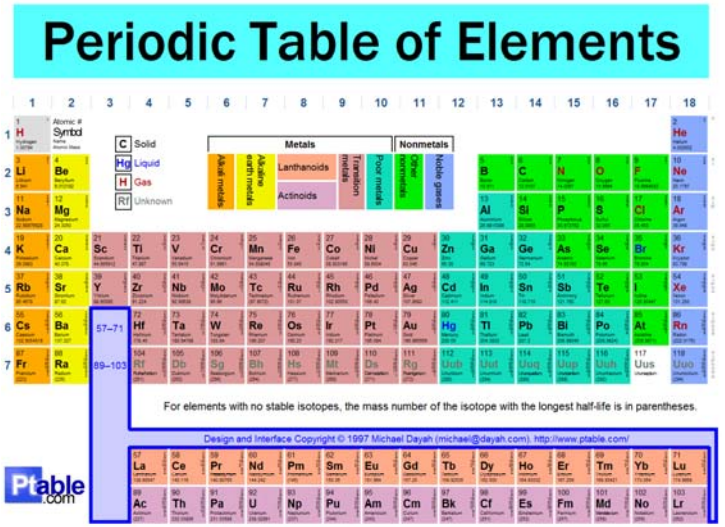
Metal Ions In Medicine



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2010
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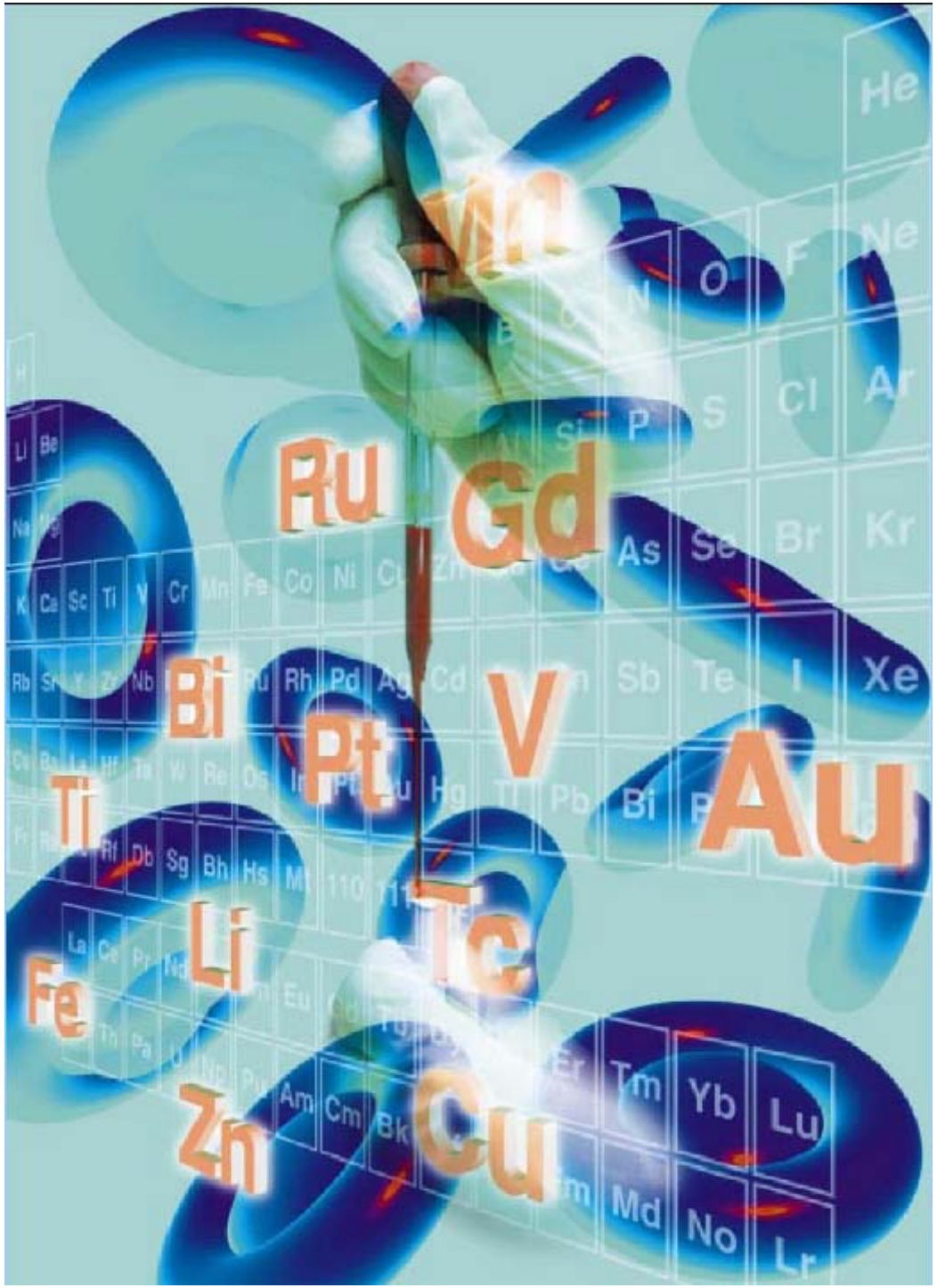
…literature…

1) Chris Jones, John Thornback, *Medicinal Applications of Coordination Chemistry*, RSC Publishing, Cambridge, 2007.

2) *Uses of Inorganic Chemistry in Medicine*. Ed: Nicholas P. Farell, RSC Publishing, Cambridge, 1999.

3) Thomas Nogrady, Donald F. Weaver, *Medicinal Chemistry: A Molecular and Biochemical Approach*, Oxford University Press, New York 2005.


Mn
Ru
Gd
Bi
Pt
V
Au
Ti
Tc
Li
Fe
Zn
Cu
He
Ne
O
F
Cl
Ar
As
Se
Br
Kr
Sb
Te
I
Xe
Tm
Yb
Lu
Md
No
Lr

Bioinorganic chemistry involves the understanding of all aspects of the role of metal ions in biology.

For example: their processing, incorporation into protein and the nature and function of metalloproteins.

Medicinal chemistry requires detailed knowledge of metabolism, stability and target interactions of the drug.

…define Medicine…

ars medicina = the art of healing

The science of healing…and preventing…

3 main objectives…

1) **Maintain health**
2) **Restore health**
3) **Prevent illness**

Modern Medicine

Health Science…nutrition

Biomedical Research…chemistry, biology, physics

Medical Technology…diagnostic and therapeutic science

Metals in Medicine

1. The use of chelating agents

2. Modulation of cellular responses by metal containing drugs

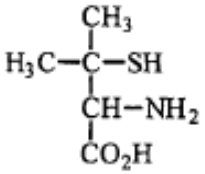
3. Metal based chemotherapeutic drugs

4. Metal complexes as diagnostic agents

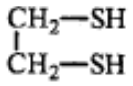
…chelating agents…

Many metals are essential for the human organism…however, **uncontrolled** mobilization may lead to the presence of **excess free metal ion**, with subsequent **health problems**…

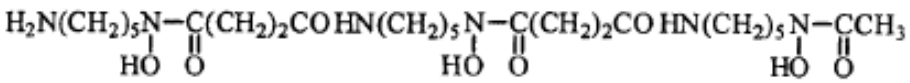
Old time classics: **Fe** and **Cu** overload.
Cu: Wilson's disease… autosomal disorder of Cu accumulation, untreated is fatal



D- Penicillamine



Cysteamine



Desferrioxamine B

Structures of some clinically used chelating agents for treatment of copper and iron overload

…modulation of cellular responses by metal containing drugs…

Inorganic drugs may be recognized as acting through a **pharmacodynamic mechanism** – modulating cellular responses …*e.g.* Li_2CO_3

PD: "what the drug does to the body": the drug action must be rapid and essentially reversible…*e.g. a patient who submits to an anesthetic does not expect to be deprived of feeling for ever.*

In addition: a graded response is required to balance effects…*e.g. a drug to reverse a stroke must be aware of the severity of that stroke and concentrations adjusted accordingly.*

Chemotherapeutic agents on the other hand involve cell killing, an irreversible process.

… Chemotherapeutic agents …

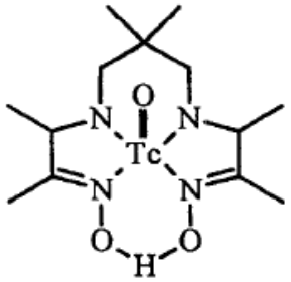
Chemotherapy is the use of drugs to injure an invading organism without injury to the host…involves cell killing, an irreversible process.

It covers: antibacterial, antiviral and anticancer agents. In the first two, the invading organism is clearly distinct from the host! In the case of cancer, a family of diseases characterized by uncontrolled cellular proliferation, the organism is strictly not different but the treatment has a common aim; the elimination of unwanted cells. Thus, chemotherapeutic drugs, **in contrast to pharmacodynamic drugs** must induce an irreversible cytotoxic effect.

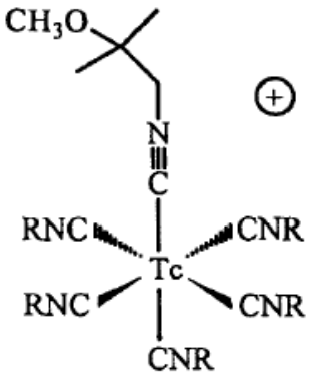
… Metal complexes as Diagnostic Agents…

…no pharmacodynamic or chemotherapeutic and is desired: imaging of tissue is achieved. The two principal sets are: technetium-based imaging agents and paramagnetic MRI contrast agents….

Stability and water solubility are paramount…

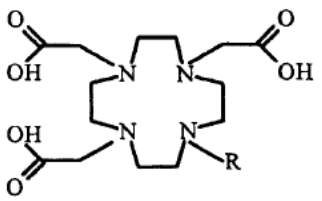


Tc- (HMPAO)

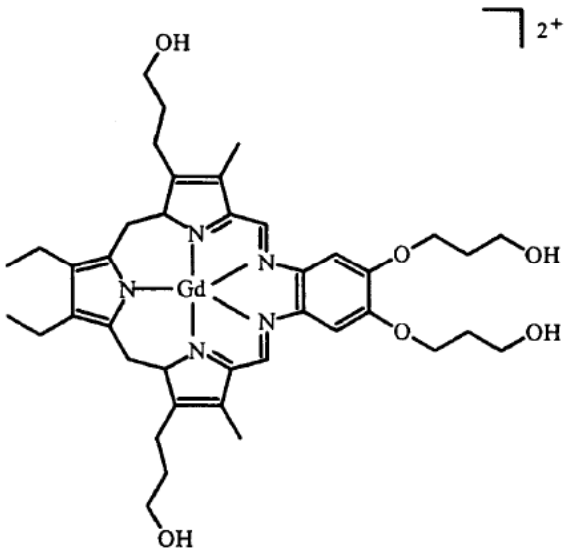


Tc- (MIBI)

Structures of clinically useful technetium imaging agents



R = H DO3A
R = $CH_2CH(OH)CH_3$ HP-DO3A
R = CH_2COOH DOTA

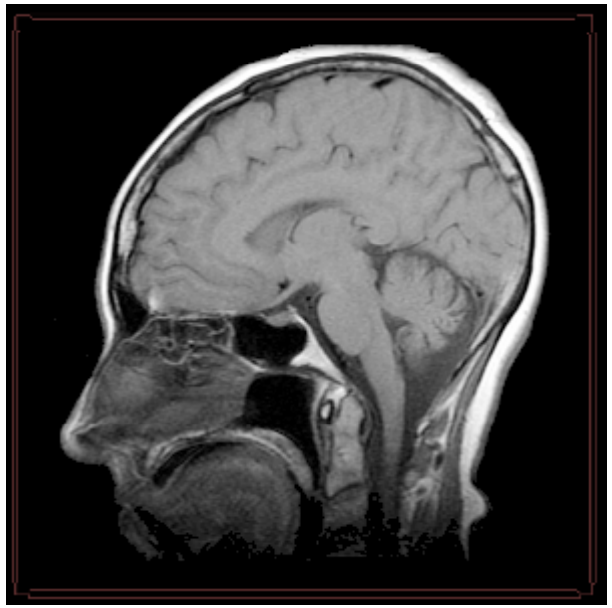


Structures of Gd-based MRI contrast agents

Metal Ions In Medicine

Diagnosis

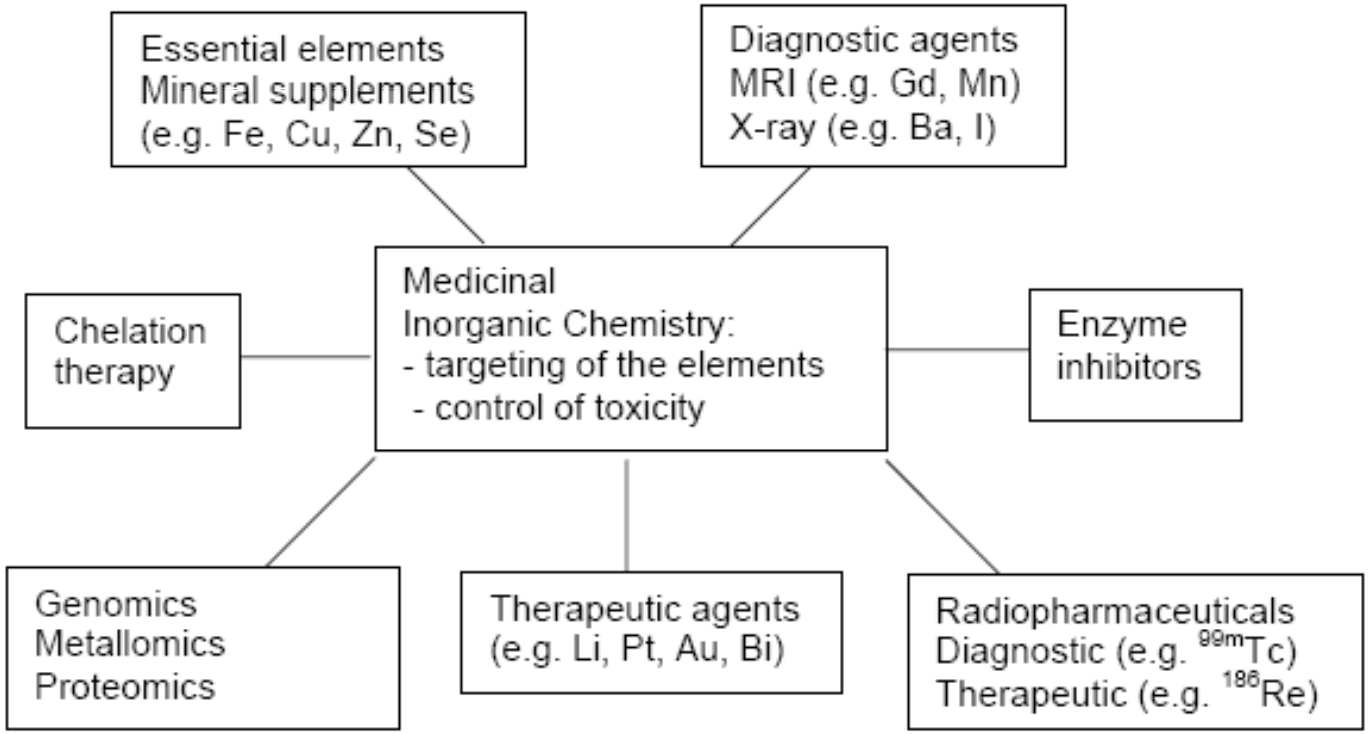
Magnetic Resonance Imaging (MRI)



Treatment

Metal-based drugs

Anti-cancer drugs
Anti-inflammatory drugs
Anti-virus drugs
Alzheimer's drugs
Lanthanide-based drugs
Li-based drugs
V-based insulin regulators
Radiopharmacology


Essential elements
Mineral supplements
(e.g. Fe, Cu, Zn, Se)
Diagnostic agents
MRI (e.g. Gd, Mn)
X-ray (e.g. Ba, I)
Chelation therapy
Medicinal
Inorganic Chemistry:
- targeting of the elements
- control of toxicity
Enzyme inhibitors
Genomics
Metallomics
Proteomics
Therapeutic agents
(e.g. Li, Pt, Au, Bi)
Radiopharmaceuticals
Diagnostic (e.g. ^{99m}Tc)
Therapeutic (e.g. ^{186}Re)

Metal-Based Drugs

$CuSO_4 \cdot 5H_2O$: Ancient Egypt as potion, sterilizing effect
Au: Arabia and China (2500 BC)
Hg: Europe (15^{th} century) to treat syphilis

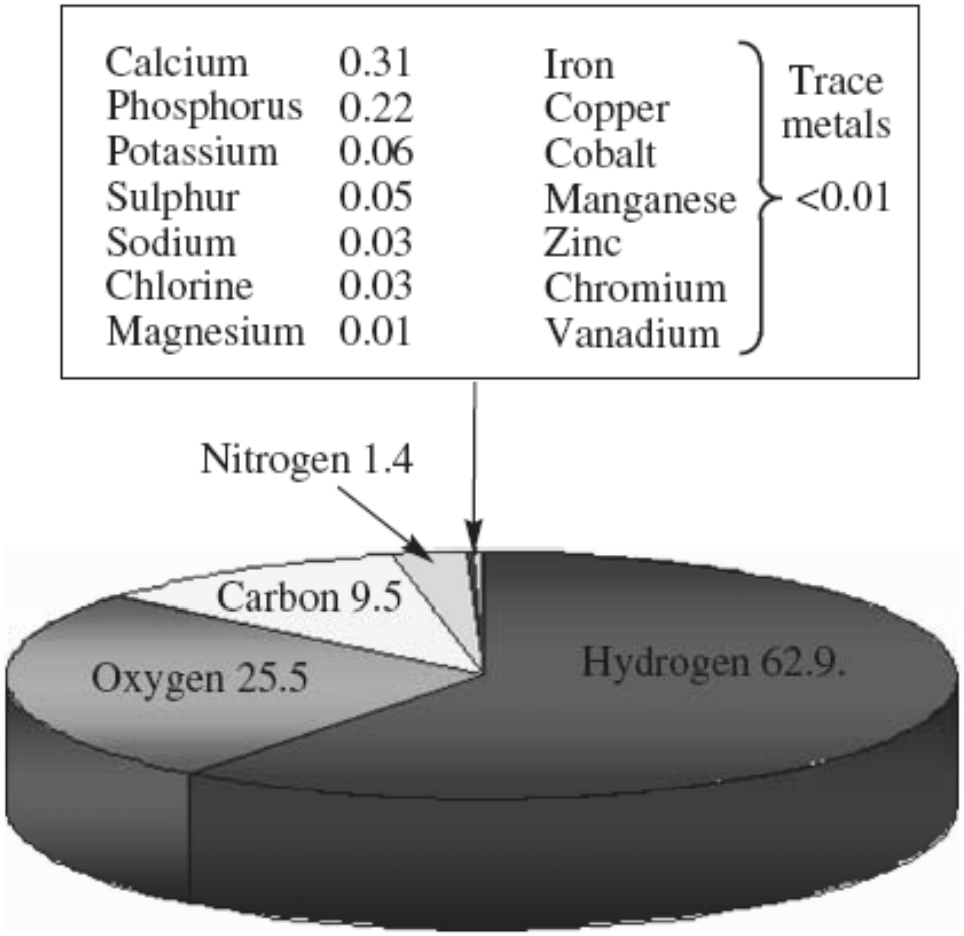
1890s: Koch's observation for bactericidal action of Au compounds
1909: Erlich used As(III) cmps. to treat syphilis
1921: Bi(III) cmps to treat syphilis
1930s: Au drugs against rheumatoid arthritis

1953: Korngold and Pressman showed that radioactive iodine can target tumours in rats
1964: *MSU*, Barnett Rosenberg found that Pt(II) inhibits cell division…1974 *cis*-$[Pt(NH_3)_2Cl_2]$ approved by FDA for testicular and ovarian cancer.

"magic bullet" P. Erlich: a dye carrying a toxic heavy metal which would target disease causing agents, while leaving healthy cells unharmed…in 2002 FDA approved a radioactive Y compd. for radioimmunotherapy.

Today…

Gold drugs to treat rheumatoid arthritis…
Lithium for depression…
Platinum to treat certain cancer types…
Bismuth for stomach ulcers…
Vanadium for diabetes…
Iron for anaemia…
Iron to control blood pressure…
Cobalt in Vitamin B_{12} to treat pernicious anaemia…
Radioactive metals for cancer…



Approximate elemental composition as percentages of the total number of atoms.

The elemental composition of a typical human

Table 1 *Trace metals in humans*

Metal	*Mass*[a] *(mg)*	*Daily intake*[b] *(mg day^{-1})*	*Examples of some biological rôles*
Iron	4200	12 (male) 15 (female)	Dioxygen storage and transport, cytchromes enzymes – oxidases, reductases, hydrogenases
Zinc	2300	15	Structural control in proteins, enzymes involved in the chemical addition of water, alcohol dehydrogenase
Copper	72	2	Dioxygen storage and transport, electron transfer proteins
Nickel	15	–	Enzymes – urease, hydrogenases
Chromium	14	0.05–0.2	May be essential in mammalian glucose metabolism
Manganese	12	2	Enzymes – phosphatase, mitochondrial superoxide dismutase
Molybdenum	5	0.075–0.25	Enzymes – reductases, hydroxylases, nitrogenases
Cobalt	3	3(as vitamin B_{12})	Enzymes – as vitamin B_{12} coenzyme
Vanadium	0.11	–	Enzymes – nitrogenases, haloperoxidases

[a] Approximate amount in 70 kg average adult human
[b] Recommended adult daily intake requirement.

Intake of some metals and their effects.

