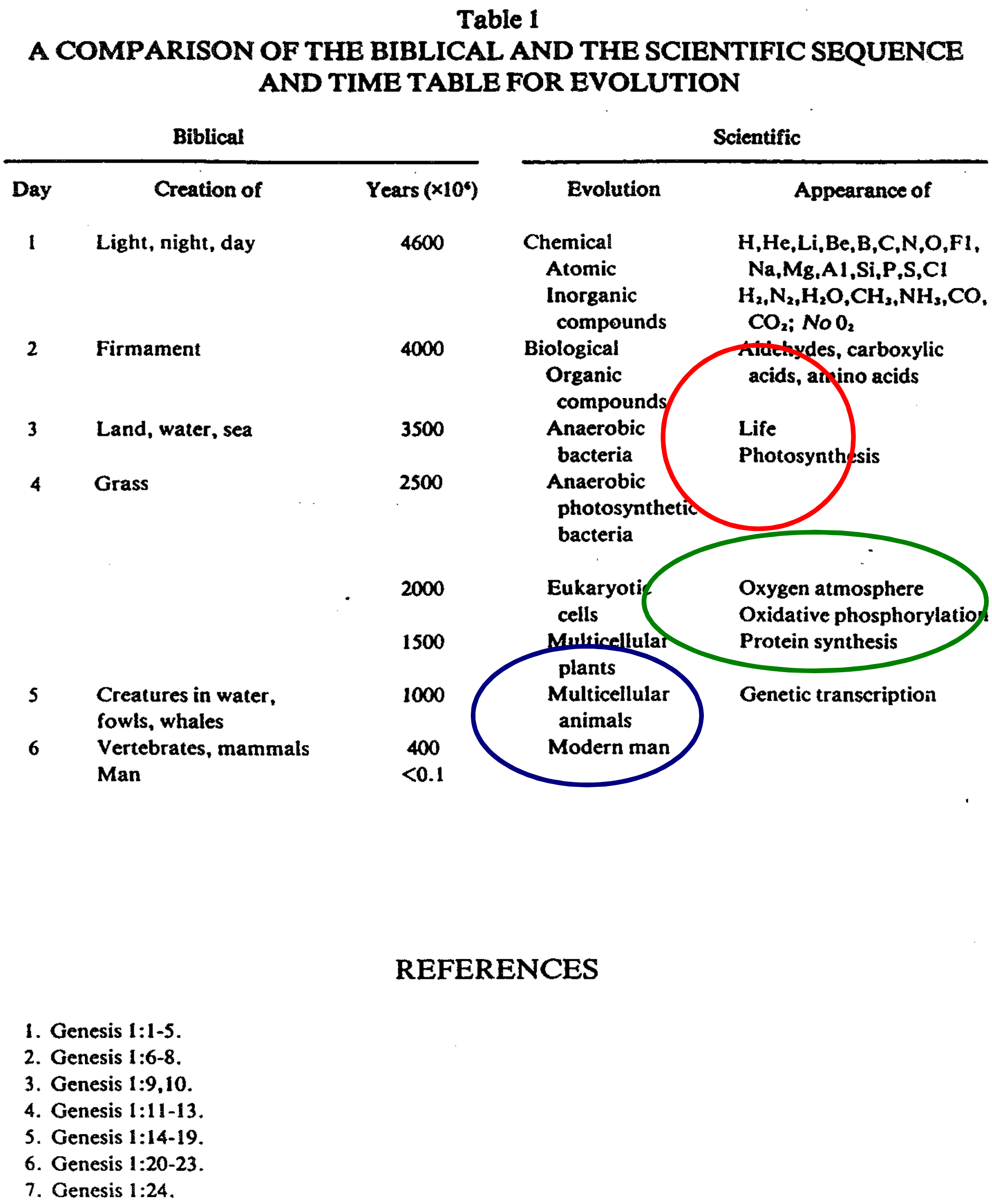


Table 1

A COMPARISON OF THE BIBLICAL AND THE SCIENTIFIC SEQUENCE AND TIME TABLE FOR EVOLUTION

Biblical			Scientific	
Day	Creation of	Years (×10^6)	Evolution	Appearance of
1	Light, night, day	4600	Chemical Atomic Inorganic compounds	H,He,Li,Be,B,C,N,O,Fl, Na,Mg,Al,Si,P,S,Cl H_2,N_2,H_2O,CH_3,NH_3,CO, CO_2; *No* 0_2
2	Firmament	4000	Biological Organic compounds	Aldehydes, carboxylic acids, amino acids
3	Land, water, sea	3500	Anaerobic bacteria	Life Photosynthesis
4	Grass	2500	Anaerobic photosynthetic bacteria	
		2000	Eukaryotic cells	Oxygen atmosphere Oxidative phosphorylation
		1500	Multicellular plants	Protein synthesis
5	Creatures in water, fowls, whales	1000	Multicellular animals	Genetic transcription
6	Vertebrates, mammals	400	Modern man	
	Man	<0.1		

REFERENCES

1. Genesis 1:1-5.
2. Genesis 1:6-8.
3. Genesis 1:9,10.
4. Genesis 1:11-13.
5. Genesis 1:14-19.
6. Genesis 1:20-23.
7. Genesis 1:24.

The Periodic Table

3092

Parts of the Periodic Table we must learn

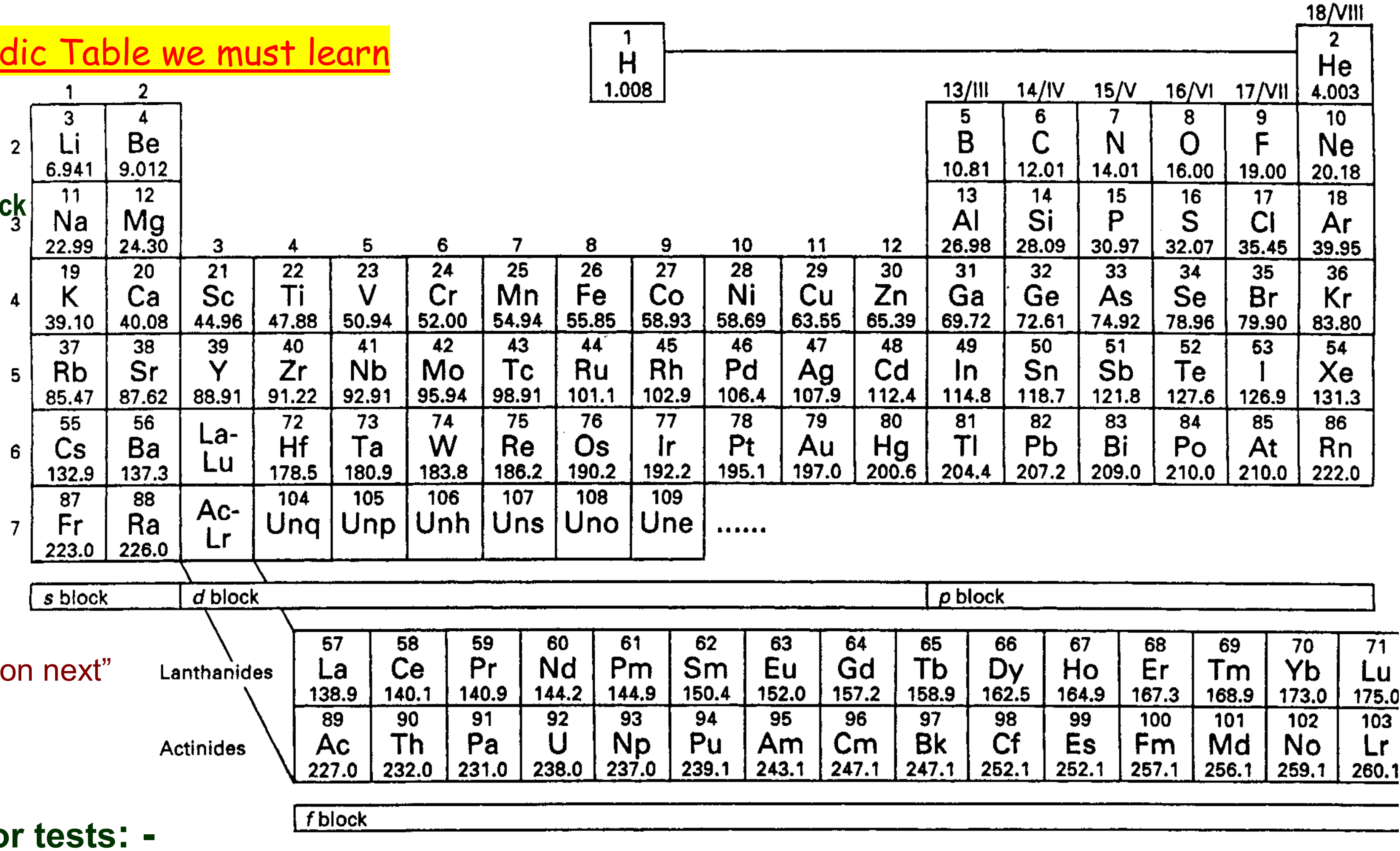
1. Gp 1 & 2
2. Selected Row 4 d-block Elements

Note key metals

3. Essential
4. In medicine
5. Toxic

-see “Key points section next”

6. Need to learn for tests: -



Period	1	2	3	4	5	6	7	8	9	10	11	12	13/III	14/IV	15/V	16/VI	17/VII	18/VIII
	1 H 1.008																	2 He 4.003
2	3 Li 6.941	4 Be 9.012											5 B 10.81	6 C 12.01	7 N 14.01	8 O 16.00	9 F 19.00	10 Ne 20.18
3	11 Na 22.99	12 Mg 24.30											13 Al 26.98	14 Si 28.09	15 P 30.97	16 S 32.07	17 Cl 35.45	18 Ar 39.95
4	19 K 39.10	20 Ca 40.08	21 Sc 44.96	22 Ti 47.88	23 V 50.94	24 Cr 52.00	25 Mn 54.94	26 Fe 55.85	27 Co 58.93	28 Ni 58.69	29 Cu 63.55	30 Zn 65.39	31 Ga 69.72	32 Ge 72.61	33 As 74.92	34 Se 78.96	35 Br 79.90	36 Kr 83.80
5	37 Rb 85.47	38 Sr 87.62	39 Y 88.91	40 Zr 91.22	41 Nb 92.91	42 Mo 95.94	43 Tc 98.91	44 Ru 101.1	45 Rh 102.9	46 Pd 106.4	47 Ag 107.9	48 Cd 112.4	49 In 114.8	50 Sn 118.7	51 Sb 121.8	52 Te 127.6	53 I 126.9	54 Xe 131.3
6	55 Cs 132.9	56 Ba 137.3	La- Lu	72 Hf 178.5	73 Ta 180.9	74 W 183.8	75 Re 186.2	76 Os 190.2	77 Ir 192.2	78 Pt 195.1	79 Au 197.0	80 Hg 200.6	81 Tl 204.4	82 Pb 207.2	83 Bi 209.0	84 Po 210.0	85 At 210.0	86 Rn 222.0
7	87 Fr 223.0	88 Ra 226.0	Ac- Lr	104 Unq	105 Unp	106 Unh	107 Uns	108 Uno	109 Une	……								

s block | *d* block | *p* block

Lanthanides	57 La 138.9	58 Ce 140.1	59 Pr 140.9	60 Nd 144.2	61 Pm 144.9	62 Sm 150.4	63 Eu 152.0	64 Gd 157.2	65 Tb 158.9	66 Dy 162.5	67 Ho 164.9	68 Er 167.3	69 Tm 168.9	70 Yb 173.0	71 Lu 175.0
Actinides	89 Ac 227.0	90 Th 232.0	91 Pa 231.0	92 U 238.0	93 Np 237.0	94 Pu 239.1	95 Am 243.1	96 Cm 247.1	97 Bk 247.1	98 Cf 252.1	99 Es 252.1	100 Fm 257.1	101 Md 256.1	102 No 259.1	103 Lr 260.1

f block

Expectations from this unit	**Where and how**
Know that very many metals are present in natural organisms – with amounts that vary by 10,000’s (in a human 44 kg Ca to 2 mg Se)	Opening lecture And first chapters of each reference book in the library
Understand the difference between ‘what’s found when you grind up an organism’ and ‘what’s essential nutrition for an organism’s well-being’	First few pages and discussions from the lecture and by reading the early pages on the reference books – could use the Internet too
Know that there are essential metals and really toxic metals	Examples?
Know your way round the Periodic Table – which metals are – macro levels (>5 gms) which are μ levels, which are ultra-trace – mg levels	Need to remember the Periodic Table (exact elements will be provided by Dr Stillman) no Periodic Table in Tests.
Know that metals are absorbed from foods	Know at least one food per metal
Know that evolution resulted in iron being used in many proteins – evn though today that would be unlikely to happen	Opening – means iron in our diet is very important
Know the difference between ‘free’ and ‘coordinated’ metal ions	Be able to describe what’s shown on pages 19 or so
Know the Bertrand Diagram as a tool	
Know some examples of metals used therapeutically	May need to do a search for extra examples.

