Principles of Molecular Recognition

2014/2015 Fall term

General information

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- Lectures are available at: http://http://chembiol.ttk.mta.hu/education.html
- Oral exam (officially January 28, 2015 – upon arrangement)

Useful literature

- Lakowicz, Joseph: Principles of fluorescence spectrosopy
- Valeur, Bernard: Molecular fluorescence
- Wang, Anslyn: Chemosensors

Chemosensing, chemosensors

- Field of chemosensing is rapidly growing
- Medical diagnostics, environmental monitoring, toxicological analysis, forensics, cell biology, biochemistry etc.
- Chemosensing is interdisciplinary (e.g. chemistry, physics, biology)
- Supramolecular chemistry - mainly non-covalent interactions

Sensors - chemsensors

- **Sensor in analytical chemistry**: a chemical indicator in an instrument that produces signal indicative of the presence of an analyte

- **Sensor in supramolecular chemistry**: is a host molecule (receptor) that changes color, emission, redox potential etc. upon binding of an analyte (quantification still requires instrumentation)

Chemsensor modules

- **Receptor** (Host): recognizes the analyte (Guest) – synthetic receptors - design, creation (chemistry)
- **Transducer**: linker (transfers the changes)
- **Signaling unit**: produces signal upon guest induced changes (physics)

Molecular recognition

- Receptor – analyte interaction (Host-guest)
- Reversibility / reusability is of utmost importance
- Interactions work together to form stable intramolecular / intermolecular configurations
- Mostly noncovalent forces (but: sugars – boronic acids)

Governing forces in supramolecular chemistry

- van der Waals interactions
- Ionic interactions
- Hydrogen bond
- π-cation interaction
- Metal chelation
- Covalent interaction

van der Waals Interactions

- Weakest, but can be predominant in aqueous media
- A collective term for noncovalent forces, inversely proportional to the inverse of the sixth power of separation
- Formerly, used interchangeably with London forces
- Van der Waals: London, Debye, Keesom) sum of attractive and repulsive interactions

van der Waals Interactions

- $E \sim 1 / r^6$
- Dipole - dipole interactions of freely rotating dipoles (orientational force, Keesom force)
- Dipole - induced dipole (induction force, Debye force)
  - A nonpolar and a polar molecule with permanent dipole

van der Waals Interactions

- Induced dipole - induced dipole (London forces, dispersion forces)
  - Present in all atoms and molecules
  - Due to the presence of instantaneous dipoles
  - One instantaneous dipole induces the other
  - Can be attractive or repulsive

Cation – π interactions

- A cation and an aromatic π electron cloud
- In the gas phase mainly electrostatic interaction
- In the solution phase electrostatic + dispersion and inductive forces (London and Debye) also important
- In nature (e.g. Lys-Trp, Arg-Phe etc.)

Hydrogen bond

- Strongest secondary interaction
- Strongly polarized H-atom (H-donor)
- Lone pairs of N, F, O (H-acceptor)
- Residual positive and negative charges
- Reasons to form (electrostatic, or covalent bond??)

Hydrophobic effect – a disputed phenomena

- Interaction of non-polar moieties in water

- Formation of water-water interactions (strong H-bond) at the expense of weak water-non-polar interaction (ΔH-favored)

- Oriented H-bonds (ΔS-disfavored)

- Although: removal of non-polar from water and water released to the bulk is ΔS favored (less ordered)

Ionic interactions

- Classical electronic (Coulombic) interaction
  - Classical ionic
  - Salt bridges (balancing of electrostatic forces between three or more entities)
    - E.g. Asp-Lys-Glu (COO^- - $NH3^+$ - COO^-)

Covalent interactions

- Restricted to a few special reversible reactions
- Strong affinity
- In aqueous solutions
- Intrinsic functional group selectivity

Boronic acid based chemosensors

- Boronic acids have strong affinity to Lewis bases

  - Diols (sugars)
  - Aminoalcohols
  - Hydroxy acids
  - Amino acids
  - Alcohols
  - Fluoride, cyanide

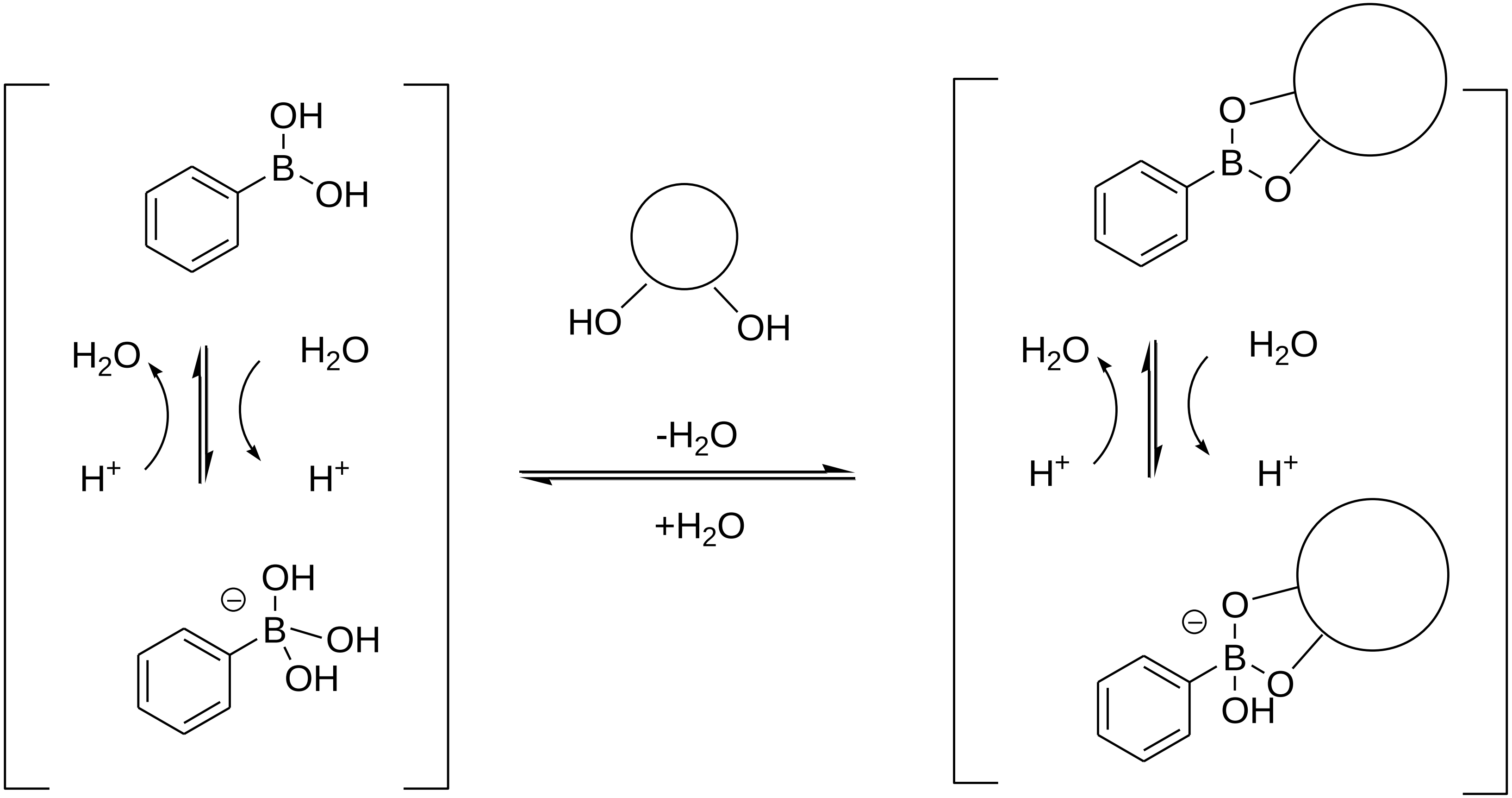
Boronic acid based chemosensors

- Special electronic features
- Boron has an open shell with 3 valence electrons in trigonal form (sp^2 hybridized + empty p orbital)
- Lewis acidic properties (can bind Lewis bases / nucleophiles)
- Several factors affect affinity