Metal	Recommended daily dose (US)	Result of deficiency	Toxic level	Toxic effects
Ca	1 g	Bone deterioration	> 2.5 g/ day	Magnesium deficiency
Cr	5-200 μg	May regulate insulin levels	> 70 mg (Cr(III))	Irregular heartbeat
Fe	10-15 mg	Anaemia	> 60mg/kg	Anorexia
Cu	ca. 2 mg	Brain disease, anaemia, heart disease	7.5 g (death)	Haemolytic anaemia
Zn	15 mg	Growth retardation, skin changes	> 500 mg/day	Heavy vomiting

Metallopharmaceuticals…

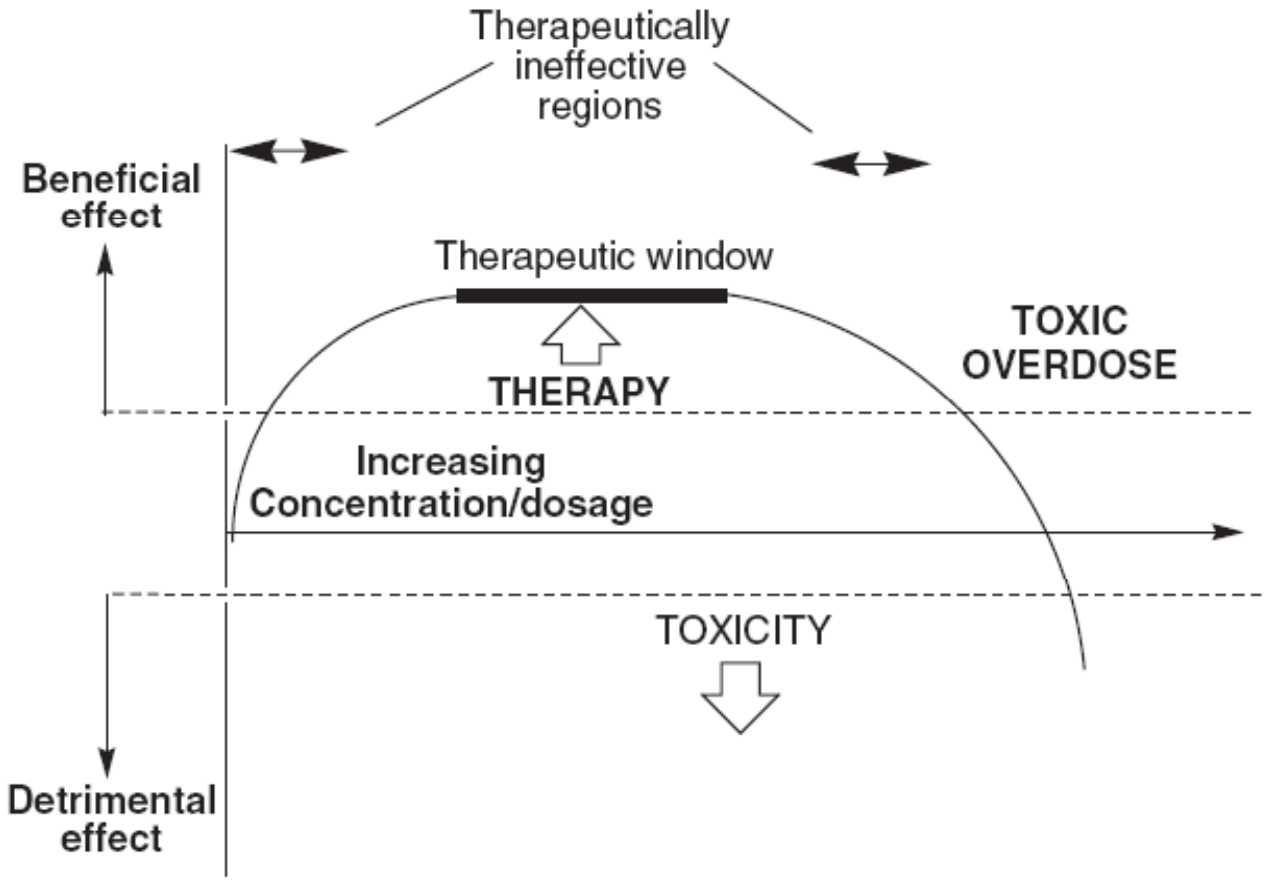
Metals are in general toxic and unstable…in the old days treatment with metals was as dangerous as the disease!!!

1) **Maximum effect with minimum dose and minimal toxic side-effects**.

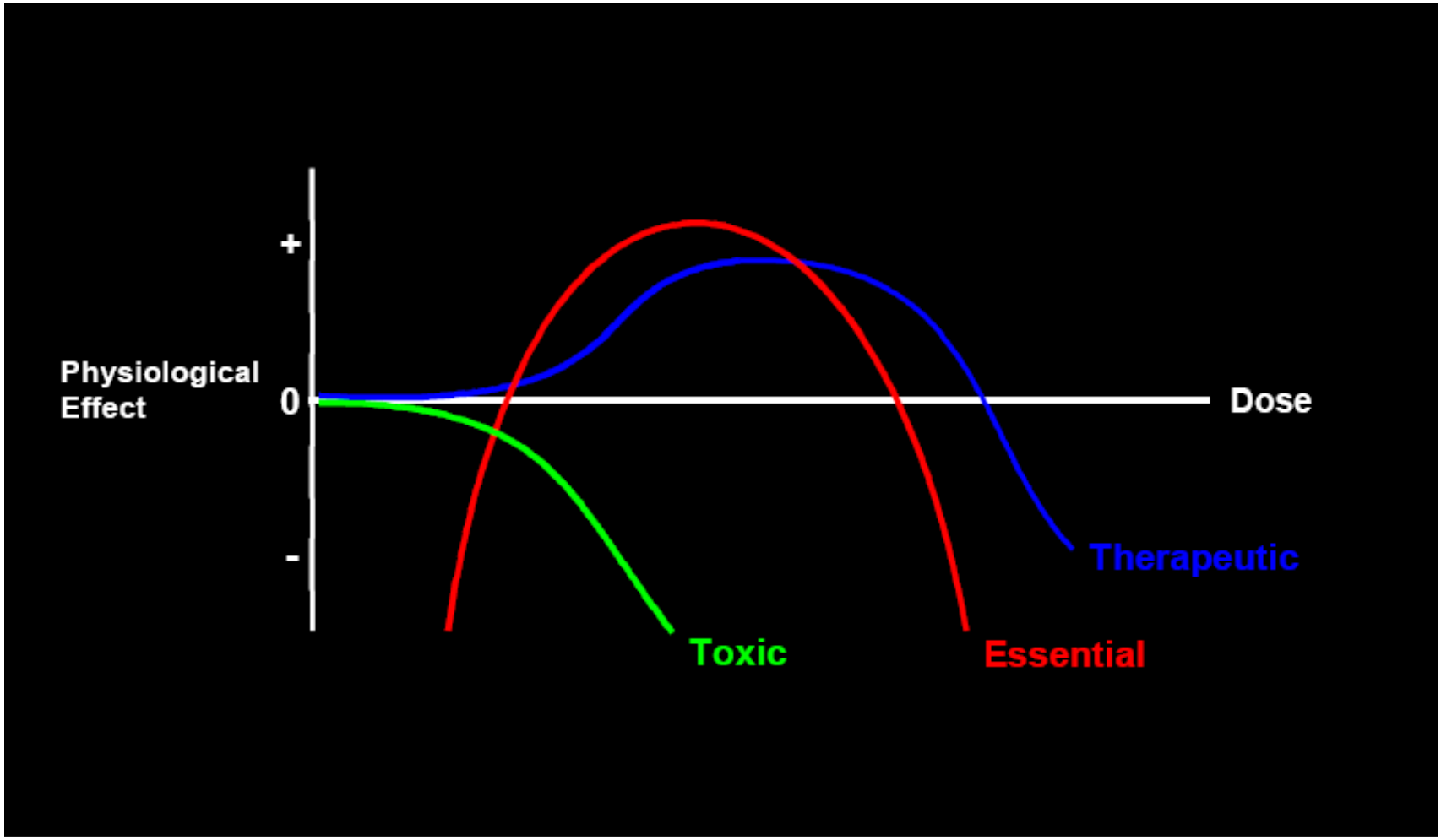
Therapeutic Index= LD_{50}/ED_{50} Small or big????anything "strange"??

Increasing the dose of the drug does not mean increasing its beneficial effect! We have to consider the "*therapeutic window*"

…e.g. carrots and Vitamin A



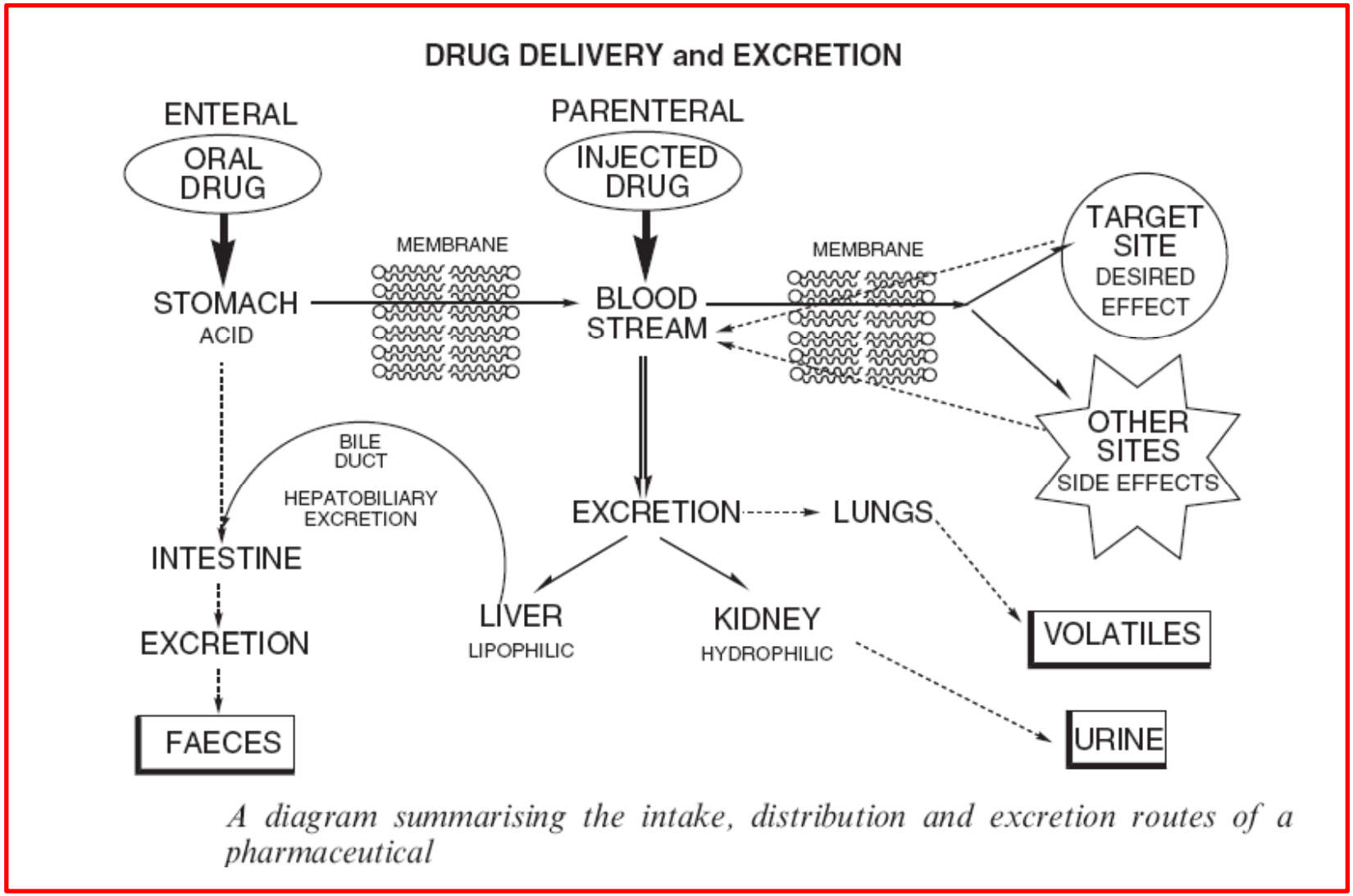
The effect of increasing pharmaceutical dosage, or concentration in vivo, on benefit to the patient. Initially the beneficial effect increases with increasing concentration but at high doses, toxic effects predominate. Dosage regimes need to be adjusted to keep concentrations within the therapeutic window



The Bertrand Diagram.

2) Bioavailability and biodistribution

Absorption, distribution, metabolism, elimination: *pharmokinetics*



A diagram summarising the intake, distribution and excretion routes of a pharmaceutical

3) In vivo stability

"Prodrugs" convert to drugs in the body

Have to consider:

i) The drug has to be soluble in the blood…

ii) The interactions with the proteins have to be taken seriously…!!!...especially for metal-containg drugs!

iii) Natural metabolic processes may cause the release of the metal…toxicity rises then!!

Preclinical Testing…

1. Acute toxicity — acute dose that is lethal in 50% of animals; usually two species, usually two routes of administration
2. Subacute toxicity — physiology, histology, autopsy studies; two species, sometimes with dosings over a 6 month time period
3. Chronic toxicity — detailed organ evaluation; two species, sometimes studied for 1–2 years
4. Mutagenic potential — effects on genetic stability of bacteria (Ames test) of mammalian cells in culture
5. Carcinogenic potential — required if drug is to be administered for prolonged periods of time
6. Reproductive performance effects — effects on animal progeny, production of birth defects

Clinical Trials…tough one!

Phase I: Small group of **healthy** people take the drug to test its absorption, biodistribution, pharmokinetics, accumulation, side-effects and dosage. (Volunteers!!!)

Phase II: Small group of **patients** receive the drug to test its activity. Optimum dosage and adverse reactions are assessed.

Phase III: Large groups of **patients** are evaluated. Double trials, blinds, placebo.

Phase IV: **Patients** are still monitored…approval follows…fine-tuning of procedures

cis-platin took **14 years** to hit the shelves since it was first discovered in 1964.

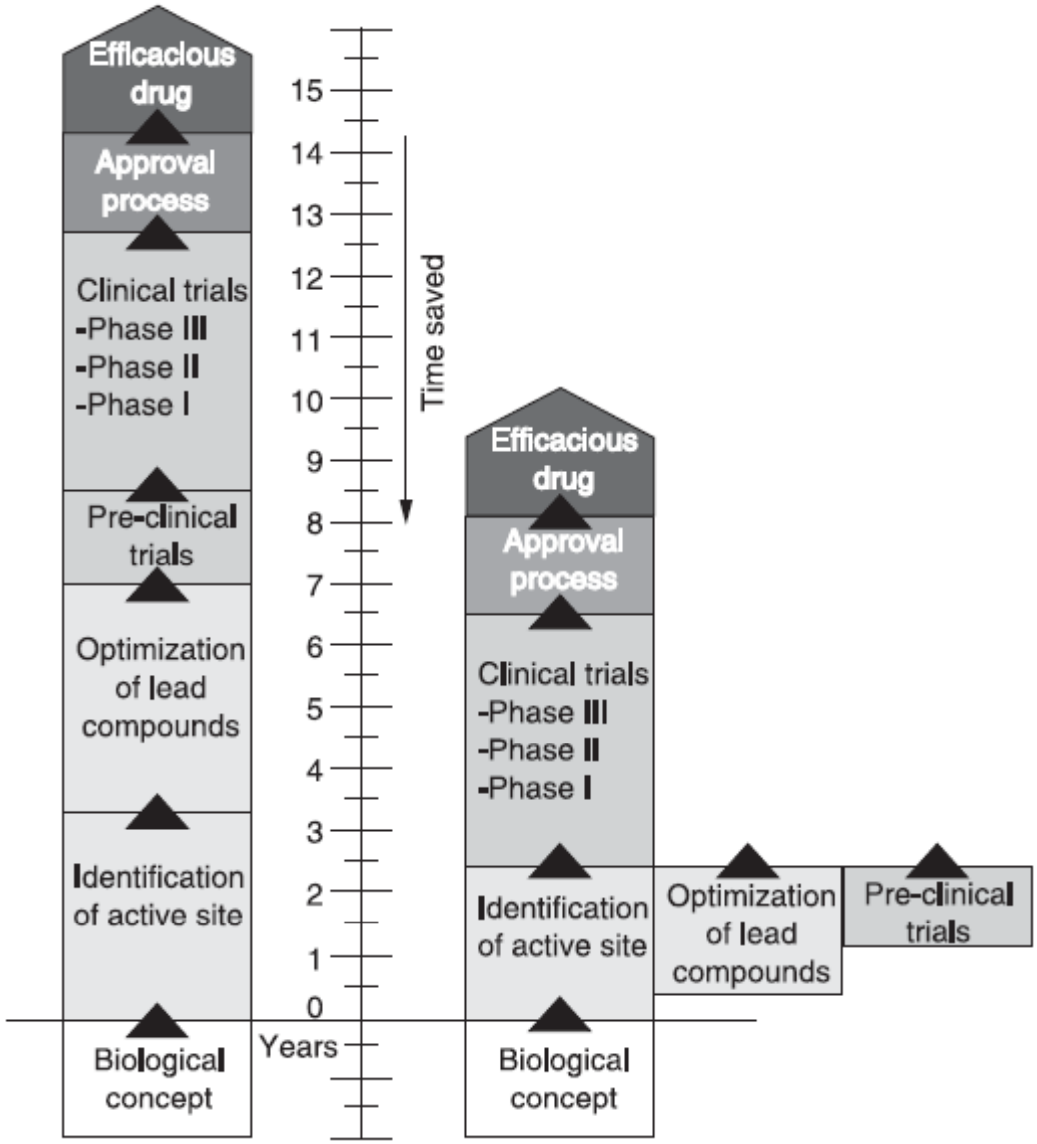
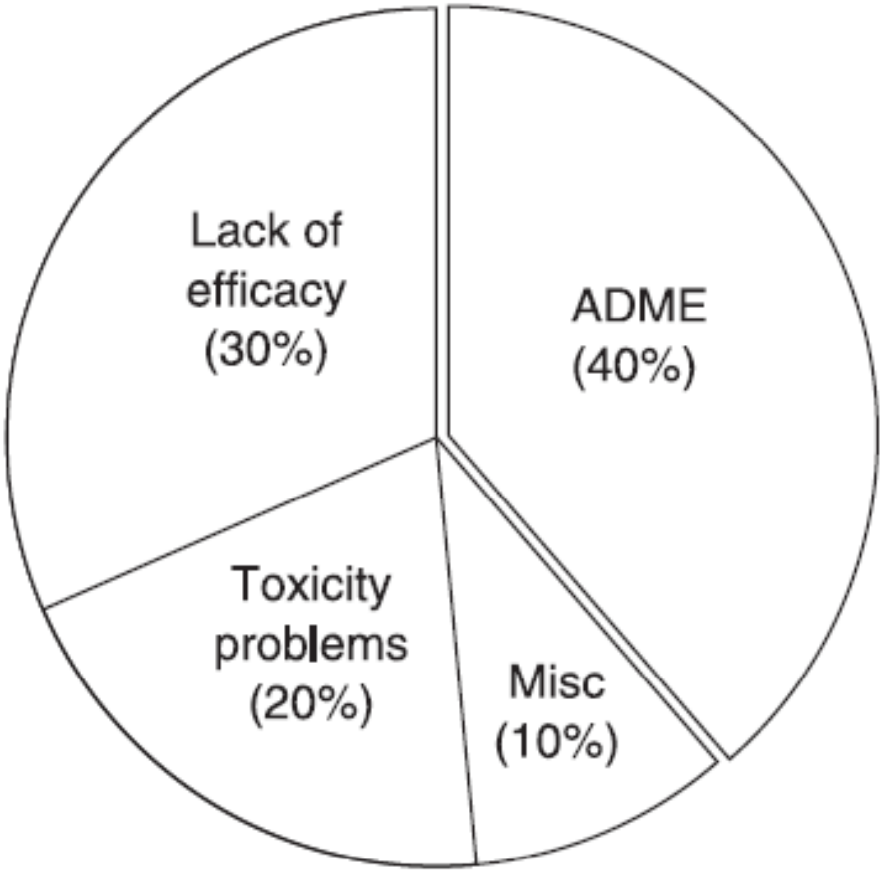

Efficacious drug
Approval process
Clinical trials
-Phase III
-Phase II
-Phase I
Pre-clinical trials
Optimization of lead compounds
Identification of active site
Biological concept
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Years
Time saved
Efficacious drug
Approval process
Clinical trials
-Phase III
-Phase II
-Phase I
Identification of active site
Optimization of lead compounds
Pre-clinical trials
Biological concept

Table 3.2 Drugs Producing Adverse Effects on the Fetus

Drug	Effect
ACE inhibitors	Kidney damage
Amphetamines	Abnormal developmental patterns
Androgens	Masculinization of female
Busulfan	Congenital malformations
Carbamazepine	Neural tube defects affecting brain formation
Cocaine	Stroke in fetus
Cyclophosphamide	Congenital malformations
Cytarabine	Congenital malformations
Diethylstilbestrol	Vaginal adenocarcinoma in child
Ethanol	Risk of fetal alcohol syndrome
Etretinate	High risk of multiple congenital malformations
Iodine	Congenital goiter, hypothyroidism
Isotretinoin	High risk of face, ear, and other malformations
Methotrexate	Multiple congenital abnormalities
Methylthiouracil	Hypothyroidism in child
Metronidazole	May be mutagenic (animal studies show no evidence for mutagenic or teratogenic effects in humans)
Penicillamine	Congenital skin malformations
Phenytoin	Fetal hydantoin syndrome
Propylthiouracil	Congenital goiter
Streptomycin	Eighth nerve toxicity (deafness) in child
Tamoxifen	Increased risk of spontaneous abortion or fetal damage
Tetracycline	Discoloration and defects of teeth and altered bone growth
Thalidomide	Phocomelia (shortened bones of the limbs)
Trimethadione	Multiple congenital abnormalities
Valproic acid	Neural tube defects of the brain

Table 3.3 Approved Drugs Withdrawn Because of Toxicity

Drug	Year	Adverse reaction
Astemizole	1998	Interactions (e.g., with grapefruit juice)
Benoxaprofen	1982	Liver damage
Centoxin	1993	Increased mortality
Cerivastatin	2001	Muscle breakdown
Cisapride	2000	Cardiac arrhythmias
Clioquinol	1975	Optic neuropathy (eye problem)
Dexfenfluramine	1997	Cardiac valve abnormalities
Fenfluamine	1997	Cardiac valve abnormalities
Flosequinan	1993	Increased mortality
Indoprofen	1984	Gastrointestinal bleeding/perforation
Metipranolol 0.6% eyedrops	1990	Anterior uveitis (eye problem)
Mibefradil	1998	Many drug interactions
Nomifensine	1986	Hemolytic anemia
Noscapine	1991	Gene toxicity
Remoxipride	1994	Aplastic anemia
Sertindole	1998	Cardiac arrhythmias
Suprofen	1987	Renal impairment
Temafloxacin	1992	Various serious adverse effects
Terodiline	1991	Cardiac arrhythmias
Tolcapone	1998	Hepatobiliary disorders
Triazolam	1991	Psychiatric disorders
Troglitazone	1997	Hepatic disorders
Zimeldine	1983	Hypersensitivity
Zomepirac	1983	Anaphylaxis