Key points from this unit

1	Many Essential Metals; H, Na, K, Mg, Ca, Cr, Mn, Fe, Co, Ni, Cu, Zn, and a many others – some we don't know about like Cd - over 35 different elements in the typical organism. Metals come from different parts of the Periodic Table – the region of the Periodic Table controls the chemical properties – identify typical chemistry from Groups 1&2; 16 &17; 2-12.
2	Both essential and toxic? Almost all for sure, but 'strangely' at low levels, Cr, Co, Cu, Cd, As, Se and others.
3	Therapeutic – Pt, Au, Ag, Li, Cu, Fe, Bi
4	Toxic for sure: Cd, Hg, As, Pb, and many others, especially at high concentrations.
5	Metals are attached to ligands most of the time. Which are typical atoms for good ligands? Why are they good? What is the key requirement? Which molecules would you find those atoms in in biological systems? Some metals are not bound all the time – which metals are they? Some metals – a few – exist as the ions under certain conditions and are bound tightly to ligands to work – which metals are they?
Study questions from the lectures to date	
Lectures	What do the alkali metals do? What does Fe do?Mg is different in plants and mammals, identify a key difference in chemistry of Mg^{2+} in mammals and plants.
Key questions to	Ch 1 in KSK – 'what do we mean by the interface between inorganic chemistry and biology?'. Give a definition of bioinorganic chemistry

consider on this unit	Give two examples What is not an example taken from the real world Separate the concentration of metals into bulk, trace and ultra trace Name one metal from each class Approximate limits on each class? In a 70 kg human: 10’s-1000’s g; >20 mg; <20 mg Is the role of each metal now defined? Coordination means shape – that comes from the ligands attached – name 3 ligand molecules identifying the attached atom (see below as well) In figure3081 here p 10 approx we see that Fe is high in the crust, and quite high in man, butFe is very low in seawater today. Explain this. How did mammals evolve to use Fe then? Account for the properties of the atmosphere. Reducing then, oxidizing now. Account for how the pH affected incorporation of elements like Mo, Al and Ti Identify 5 foods containing different metals using the textbook or the Internet. How is vitB12 connected with the toxicity of mercury? Glutamate mutase - as the example of B12 action What is a vitamin? Why do we need them? We are what we eat – Identify the food source, bodily functions; deficiency symptoms for: Ca, Cr, Cu, iodine, Fe, Mg, K, Na, Zn Which metals are unexpected? Search the Internet for each metal AND one specific function – metal & molecule &

activity

Coordination of metals

Identify 3 different ways metals are attached to ligands in biological materials

Explain the dose-response curve commonly called the Bertrand diagram

Sketch the curve for mercury; sketch for Zn

Periodic Table – know the 4 major alkali metal and alkaline earth metals – d block metals –know 3 key and essential –

Know 2 metals used in medicine

Know 4 really toxic metals

Some useful definitions - A **nutrient** is a chemical that an organism needs to live and grow or a substance used in an organism's metabolism which must be taken in from its environment.[1]
organic - fats, sugars, proteins, amino acids, vitamins
inorganic- minerals

Macronutrients - needed in large amounts - are defined in several different ways.

- The chemical elements humans consume in the largest quantities these are - are carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulfur. CHNOPS
- The classes of chemical compounds humans consume in the

Together, the "Big Six" are the elemental **macronutrients** for all organisms CHNOPS

- macrominerals.

Calcium, salt (sodium and chloride), magnesium, and potassium (along with phosphorus and sulfur) are sometimes added to the list of macronutrients because they are required in large quantities compared to other vitamins and minerals.

largest quantities and which provide bulk energy are carbohydrates, proteins, and fats. ▪ ▪ *Water and atmospheric oxygen also must be consumed in large quantities, but are not always considered "food" or "nutrients".* ▪	The remaining vitamins, minerals, fats or elements, are called **micronutrients** because there required in relatively small quantities. micronutrients Silicon, chloride, sodium, copper, zinc, and molybdenum are sometimes also included, but are in other cases considered .[10]

Now to Inorganic chemistry. This will also span a number of lectures.

B) Important chemistry and special inorganic chemistry for bioinorganic chemistry

a. Periodic table
b. Elements, transition metals, trends, electronic configurations, d orbitals
c. Special molecules that bind metals
    a. Ligands – special features of ligands
    b. Hard and Soft metals and ligands
    c. Shapes of complexes
d. Kinetics – 1st order reactions – ½ lives – enzyme kinetics
e. Metal-Ligand complex formation
    a. Equilibrium constants

End ✓
2017
Jan
19

KSK p 14 onwards

BioInorganic Chemistry
Chemistry 3391B

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marked up
(2017) pdf
Feb 7
w/

Instructor: Martin Stillman ChB064
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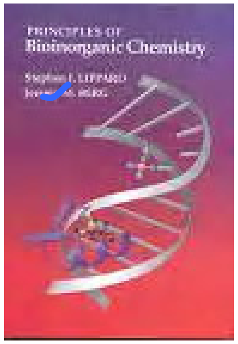
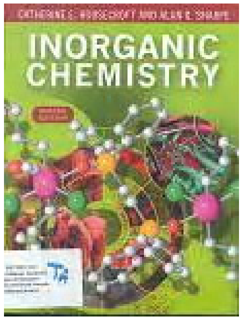
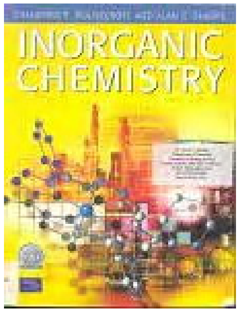
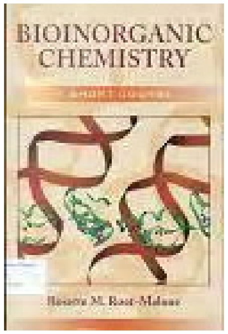
B) Important chemistry and special inorganic chemistry for bioinorganic chemistry

1. Periodic table
    a. Elements, transition metals, trends, electronic configurations, d orbitals
    b. Hard and Soft metals and Ligands
    c. Sizes of cations, atoms, anions; size to charge ratio
2. Metal-Ligand complex formation
    a. Special molecules that bind metals
        1. Ligands – special features of ligands
        2. Shapes of complexes
    b. Equilibrium constants
        1. K_F
        2. Chelate effect
        3. K's for multiple Ligands
        4. pK_a









Recommended text Books

Principles of Bioinorganic chemistry by Lippard & Berg. TAYSTK QU 130.L765 1994 (On heavy demand (2-hour loan) at the Taylor Library and in the book store.)

**Bioinorganic chemistry: a short course by Roat-Malone. QU130.R628b (On heavy demand (2-hour loan) at the Taylor Library and in the book store.)

Bioinorganic chemistry: inorganic elements in the chemistry of life: an introduction and guide by Kaim and Schwederski. (On heavy demand (2-hour loan) at the Taylor Library.)
The biological chemistry of the elements: the inorganic chemistry of life by da Silva and Williams. QU4.S586b 2001 (On heavy demand (1-day loan) at the Taylor Library)

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To start then

1. Periodic table
    i. Elements, transition metals, trends, electronic configurations, d orbitals
    ii. Hard and Soft metals and ligands
    iii. Sizes of cations, atoms, anions; size to charge ratio

Summary : This section provides the background necessary to understand the following scenarios:

1. Zn exists as the 2+ cation only and binds to sulfur in cysteine as well as to nitrogen in histidine but Na exists only as the 1+ cation and never binds to cysteines, rather preferentially to oxygen in water, and even better, to oxygen in carboxylic acids, the O^-.
2. The electronic configuration of each element and its place in the Periodic Table controls its chemistry.
3. For metals in Groups 3-12 (V – Zn) the key to the chemical properties is the arrangement of the 5 3d orbitals** and the electron distribution in the d-orbitals.
4. Equilibrium is a thermodynamic property that tells us energetically which way the reaction will go but not how fast.
5. The chelate effect is very important as biological reactions benefit from the enhancement in binding constant. Reaction rates tell us how fast the reaction takes place.

**By "arrangement", I mean the energy of each of the 5 3d orbitals when the metal is part of a complex – see slide 41.

L-B	R-M	K-S	In Housecroft 2nd ed.	Problems to do
1-2			See ch. 1, p 20-21; Ch. 20, p 557-564.	If blank – see later

3094b

The Periodic Table…

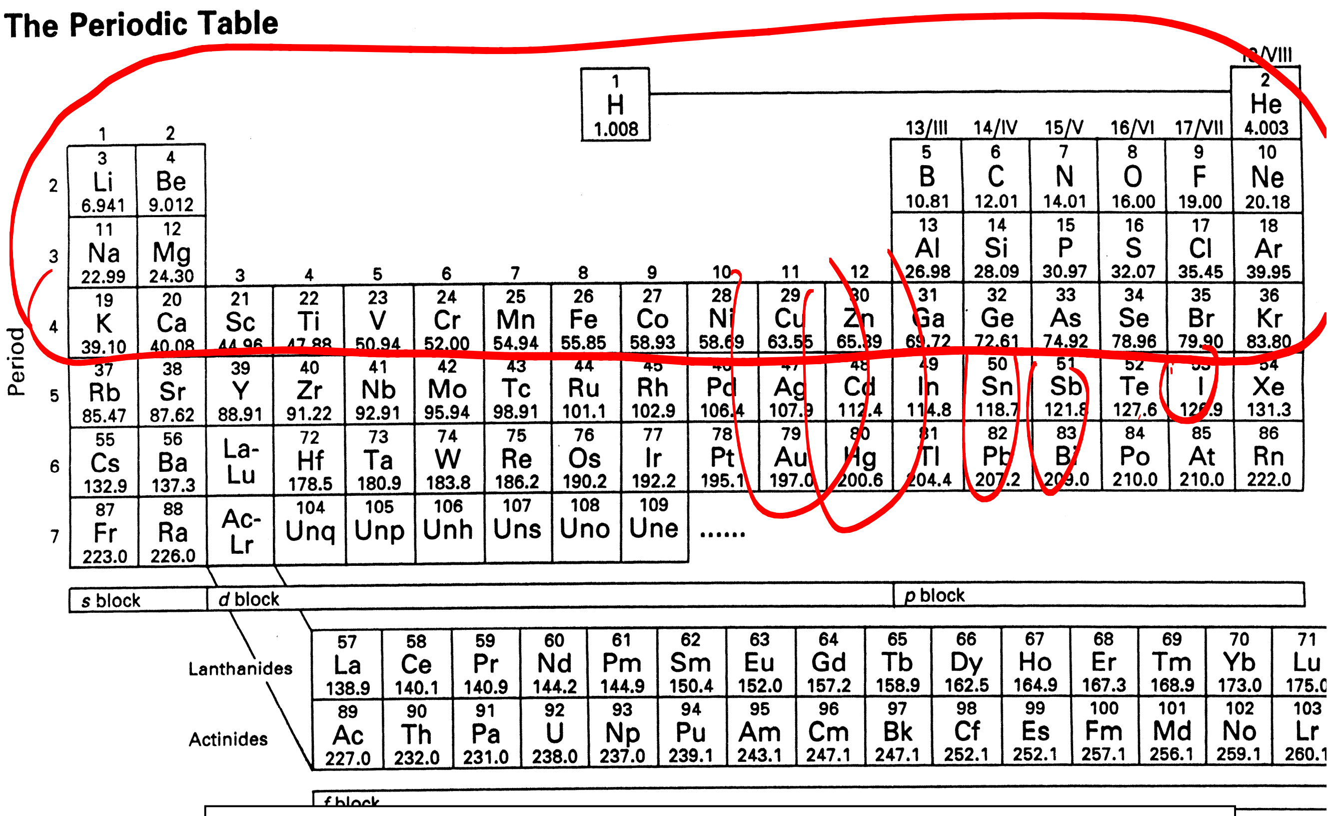
1. We know about Rows and Columns
2. Rows: Periods – generally the only link is the same (s, p) or 1 less (d) valence shell is being filled – so these elements are of similar size (always decreasing) BUT their properties are completely different.
3. The columns indicate the Atomic Orbital (AO) being filled 1 & 2 –s; 3-12 (d) (or (f)); 13-18 p
4. GROUPS – have numbers & names

Alkali metals (1) Alkaline earths (2)
Chalcogens (16), Halogens (17) (18) Rare gases

All MAIN groups (13-18)

8. Groups 3-12 –d-block elements called either Transition Metals or d-block metals (dbMs) – see →
9. Major groups we will study (learn) 1, 2, 12, 17 + all the others see below…

So where are our key metals? Next slide



→ Why not all called Transition Metals? Well, the definition requires at least 1 d-electron. So, many oxidation states (which ones?   ) and Zn^{2+} don't fit. D-block metal (dbM) includes all elements groups 3-12.