Boronic acid based chemosensors

- Small O-C-C-O dihedral angle
- Low pKa of the diol and boronic acid favor binding at neutral pH
- pKa effect is not unidirectional (bell shaped relationship between the diol and the boronic acid) ~ between the pKa of the two
- Combined effect of pKa and diehdral angle : catechol > *cis*-diols on five membered rings > linear diols > *cis*-diols on six membered rings
- Strong B-O bond is formed (rehybridizes to sp^3)

Boronic acid based chemosensors



Metal chelation chemistry

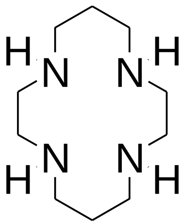
- Metal coordination to the host framework
- Binding affinity of host (ligand) towards analyte
- Principles of metal chelation
    - Hard-soft acid-base concept (HSAB)
    - Hard and soft refer to polarizability of LA-LB pairs associated through dative bonds
    - Hard acids prefer hard bases, soft bases prefer soft acids
    - E.g. alkali, alkali earth metals prefer O, amine, amide N; late transition metals prefer imine N, and S donors

Ligands (Hosts)

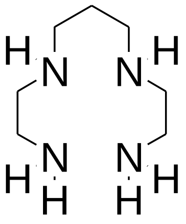
- Ligands are classified by the number of coordinating (donor) atoms
- E.g. bidentate ligand (bite angle, chelate ring -5 or 6 membered (less torsion))
- Chelates of higher denticity
  - By linear repetition of bidentate motifs
  - Branching from common bridgehead atom
- Chelate effect: refers to the enhanced stability of metal complexes of multidentate ligands as compared to those of monodentate ligands

The macrocyclic effect

- Increasing denticity with proper bite angle enhances stability of the complex
- Preorganized cyclic ligands have stronger binding affinity than acyclic ligands (Entropy)



Cyclam, **1**



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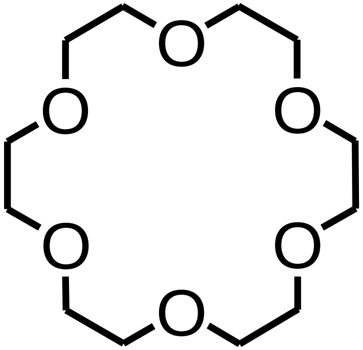
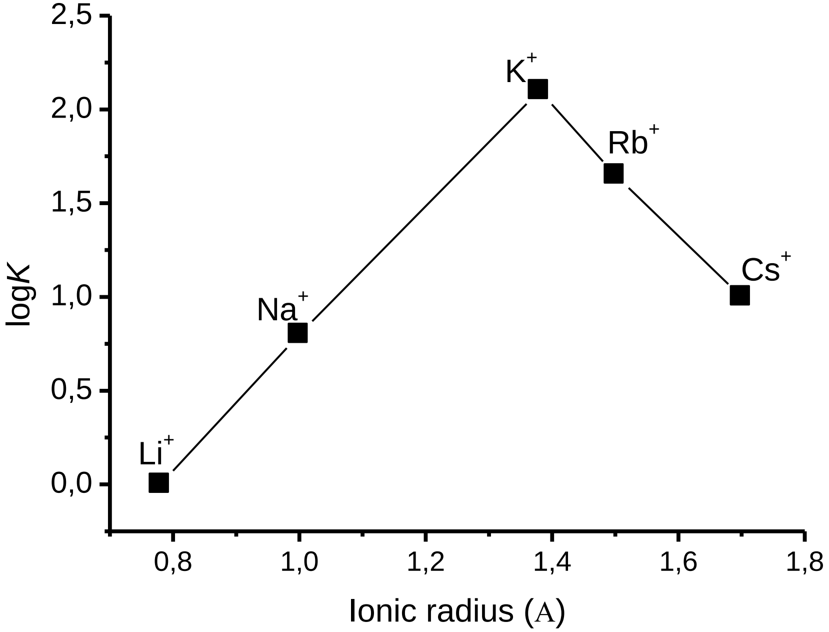
$1 \quad + \quad \mathrm{Ni(II)} \rightleftharpoons [\mathrm{Ni}(\mathbf{1})]^{2+}$ logK = 22.2; ΔH = -24.1 kcal/mol; ΔS = +21cal/K/mol

$2 \quad + \quad \mathrm{Ni(II)} \rightleftharpoons [\mathrm{Ni}(\mathbf{2})]^{2+}$ logK = 16.1; ΔH = -17.9 kcaklmol; ΔS = +15cal/K/mol

The macrocyclic effect

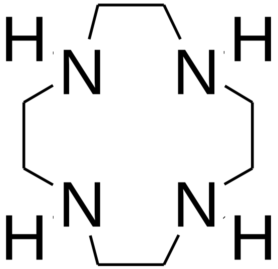
- Ion-cavity concept : complementarity between host cavity and metal ion size
- Rule of three (three-point binding)
- E.g. 18-crown-6 ether binds K^+ the best



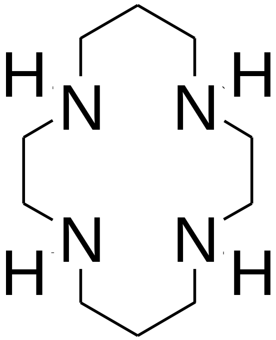


The macrocyclic effect

- Deviation from this for cyclenes
- E.g. cyclen binds larger metal ions better than cyclam



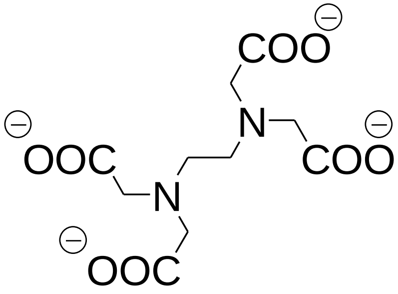
Cyclen

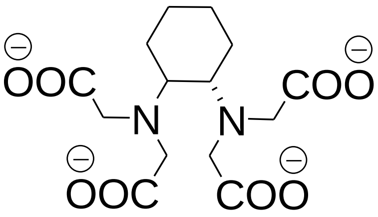


Cyclam

Preorganization of donor atoms

- Binding is more favorable when ground-state conformation of the ligand resembles that in the complex
- Restricted torsional motions facilitates appropriate conformations
- Enthalpy vs. entropy