Absorption
Distribution
Metabolism
Excretion

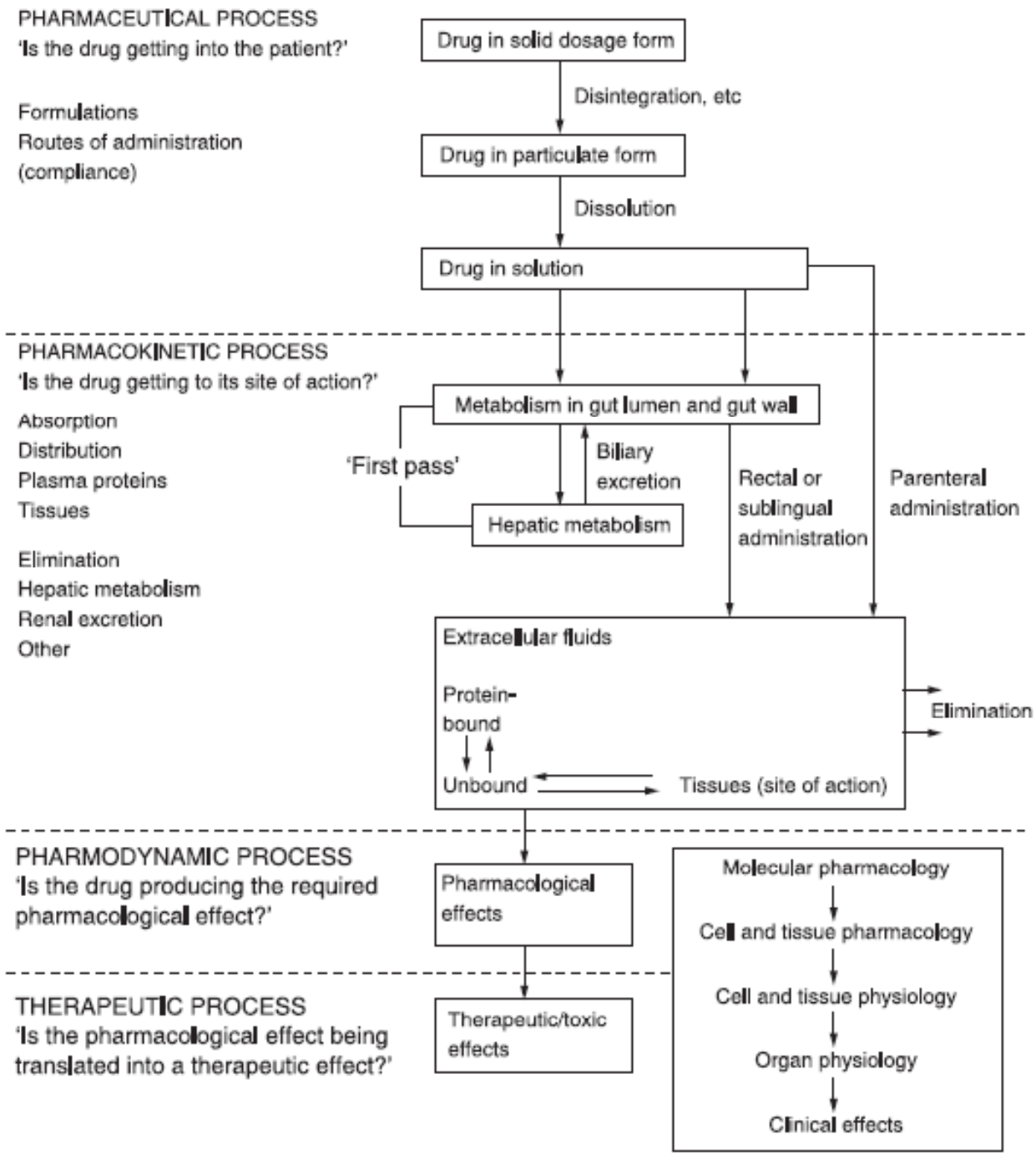
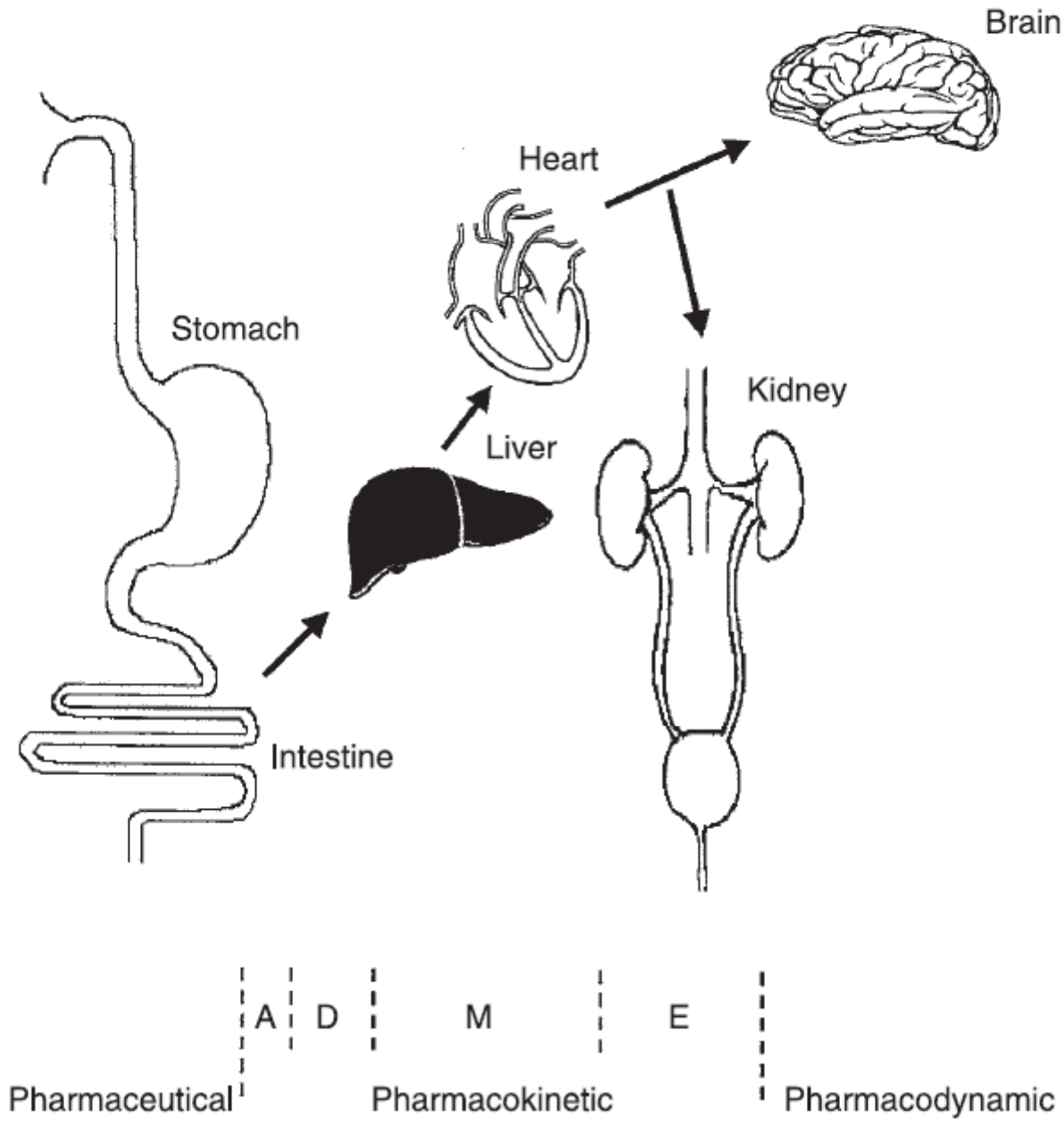

PHARMACEUTICAL PROCESS
'Is the drug getting into the patient?'
Formulations
Routes of administration
(compliance)
Drug in solid dosage form
Disintegration, etc
Drug in particulate form
Dissolution
Drug in solution
PHARMACOKINETIC PROCESS
'Is the drug getting to its site of action?'
Absorption
Distribution
Plasma proteins
Tissues
Elimination
Hepatic metabolism
Renal excretion
Other
Metabolism in gut lumen and gut wall
'First pass'
Biliary excretion
Hepatic metabolism
Rectal or sublingual administration
Parenteral administration
Extracellular fluids
Protein-bound
Unbound
Tissues (site of action)
Elimination
PHARMODYNAMIC PROCESS
'Is the drug producing the required pharmacological effect?'
Pharmacological effects
Molecular pharmacology
Cell and tissue pharmacology
Cell and tissue physiology
Organ physiology
Clinical effects
THERAPEUTIC PROCESS
'Is the pharmacological effect being translated into a therapeutic effect?'
Therapeutic/toxic effects

Table 1.1 pH Values for Tissue Fluids

Fluid	pH
Aqueous humor (eye)	7.2
Blood, arterial	7.4
Blood, venous	7.4
Blood, maternal umbilical	7.3
Cerebrospinal fluid	7.4
Duodenum	4.5–7.8
Intestine	6.0–8.3
Lacrimal fluid (tears)	7.4
Milk, breast	7.0
Nasal secretions	6.0
Prostatic fluid	6.5
Saliva	6.4
Semen	7.2
Stomach	1.8
Sweat	5.4
Urine	5.6–7.0
Vaginal secretions, premenopause	4.5
Vaginal secretions, postmenopause	7.0

THE PHYSIOLOGICAL SYSTEMS

1. Cardiovascular system (angina, myocardial infarction, arrhythmias, arterial hypertension, valvular heart disease)
2. Dermatological system (erythroderma, icthyosis, Stevens–Johnson syndrome, Behcet's disease, acute blistering diseases)
3. Endocrine system (Cushing's disease, Addison's disease, carcinoid syndrome, diabetes, hyperthyroidism, Grave's disease, hypothyroidism)
4. Gastrointestinal system (inflammatory bowel disease [ulcerative colitis, Crohn's disease], peptic ulcer, pancreatitis, cholecystitis, hepatitis, choledocholithiasis)
5. Genitourinary system (nephrologic—glomerulonephritis, chronic renal failure; urological—benign prostatic hypertrophy, prostatitis)
6. Hematological system (anemia, polycythemia, thrombocytopenia, leukemia, lymphoma, multiple myeloma)
7. Immune system (allergic rhinitis, polymyositis, autoimmune diseases [systemic lupus erythmatosus], graft vs. host disease)
8. Musculoskeletal system (rheumatoid arthritis, ankylosing spondylitis, Sjogren's syndrome, osteoporosis)
9. Nervous system (dementia, stroke, epilepsy, extrapyramidal diseases [Parkinson's], demyelinating diseases [multiple sclerosis], neuropathy, myasthenia gravis, psychosis, schizophrenia)
10. Respiratory system (chronic obstructive pulmonary disease [COPD; emphysema, chronic bronchitis], acute obstructive lung disease [asthma], chronic restrictive lung disease [connective tissue lung disease])


Brain
Heart
Stomach
Kidney
Liver
Intestine
A
D
M
E
Pharmaceutical
Pharmacokinetic
Pharmacodynamic

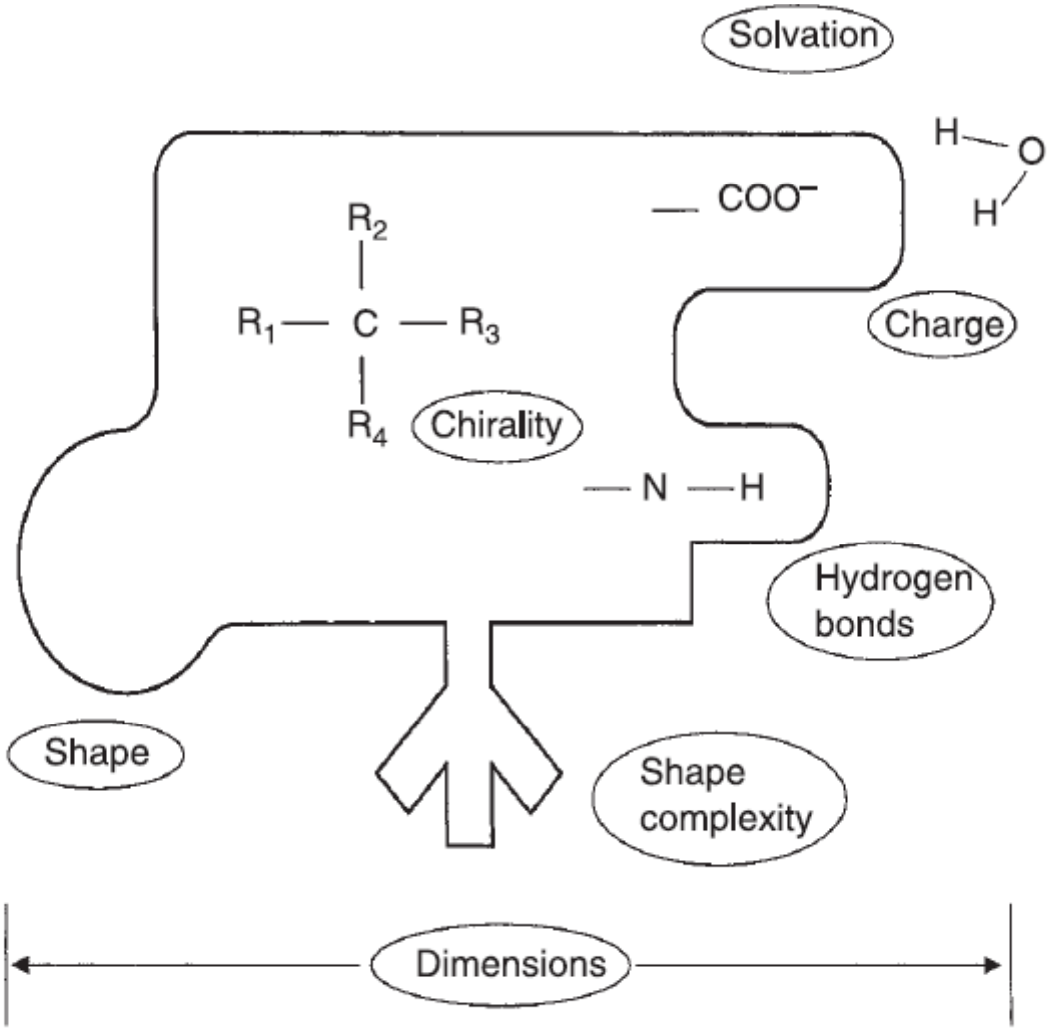

Solvation
H
O
H
— COO⁻
R2
R1 — C — R3
R4
Chirality
Charge
— N —H
Hydrogen bonds
Shape
Shape complexity
Dimensions

Table 3.1 Drug Discoveries, 1842–2000

1842	Long introduces ether as an anesthetic
1857	Locock accidentally discovers bromides as anticonvulsants
1867	Lister pioneers use of phenol as a surgical antiseptic
1869	Liebreich discovers hypnotic effects of chloral hydrate
1876	Stricker uncovers analgesic properties of salicylic acid
1882	Guthzeit and Conrad synthesize a series of barbiturates
1891	Erlich pioneers concepts of "receptor" and "chemotherapy"
1899	Meyer and Overton discover effect of lipid solubility on anesthetic action
1903	Fischer and von Mering identify hypnotic properties of barbiturates (see 1882)
1906	Hunt and Taveau synthesize and study acetylcholine
1912	Hauptmann accidentally discovers barbiturates as anticonvulsants (see 1903, 1882)
1921	Loewi demonstrates that acetylcholine is a neurotransmitter
1922	Banting and Best purify insulin as treatment for diabetes
1927	Szent-Gyorgyi isolates ascorbic acid (Vitamin C)
1929	Fleming serendipitously discovers antibacterial properties of penicillin
1932	Mietzach, Klarer, Domagk introduce first anti-streptococcal drug
1934	Ruzicka first synthesizes progesterone
1938	Merritt and Putnam use screening to identify hydantoins as anticonvulsants
1940	Chain and Florey introduce manufactured penicillin
1942	Ehrhard and Schauman produce synthetic analgesics (meperidine, methadone)
1945	Woodward and Doering synthesize quinine
1947	Lands introduces isoproterenol as a bronchodilator
1952	Charpentier identifies tricyclic phenothiazines as antipsychotics
1953	Watson and Crick deduce structure of DNA
1959	Beecham Laboratories develops semisynthetic penicillins
1959	Searle introduces the birth control pill
1960	Hoffmann-La Roche tests benzodiazepines as anxiolytics (Librium, Valium)
1962	Hansch develops principle of quantitative structure–activity relationships
1962	Pullman introduces quantum mechanics to drug design
1967	Cotzias pioneers the use of L-DOPA for treatment of Parkinson's disease
1975	Biochemically driven rational drug design begins to flourish as method
1985	Improved computers enable computer-aided drug design to advance
1995	Advances in combinatorial chemistry advance high throughput screening
2000	Widespread use of cholinesterase inhibitors for symptomatic treatment of Alzheimer's disease

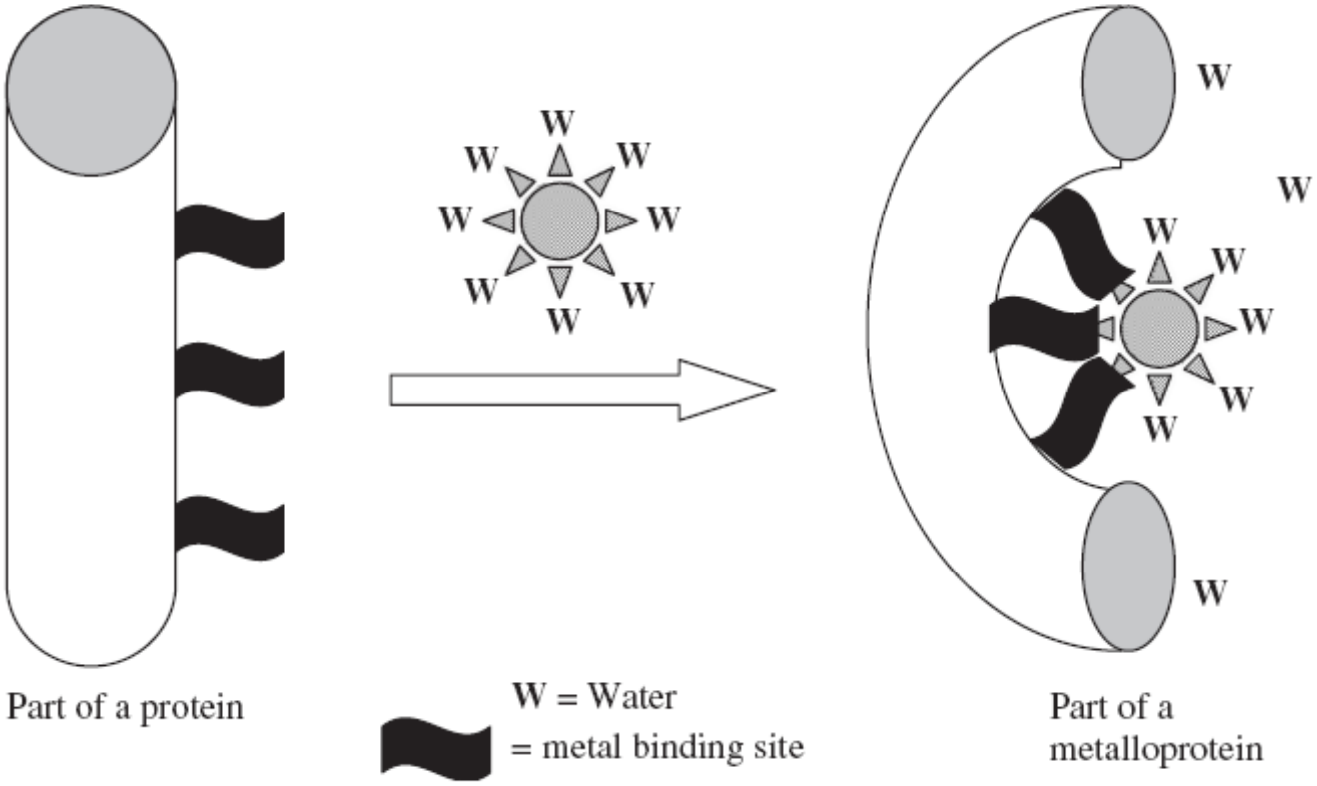
Few properties of Metals!

Lewis acids

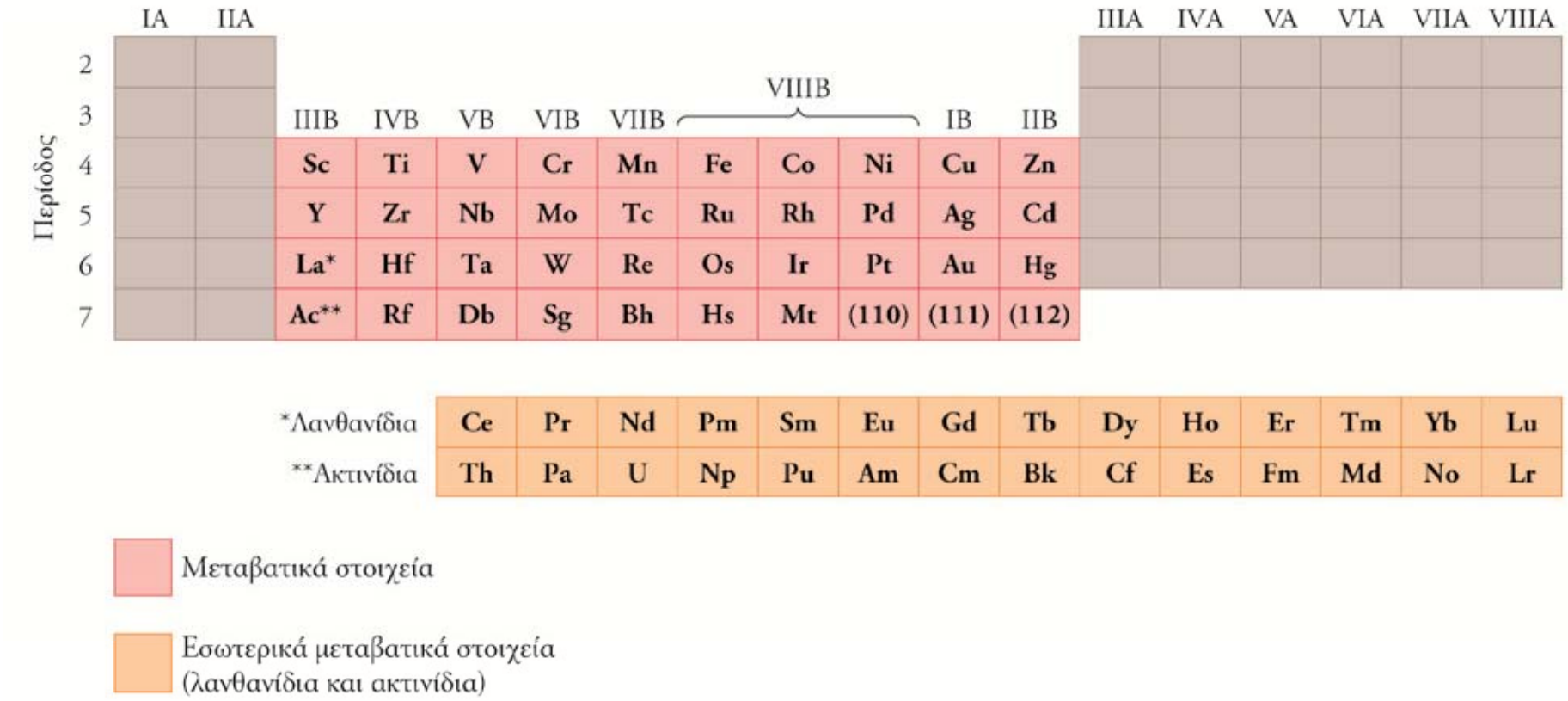
Can form reactive centers inside the proteins

Redox active

Bind and activate small



Few basics about Transition Metals!