L-B	R-M	K-S	Problems to do
1-2			Check – Housecroft & Sharpe Inorganic Chemistry 2nd Ed – p 20 -

These are the metals that are found throughout biology and for which we know the oxidation state and some of the complexes that form.

For a metal complex, we need to know:

1) The oxidation state of the metal in the complex
2) The electronic configuration of this oxidation state
3) The electron distribution if this a dbM – we need to know which 3d orbitals the electrons occupy – to do this we need to know:
4) The 3d splitting pattern for that geometry
5) The ligand field strength(s)* of the ligands
6) Determine whether the electrons are spin parallel or paired up (high or low spin)

*essentially the electron donor strength

Hard/ Int/Soft? Complete later	Preference for ligand donor group?	M	+1	+2	+3	+4	Example of molecules in biology	Example species where this molecule is found
		Na	+1				Nerves all cell membranes	all arganisms
		Mg		+2			Chlorophyll; ATP activation	Plants and all organisms
		K	+1				Nerves – cell membranes	All organisms
		Ca		+2			Muscle action – bone formation – shell formation	
		Sc						
		Ti						
		V		+2				
		Cr			+3		+6 – highly toxic +3 insulin production	humans
		Mn		+2				
		Fe		+2	+3	+4	Hemoglobin – myoglobin; +3 and + 4 catalase	mammals
		Co	+1	+2	+3		Vit B12 (CN^-)	All mammals
		Ni		+2				
		Cu	+1	+2			Hemocyanin – superoxide dismutase ($O_2^- \rightarrow H_2O_2$) Cytochrome oxidase	Invertebrates – lobsters, crabs – blue blood; mammals
		Zn		+2			Carbonic anhydrase (1 Zn per molecule)	mammals 
		Cd		+2			+2 – toxic	
		Hg	0 and +1	+2			0 & +1 & +2 and methylated (CH_3Hg^+) – all toxic – worst is methylHg$^+$	
		Pb		+2		+4	+2 & +4 – both toxic	
		As			+3		+3 (& +5) – toxic	

Comparison of cations and anions

We can identify the biologically important elements from Group 1 and 2 , dBM and Group 13, 14, 16 and 17.

The size to charge ratio is important in biological coordination chemistry

Biological ligands recognise metals often by the charge/size ratio alone

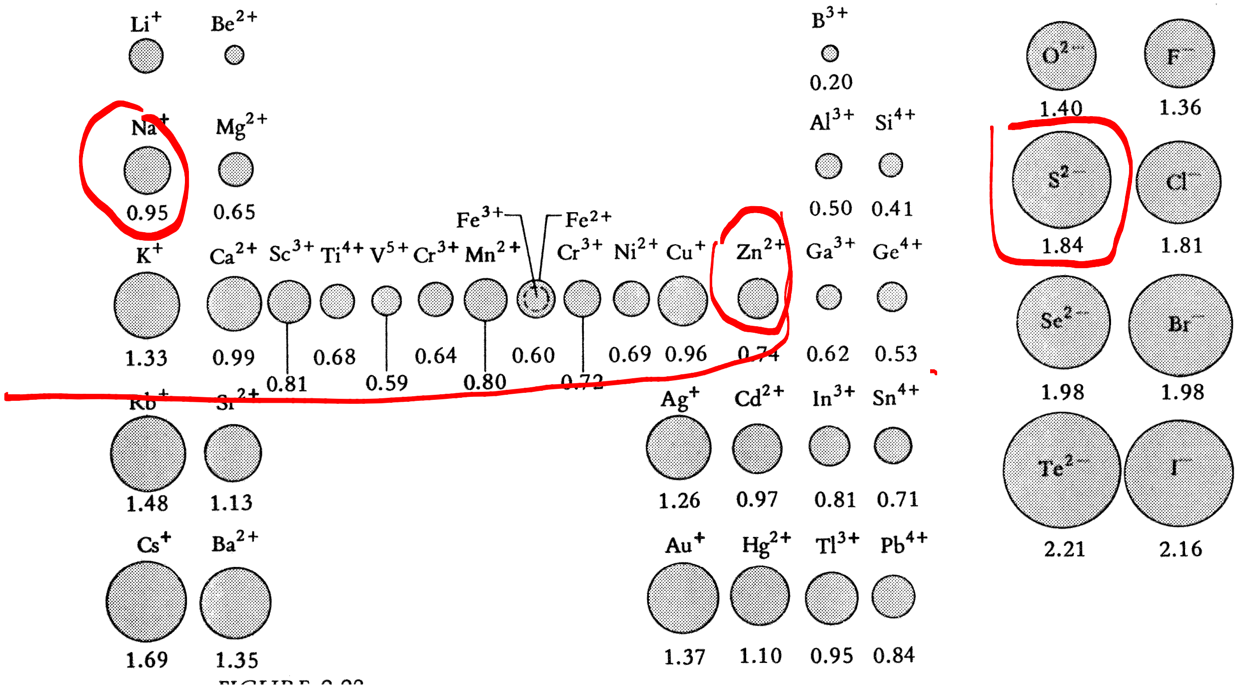
Trends:

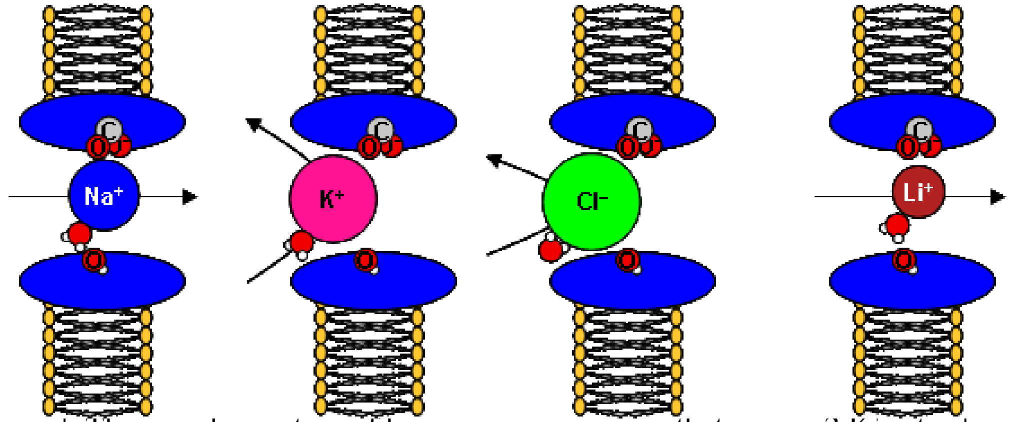
1. Down the groups – always larger whether neutral, cation or anion because of the extra protns and neutrons and core electrons.
2. Across rows: different trends not so easy – track the 1st IE - high IE=smaller.
3. The greater the positive charge = smaller; negative charge = larger.
4. So Ca^{2+} is smaller than ...... K^+
5. And S^{2-} is larger than .... O^{2-}
6. BUT d-block metals (dBM) all about the same.

This fig also emphasizes that isomorphous replacement can take place – substitute one cation for a cation of the same size – Pb^{2+} for Ca^{2+}.

Needs **hard-soft** rules followed though. So less likely to substitute Cd^{2+} for Ca^{2+} - why not? (See below)

Soft Hard





This is a description of how an enzyme pump that pumps 2 K^+ into a cell and pumps 3 Na^+ out of a cell works. This is a 'passive' mechanism. We will see more complex mechanism in the Biology unit (section 3). See also the cyclic polyethers and the antibiotics – valinomycin as synthetic examples of ion selectivity based on size.

Special molecules that bind metals ☐

Ligands – special features of ligands

1. Control the function of the metal
2. Change the shapes of complexes Oh Td
3. There is an effect of shape on the energies of 3d orbitals (dbM's) = = ≡ =
4. Equilibium reactions – the equilibrium constant, $K_{\cancel{s}}$ F
5.

Ligands – special features of ligands

(i) Biologically important ligands

N- (as R_2N:) 3 NH_3

S- (as RS:R and RSH and RS⁻)

O- containing (as RC=O:, RO:R,

ROH, and esp RO⁻)

and also water

OK – let us look at a typical small complex

(ii) Chelating ligands used to detoxify metals

BAL - soft (S)

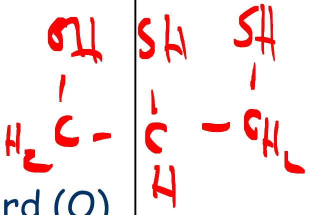
D-penicillamine – medium (N)

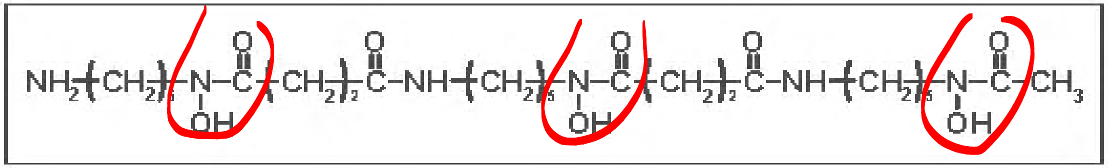
EDTA – hard (O)

Desferrioxamine B see LB p 13-14 – hard (O)

(All these structures coming up in 5 pages)

And note – later in "Chelators" in "Toxic Metals"



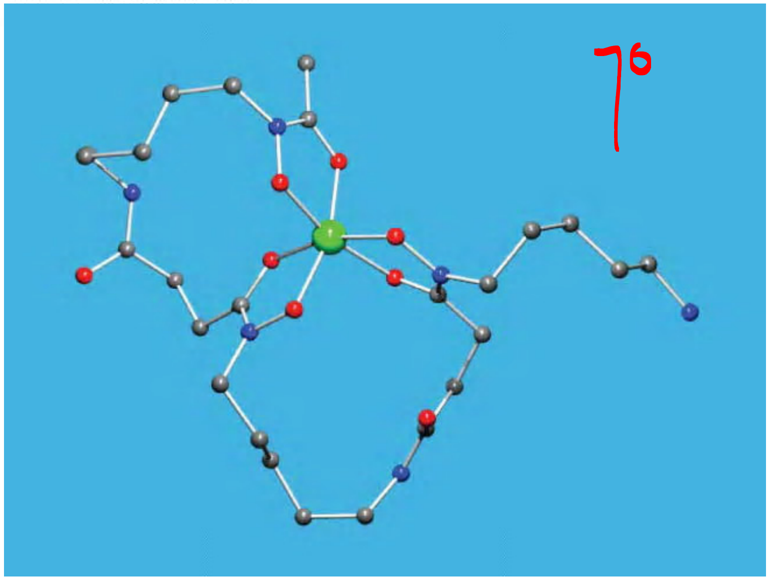


$$NH_2\text{-}(CH_2)_5\text{-}N(OH)\text{-}C(=O)\text{-}(CH_2)_2\text{-}C(=O)\text{-}NH\text{-}(CH_2)_5\text{-}N(OH)\text{-}C(=O)\text{-}(CH_2)_2\text{-}C(=O)\text{-}NH\text{-}(CH_2)_5\text{-}N(OH)\text{-}C(=O)\text{-}CH_3$$

Desferrioxamine

Desferrioxamine B complex with Fe(III) used to remove excess iron in humans – a hexadentate chelator

Hexadentate chelate



7^{6}

Are there any systematic ways of predicting which metal binds to which ligand?

In synthetic chemistry, it's not too easy - change the conditions and almost any ligand will coordinate any metal, BUT in biology, nature took the easy way out most of the time, or, why take chances and - take the easy route and react ligand sand metals that always react together...