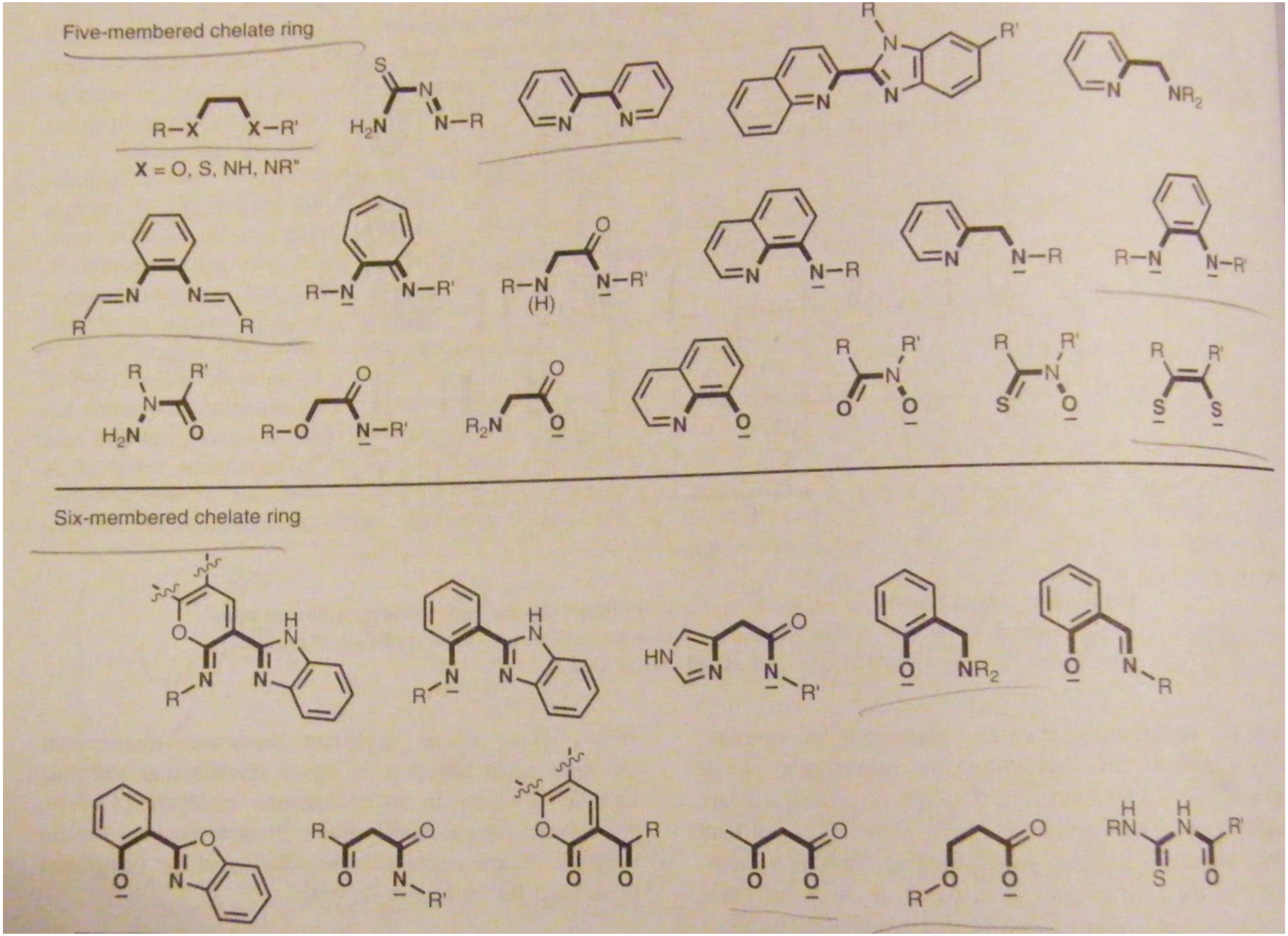




	EDTA	CDTA
logK for Cu(II) complexes:	18.7	21.9
logK for Fe(II) complexes:	25.0	30.0

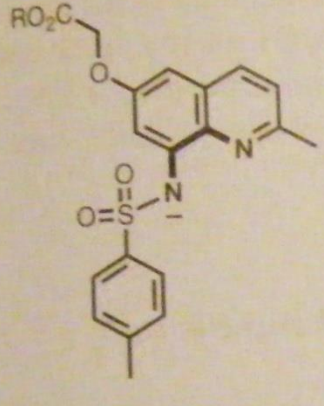
Examples for receptors (ligands, hosts)

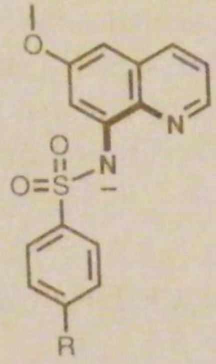
Bidentate ligands (Often 1:2; 1:3 stoichiometry)

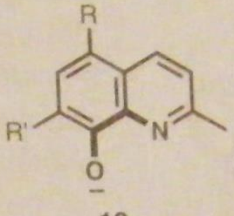


Bidentate ligands (Often 1:2; 1:3 stoichiometry)

Cu(II) and Co(II) binding ligands (Hard)


Zinquin A (R = H), **14**
Zinquin E (R = Et), **15**


TSQ (R = Me), **16**
TFLZn (R = CO_2H), **17**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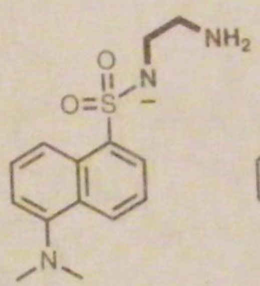
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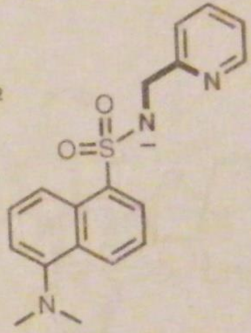
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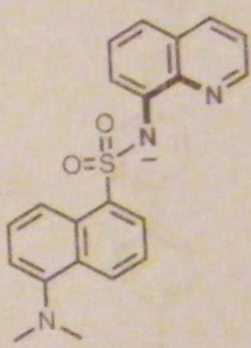
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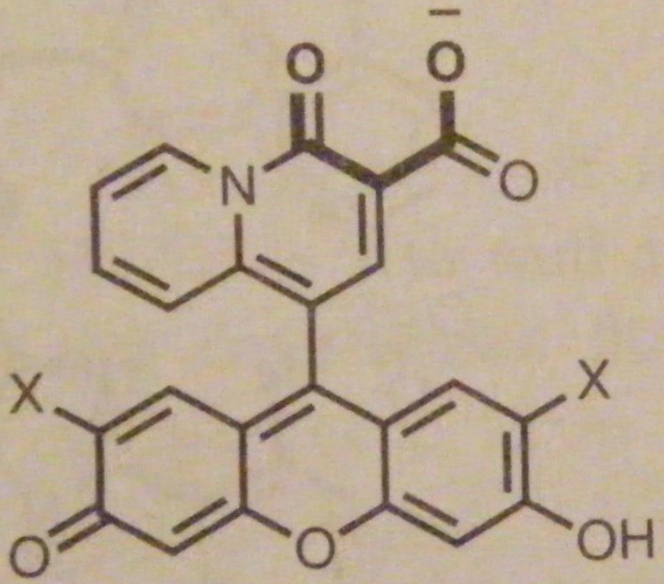
Bidentate ligands (Often 1:2; 1:3 stoichiometry)

Changing donor atoms…

Mg(II) (hard)



X = H; F; Cl

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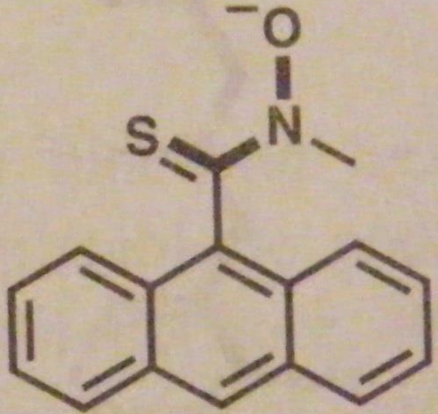
Pb(II) (mixed)



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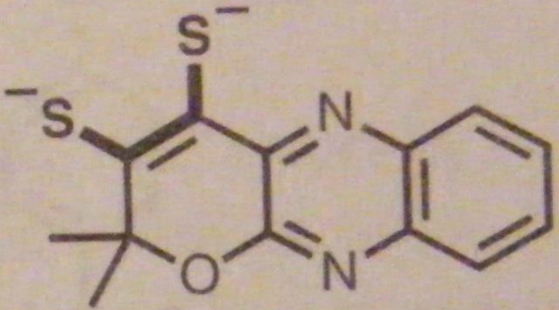
Pb(II) (Soft)