ΠΙΝΑΚΑΣ 23.1

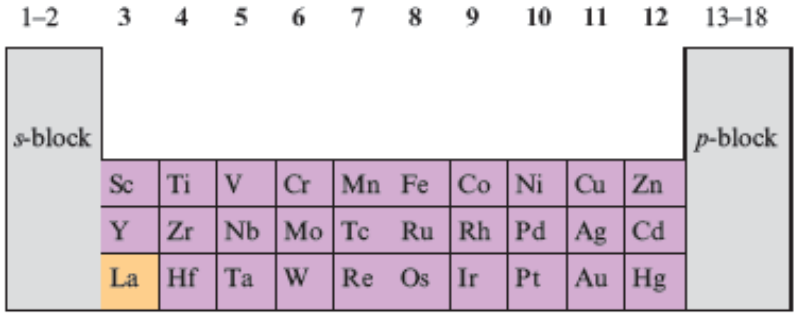
Ιδιότητες των μεταβατικών στοιχείων της τέταρτης περιόδου

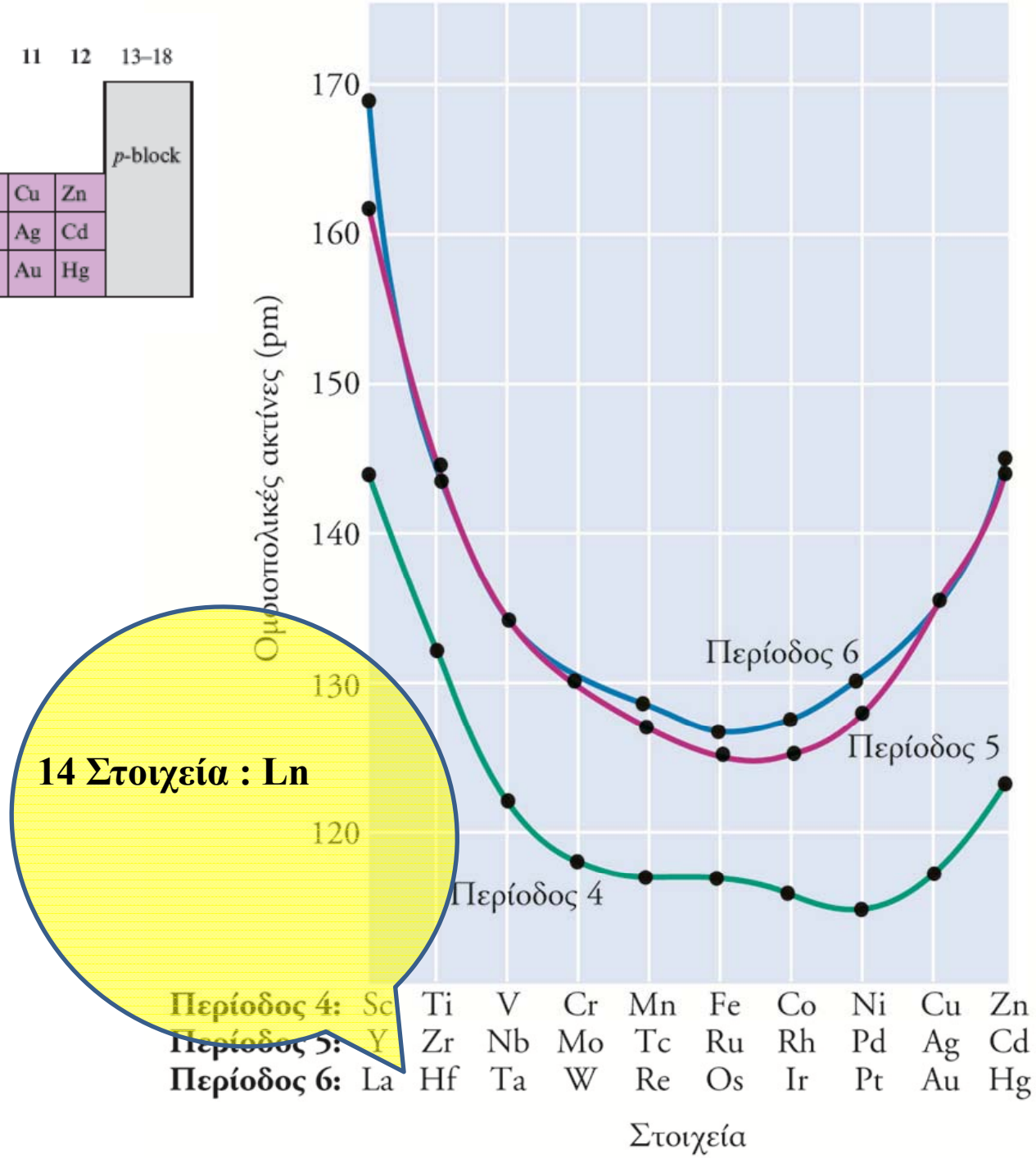
Ιδιότητα	Σκάνδιο	Τιτάνιο	Βανάδιο	Χρώμιο	Μαγγάνιο
Ηλεκτρονική δομή	$[Ar]3d^1 4s^2$	$[Ar]3d^2 4s^2$	$[Ar]3d^3 4s^2$	$[Ar]3d^5 4s^1$	$[Ar]3d^5 4s^2$
Σημείο τήξεως, °C	1541	1660	1890	1857	1244
Σημείο ζέσεως, °C	2831	3287	3380	2672	1962
Πυκνότητα, g/cm^3	3,0	4,5	6,0	7,2	7,2
Ηλεκτραρνητικότητα (κλίμακα Pauling)	1,3	1,5	1,6	1,6	1,5
Ομοιοπολική ακτίνα, pm	144	132	122	118	117
Ιοντική ακτίνα (για M^{2+}), pm	—	100	93	87	81

ΠΙΝΑΚΑΣ 23.1

(συνέχεια)

Ιδιότητα	Σίδηρος	Κοβάλτιο	Νικέλιο	Χαλκός	Ψευδάργυρος
Ηλεκτρονική δομή	$[Ar]3d^6 4s^2$	$[Ar]3d^7 4s^2$	$[Ar]3d^8 4s^2$	$[Ar]3d^{10}4s^1$	$[Ar]3d^{10}4s^2$
Σημείο τήξεως, °C	1535	1495	1453	1083	420
Σημείο ζέσεως, °C	2750	2870	2732	2567	907
Πυκνότητα, g/cm^3	7,9	8,9	8,9	8,9	7,1
Ηλεκτραρνητικότητα (κλίμακα Pauling)	1,8	1,8	1,8	1,9	1,6
Ομοιοπολική ακτίνα, pm	117	116	115	117	125
Ιοντική ακτίνα (για M^{2+}), pm	75	79	83	87	88


1–2
3
4
5
6
7
8
9
10
11
12
13–18
s-block
p-block
Sc Ti V Cr Mn Fe Co Ni Cu Zn
Y Zr Nb Mo Tc Ru Rh Pd Ag Cd
La Hf Ta W Re Os Ir Pt Au Hg


Ομοιοπολικές ακτίνες (pm)
170
160
150
140
130
120
Περίοδος 6
Περίοδος 5
Περίοδος 4
14 Στοιχεία : Ln
Περίοδος 4: Sc Ti V Cr Mn Fe Co Ni Cu Zn
Περίοδος 5: Y Zr Nb Mo Tc Ru Rh Pd Ag Cd
Περίοδος 6: La Hf Ta W Re Os Ir Pt Au Hg
Στοιχεία

ΠΙΝΑΚΑΣ 23.3

Οξειδωτικές καταστάσεις των μεταβατικών στοιχείων της τέταρτης περιόδου

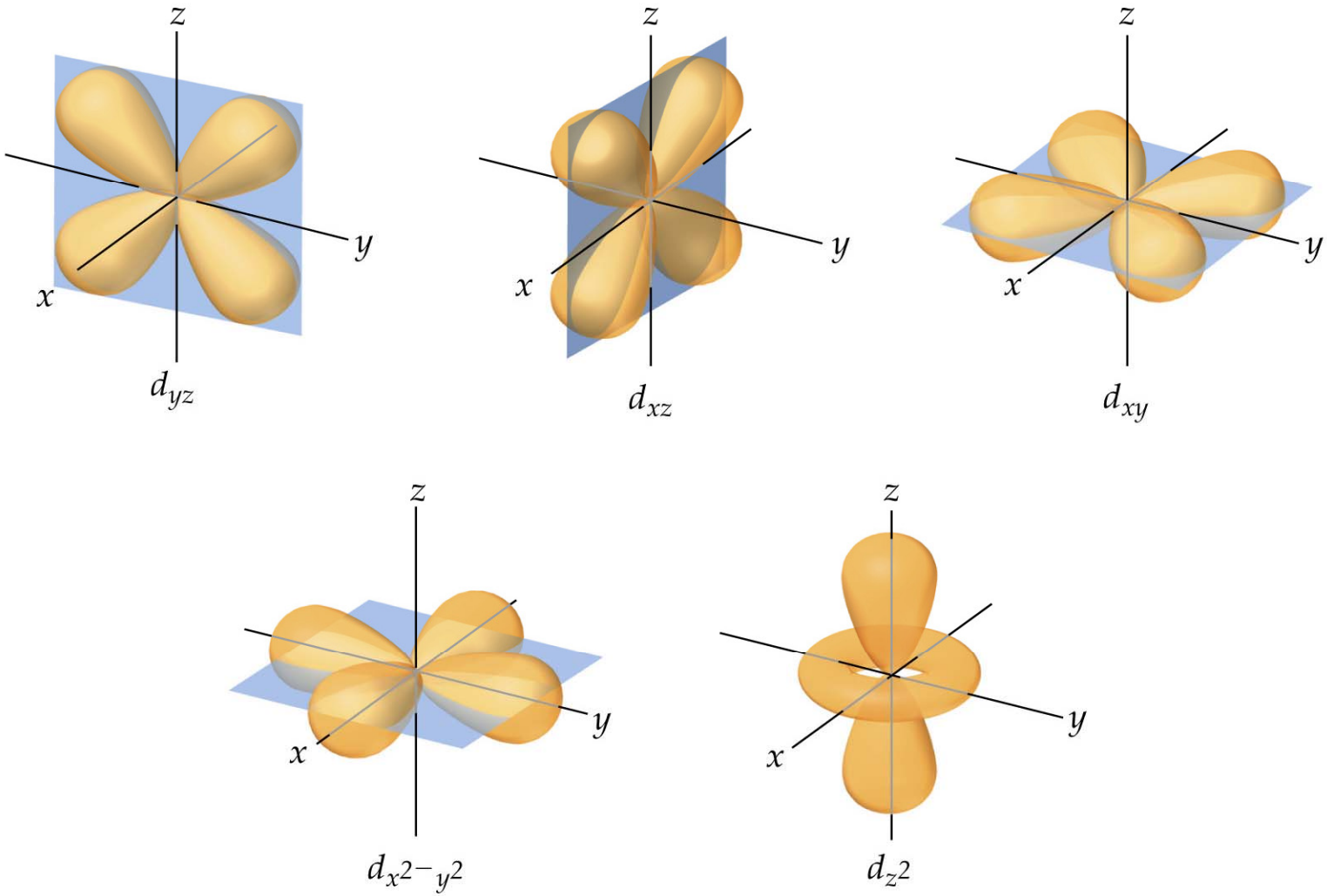
IIIB	IVB	VB	VIB	VIIB	VIIIB			IB	IIB
Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
							+1	**+1**	
	+2	+2	**+2**	**+2**	**+2**	**+2**	**+2**	**+2**	**+2**
+3	+3	**+3**	**+3**	+3	**+3**	**+3**	+3	+3	
	+4	**+4**	+4	**+4**	+4	+4	+4		
		+5	+5	+5	+5				
			+6	+6	+6				
				+7					

ΠΙΝΑΚΑΣ 23.4

Μεταβατικά μέταλλα απαραίτητα στη διατροφή του ανθρώπου

Στοιχείο	Μερικές βιοχημικές ουσίες	Λειτουργία
Χρώμιο	Παράγοντας ανοχής γλυκόζης	Χρησιμοποίηση γλυκόζης
Μαγγάνιο	Ισοκιτρική αφυδρογονάση	Ενεργητική κυττάρου
Σίδηρος	Αιμοσφαιρίνη και μυοσφαιρίνη	Μεταφορά και αποθήκευση οξυγόνου
	Κυτόχρωμα *c*	Ενεργητική κυττάρου
	Καταλάση	Διάσπαση υπεροξειδίου του υδρογόνου
Κοβάλτιο	Κοβαλαμίνη (βιταμίνη B_{12})	Ανάπτυξη ερυθρών αιμοκυττάρων
Χαλκός	Χαλκοπλασμίνη	Σύνθεση αιμοσφαιρίνης
	Κυτοχρωμική οξειδάση	Ενεργητική κυττάρου
Ψευδάργυρος	Καρβοανυδράση	Απόσπαση διοξειδίου του άνθρακα
	Καρβοξυπεπτιδάση Α (παγκρεατικό υγρό)	Πέψη πρωτεϊνών
	Αλκοολική αφυδρογονάση	Οξείδωση αιθανόλης

Ας θυμηθούμε τα σχήματα των 3d τροχιακών



The Nobel Prize in Chemistry 1913

Alfred Werner (University of Zurich, Switzerland)

"in recognition of his work on the linkage of atoms in molecules by which he has thrown new light on earlier investigations and opened up new fields of research especially in inorganic chemistry"

Πριν το Werner δεν ήταν γνωστό **πως** συνδέονται τα άτομα στο μόριο $Pt(NH_3)_2Cl_2$

Οι μέχρι τότε θεωρίες υποστήριζαν γραμμική σύνδεση

$[Pt\text{-}NH_3\text{-}NH_3\text{-}Cl]Cl$ ή $Cl\text{-}NH_3\text{-}Pt\text{-}NH_3\text{-}Cl$

Ο Werner με μία σειρά πειραματικών μετρήσεων πρότεινε **δύο διαφορετικούς τύπους δεσμών στην ανόργανες ενώσεις**

Πρωτεύον σθένος: καθορισμένος αριθμός, προερχόμενος από την εξουδετέρωση φορτίου

Δευτερεύον σθένος: καθορίζεται από το κεντρικό μέταλλο, είναι μη ιοντικοί και έχουν συγκεκριμένο προσανατολισμό στο χώρο άρα μελετώνται με εφαρμογή δομικών αρχών

Δομές που μελέτησε ο Werner

ΠΙΝΑΚΑΣ 23.6
Μερικά σύμπλοκα του λευκοχρύσου(IV) που μελετήθηκαν από τον Werner

Παλιός τύπος	Σύγχρονος τύπος	Αριθμός ιόντων	Αριθμός ελεύθερων ιόντων Cl^-
$PtCl_4 \cdot 6NH_3$	$[Pt(NH_3)_6]Cl_4$	5	4
$PtCl_4 \cdot 4NH_3$	$[Pt(NH_3)_4Cl_2]Cl_2$	3	2
$PtCl_4 \cdot 3NH_3$	$[Pt(NH_3)_3Cl_3]Cl$	2	1
$PtCl_4 \cdot 2NH_3$	$[Pt(NH_3)_2Cl_4]$	0	0

Alfred Werner και η θεωρία του για τις ενώσεις σύνταξης

Παλαιός τύπος	*m*	*n*	Τύπος Werner	Ιόντα	
$PtCl_4 \cdot 6NH_3$	4	5	$[Pt(NH_3)_6]Cl_4$	$[Pt(NH_3)_6]^{4+}$	4 Cl^-
$PtCl_4 \cdot 5NH_3$	3	4	$[Pt(NH_3)_5Cl]Cl_3$	$[Pt(NH_3)_5Cl]^{3+}$	3 Cl^-
$PtCl_4 \cdot 4NH_3$	2	3	$[Pt(NH_3)_4Cl_2]Cl_2$	$[Pt(NH_3)_4Cl_2]^{2+}$	2 Cl^-
$PtCl_4 \cdot 3NH_3$	1	2	$[Pt(NH_3)_3Cl_3]Cl$	$[Pt(NH_3)_3Cl_3]^{+}$	1 Cl^-
$PtCl_4 \cdot 2NH_3$	0	0	$[Pt(NH_3)_2Cl_4]$	δεν δίνει ιόντα	

m = moles AgCl που καθιζάνουν ανά mole ενώσεως, μετά από προσθήκη περίσσειας $AgNO_3(aq)$ (από σταθμική ανάλυση)

n = αριθμός ιόντων ανά τυπική μονάδα ενώσεως (από μετρήσεις αγωγιμότητας)

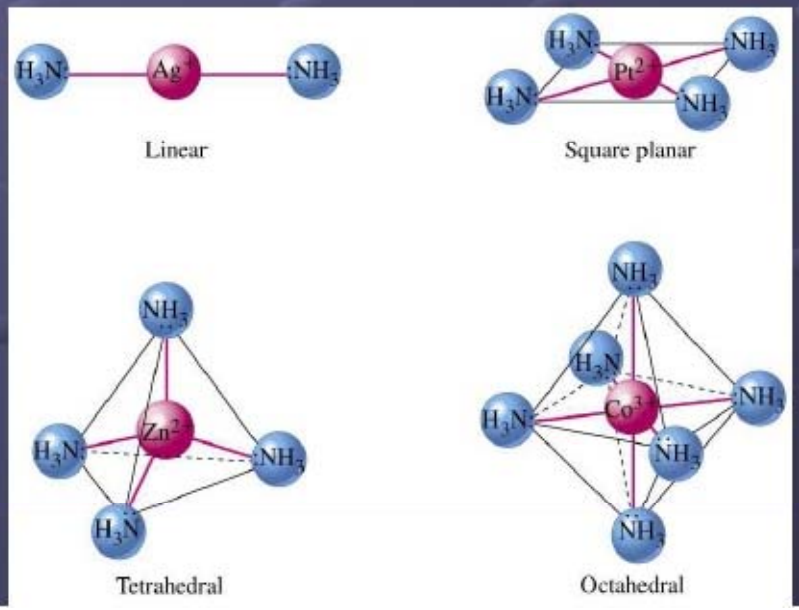
Σήμερα

Ενώσεις συναρμογής : μεταλλικές ενώσεις που σχηματίζονται με αλληλεπιδράσεις οξέος –βάσης κατά Lewis

Σύμπλοκα : έχουν ένα κεντρικό μέταλλο ενωμένο με ένα αριθμό υποκατασταtών. Τα σύμπλοκα ιόντα μπορεί είναι φορτισμένα π.χ. **$[Ag(NH_3)_2]^+$.**

Υποκαταστάτες: βάσεις κατά Lewis

Σφαίρα συναρμογής : το μέρος του χώρου που περιέχει το μέταλλο και τους υποκατασtάτες



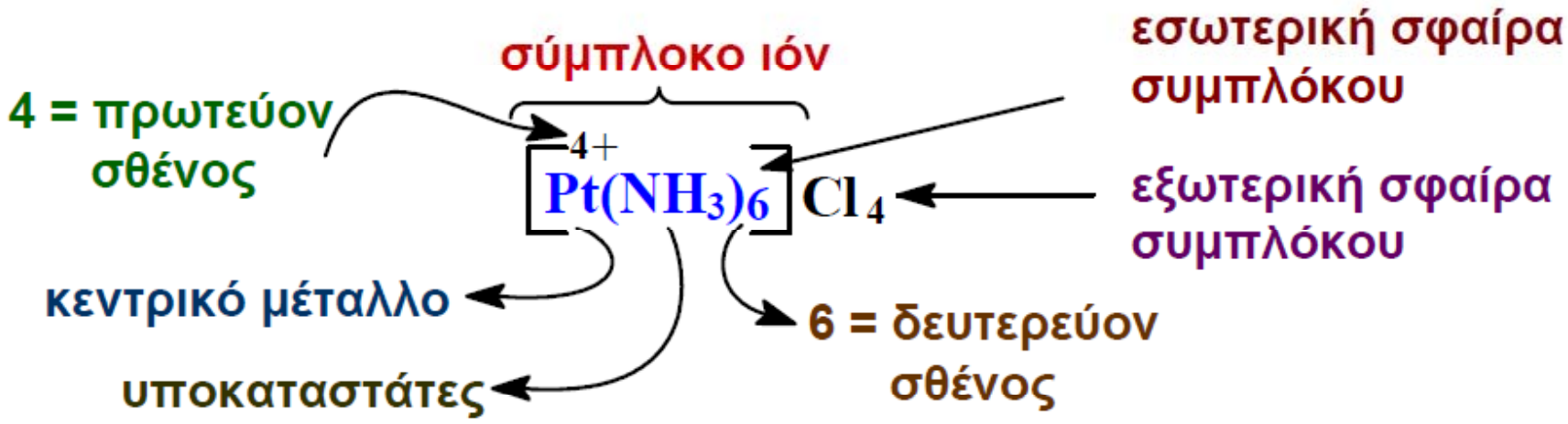
ΠΙΝΑΚΑΣ 23.5

Παραδείγματα συμπλόκων διαφόρων αριθμών σύνταξης

Σύμπλοκο	Αριθμός σύνταξης
$Ag(NH_3)_2^+$	2
HgI_3^-	3
$PtCl_4^{2-}$, $Ni(CO)_4$	4
$Fe(CO)_5$, $Co(CN)_5^{3-}$	5
$Co(NH_3)_6^{3+}$, $W(CO)_6$	6
$Mo(CN)_7^{3-}$	7
$W(CN)_8^{4-}$	8

Alfred Werner και η θεωρία του για τις ενώσεις σύνταξης

Αποσαφήνιση των βασικών όρων της θεωρίας του Werner στο παράδειγμα του συμπλόκου $Pt(NH_3)_6Cl_4$



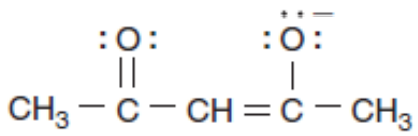
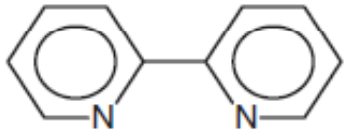
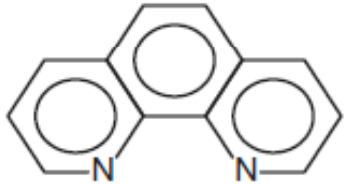
Υποκαταστάτης-ligand :