Hard acid - Soft base theory

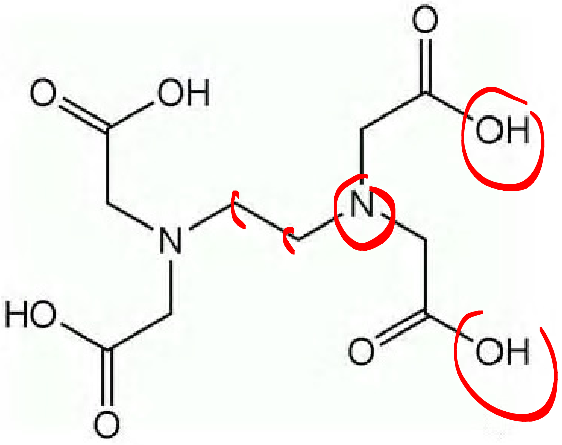
Hard acids react with hard bases and

Soft acids react with soft bases

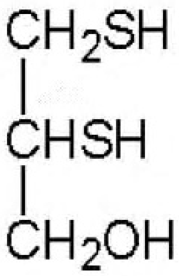
And intermediate acids and bases? Well, they react with everything.

Extremes - very hard, why?

Very soft, why?



$EDTAH_4$



BAL

3103

Hard-Soft Metals and Ligand atoms

1. Pearson Hard-Soft (Acid-Base) theory applied to metals and ligands – a critically important aspect of biological metal-based chemistry
2. Ca … Mg…
   Co… Cu ..
3. But, Cu^+ and Hg^{2+} are really soft
4. So bind preferentially with ?
5. Although the metals are the same in biology, the ligands include amino acid side groups – come back to here once we have covered the amino acid section and add in the amino acids that bind metals –
6. remembering that uncharged N is intermediate, so binds all metals.

Table 2. Classification of Hard and Soft Acceptors and Donors [3]

Hard	Acceptor Intermediate	Soft
H^+, Na^+, K^+, Be^{2+}, Mg^{2+}, Ca^{2+}, Mn^{2+}, Al^{3+}, Cr^{3+}, Co^{3+}, Fe^{3+}, As(III) As^{3+} (with RO^-)	Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}	Cu^+, Ag^+, Au^+, Tl^+, Hg^{2+}, CH_3Hg^+ As^{3+}(with RS^-) Cd^{2+}
	Donor Intermediate	Soft
H_2O, OH^-, F^-, Cl^-, PO_4^{3-}, SO_4^{2-}, CO_3^{2-}, O^{2-}	Br^-. NO_2^-, SO_3^{2-}	HS^-, S^{2-}, RS^-, CN^-, SCN^-, CO, R_2S, RSH Cys Met

becomes harder

d^{10}

2+

Fe^{2+} – bind to
O^-
N:
S

form covalent bonds

Soft when reacting metals – city

L-B	R-M	K-S	Problems to do
21-23; 24-25	Table 1.7, p 6	P 15; also 13-20 generally	Which metals do you predict will bind to metallothionein? See Fig 2.1 in L-B – why – search the web – what other metals bind to metallothionein??

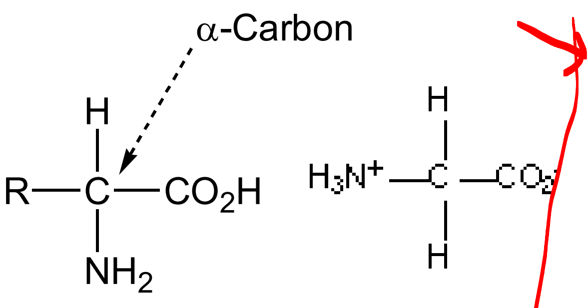
strong σ donor – also have some π overlap

Fe 2+

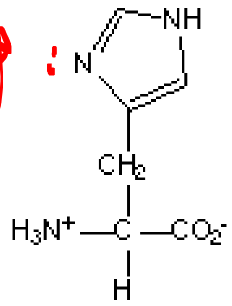
Biological Ligand molecules

Excellent source for information http://en.wikipedia.org/wiki/List_of_standard_amino_acids

We'll jump ahead by bringing in those amino acids likely to bind metals as well here.

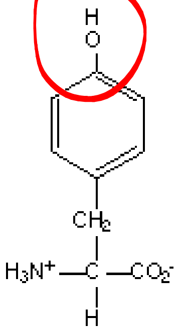


GLYCINE



HISTIDINE

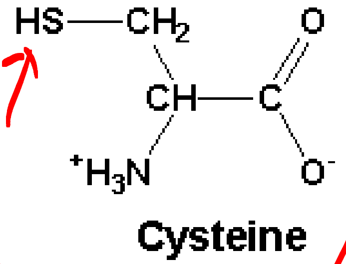
HIS - imidazole group N



TYROSINE

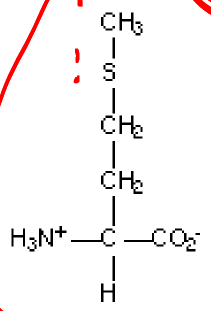
TYR O⁻

Fe 3+



CYSTEINE

CYS S



METHIONINE

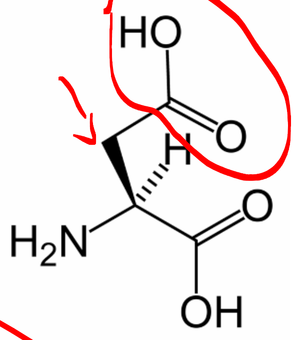
MET S

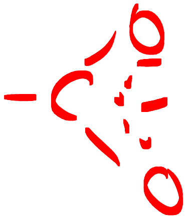
Oxygen from Asp – aspartic acid and

Which are the donor atoms?

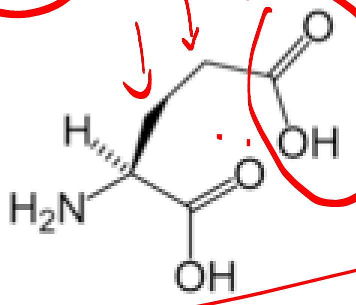
Hard, Int or Soft?

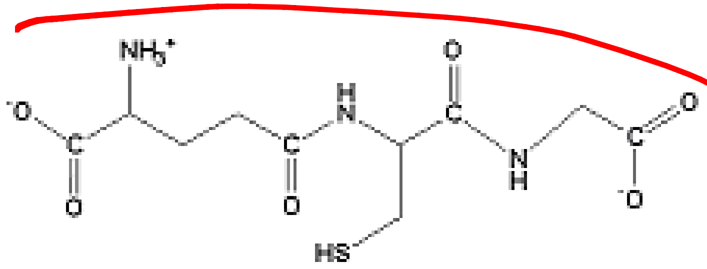
Then there are these biological ligands:





Glu, glutamic acid

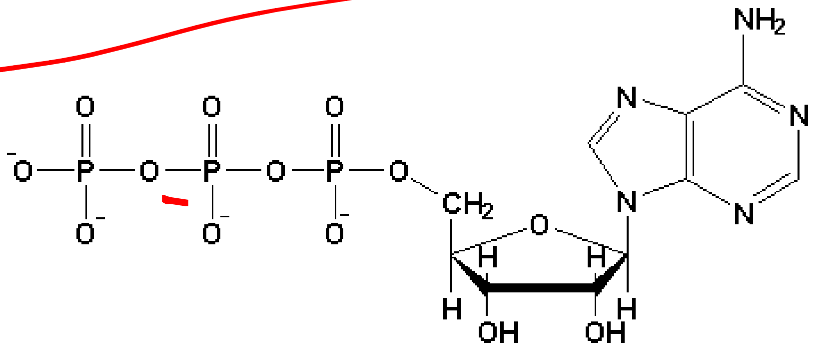




Glutathione

L-B	R-M	K-S	Problems to do
22 44; 46; 47		15-16; 16-38 everything about ligands,and metals, and rings; also 3d splitting	If blank – see later

Thr.



Adenosine triphosphate (ATP)

Structural form of the metal changes the function (from before)

1. Coordination by **ligands** – ligands are either neutral with nonbonding pairs (like NH_3) or anions like OH^- to stabilize the metal cation.

2. The more oxidized the metals, the more anionic the ligands have to be.

3. Biological LIGANDS – see after Hard-Soft slide – we must relate Hard-Soft character to the metal cation and the ligand

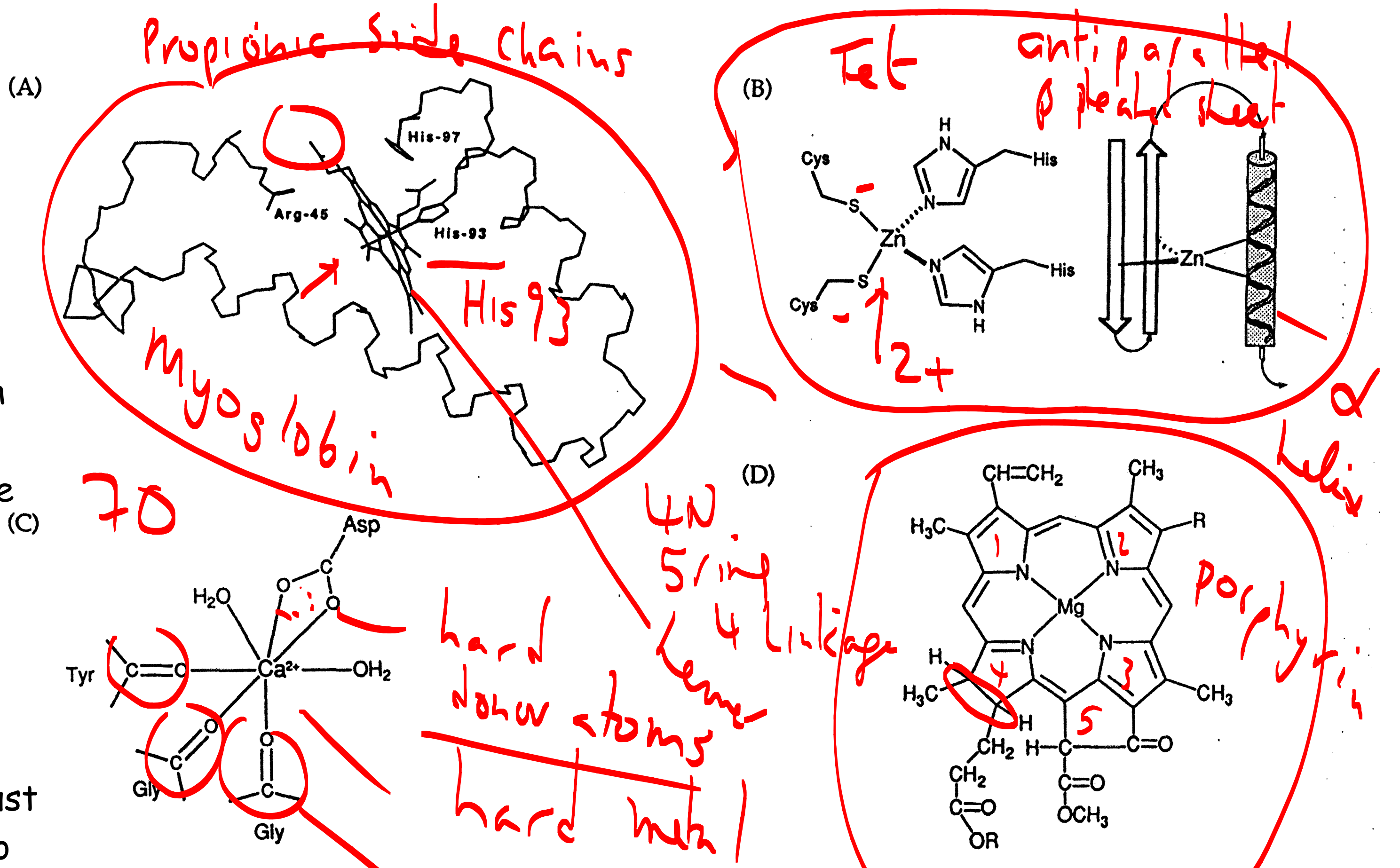


Figure 1.15 Coordination modes for metal binding to metalloproteins and peptides. (A) The heme prosthetic center and a portion of the backbone in myoglobin. (B) Bound Zn^{2+} in a zinc finger. On the right the portion of the protein backbone that forms the "finger" is traced. Figure 1.19 gives more details on such schematic diagrams. (C) The metal-binding domain of a Ca^{2+}-activated enzyme (phospholipase A_2) showing coordination of a chelating carboxylate, two water molecules, and three backbone carbonyls. (D) Chlorophyll from the light-harvesting complex of the photosynthetic reaction center.