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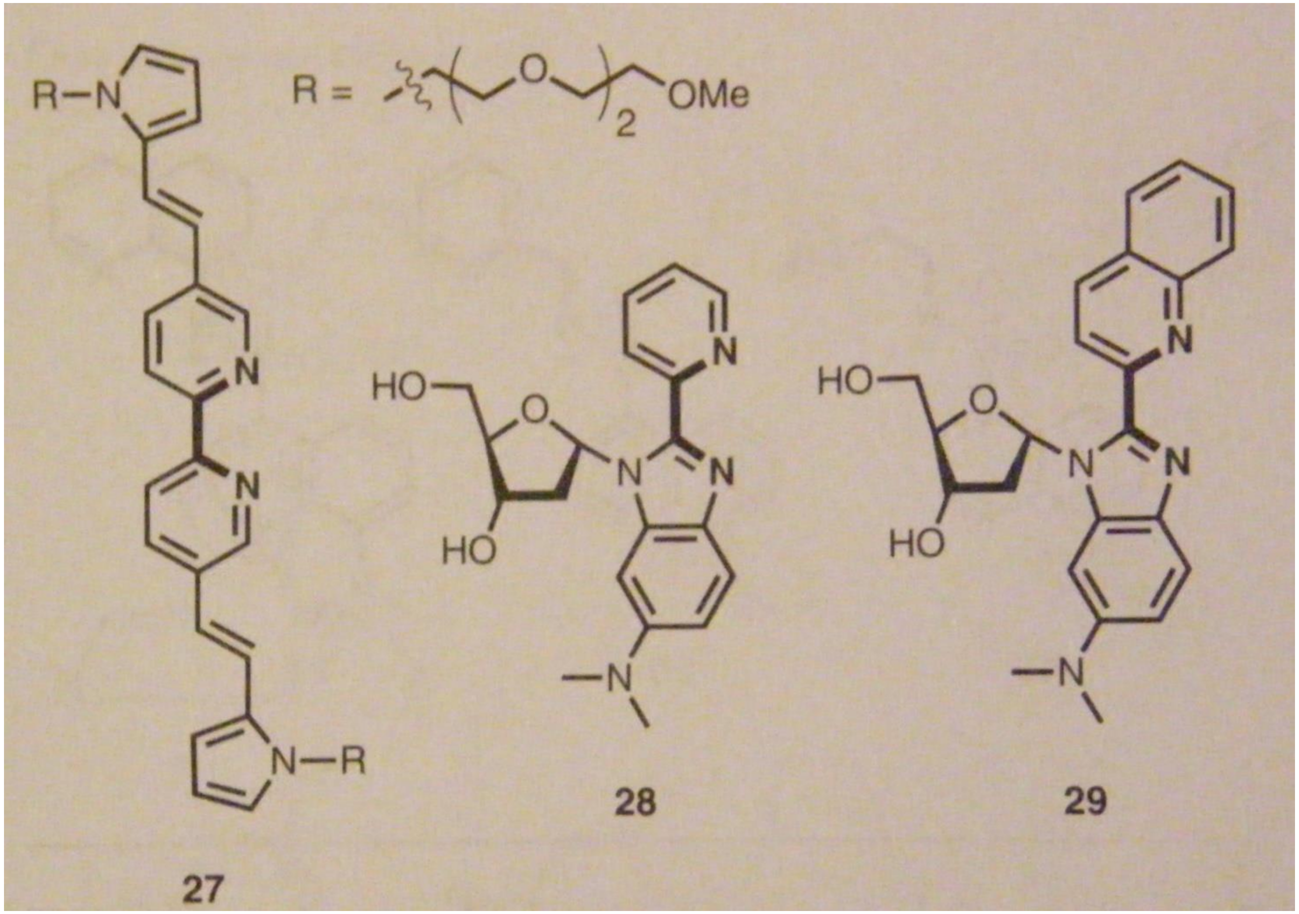
Bidentate ligands (Often 1:2; 1:3 stoichiometry)

Neutral imine: Borderline hard/soft

Zn(II)

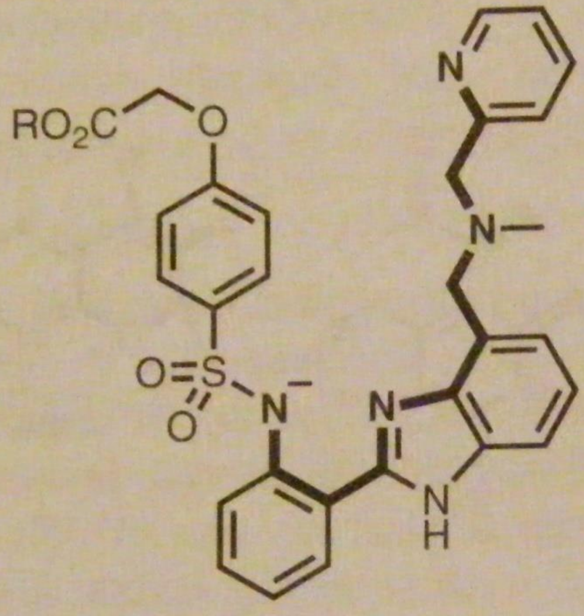


27 **28** **29**

Acyclic multidentate ligands

Wrap around the metal

Zn(II)



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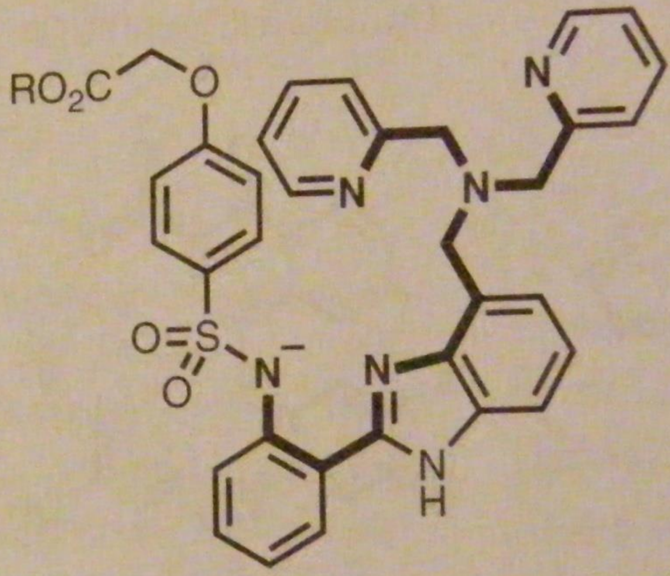

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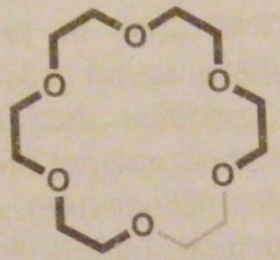
Acyclic multidentate: Linear chelates

Less selective for size

Pb(II)

1:1 with **38**
2:1 with **39**



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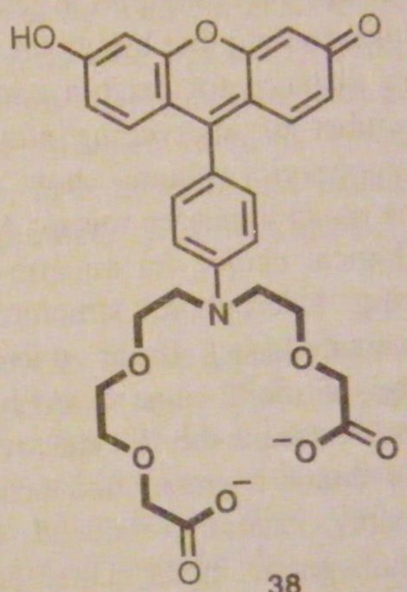