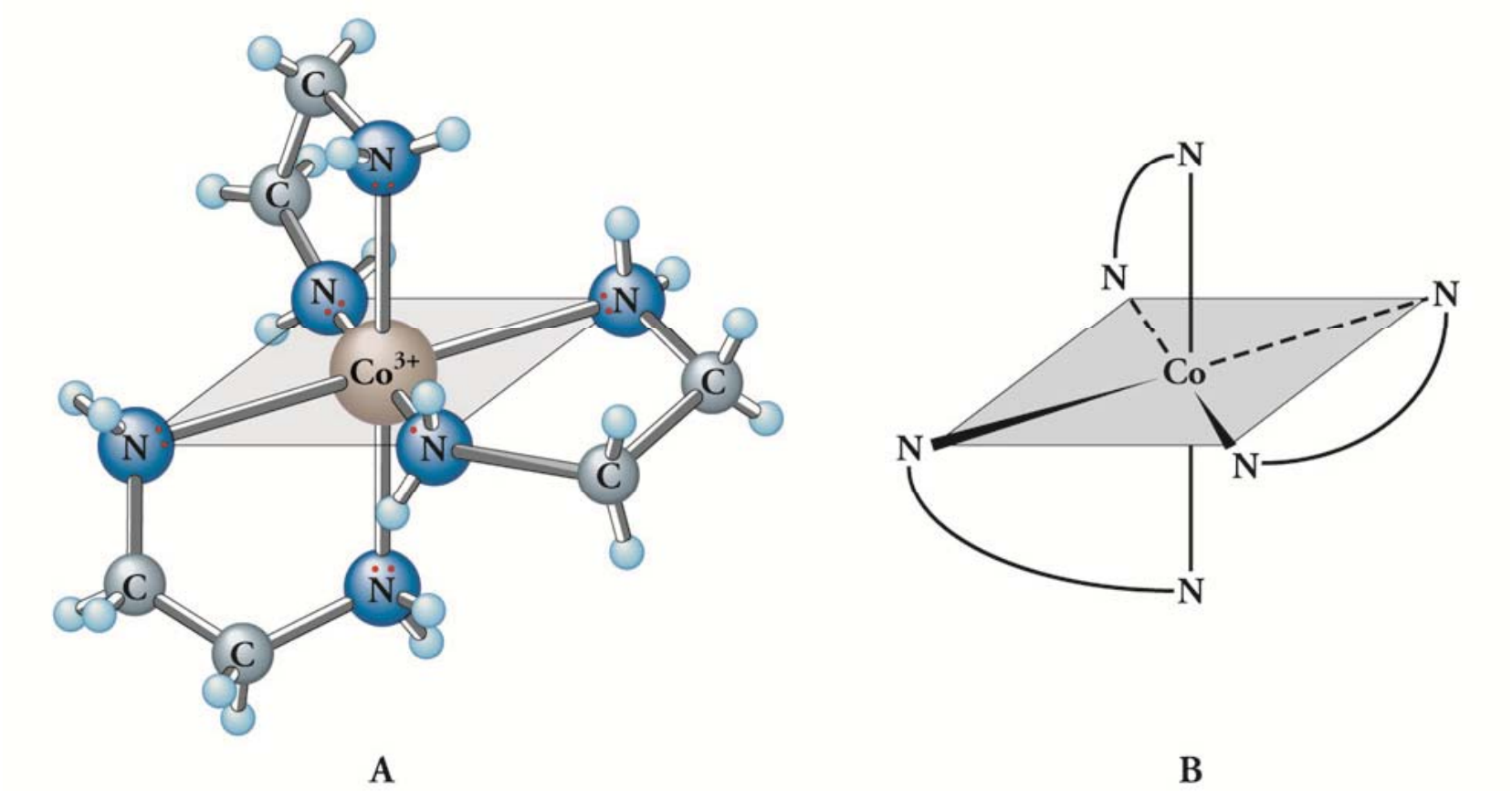
✦ μπορεί να είναι ιόν ή μόριο ή άτομο που ενώνεται με το κεντρικό μέταλλο

✦Είναι βάση κατά Lewis και δίνει ηλεκτρόνια στο κεντρικό μέταλλο

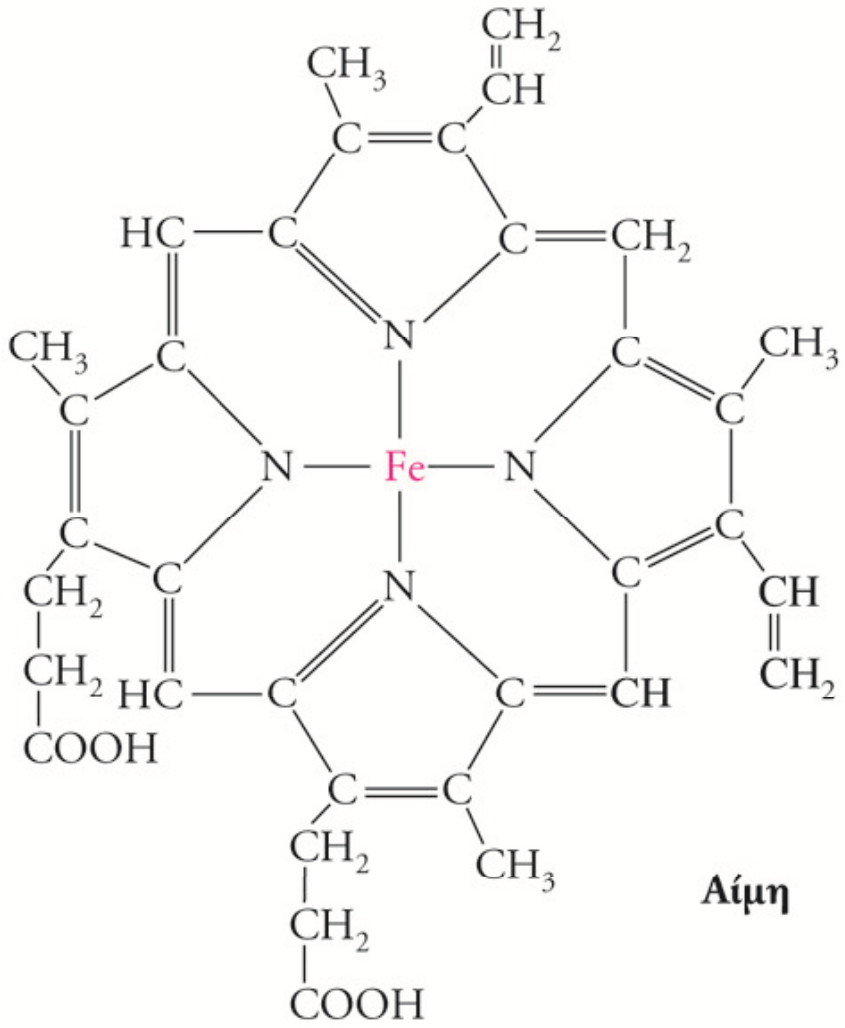
✦ Ανάλογα με τον αριθμό των μονήρων ηλεκτρονίων οι υποκαταστάτες μπορεί να είναι **μονοδοντικοί (**συνδέονται με το μέταλλο με ένα δεσμό), **διδοντικοί….ή πολυδοντικοί**

Table 16.1 Some of the Most Common Ligands.

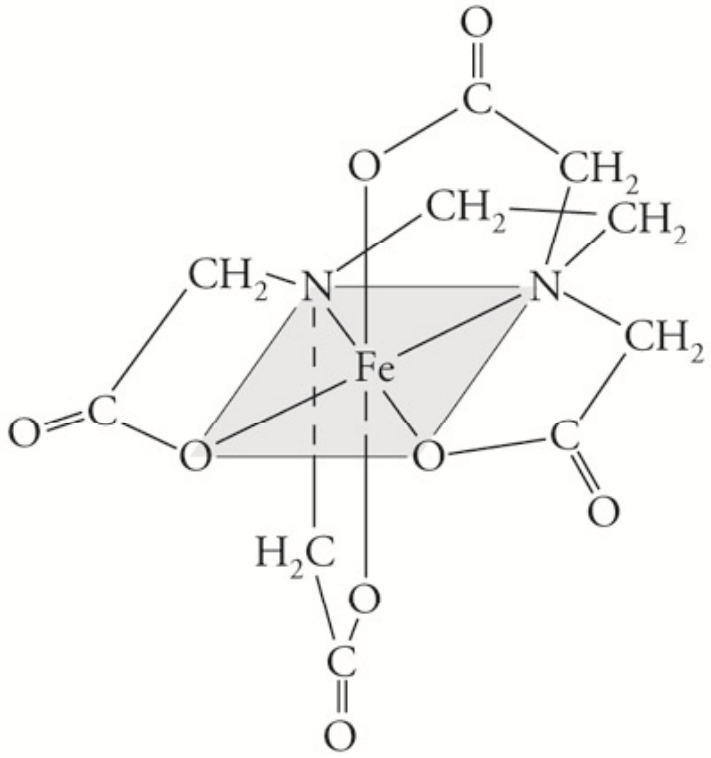
Group	Formula	Name
Water	H_2O	aqua
Ammonia	NH_3	ammine
Chloride	Cl^-	chloro
Cyanide	CN^-	cyano
Hydroxide	OH^-	hydroxo
Thiocyanate	SCN^-	thiocyanato
Carbonate	CO_3^{2-}	carbonato
Nitrite	NO_2^-	nitrito
Oxalate	$C_2O_4^{2-}$	oxalato
Carbon monoxide	CO	carbonyl
Nitric oxide	NO	nitrosyl
Ethylenediamine	$H_2\ddot{N}CH_2CH_2\ddot{N}H_2$	ethylenediamine
Acetylacetonate		acetylacetonato
2,2′-Dipyridyl		2,2′-dipyridyl
1,10-Phenanthroline		1,10-phenanthroline



Γιατί είναι σταθεροί οι χηλικοί δακτύλιοι?



Αίμη

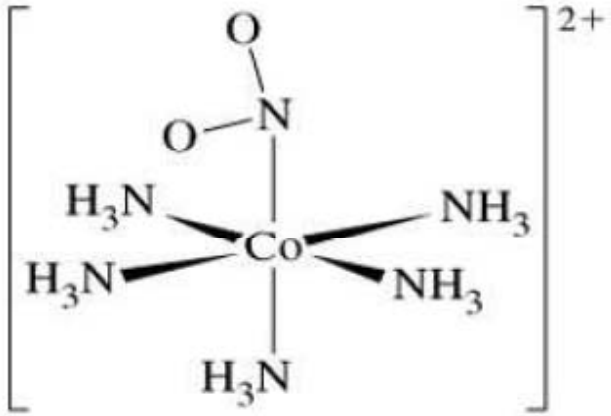


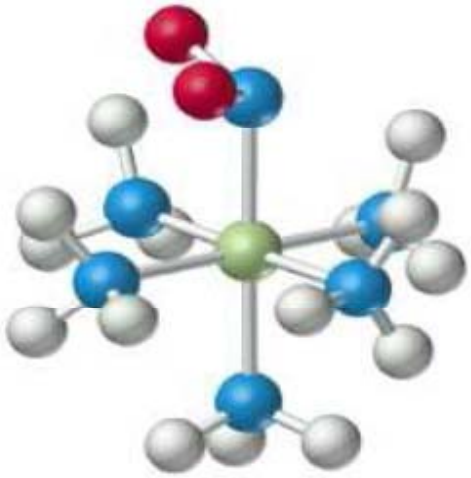
Σύμπλοκο του Fe^{2+} με EDTA

Ισομέρεια

Δομική ισομέρεια

- Ορισμένα ligands συναρμόζονται με διαφορετικούς τρόπους δηλαδή το ligand μπορεί να συναρμοστεί με το μέταλλο με διαφορετικά άτομα δίνοντας την **ισομέρεια σύνδεσης**.
- Παράδειγμα: NO_2^- συναρμόζεται μέσω
- του N ή του O (π.χ.στο σύμπλοκο $[Co(NH_3)_5(NO_2)]^{2+}$ δύο σύμπλοκα είναι πιθανά
- Όταν ενώνεται μέσω του N ονομάζεται –νιτρο (nitro).
  - Πενταάμινο νίτρο κοβάλτιο (III) και είναι κίτρινο
- όταν ONO^- συναρμόζεται μέσω του O ονομάζεται νιτριδο.
  - Πενταάμινο νιτριδοκοβάλτιο (III) και είναι κόκκινο

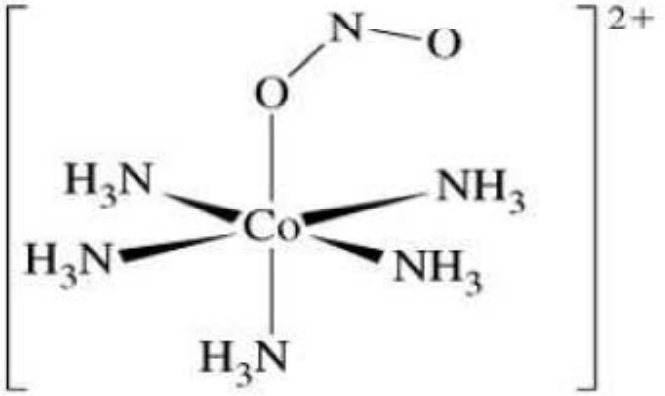


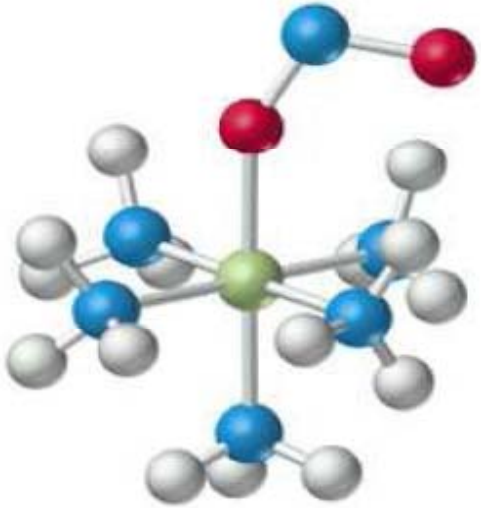


(a) $[Co(NO_2)(NH_3)_5]^{2+}$

χλωρίδιο του πενταμμινο-
νιτροκοβαλτίου(III)
$[Co(NH_3)_5(NO_2)]Cl_2$

$$[Co(NH_3)_5ONO]^{2+} \rightarrow [Co(NH_3)_5NO_2]^{2+}$$
red, nitrito → yellow, nitro





(b) $[Co(ONO)(NH_3)_5]^{2+}$

χλωρίδιο του πενταμμινο-
νιτριτοκοβαλτίου(III)
$[Co(NH_3)_5(ONO)]Cl_2$

Υποκαταστάτες ικανοί για ισομερή σύνδεσης:

NO_2^-	–NO_2 (νιτρο),	–ONO (νιτριτο)
CN^-	–CN (κυανο),	–NC (ισοκυανο)
SCN^-	–SCN (θειοκυανατο),	–NCS (ισοθειοκυανατο)

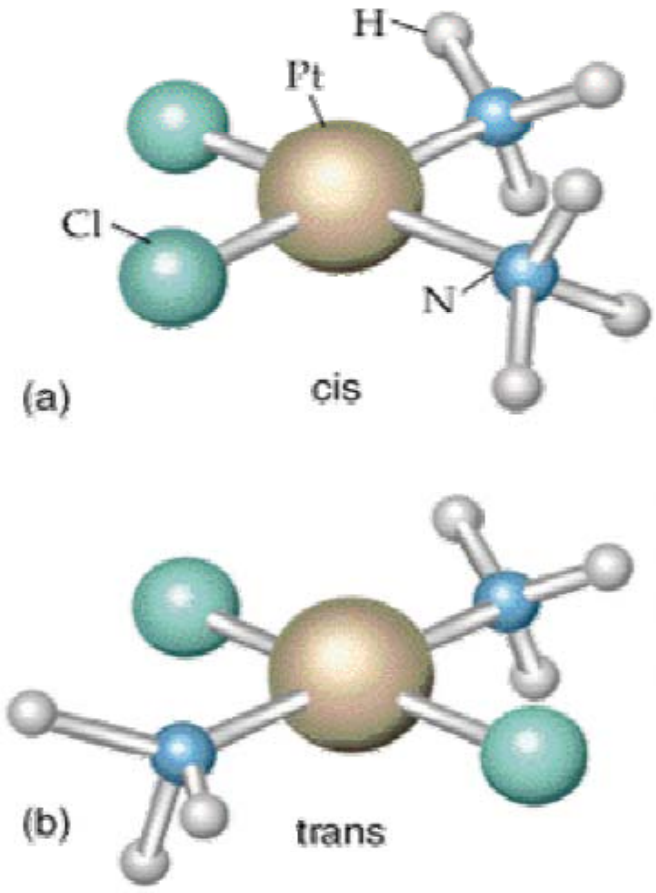
Γεωμετρική ισομέρεια

Επίπεδα τετραγωνικά

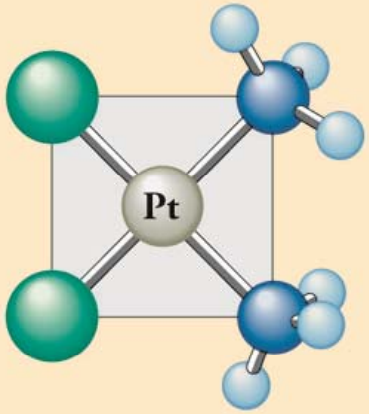
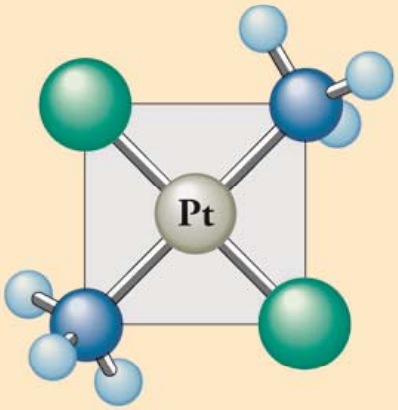
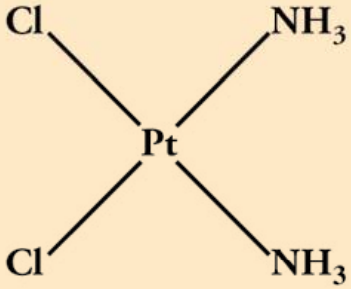
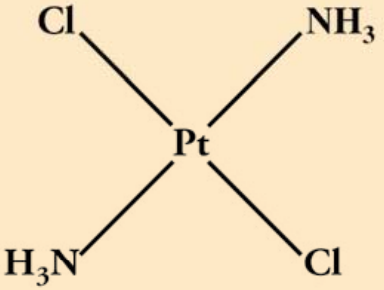
Cis-trans ισομέρεια

Γωνία 90°

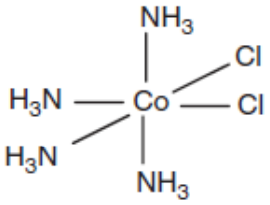
Γωνία 180°



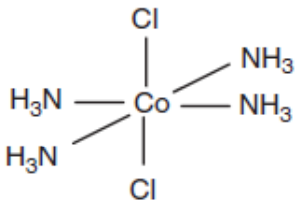
Χρησιμοποιείται στη χημειοθεραπεία

	cis	*trans*
Μοντέλο σφαίρας–ράβδου		
Συντακτικός τύπος		
Χρώμα	Πορτοκαλοκίτρινο	Ωχροκίτρινο
Διαλυτότητα	0,252 g/100 g H_2O	0,037 g/100 g H_2O

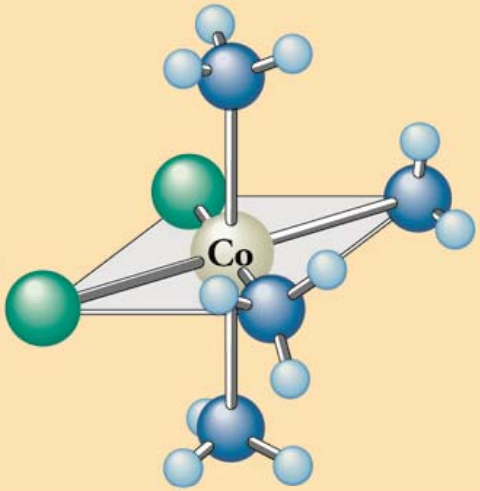
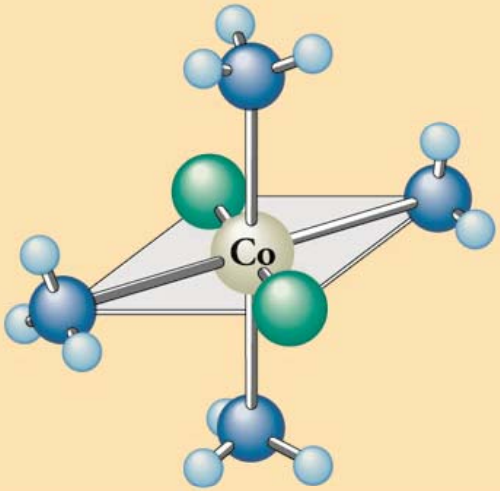
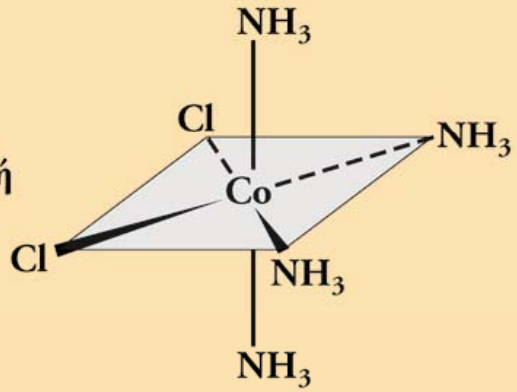
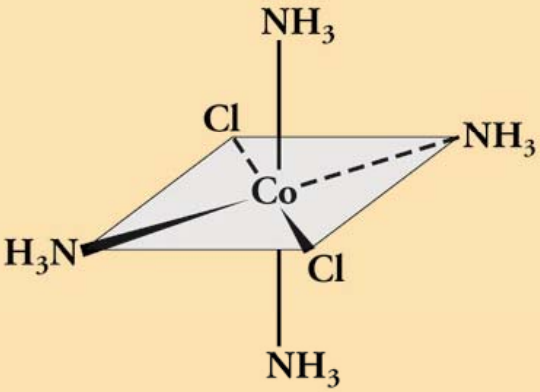
MX_2Y_2



Cis (violet)