What are the ligands – the atoms next to the metals in these examples? Write out the molecules without the metals in B, C and D. You'll need to check your biochemistry book for the amino acids – also coming in 3 lectures here.:

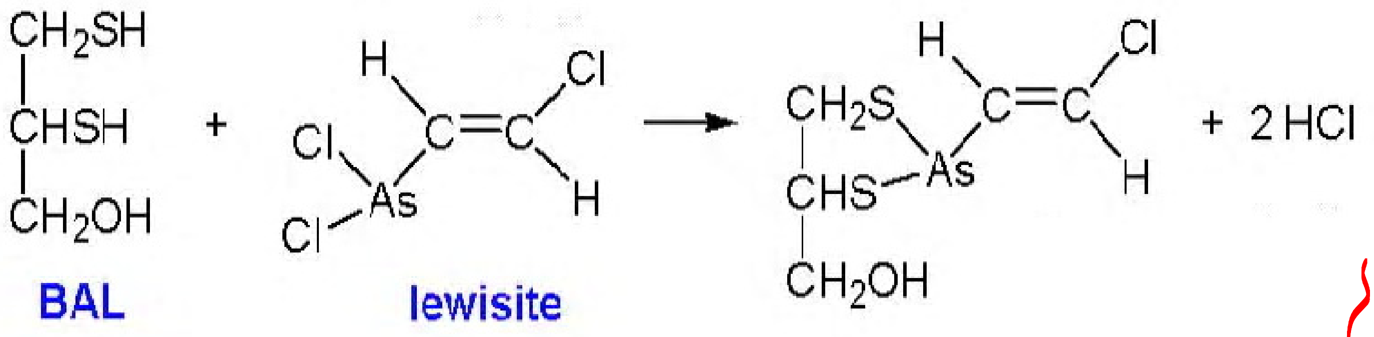
L-B	R-M	K-S	Problems to do

Rephil

$-NH-C-C^{:O}$

The role of the Ca^{2+} is to set up the "lock" shape.

So, how does BAL work with Lewisite?



Chelation in action .... Didentate attachment of the BAL to the As

oxidation numbers for all atoms

Nature 156, 616-619 (24 November 1945) | doi:10.1038/156616a0

British Anti-Lewisite (BAL)

R. A. PETERS , L. A. STOCKEN & R. H. S. THOMPSON

Abstract

IN the first fortnight of the War (1939) fundamental research was initiated in the Oxford Department of Biochemistry by Peters and carried out under his direction by a group of workers as an extra-mural research with the support of and for the Chemical Defence Research Department, Ministry of Supply; the object was to find antidotes for vesicants, both arsenical such as lewisite (CH.Cl: CH.As.Cl_2) and also those of the mustard gas type. In this brief review, the main facts are given about the discovery of the antidote to lewisite known as *BAL*, owing to its medical importance; more detailed papers based upon the original reports are being prepared. An attempt is made to include the more relevant work from elsewhere and also to focus the main stages in this discovery, as this may prove useful in planning future work of this type.

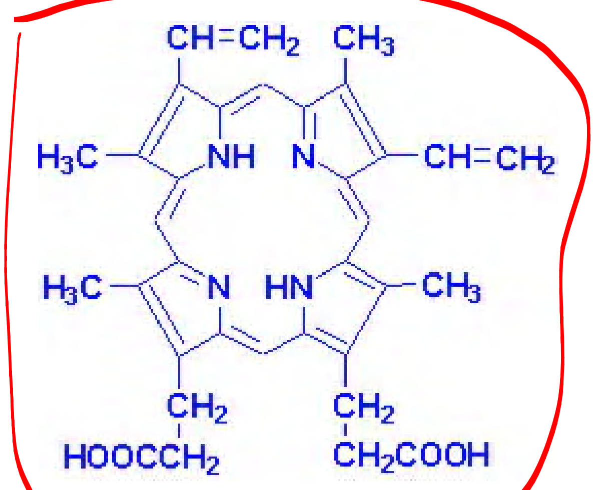
Some of the many different Porphyrin rings in biology - see LB 131

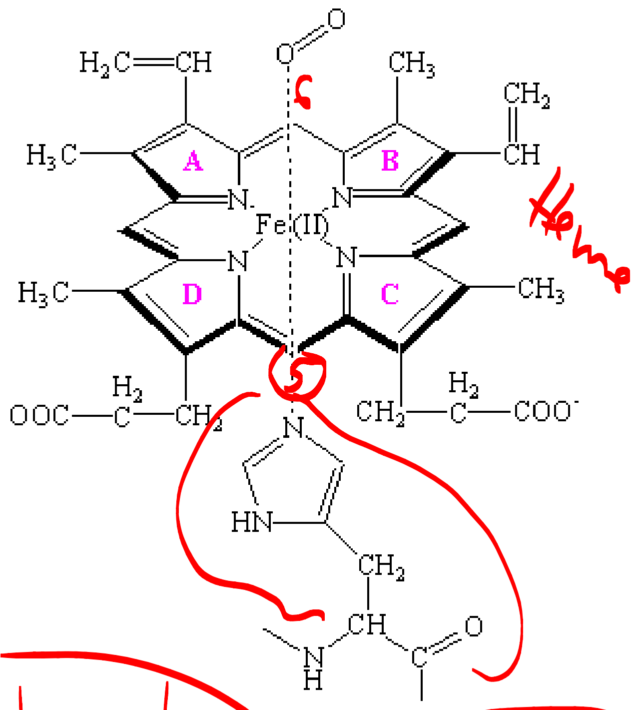
Heme= iron protoporphyrin IX freebase

protoporphyrin IX

-see next slide

how to memorize





Heme b

Cobalt Corrin

Vit B12

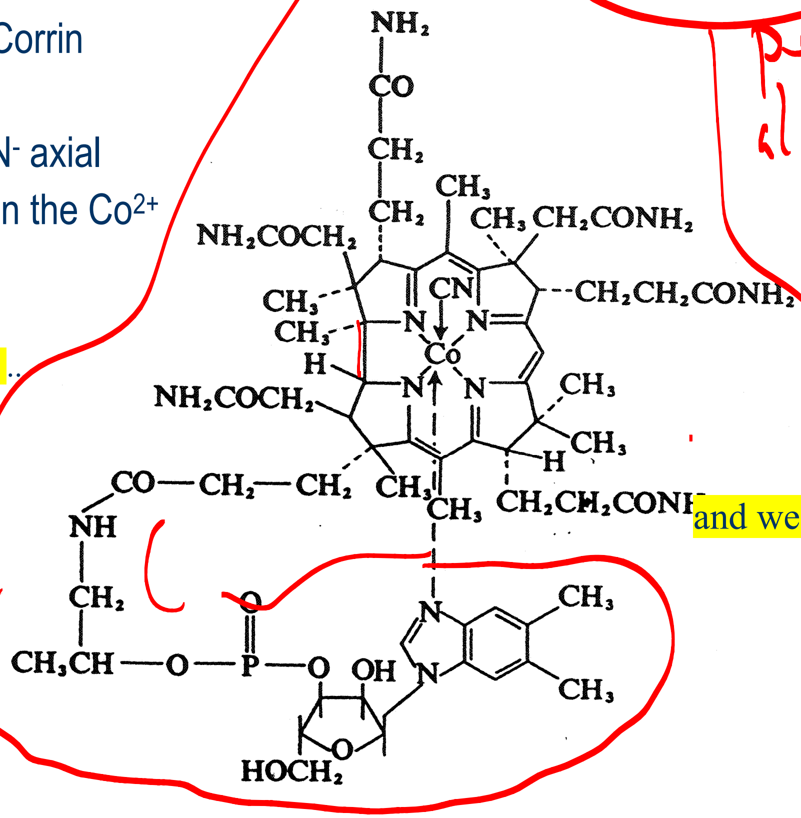
Note CN- axial ligand on the Co2+

4 N

4 rings

3 linkages

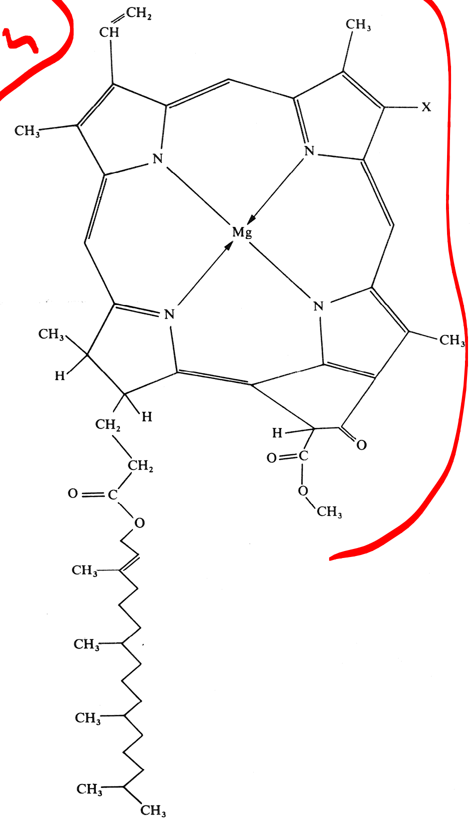
1150



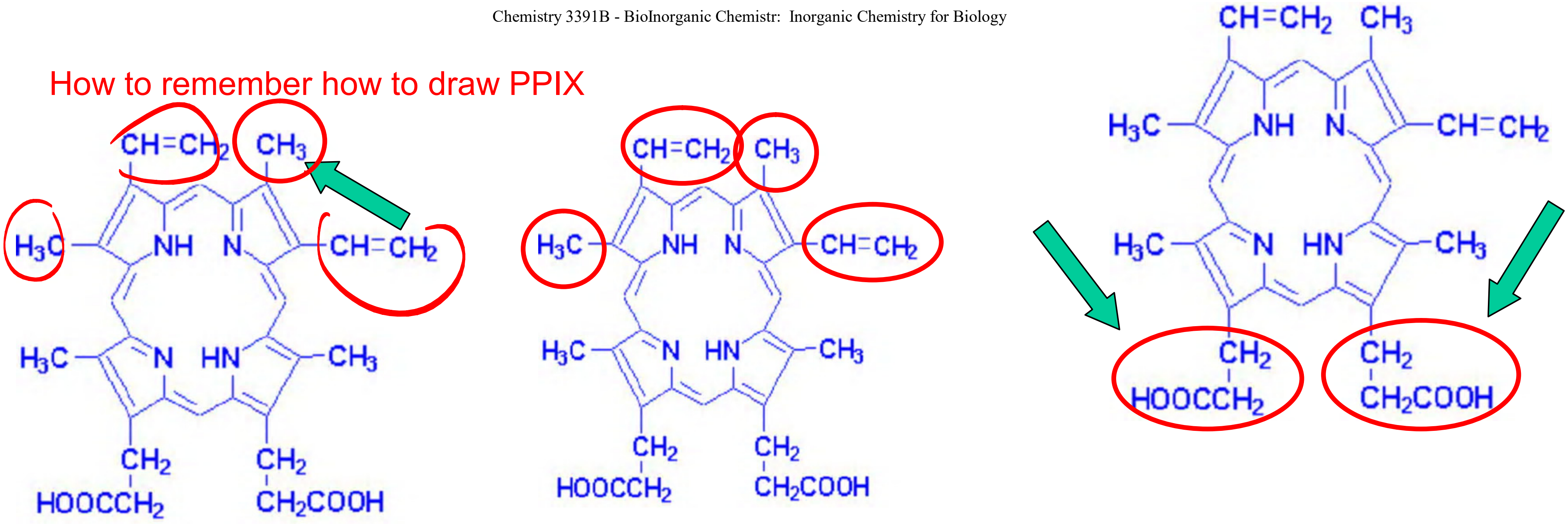
Peripheral decoration allows for electronic tuning of the metal oxidation states

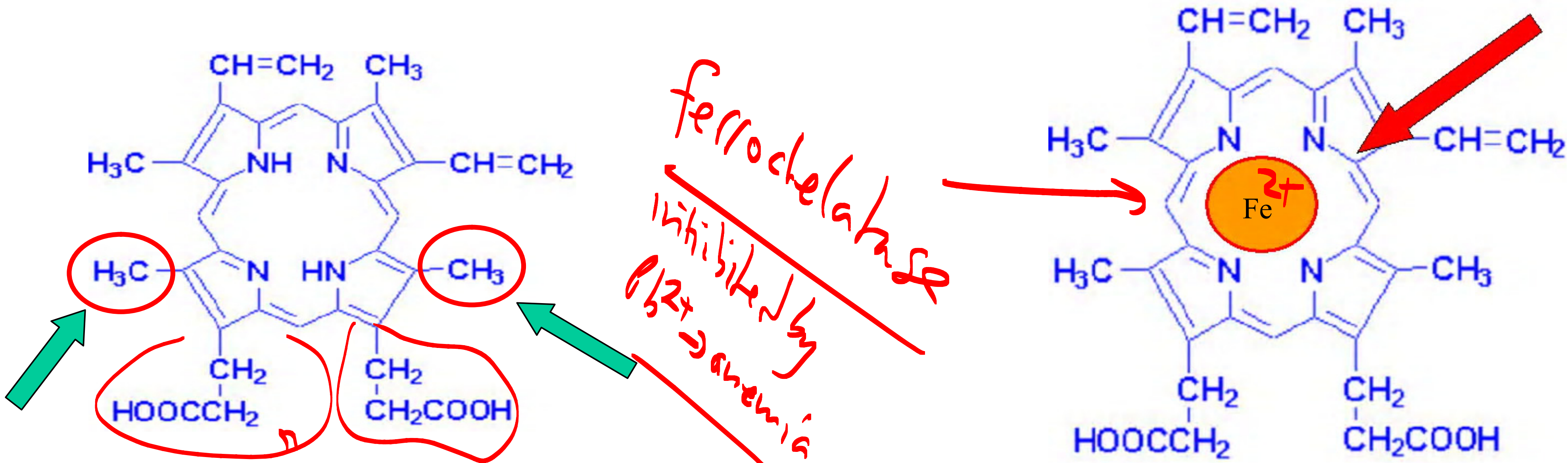
Chlorin in chlorophyll→

and we must draw what??