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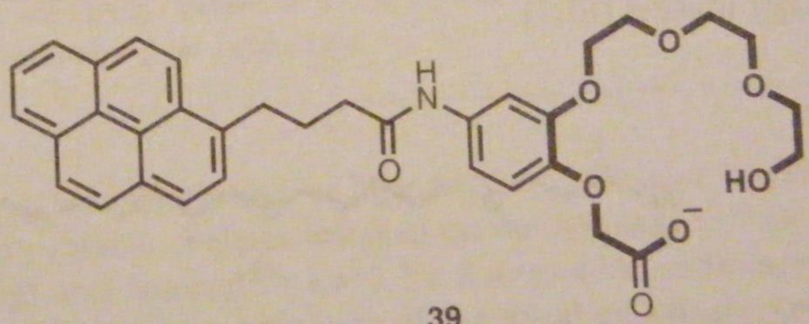

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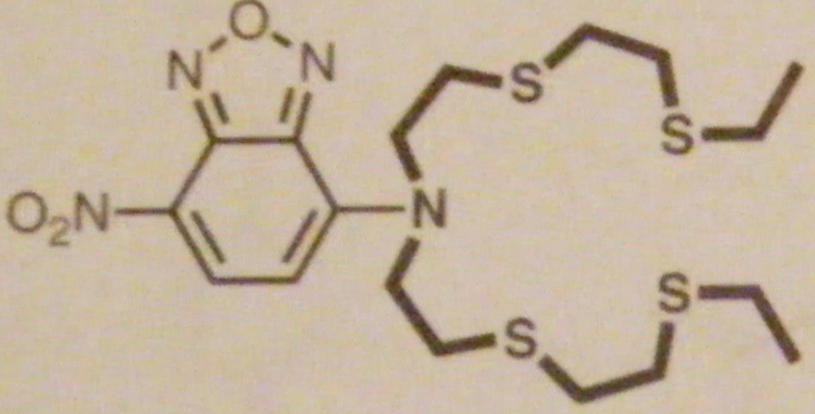
Acyclic multidentate: Linear chelates

Soft binders

Ag(I) and Hg(II)

Cu(I)



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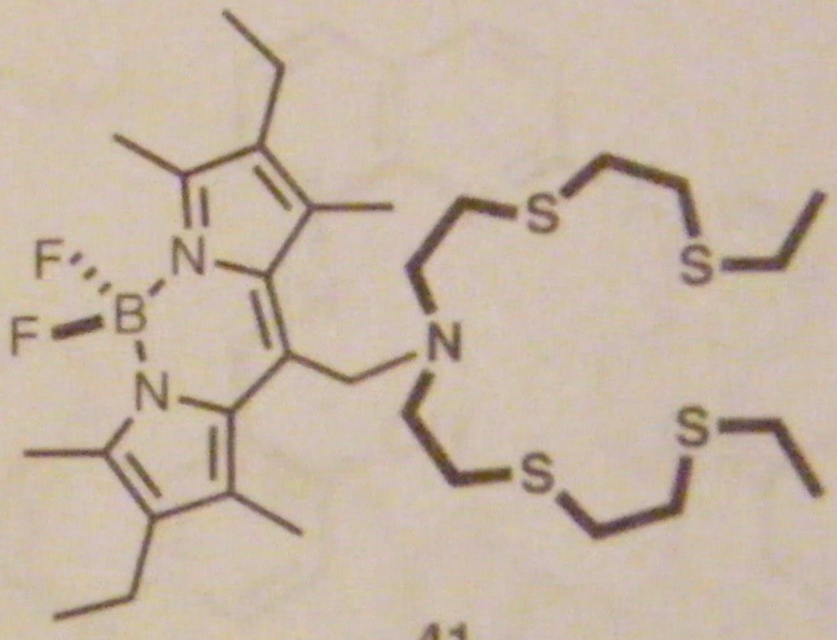

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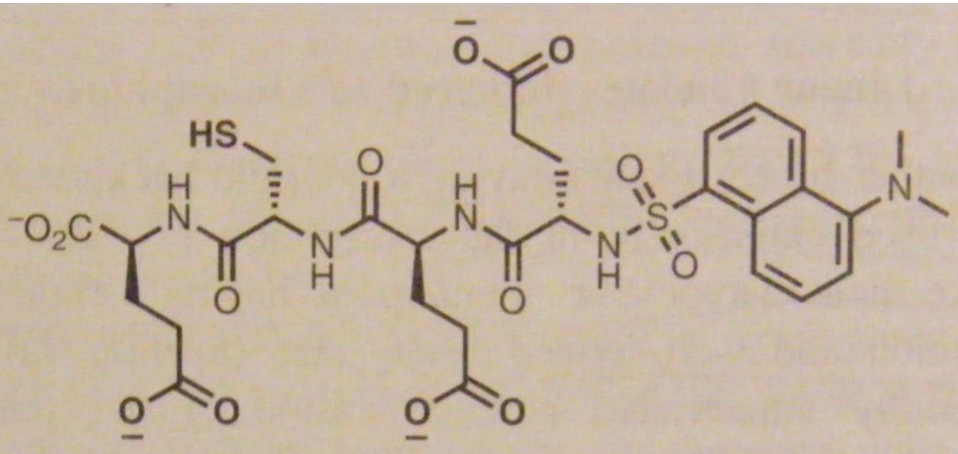
Acyclic multidentate: Linear chelates

Tetrapeptide motif

Pb(II)



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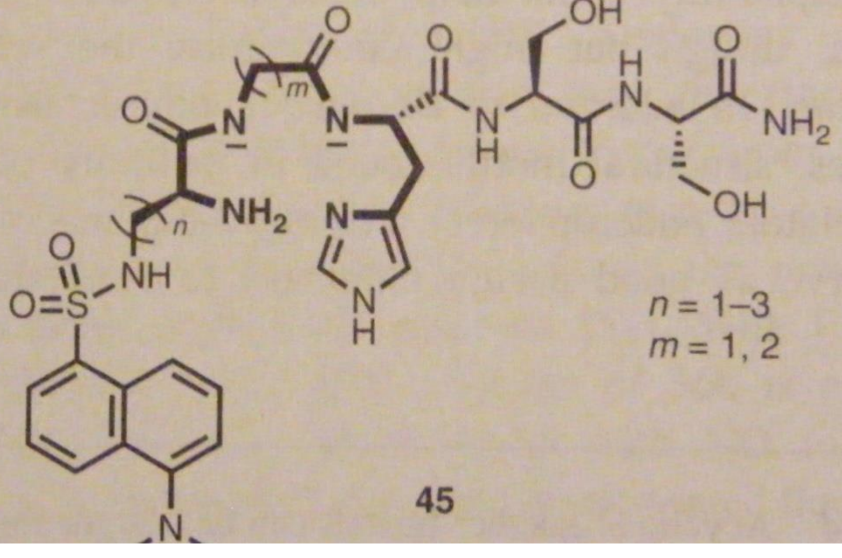
Cu(II)

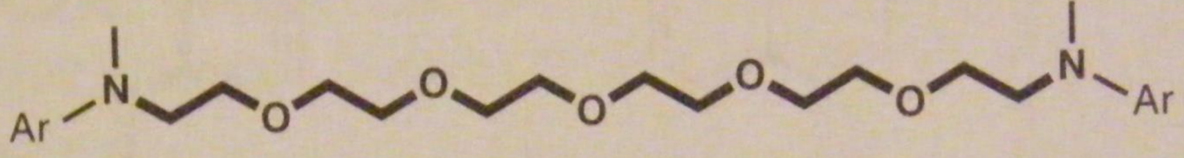


$n = 1\text{–}3$
$m = 1, 2$

45

Acyclic multidentate: Linear chelates

Ca(II)