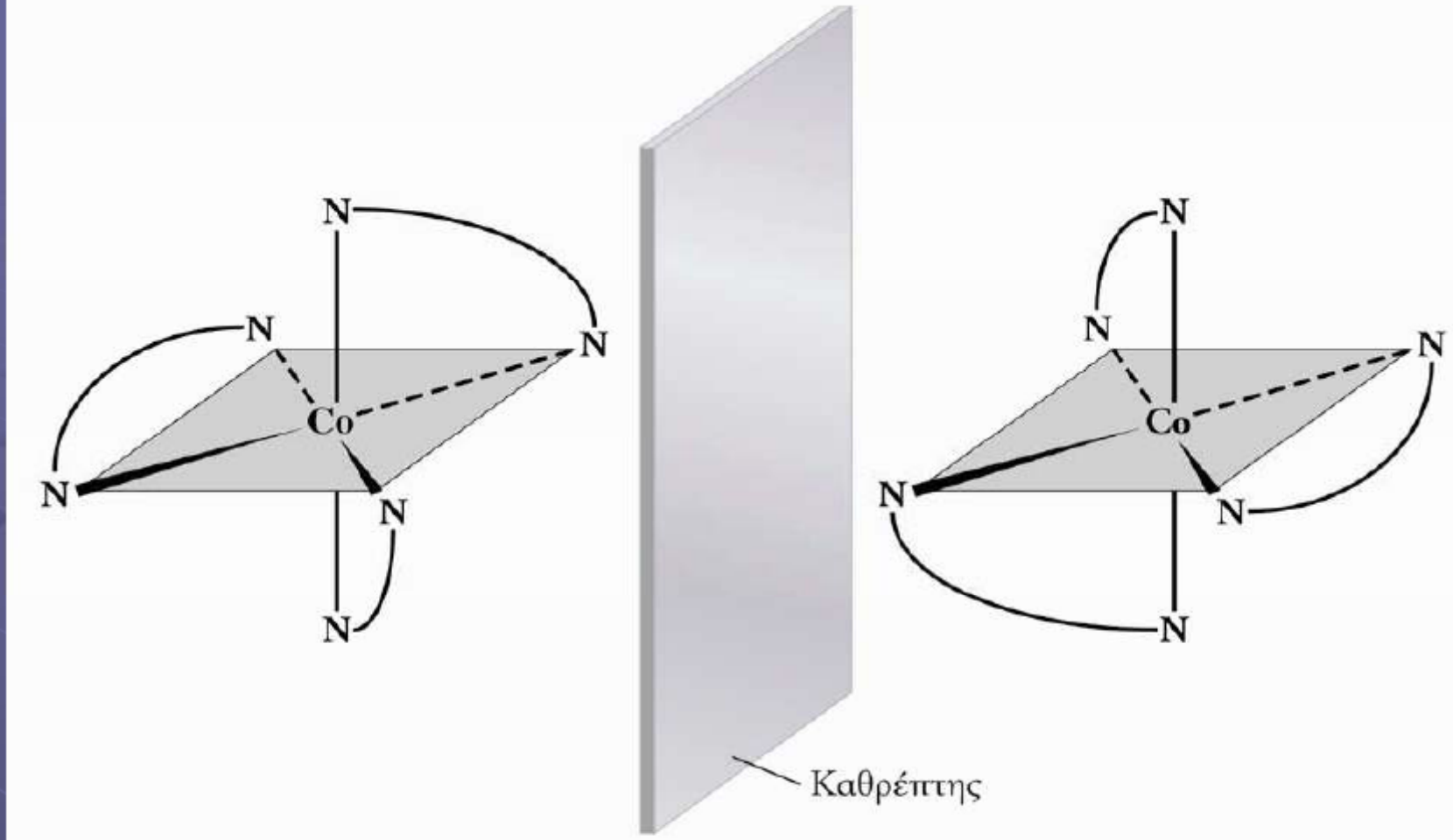


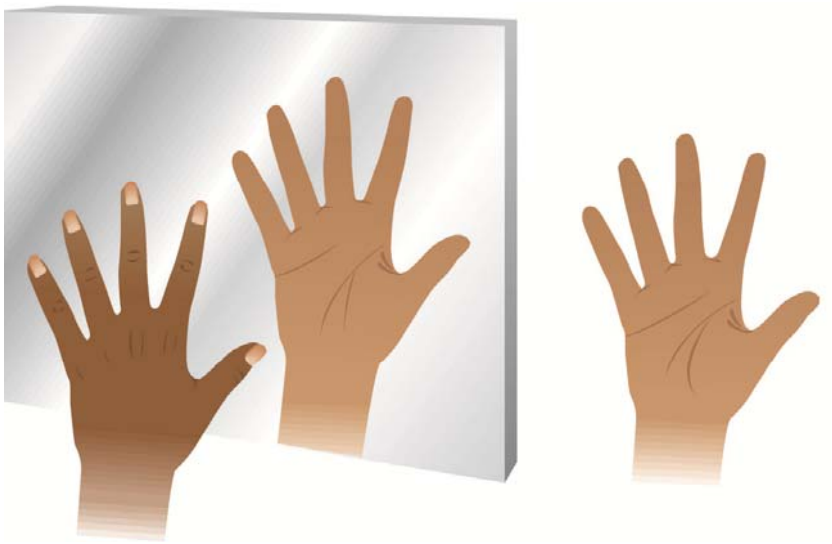
Trans (green)

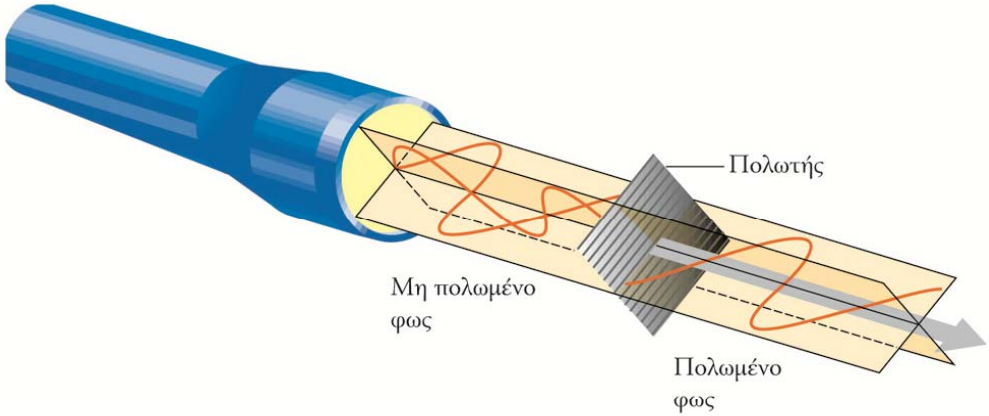
	cis	***trans***
Μοντέλο σφαίρας–ράβδου		
Συντομογραφική απεικόνιση		
Χρώμα	Πορφυρό	Πράσινο

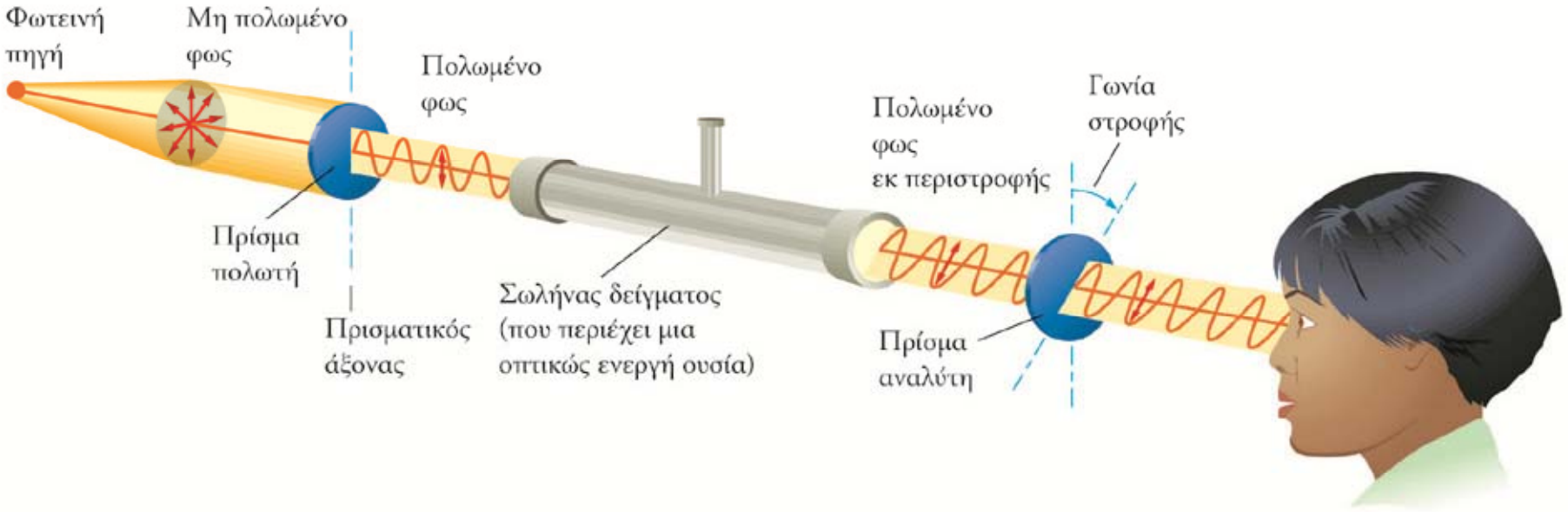
MX_4Y_2

Οπτικά ισομερή

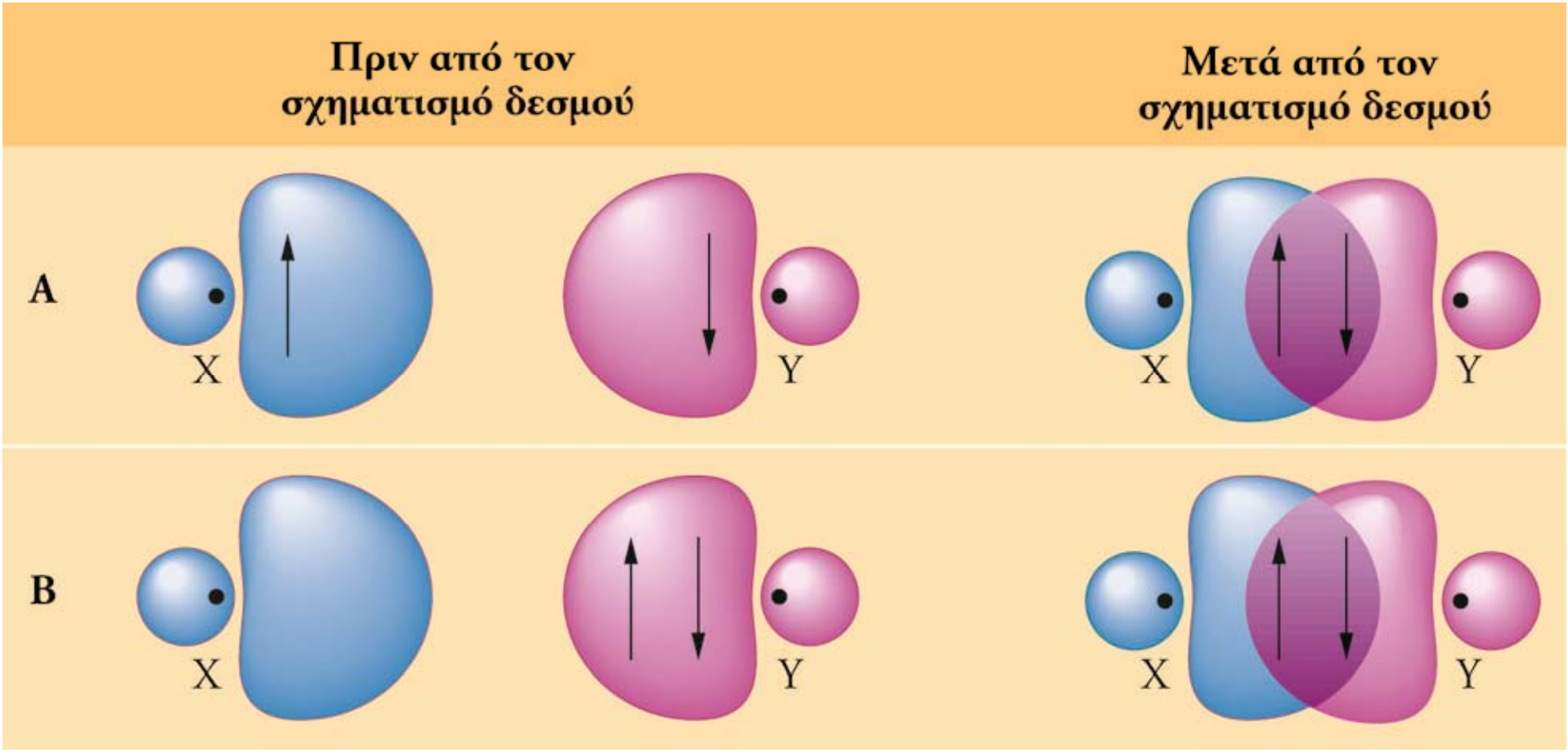


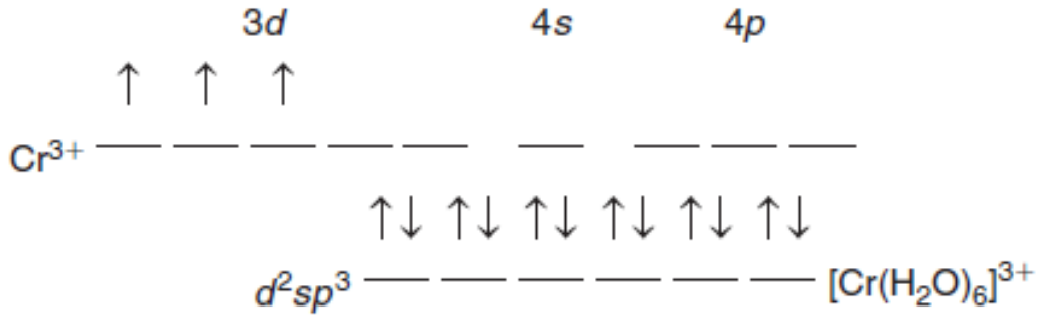


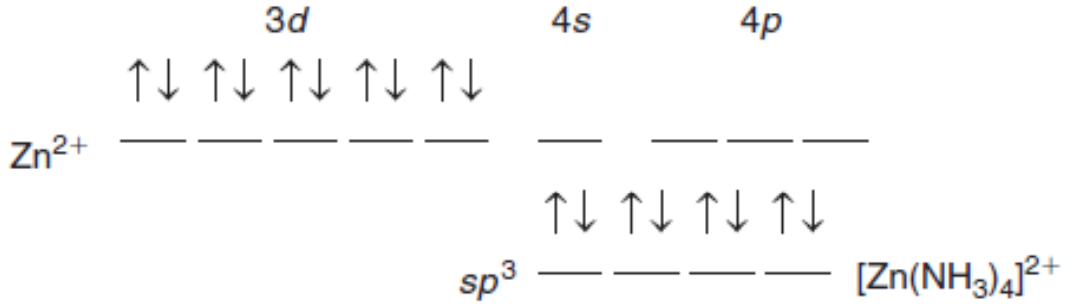

Πολωτής
Μη πολωμένο φως
Πολωμένο φως

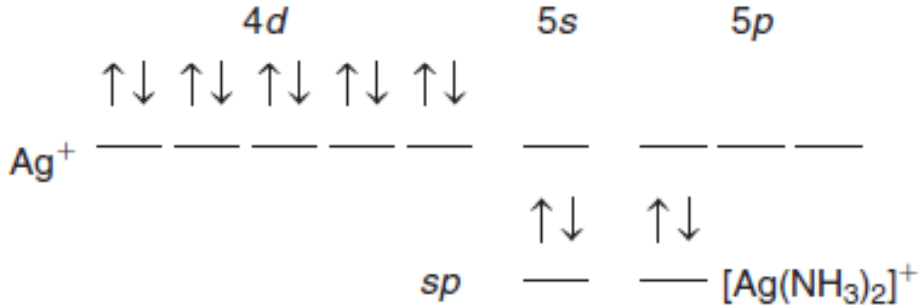

Φωτεινή πηγή
Μη πολωμένο φως
Πολωμένο φως
Πολωμένο φως εκ περιστροφής
Γωνία στροφής
Πρίσμα πολωτή
Πρισματικός άξονας
Σωλήνας δείγματος (που περιέχει μια οπτικώς ενεργή ουσία)
Πρίσμα αναλύτη

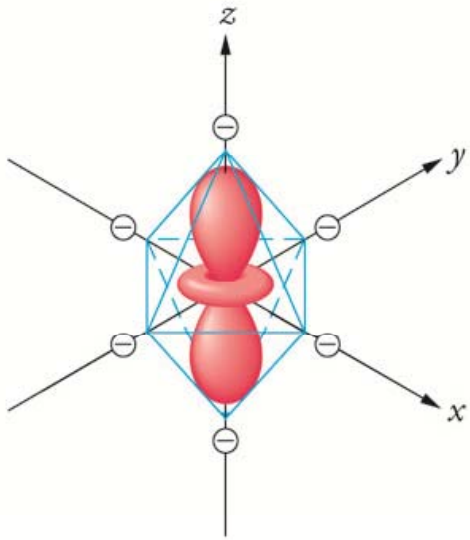
Η θεωρία του δεσμού σθένους στα σύμπλοκα