How to remember how to draw PPIX





ferrochelatase

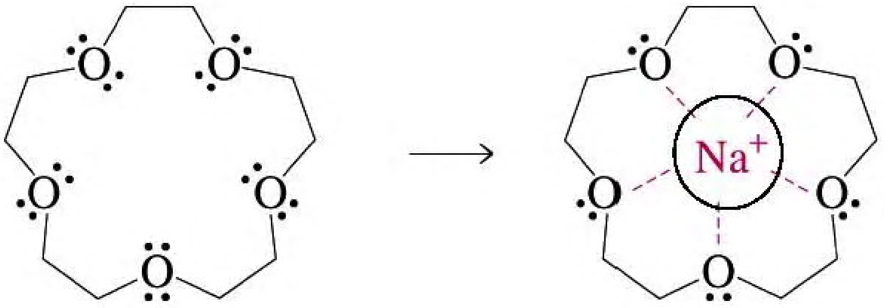
inhibited by Pb^{2+} → anemia

Iron protoporphyrin IX – usually called 'heme' – Fe can be 2+, 3+ or 4+
Key to heme proteins – see myoglobin, hemoglobin, catalase, and many others – variations in the peripheral groups are found in proteins like cytochrome c. Many here proteins use the imidazole nitrogen (HIS) for the 'proximal', 5th position amino acid.

heme c

How do cyclic polyethers "crown ethers" work?

Na^+
guest
Na^+ 1.80Å



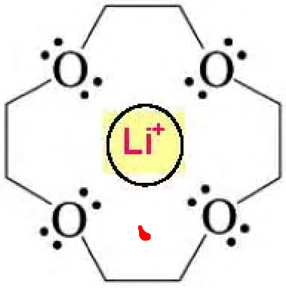
host
[15]-crown-5
cavity diameter = 1.7–2.2 Å

inclusion compound

50

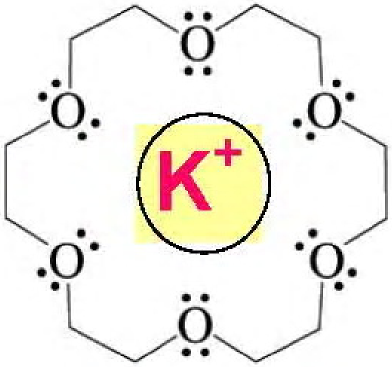
40 Li^+
50 Na^+
60 K^+

Li^+ 1.20Å



40

K^+ 2.66Å

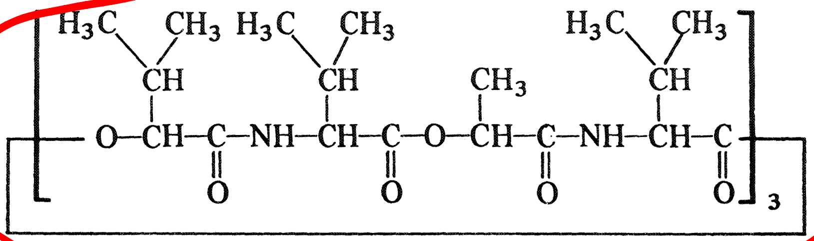


60

[12]-crown-4
cavity diameter = 1.2–1.5 Å

[18]-crown-6
cavity diameter = 2.6–3.2 Å

antibiotics that function to disrupt the membrane transport


$[-O-CH(CH(CH_3)_2)-C(=O)-NH-CH(CH(CH_3)_2)-C(=O)-O-CH(CH_3)-C(=O)-NH-CH(CH(CH_3)_2)-C(=O)-]_3$

Valinomycin

The ionic radii of the group I & II metals plus others like Al^{3+} can be selectively coordinated to the crown ether -

So in the previous page we see that the 15-crown-5 (a ring of 15 atoms with 5 oxygen) binds selectively Na^+ (but it will also bind K^+ but in competition the Na^+ will win)

The smaller cavity of 12-crown-4 means that Li^+ is selected with a larger K_F.

Special molecules that bind metals:

Shapes of complexes

Ca^{2+}

1. Forming complexes is the key to many biologically important reactions. *
2. In fact even metals not thought to form well-defined complexes (Group 1 & 2), preferring to exist as isolated ions, are always surrounded by water – a shell of 6 – 8 water molecues, and in their biological passage – these molecules are transported often into and then out of of cells, these transporters or pumps have tuned groups to bind to the metals – **hard metals so hard attaching atoms – a good guess would be?** O^- O:
3. Group 1 and 2 metals maintain osmotic pressure across membranes, this same atom is part of an enzyme molecule used to move these metals through a lipid bilayer that is the membrane.
4. On the other hand, the dBMs are always coordinated to something – being transported or functioning. The chemical nature of the attached ligands and the shape **control function.**
5. We are interested in:
    a. The possible shapes of complexes that form
    b. The atoms that bind the metals and the molecule that inludes those atoms – the ligands
    c. The effect this shape has on the atomic orbitals of the coordinated metal – most significantly, the effect on the 5 3d orbitals of the dBMs
    d. The binding constants, the K_F, showing especially the relative bind strengths. (In a competition, the metal with the greater K_F will win the ligand!)
    e. The form of the ligand depends on its state in acidic, neutral and basic conditions, this is controlled by pK_a.

Zn^{2+}
often
Tet.

Fe^{2+}
often
Oh

d6 2S+1 = multiplicity ⑤

Effect of ligand field strength on the splitting of the 3d orbitals.

Weak field ligands

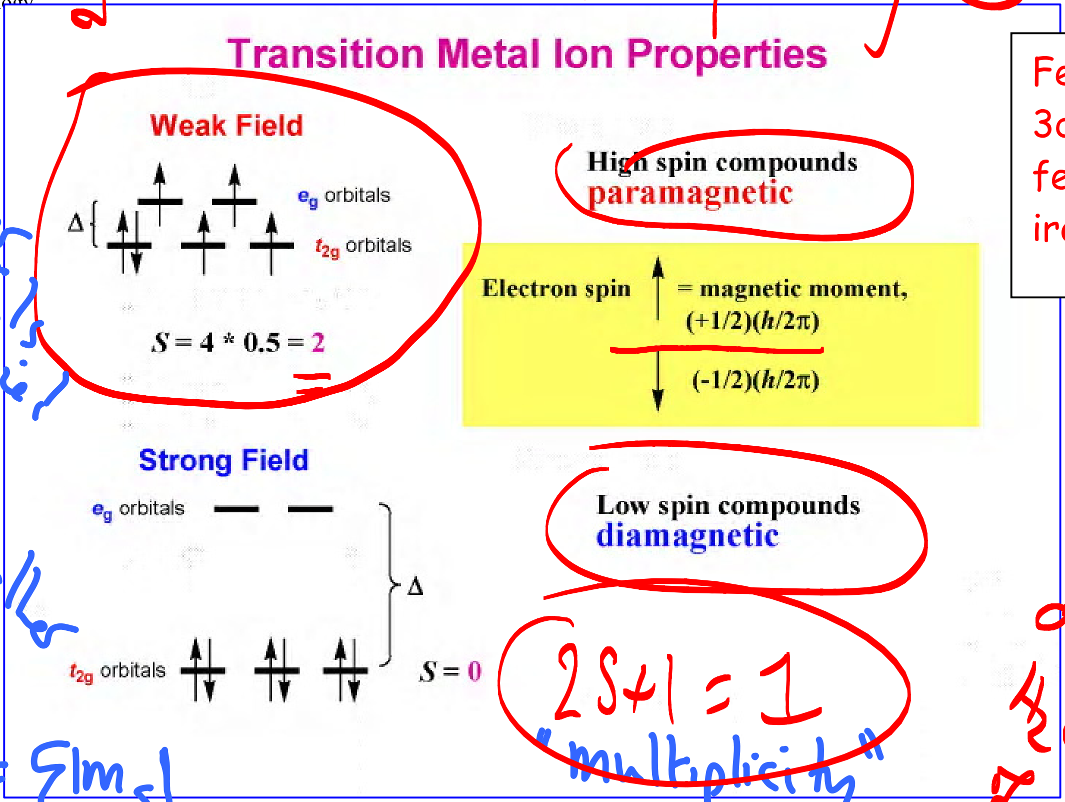
1. Strong field ligands
2. Why is this important for us to understand?
3. Myoglobin & Hemoglobin
4. There is a theoretical basis – not for us in detail – just 4 examples, “The Spectrochemical Series”
5. Weak field: fluoride, hydroxide – intermediate: water and oxides, RO^-,– Strong field: cyanide, carbon monoxide
6. (H&S p 559)
7. What does all this have to do with biological molecules? Well, the field strength controls the availability of electrons and whether the molecule is going to be DIAMAGNETIC OR PARAMAGNETIC – and we will see this in the colours. Paramagentic metals are a problem in biology = `RADICALS`.

more orbitals occupied

larger

smaller

$S = \Sigma m_s$



Transition Metal Ion Properties

Weak Field

e_g orbitals

t_{2g} orbitals

Δ

$S = 4 * 0.5 = 2$

High spin compounds
paramagnetic

Electron spin ↑ = magnetic moment, $(+1/2)(h/2\pi)$

↓ $(-1/2)(h/2\pi)$

Strong Field

e_g orbitals

t_{2g} orbitals

Δ

$S = 0$

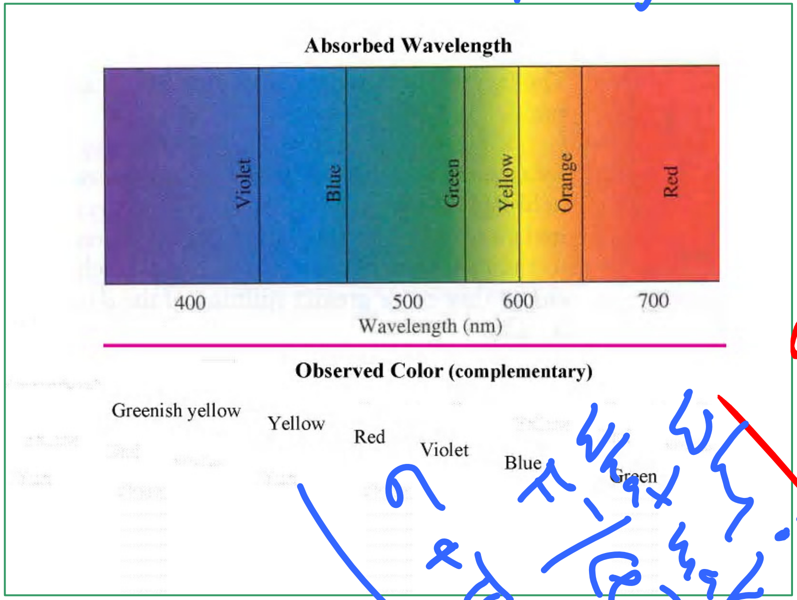
Low spin compounds
diamagnetic

2S+1 = 1
"multiplicity"

Fe^{2+}
$3d^6$
ferrous
iron

smaller

O_2 H_2O & NH_3
common in Nature
a/e similar
6 d [illegible]



σ & π ?

F⁻ / CO

What makes

Why?

L-B	R-M	K-S	Problems to do
288 - Hb			If blank – see later

Fe(III) has 5 3d electrons: $3d^5$ and is always paramagnetic whereas Fe(II) has 6 3d electrons and is only paramagentic when high spin. Intermediate spin is also possible – how? What is the value of S? (Found? In heme proteins – HRP and cyt c'?). Low spin Fe(II) is always diamagnetic (needs what type of axial ligand?)