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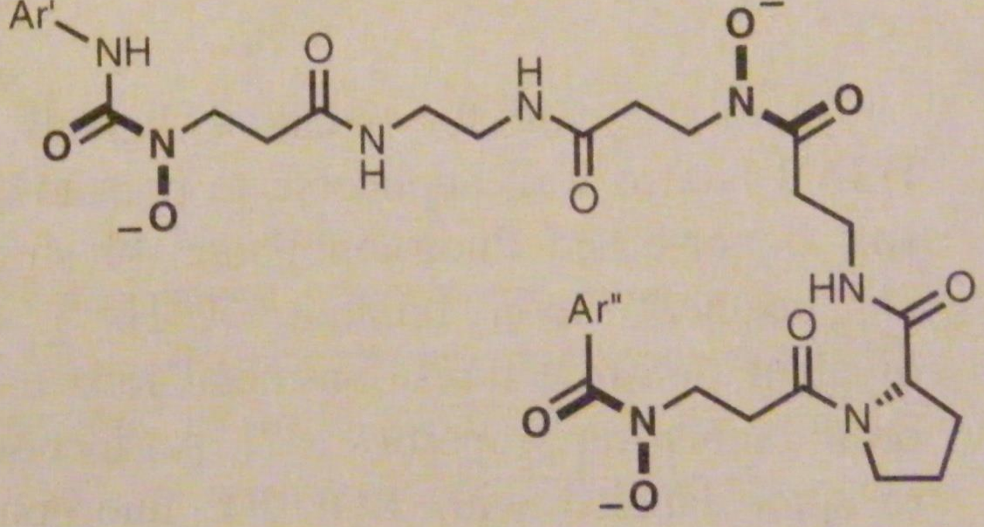
Fe(III)



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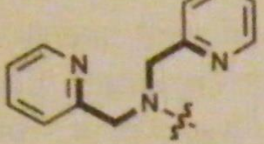
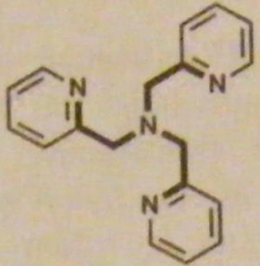
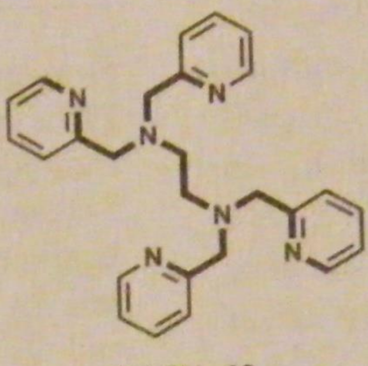
Acyclic multidentate: Branched chelates



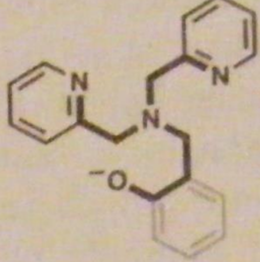
DPA, **47**



TPA, **48**



TPEN, **49**



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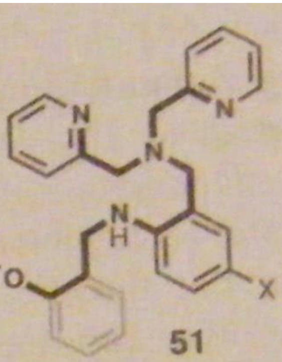

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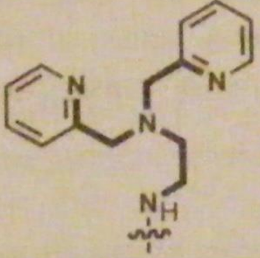

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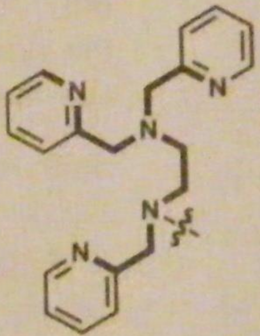

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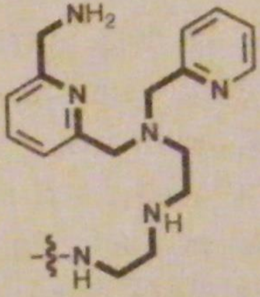

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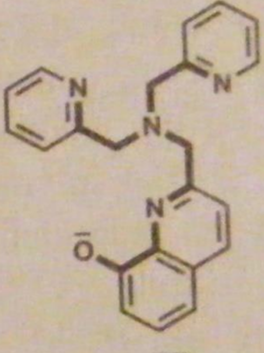

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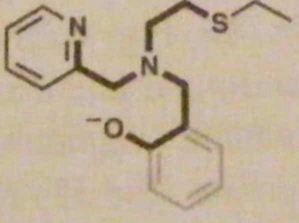
Zn(II); Cd(II) mainly



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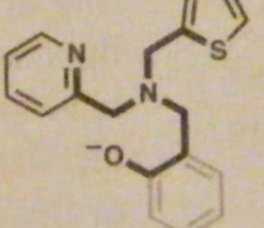

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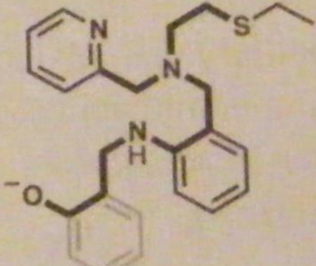

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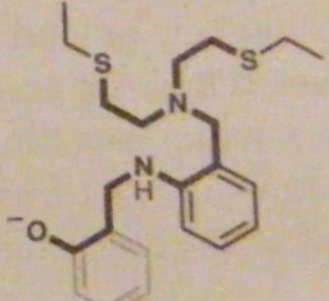

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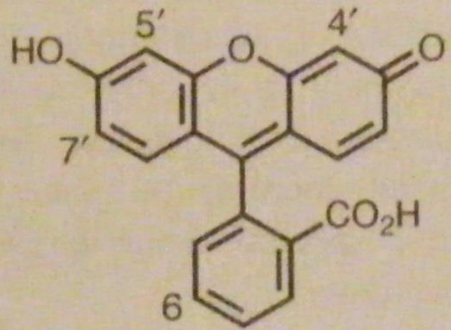
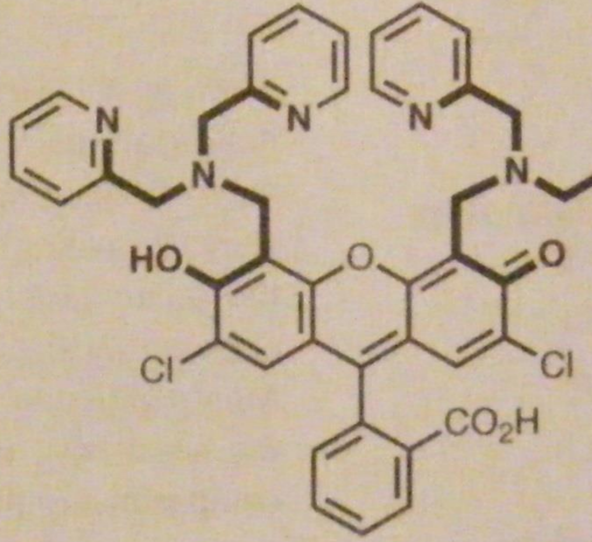
Acyclic multidentate: Branched chelates