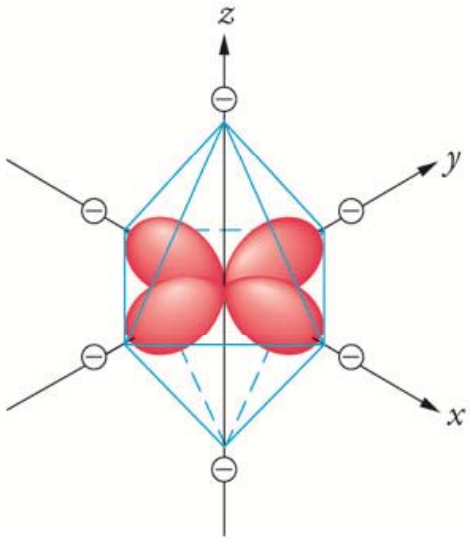

3d
4s
4p
Cr3+
d2sp3
[Cr(H2O)6]3+


3d
4s
4p
Zn2+
sp3
[Zn(NH3)4]2+

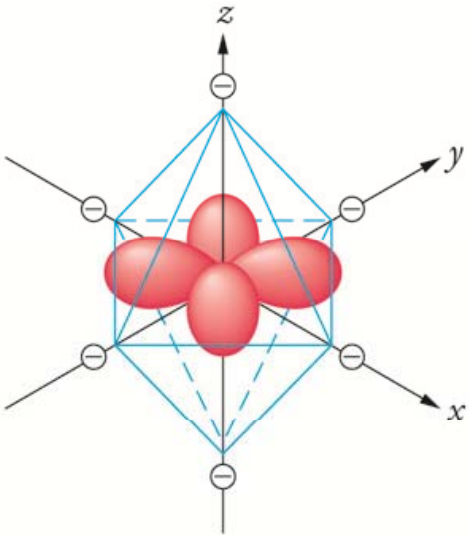

4d
5s
5p
Ag+
sp
[Ag(NH3)2]+



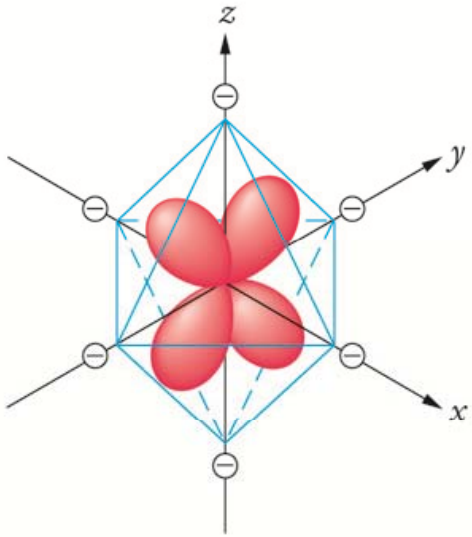
d_{z^2}



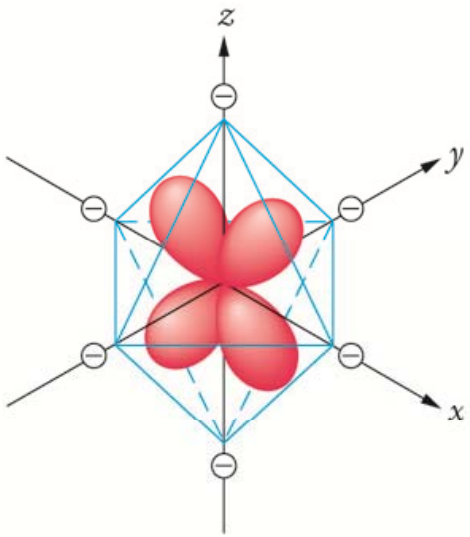
$d_{x^2-y^2}$



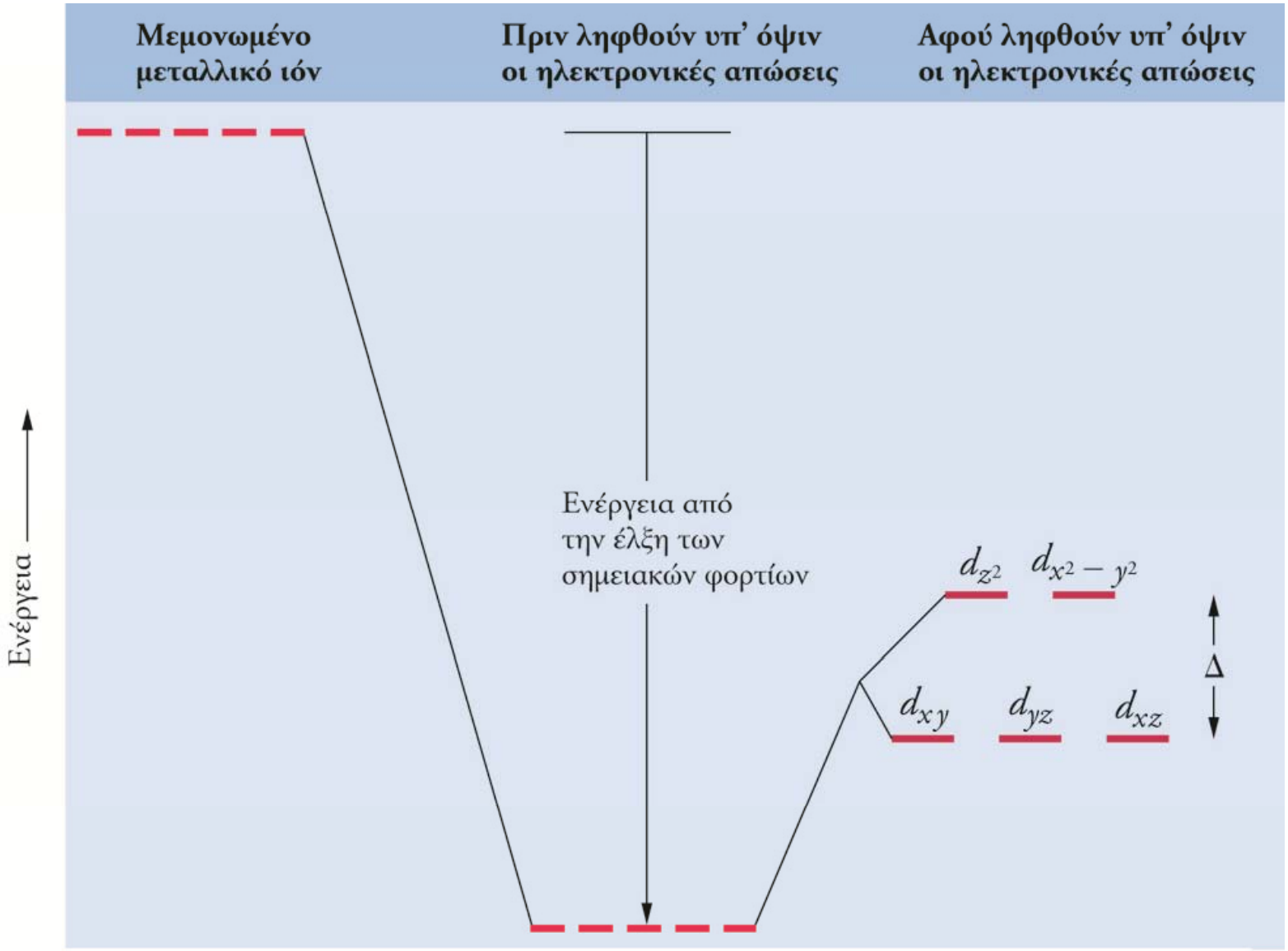
d_{xy}

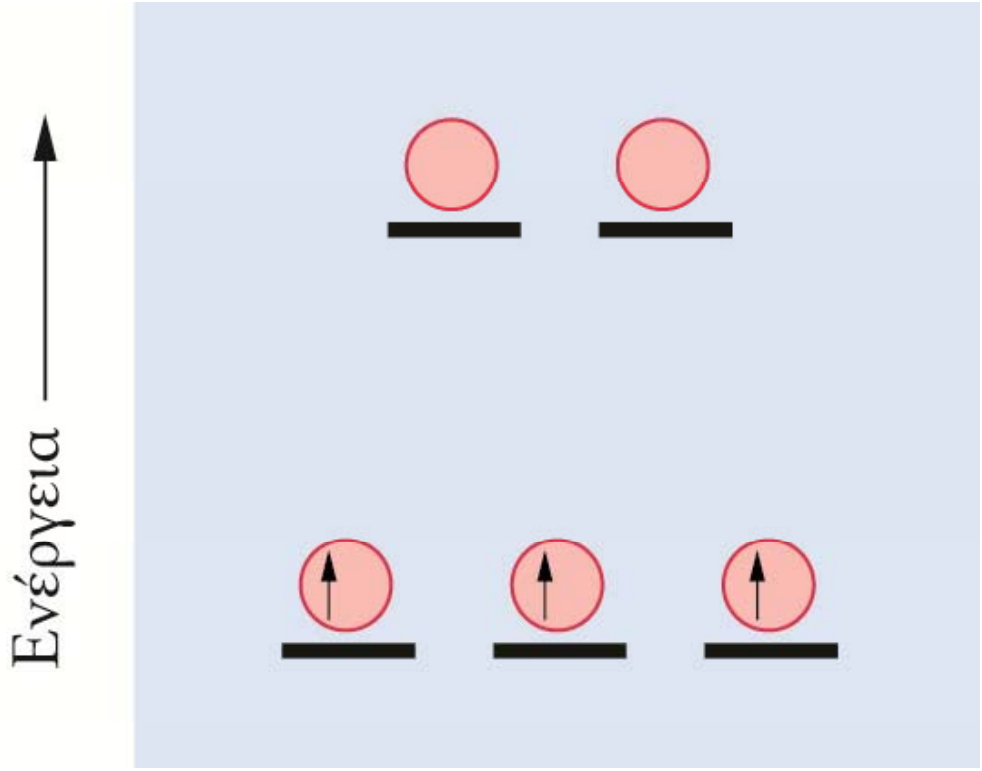


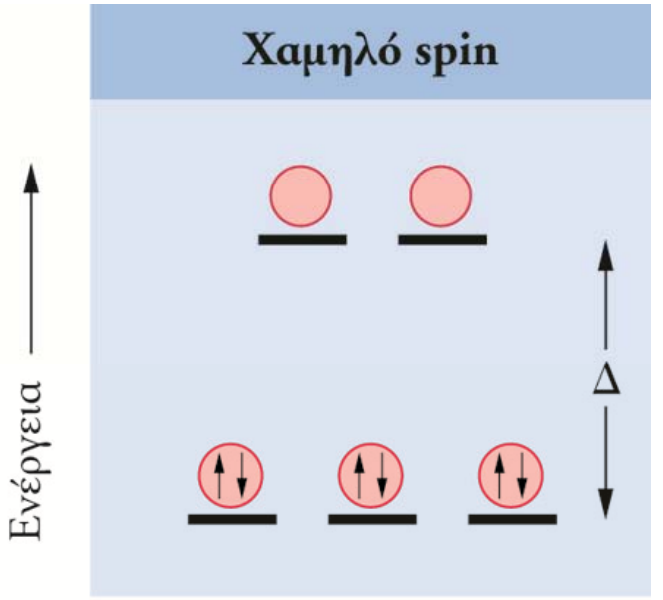
d_{yz}



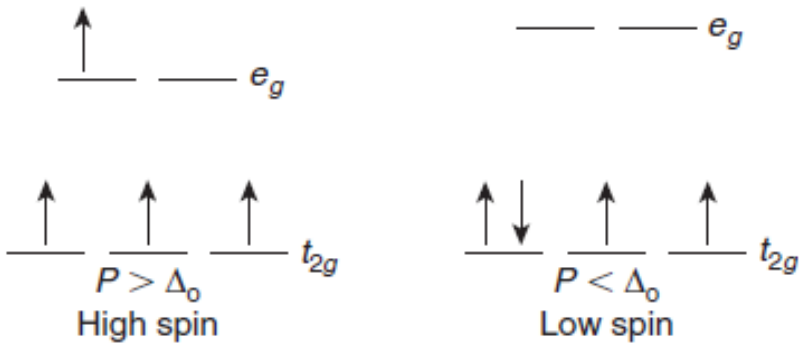
d_{xz}

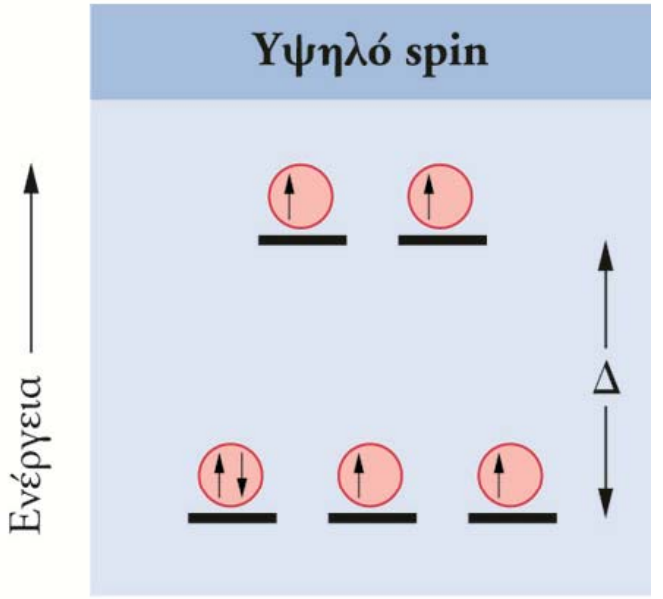

Μεμονωμένο μεταλλικό ιόν
Πριν ληφθούν υπ' όψιν οι ηλεκτρονικές απώσεις
Αφού ληφθούν υπ' όψιν οι ηλεκτρονικές απώσεις
Ενέργεια
Ενέργεια από την έλξη των σημειακών φορτίων
d_{z^2}
$d_{x^2-y^2}$
d_{xy}
d_{yz}
d_{xz}
Δ





A





B

Crystal field splitting energy compared to the electron pairing energy.

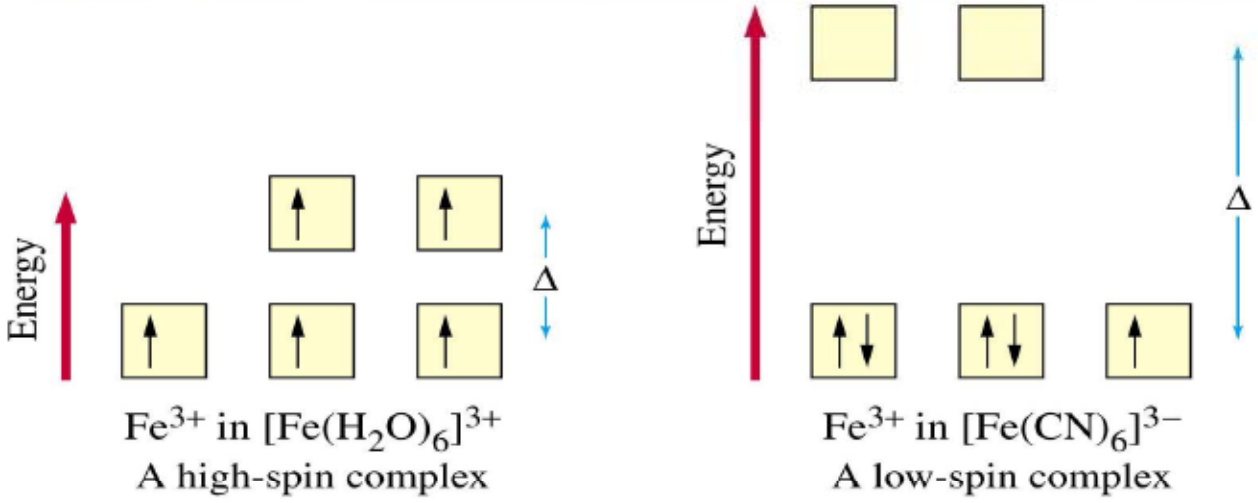
Δεσμοί στίς σύμπλοκες ενώσεις: Θεωρία κρυσταλλικού πεδίου

Η *φασματοχημική σειρά* δείχνει τη σχετική ικανότητα των ligands να διασπούν τα ενεργειακά επίπεδα των *d*-τροχιακών.

Field strength: Strong → Weak

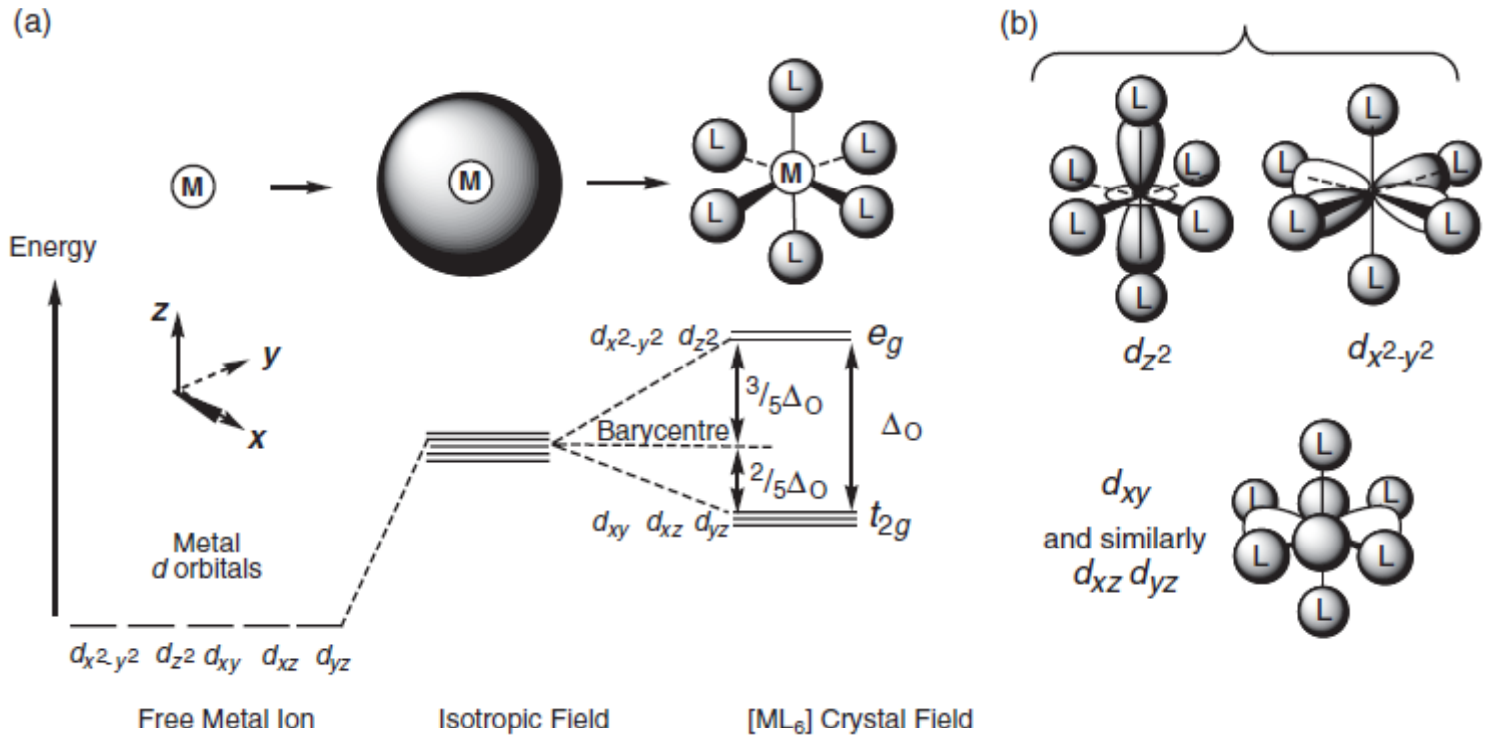
$CN^- > NO_2^- > en > NH_3 > H_2O > OH^- > F^- > Cl^- > Br^- > I^-$

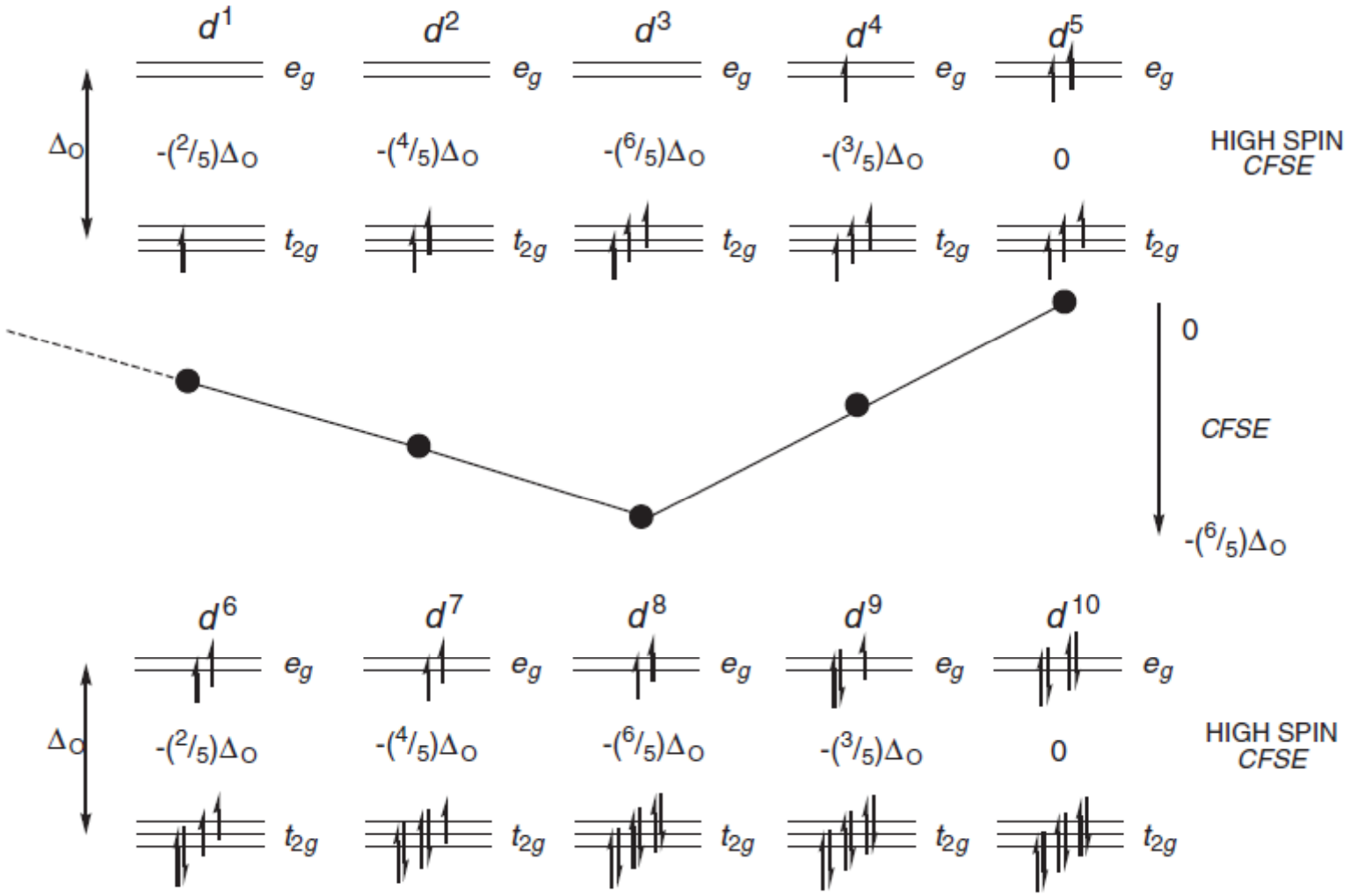
d-Level splitting, Δ: Large → Small

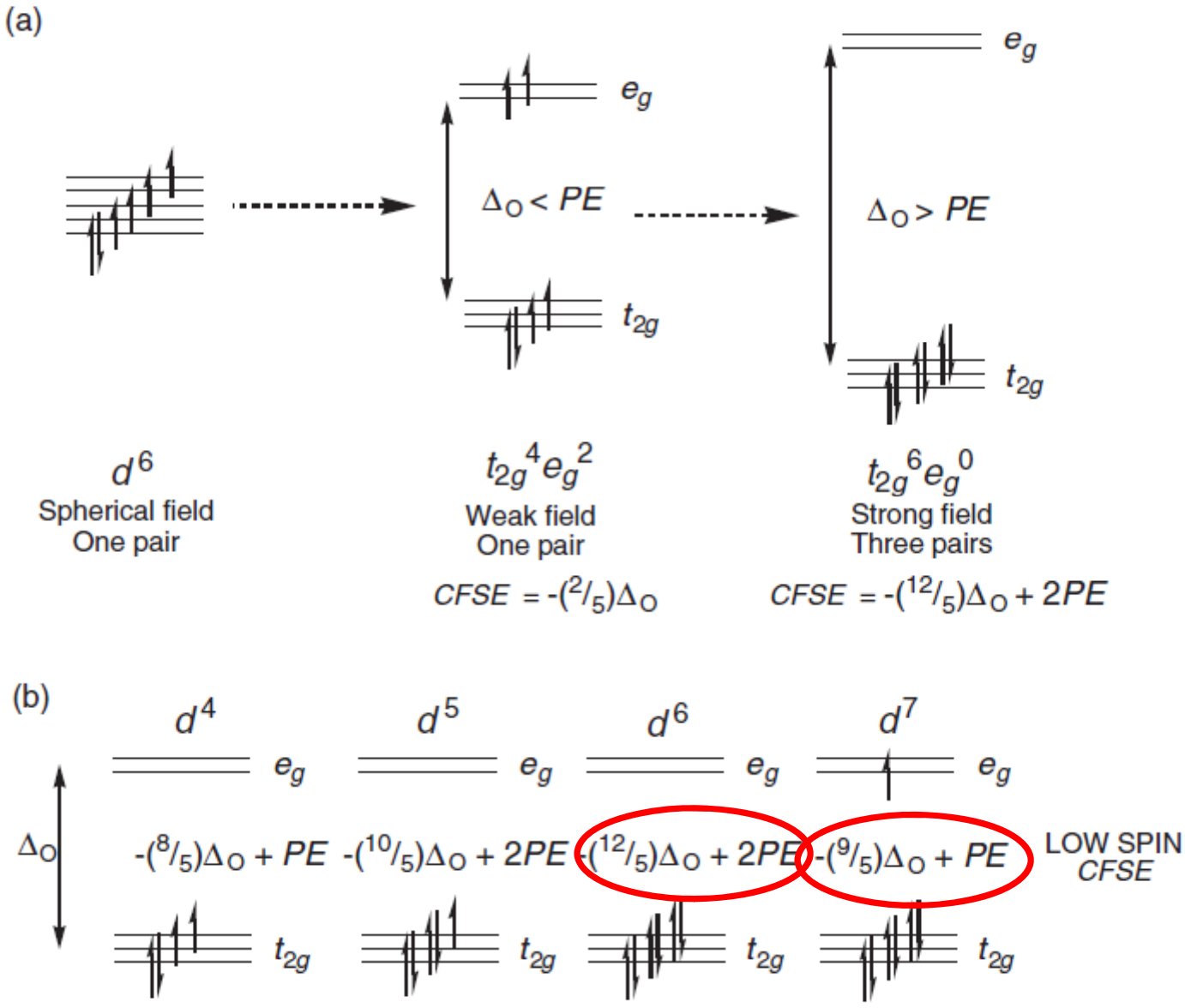


Fe^{3+} in $[Fe(H_2O)_6]^{3+}$
A high-spin complex

Fe^{3+} in $[Fe(CN)_6]^{3-}$
A low-spin complex

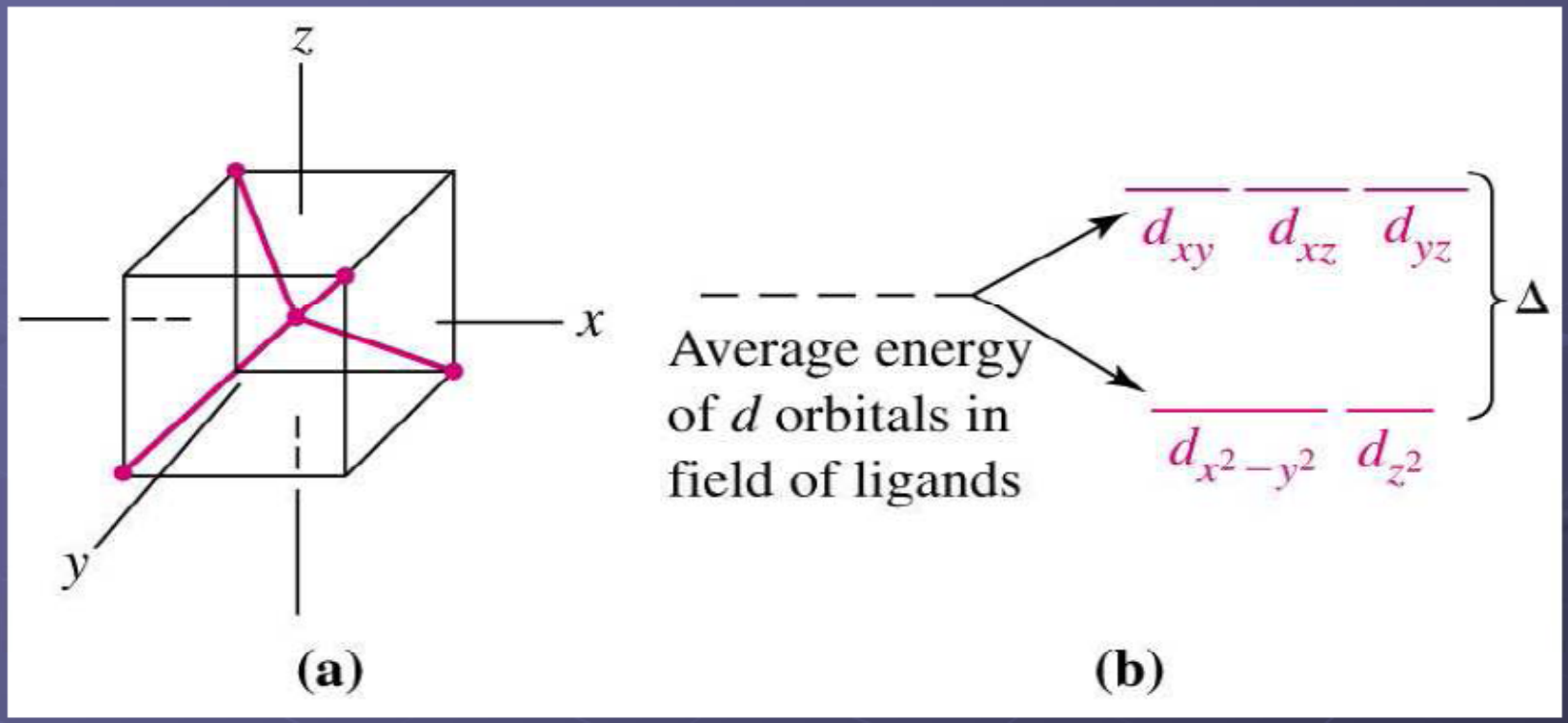

(a)
M
M
L
L
L
L
L
L
M
Energy
z
y
x
$d_{x^2-y^2}$ d_{z^2}
e_g
$^3/_5\Delta_O$
Barycentre
Δ_O
$^2/_5\Delta_O$
d_{xy} d_{xz} d_{yz}
t_{2g}
Metal
d orbitals
$d_{x^2-y^2}$ d_{z^2} d_{xy} d_{xz} d_{yz}
Free Metal Ion
Isotropic Field
[ML_6] Crystal Field
(b)
d_{z^2}
$d_{x^2-y^2}$
d_{xy}
and similarly
d_{xz} d_{yz}