For Fe(II) – add 1 electron! To make 6 here

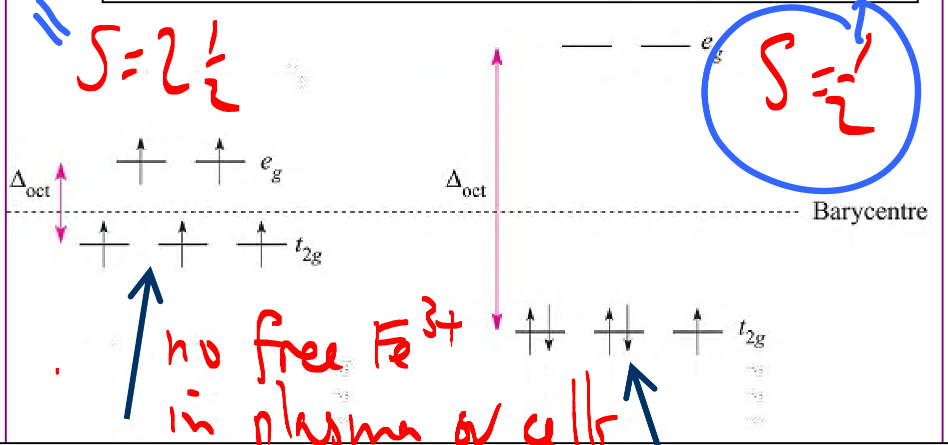
multiplicity = 2S+1 = ⑥ sextet

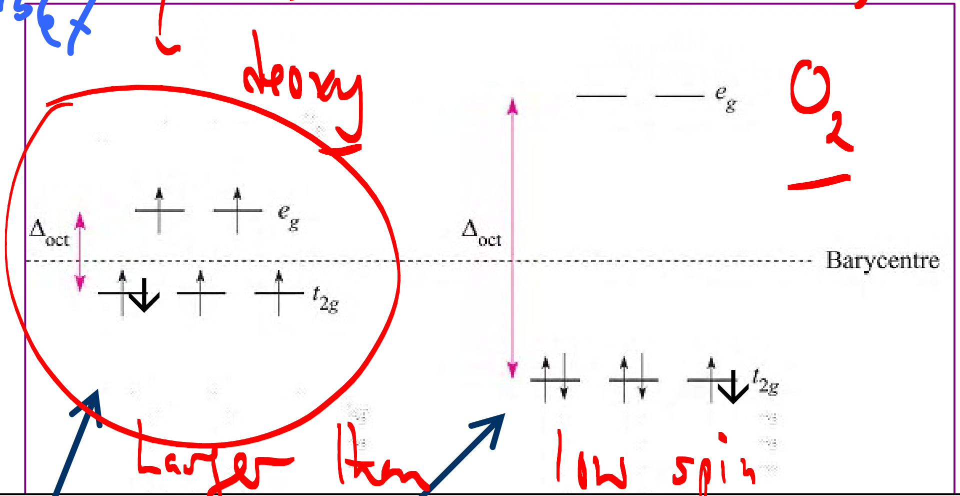
2S+1 =2 = doublet

also a radical

diamagnetic

This is Fe(III), only 5 3d electrons





Weak field (F^-, OH^-, intermediate H_2O and also 1 N from HIS plus H_2O)

Strong field CN^-

Weak field (2 x H_2O and also 1 N from HIS plus H_2O)

Strong field – dioxygen with HIS-N in 5th position and His-N plus CO

Fe(III) always unpaired electrons, therefore, always paramagnetic

Fe(II) only paramagnetic if high spin – low spin is diamagnetic

The Spectrochemical Series (for Chem 3391B)

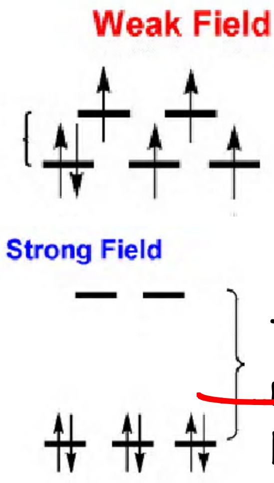
Weak F^- OH^- RO^- (RCOOH) Int H_2O NH_3 Strong PPIX-4N's O_2 CN^- CO

π donors

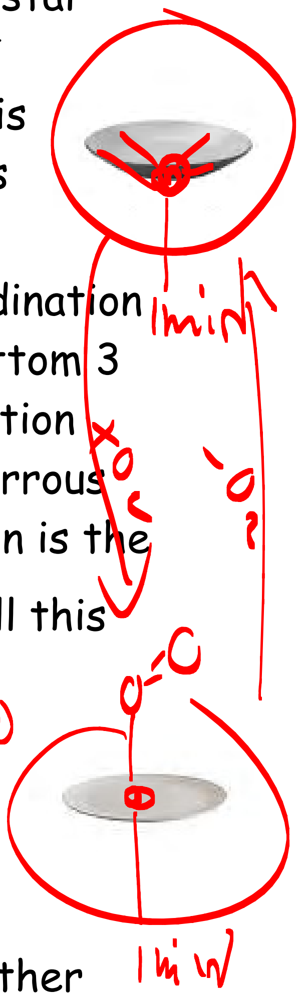
π acceptors

A quick (very quick) primer in the dioxygen chemistry of hemoglobin –see Hb section --

1) DEOXYhemoglobin (in the veins) has 1N from imidazole (proximal, or 5th position), 4 N's from the protoporphyrin IX ring (the heme ring) and nothing in the 6th position or distal position. Because of this (5-coordination not 6 = Weak Field) the 6 electrons in Fe^{2+} adopt a High Spin electronic configuration ($4 \times +\frac{1}{2}$ =sum of spins= 2). High Spin Fe^{2+} is larger than Low Spin Fe^{2+} so does not fit into the hole in the heme ring – the ferrous ion pops out of the ring a bit on the side of the proximal histidine.



When oxygen binds – this makes the OXYhemoglobin and the 6 coordination exerts a Strong Field, the energy gap between the top 2 and the bottom 3 3d orbitals increases, and the electrons pair up = Low Spin configuration (S=0).. Low Spin Fe2+ IS SMALLER THAN High Spin Fe2+ so the ferrous iron moves back into the plane of the ring. An alternative explanation is the the electron distribution in oxyHb/oxyMb= Fe(III) + O_2^-. How does all this movement control oxygenation? Well, there are four hemes in hemoglobin, and they are all connected through a hydrogen bond network. When the Fe drops out of the plane it pushes the Histidine down, this mechanically moves the protein. So, all the other hemes 'know' that one heme is not in the DEOXY-or sprung state. Conversely, when the Fe picks up the dioxygen, movement back into the plane pulls the attached Histidine and 'tells' the other hemes that it is now oxygenated. This 'spring-loaded' effect also has the property of delaying oxygenation until there is plenty of dioxygen available – so all 4 heme groups can pick up oxygen at once and then travel fully oxygen-loaded to the muscles.



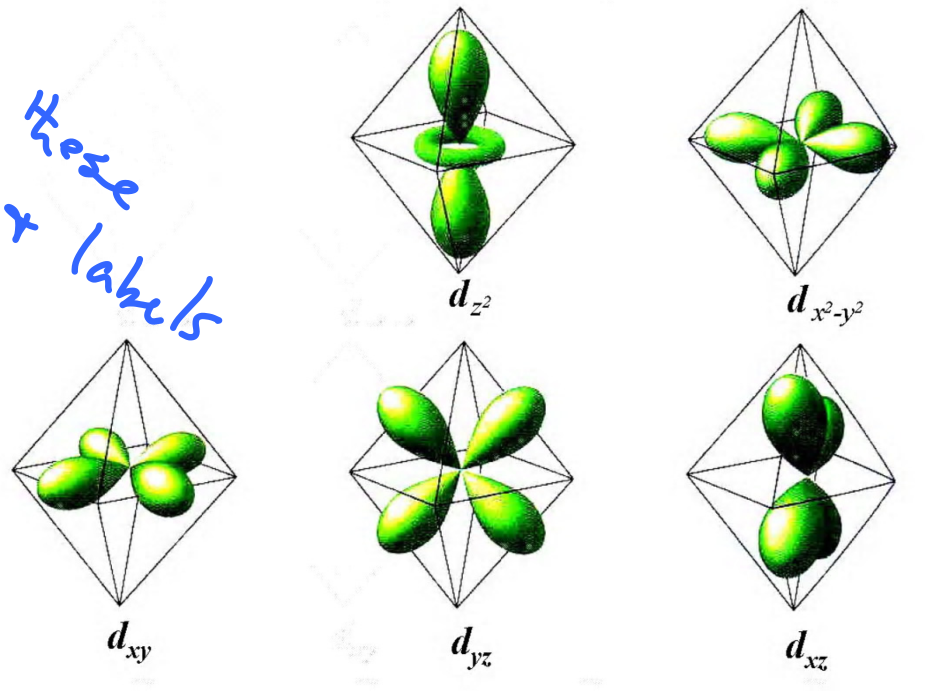
Make sure you follow this!

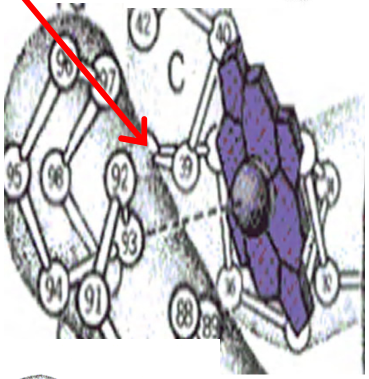
3d orbital arrangements -1 – the shapes of the 5 3d orbitals (2=the energies)

Know these shapes & labels well

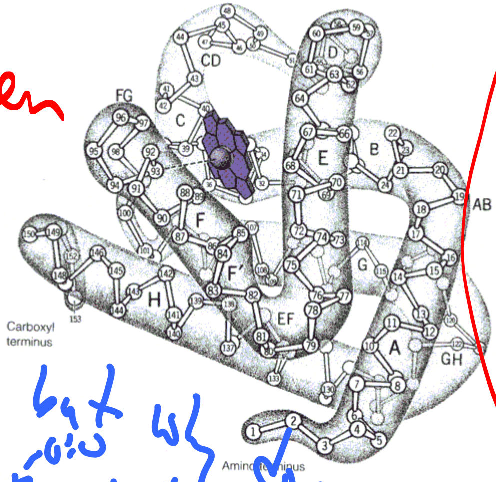
1. The lobes of the electron density in the 5 3d orbitals point at the vertices of the octahedron
2. The number of electrons in the 3d orbitals in each orbital and whether they are all the same spin (high spin) or paired up (low spin) changes the size of the cation.
3. Many dbM complexes form octahedral shapes (ML_6) the 3d orbitals will interact with those attached ligands – for example, look at the heme group in myoglobin – 6 ligands bind to the Fe^{2+}.
4. This is the basis of the dioxygen binding of myoglobin and hemoglobin because the energies of each 3d orbital (there are 5 here) can be different and depends on the ligand (or no ligand) attached. Here we have 4 the same – N's on the protoporphyrin IX ring (PPIX) or heme ring, 1 N from HisF8 or His93 histidine imidazole side chain, and 1 empty spot (the 6th position) for water, or dioxygen or CO – but tight because of HisE7.
5. To memorize – the 3d shapes and the alignment of His93 connected to the Fe –heme and the O_2 and CO in Myoglobin.

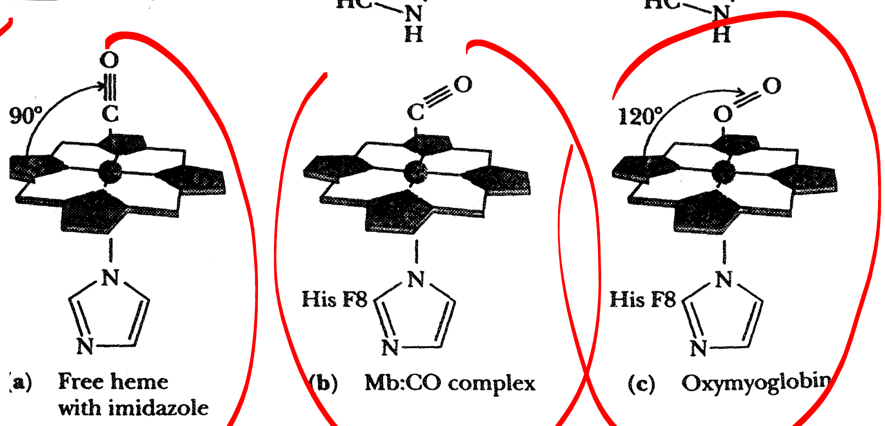
His F8, means 8th amino acid in helical coil F (6th). We will call it His93. meaning 93rd amino acid from the N-terminal. HisE7 is His64. So where is His E7





Find the 6 ligand s- 5 are N's, the 6th is the dioxygen – O_2 – see below RHS





(a) Free heme with imidazole (b) Mb:CO complex (c) Oxymyoglobin

Why is the diOxygen bent?
Because Fe II must remain Fe II –

but why does -O:O Fe do that?