fluorescein, **60**



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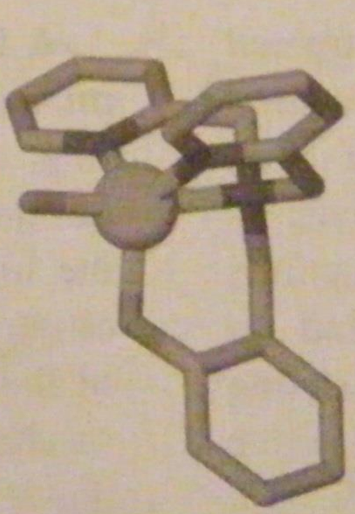
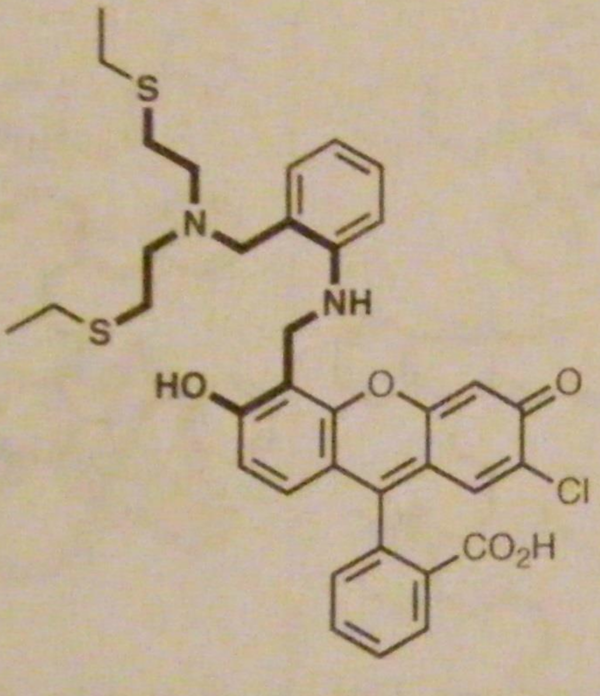
Zn(II) binders



Acyclic multidentate: Branched chelates

Hg(II) binders



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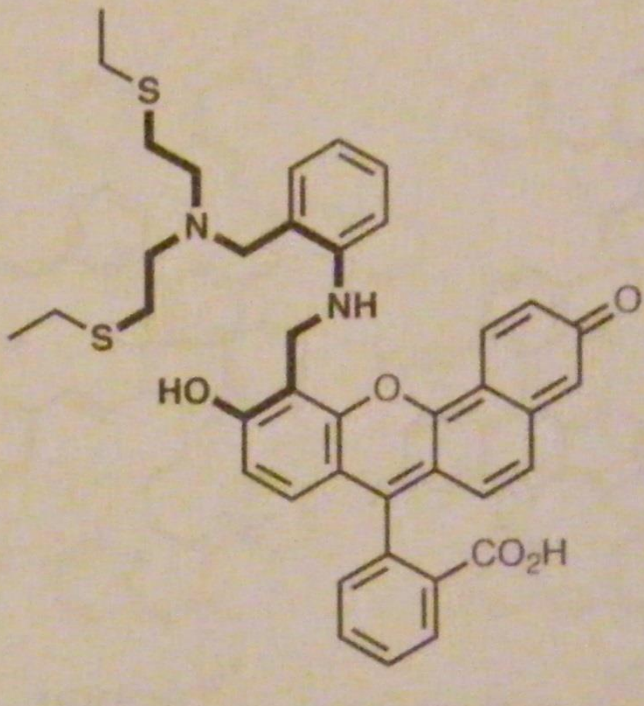

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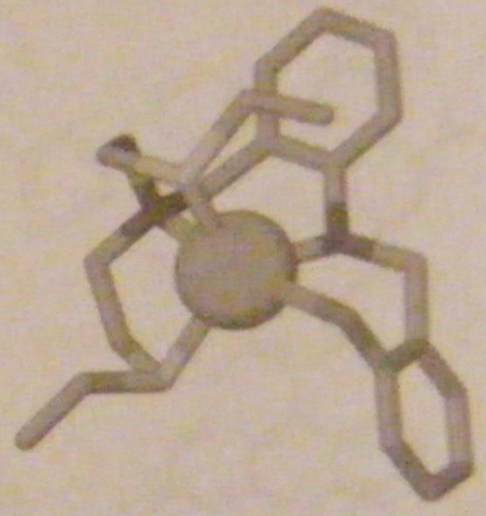
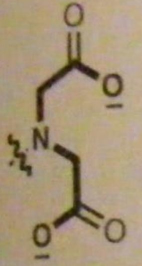
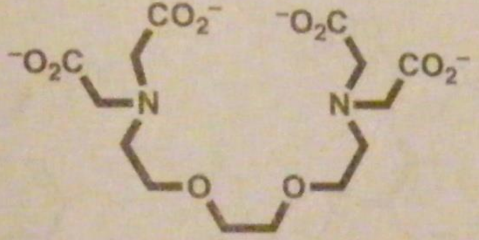


Acyclic multidentate: Branched chelates

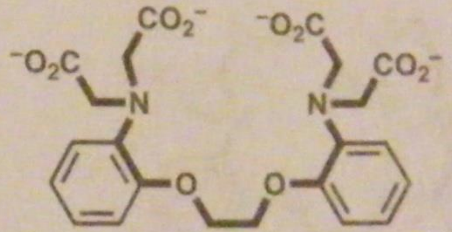
Mg(II); Ca(II) binders



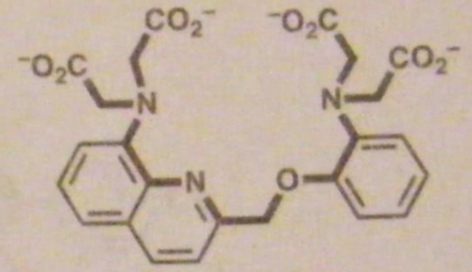
IDA, 75



EGTA, 76



BAPTA, 77



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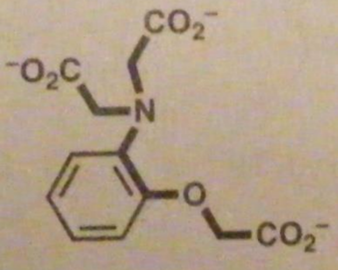
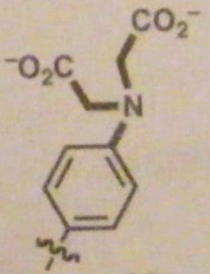


APTRA, 79



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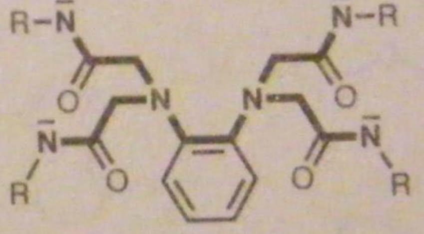
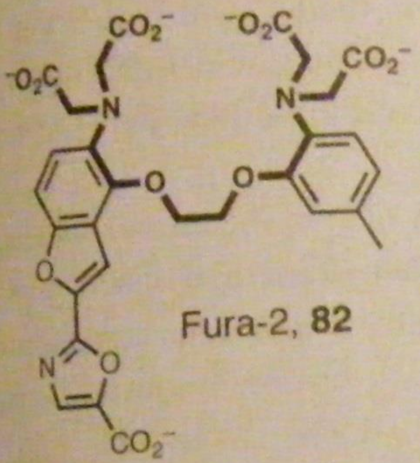