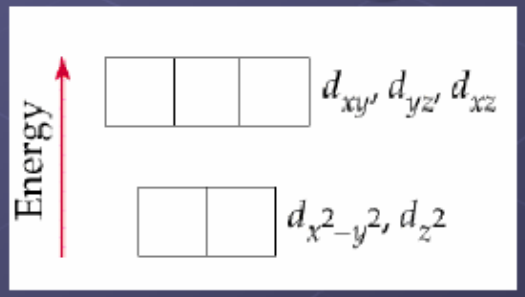

d^1
d^2
d^3
d^4
d^5
e_g
Δ_O
$-(^2/_5)\Delta_O$
$-(^4/_5)\Delta_O$
$-(^6/_5)\Delta_O$
$-(^3/_5)\Delta_O$
0
HIGH SPIN
CFSE
t_{2g}
0
CFSE
$-(^6/_5)\Delta_O$
d^6
d^7
d^8
d^9
d^{10}
e_g
Δ_O
$-(^2/_5)\Delta_O$
$-(^4/_5)\Delta_O$
$-(^6/_5)\Delta_O$
$-(^3/_5)\Delta_O$
0
HIGH SPIN
CFSE
t_{2g}


(a)
e_g
$\Delta_O < PE$
t_{2g}
e_g
$\Delta_O > PE$
t_{2g}
d^6
Spherical field
One pair
$t_{2g}^4 e_g^2$
Weak field
One pair
$CFSE = -(^2/_5)\Delta_O$
$t_{2g}^6 e_g^0$
Strong field
Three pairs
$CFSE = -(^{12}/_5)\Delta_O + 2PE$
(b)
d^4
d^5
d^6
d^7
e_g
Δ_O
$-(^8/_5)\Delta_O + PE$
$-(^{10}/_5)\Delta_O + 2PE$
$-(^{12}/_5)\Delta_O + 2PE$
$-(^9/_5)\Delta_O + PE$
LOW SPIN
CFSE
t_{2g}

ΤΕΤΡΑΕΔΡΙΚΗ ΔΙΑΤΑΞΗ

Εχουμε άρση του εκφυλισμού των d τροχιακών

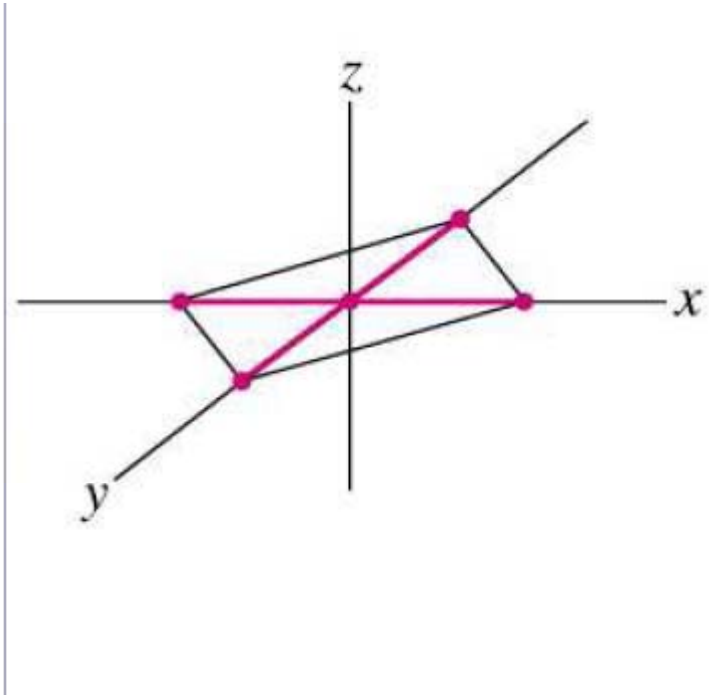


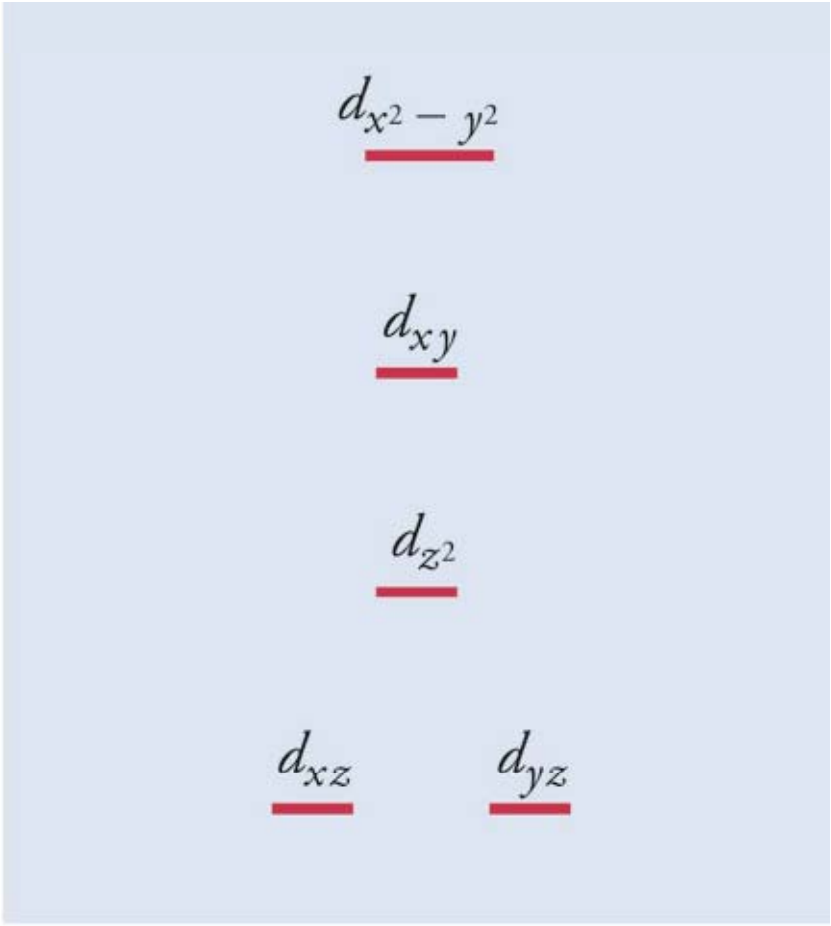


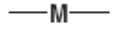
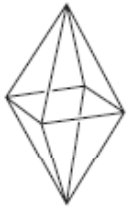
Η Δ είναι πιο μικρή και όλα τα τετραεδρικά είναι **υψηλού σπιν**

Επίπεδη τετραγωνική διάταξη

- Τα περισσότερα d^8 μεταλλικά ιόντα σχηματίζουν επίπεδα τετραγωνικά σύμπλοκα..
  - Η πλειοψηφία των συμπλόκων είναι χαμηλού spin.
  - Pd^{2+}, Pt^{2+}, Ir^{+}, Au^{3+}.





CO-ORDINATION NUMBER	GEOMETRY	POLYHEDRON	COMMENTS
2 Linear			Uncommon: found mainly with d^{10} metal ions
3 Trigonal Plane			Rare
4 Square Plane			Common for d^8 metal ions otherwise unusual
4 Tetrahedron			Common for d^{10} and some d^5 ions
5 Trigonal Bipyramid			Rare — Examples are often similar in structure and energy so may easily interconvert.
5 Square Pyramid			Rare
6 Octahedron			Very common: usually the most favoured energetically for *d*-block metal ions and gives the lowest ligand-ligand repulsions
(Octahedron = Trigonal Antiprism)			An alternative view of an octahedron down a three fold rotation axis
6 Tetragonal			A distorted octahedron elongated or flattened along one axis
6 Trigonal Prismatic			Rare not normally favoured over octahedral

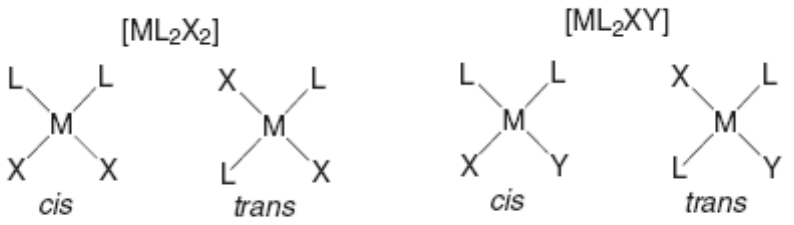
CO-ORDINATION NUMBER	GEOMETRY	POLYHEDRON	COMMENTS
7 Pentagonal Bipyramid			Uncommon
7 Monocapped Octahedron			Uncommon
8 Dodecahedron			Most sterically efficient geometric arrangement for 8 equivalent ligands
8 Square Antiprism			Uncommon
8 Cube			Rare found only with the largest metal ions
8 Hexagonal Bipyramid			Quite common for 8-coordinate complexes of metals with *trans*-dioxo ligands *i.e.* $\{O=M=O\}^{z+}$

LARGER CO-ORDINATION NUMBERS

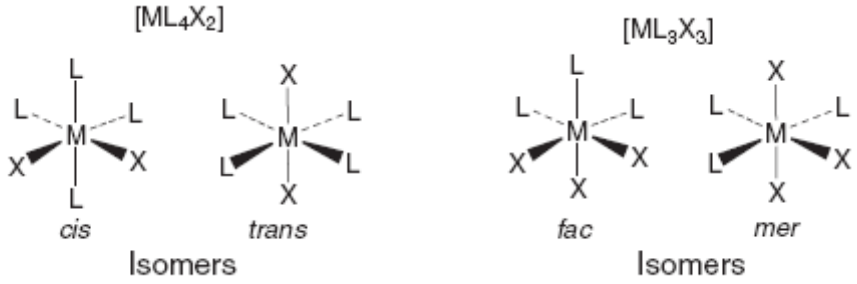
C.N.	9	10	11	12
	Tricapped trigonal prism	Bicapped square antiprism	Octadecahedron	Icosahedron
				

Most regular co-ordination polyhedra

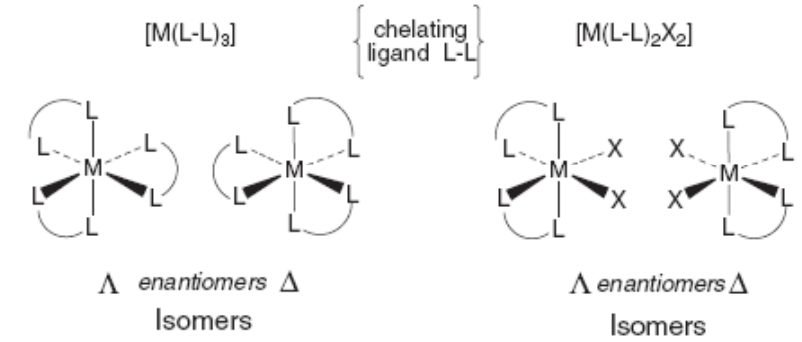
(a) Square Planar

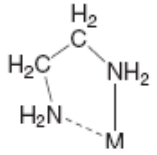


(b) Octahedral

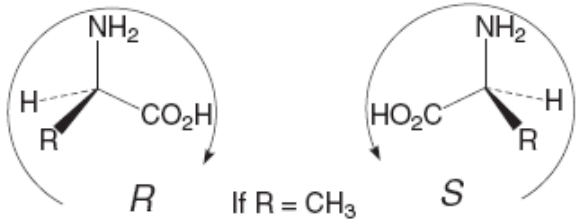


(c) Chiral complexes



for L-L = en  or represent 

(d) Chiral carbon centres



Substitution Reactions at Metal Centers…

Stability and Dissociation…

Stability: Provides info on the relative proportions of the solvated metal ion, free ligands and complex present in a solution at equilibrium.. not always good indicator…especially if "*other factors*" start affecting the complex .

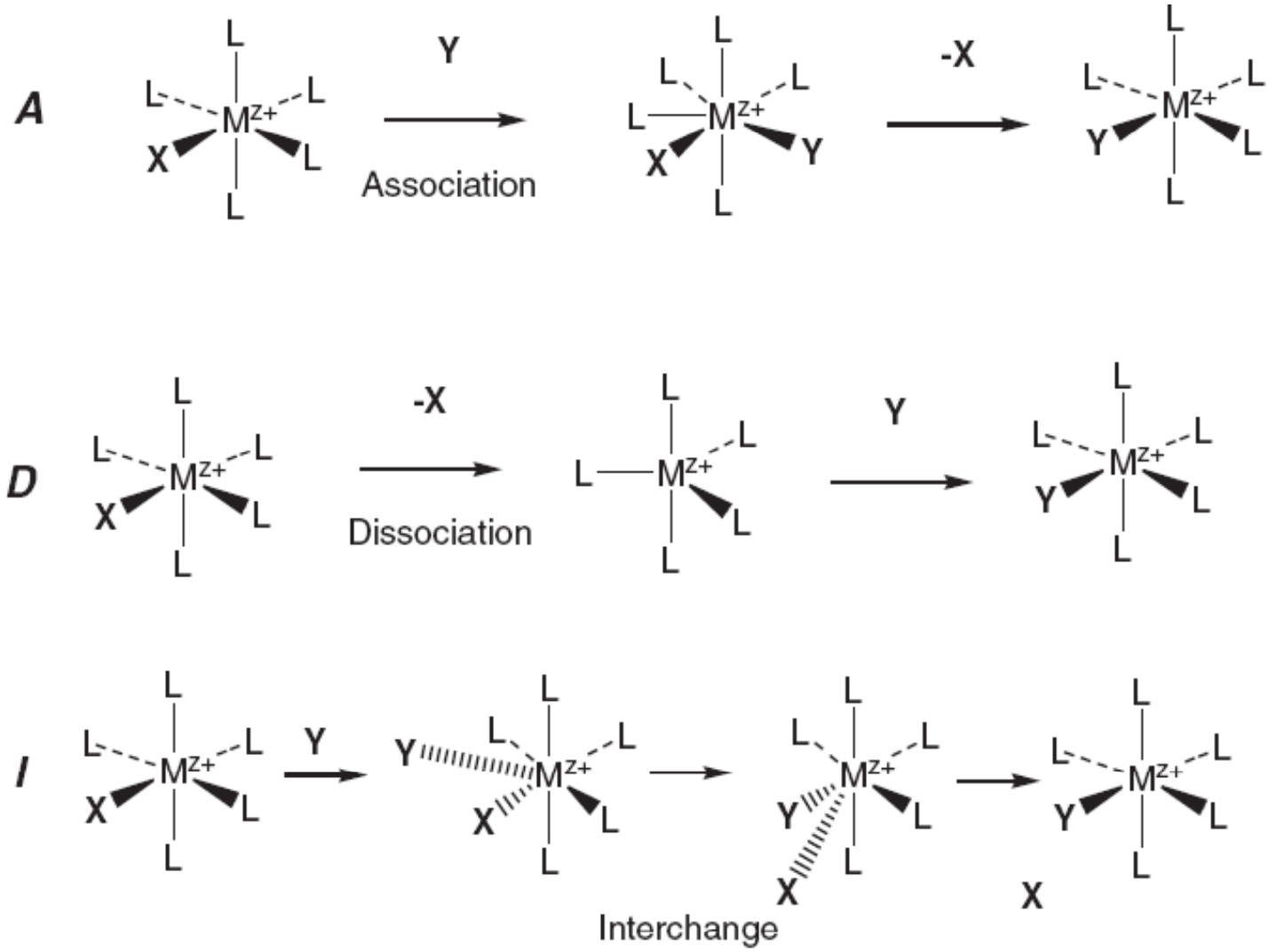
Dissociation: Provides info on *how fast* or *slow* a complex dissociates..

Stability: Stable or Unstable : THERMODYNAMICS
Dissociation: Labile or Inert : KINETICS

Labile: reactions half complete at ~ 30 sec @ 298 K

What is good for the drugs ????

Mechanisms for Substitution at Metal Centers…



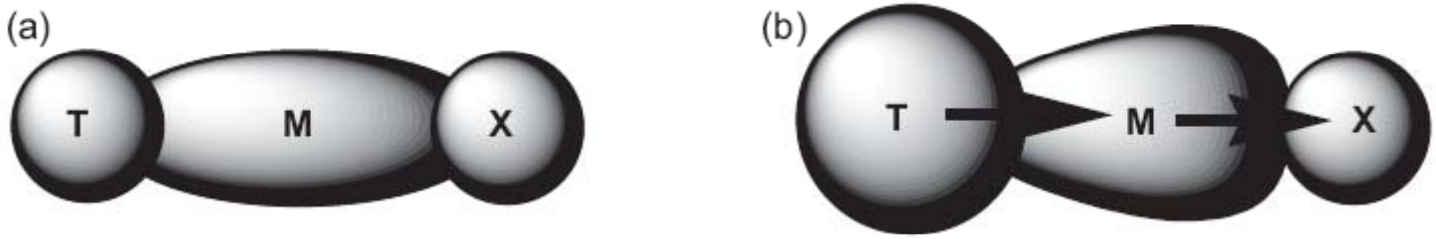
$$[ML_nX] + Sol \rightarrow [ML_n(Sol)] + X$$

$$[ML_n(Sol)] + Y \rightarrow [ML_nY] + Sol$$

$$[PtL_3X] + Sol \rightarrow [PtL_3(Sol)] + X \quad \text{slow}$$

$$[PtL_3(Sol)] + Y \rightarrow [PtL_3Y] + Sol \quad \text{fast}$$

***trans*-influence for $[ML_2XT]$…(X: Substitution-labile ligand *trans* to a less subst-labile ligand, T)**

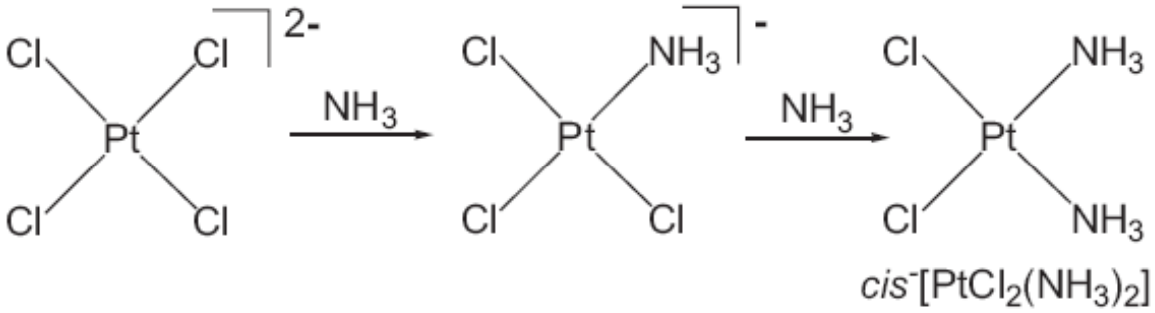


The polarisation of a metal ion by a ligand T to increase the lability of a trans-ligand, X. (a) T does not have a strong trans-influence; (b) T does have a strong trans-influence increasing the electron density at the metal centre as perceived by X

$$H_2O < OH^- < NH_3, \text{ amines} < py < Cl^-, Br^- < SCN^-, I^-, NO_2^- < C_6H_5^-$$

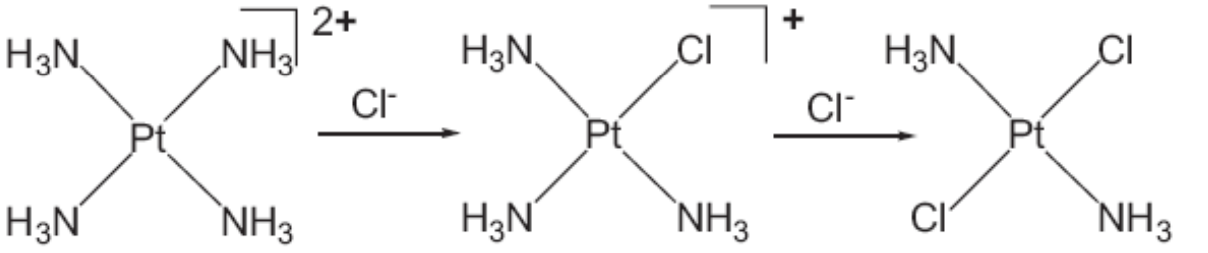
Increasing *trans*-effect ⟶

$$C_6H_5^- < CH_3^- < H^-, PR_3 < C_2H_4 < NO, CO < CN^-$$



cis-$[PtCl_2(NH_3)_2]$

Substitution *trans* to Cl^- favoured



trans-$[PtCl_2(NH_3)_2]$

An example of the trans effect