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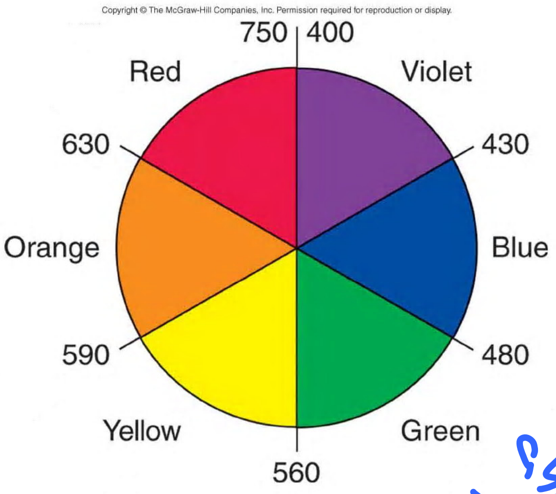
Table 23.11 Relation Between Absorbed and Observed Colors

Absorbed Color	λ (nm)	Observed Color	λ (nm)
Violet	400	Green-yellow	560
Blue	450	Yellow	600
Blue-green	490	Red	620
Yellow-green	570	Violet	410
Yellow	580	Dark blue	430
Orange	600	Blue	450
Red	650	Green	520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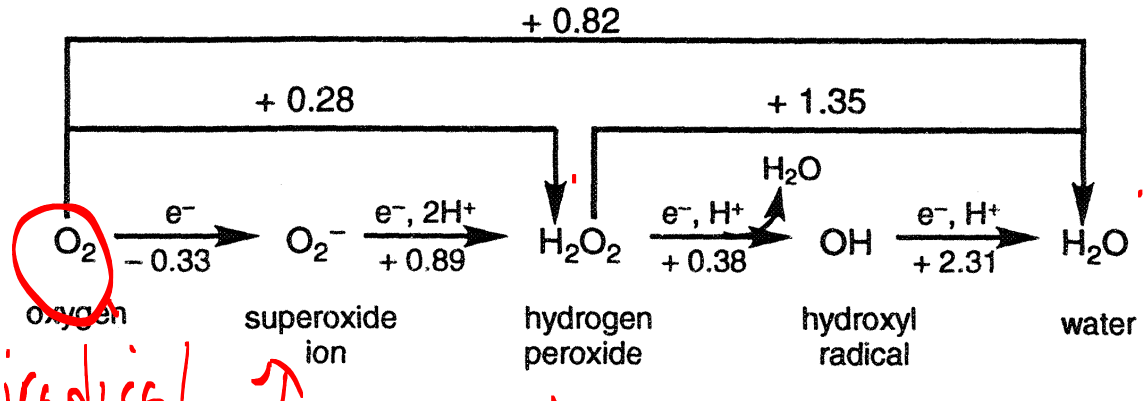
Know colours
vs spectra)
ranges -
transmitted
+ absorbed

The most important ligand and molecule – OXYGEN

1. First because oxygen in its many forms
mammalian existence we need to look at h
forms are interconnected.

2. The electrochemical potentials are only
A second molecule or atom must be conne
the 2 ½ potentials must be positive for th
react.



diradical

Chart 8.1

3. Electrochemical potentials are thermodynamically controlled – there is no information on the rate of the reaction – luckily! Why luckily? Consider what humans are made of and the composition of gas surrounding us…

all have metals permanently bound

Which biological molecules are involved with the oxygen species shown here?

(Cu, Zn) Superoxide dismutase (SOD) – breaks up $O_2^{\cdot -}$ —to H_2O_2
(Fe(III)-Fe(IV))Catalase – breaks up H_2O_2 – to O_2 and H_2O

(Fe(II)) Hemoglobin – transports O_2
(FE(II)) Myoglobin – stores O_2

Equilibrium – what does it mean?

$$aA + bB \rightleftharpoons cC + dD$$

$$K_F = \frac{[C]^c[D]^d}{[A]^a[B]^b}$$

$\rightarrow 10^{+20}$, 10^{+30}, 10^{+40}

but $K_F = \frac{k_{+1}}{k_{-1}}$ the specific rate constants.

at equilibrium $k_{+1}[A]^a[B]^b = k_{-1}[C]^c[D]^d$

ie this is a dynamic process.

Really reactions are much simpler than the above:

$$A + B \overset{K_F}{\rightleftharpoons} C \quad \text{bimolecular}$$

$$K_F = \frac{[C]}{[A][B]}$$

≡m ≡m ≡m

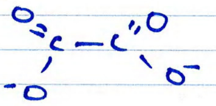
≡m = equilibrium

Equilibrium

How does the type of ligand affect K_F?

Generically, the more donor atoms on the ligand the greater K_F will be – the "chelate effect".

Polydentate ligands ← bind to metals with more than one donor atom.

oxalate  (ox) EDTA

porphyrins (see next slides)

A = chelator
B = metal

– all because of $\Delta G^\circ = -RT \ln K$

$= \Delta H^\circ - T\Delta S^\circ$

ΔH° we know – $T\Delta S^\circ$? ⊖ ⊕

Equilibrium – specifically step-wise vs cumulative equilibrium constants.

nomenclature:

$A + B \rightleftharpoons AB_1$ $K_1 = \frac{[AB_1]}{[A][B]}$

$AB_1 + B \rightleftharpoons AB_2$ $K_2 = \frac{[AB_2]}{[AB_1][B]}$

etc.
etc.

Cumulative:

$A + 2B \rightleftharpoons AB_2$

$\beta_2 = \frac{[AB_2]}{[A][B]^2} = K_1K_2$

T.O. →

$A + 3B \rightleftharpoons AB_3$

$\beta_3 = \frac{[AB_3]}{[A][B]^3} = K_1K_2K_3$

T.O. →

$A + nB \rightleftharpoons AB_n$

$K_1 \gg K_2 \gg K_3 \cdots$

eventually is st ≡m

Equilibrium "chelate effect"

$\Delta G^\circ = -RT \overset{\ln(K)}{\log_{10}(K)}$

units. $\ln = 2.303 \log_{10}$

$= \Delta H^\circ - T\Delta S^\circ$

heat of formation enthalpy

if ΔS°: ⊖ve, ⊕ve

if ⊖ve:
⊕ve:

T = K°
0°C = 273 K

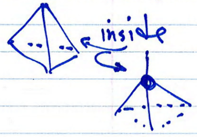
if ΔS° is very positive (J/mole/K)
then ΔG° – very negative
+ K >>> 1 … 10^6 10^{10} 10^{40}!

eg siderophores that capture Fe^{3+}

Examples

$[Cd(H_2O)_4]^{2+} + 4NH_3 \rightleftharpoons [Cd(NH_3)_4]^{2+} + 4H_2O$

CN = 4 Tetrahedral



Cumulative binding constant

β_4

$$= \frac{[\{Cd(NH_3)_4\}^{2+}]\cancel{[H_2O]^4}}{[\{Cd(H_2O)_4\}^{2+}][NH_3]^4}$$

H_2O is solvent so is not included in the value → $\beta_4 / [H_2O]^4$

K_n stepwise:

$[Cd[H_2O]_4]^{2+} + NH_3 \overset{K_1}{\rightleftharpoons} [Cd(H_2O)_3(NH_3)]^{2+} + H_2O$

etc.

Generally, $K_1 > K_2 > K_3 > K_4$ and $\beta_4 = K_1K_2K_3K_4$

Equilibrium

The chelate effect

Consider Ni^{2+} really $[Ni(H_2O)_6]^{2+}$

$$\underbrace{[Ni(H_2O)_6]^{2+} + 6NH_3}_{7 \text{ species}} \underset{\beta_6}{\rightleftharpoons} \underbrace{[Ni(NH_3)_6]^{2+} + 6H_2O}_{7 \text{ species}}$$

What happens if we use EDTA? $\left(\begin{smallmatrix} N & O & O \\ N & O & O \end{smallmatrix}\right)$

$$\underbrace{[Ni(H_2O)_6]^{2+} + EDTA^{4-}}_{1 \quad 1} \rightleftharpoons \underbrace{[Ni(EDTA)]^{2-} + 6H_2O}_{1 \quad + 6}$$

$\boxed{\Delta S = \oplus ve}$ – why $\oplus$ ve?

Equilibrium "chelate effect"

β_6 $[Ni(NH_3)_6]^{2+}$ 4.0×10^9 $\log_{10}\beta_6 = 8.61$

(large? $[Co(NH_3)_6]^{2+} \sim 4 \times 10^{33}$)

β_1 $[Ni(EDTA)]^{2-}$ 3.6×10^{18}

β_3 $[Ni(en)_3]^{2+}$ 2.1×10^{18} (?)

but 3 en same as 1 EDTA?

ΔS effects for these 3?

Chelate effect $\frac{\beta_3(en)_3}{\beta_6(NH_3)_6}$ $\frac{\beta_1(EDTA)}{\beta_6(NH_3)}$

$\frac{10^{18}}{10^9} \approx 10^9 \times$

Equilibrium "chelate effect"

$[Cd(H_2O)_4]^{2+} + 2en \rightleftharpoons [Cd(en)_2]^{2+} + 4H_2O$

if ~~$\Delta G°$~~ = −60.70 kJ/mole

$\Delta H° = -56.48$ kJ/mole

T = 25 °C = 298 K R = 8.314 J/K

Calculate β_2, $\Delta S°$

($\approx 4.4 \times 10^{10}$; +14.2 J/K)

↑ K. ↑ ΔS

Revise for mid term

Calculate yourself.

Summary of K_F —

① Think simple

The binding affinity

$K_F >> 1$ to move to the product

if $K_F << 1$ then very little product

BUT there would be some because this is $\rightleftarrows$

$$A + B \overset{K_F}{\rightleftarrows} AB$$

$$K_F = \frac{[AB]_{\equiv m}}{[A]_{\equiv m}[B]_{\equiv m}}$$

for multiple B's each K_F is a single step

so for $Cu^{II}(H_2O)_6^{2+} + 6NH_3 \rightleftarrows Cu(NH_3)_6^{2+} + 6H_2O$

there are 6 K_F's

and $\beta_6 = K_1 \cdots \times K_6$

②

Now $\Delta G^\circ = -RT\ln K$ per step

or $\Delta G^\circ = -RT\ln \beta_6$ for all 6 steps

and! $\underset{kJ}{\Delta G^\circ} = \underset{kJ}{\Delta H^\circ} - T\Delta S^\circ$ ↑ J !

if ΔS° is positive = more disorder and ΔG° will become more negative

so $\beta\uparrow$

if ΔS° is ~zero or negative, = more or less order

(β not influenced, only $\propto \Delta H^\circ$

Expectations from the material in this unit

1	Know your way round the Periodic Table – esp elements of bio-interest in Groups 1, 2, 14-17. Which are these elements? What are the configurations of the row 2 and 3 metals we are interested in? Know the orbital shapes and labels s, p, and d What is special about the ionization energies across the rows? How does this change the characteristics of the element wrt forming compounds? What happens to the size of elements when oxidized? Reduced? What is a ligand? How is it defined? Why do the hard metals lie on the LHS of the Periodic Table? And the soft metals are? And the hard ligands? And the sift ligands? What are the distinguishing features of all these types of species?
2	Predict good ligand atoms for the following dications**: Zn, Cd, Hg – which amino acids would be prime targets? And Mg, Ca – what about Pb? (See ch. 17 in K&S) **what does this mean?
3	What is BAL? Why was it used in the 1st and 2nd World Wars? What is the L in BAL? What is EDTA? What does it bind best? Why? And, deferrioxamine B – what is it? Why would you be given this as a drug? What is special about the polyether molecules? How would they 'work' in a biological system? Match the following metal ions to the preferred amino acids: K, Zn, Cd, Cu as +1.
4	Identify those amino acids most likely to bind metals – which atoms bind directly to the metal in these molecules? Be able to draw and recognise protoporphyrin IX
5	How do the 3d orbitals split? What effect does this have on the arrangement of electrons? Which of the compounds of oxygen shown in slide 1079 are important to an organism? Which would be toxic? See R-M p 205 for a start on this

Study questions Using books, the Internet and lectures – explain how dioxygen binding takes place in the heme protein myoglobin in terms of the 3d orbitals and d electron configuration