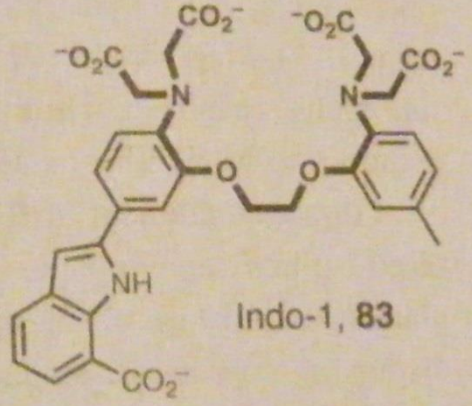
81

Acyclic multidentate: Branched chelates

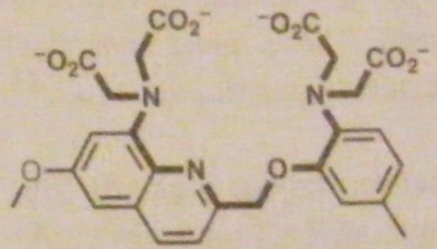
Ca(II) binders



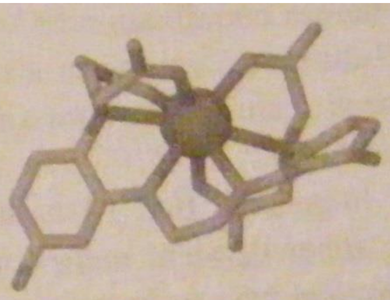
Fura-2, **82**

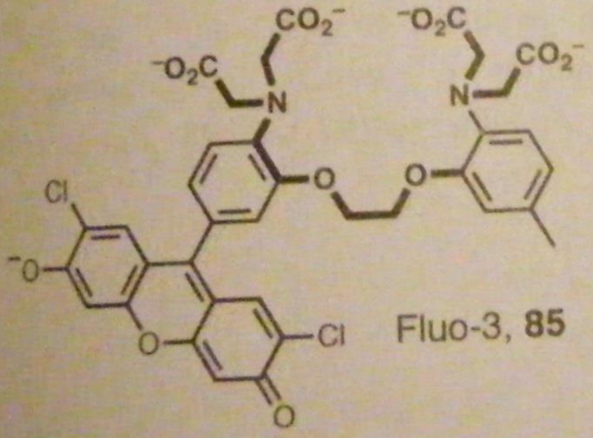


Indo-1, **83**

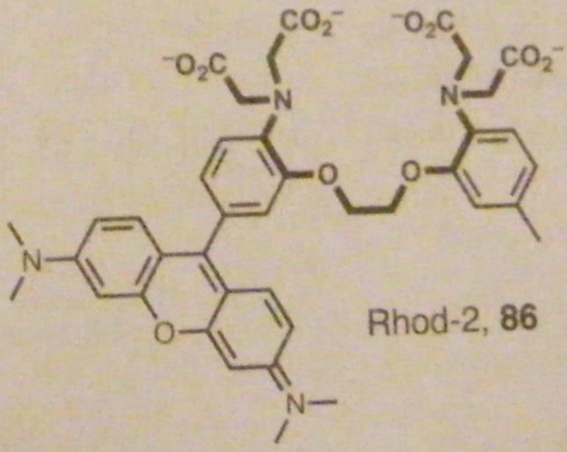


Quin-2, **84**

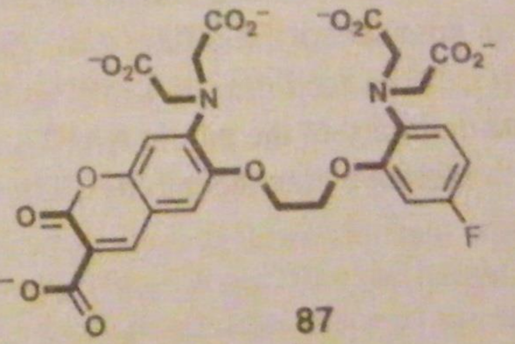




Fluo-3, **85**



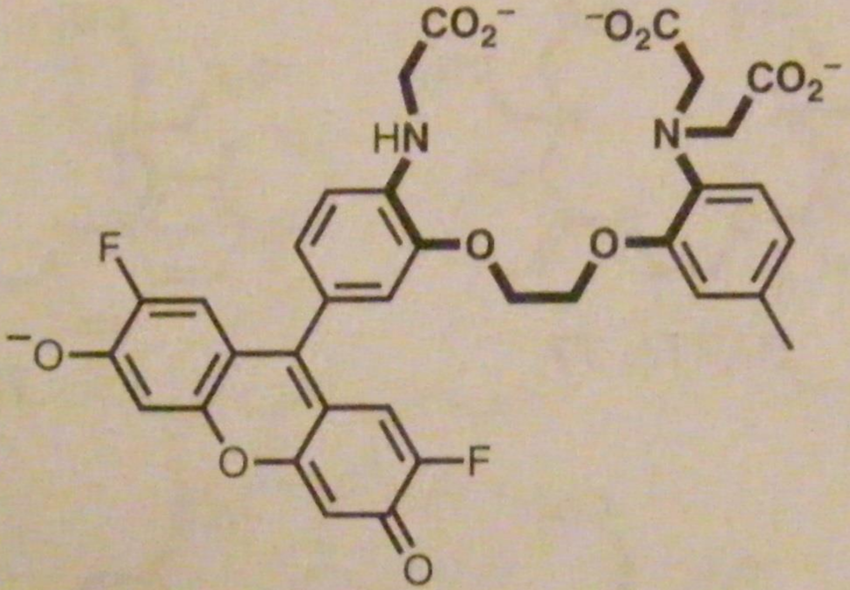
Rhod-2, **86**



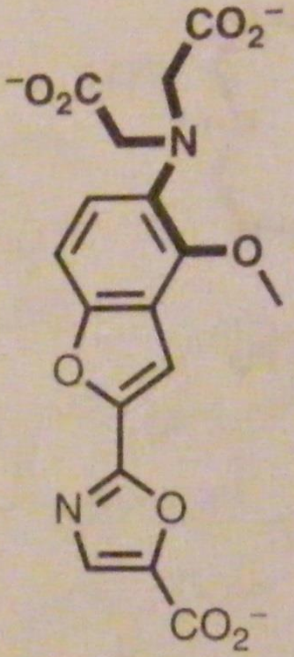
87

Acyclic multidentate: Branched chelates

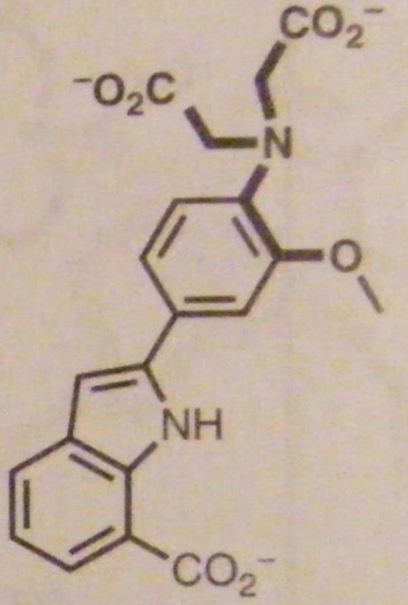
Zn(II) chelators



FluoZin-3, **88**

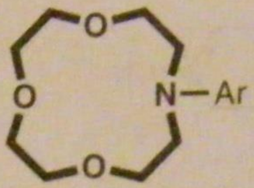


FuraZin-1, **89**



IndoZin-1, **90**

Macrocyclic ligands: (aza)crown ethers



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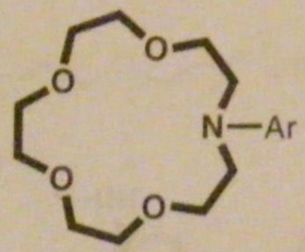

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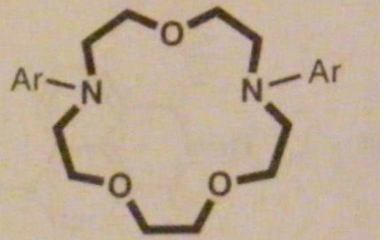
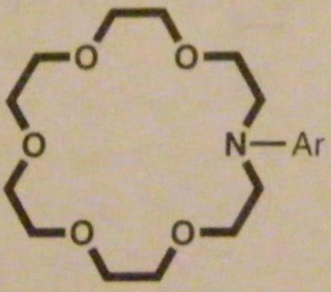


101



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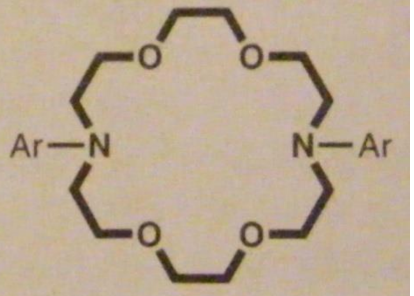
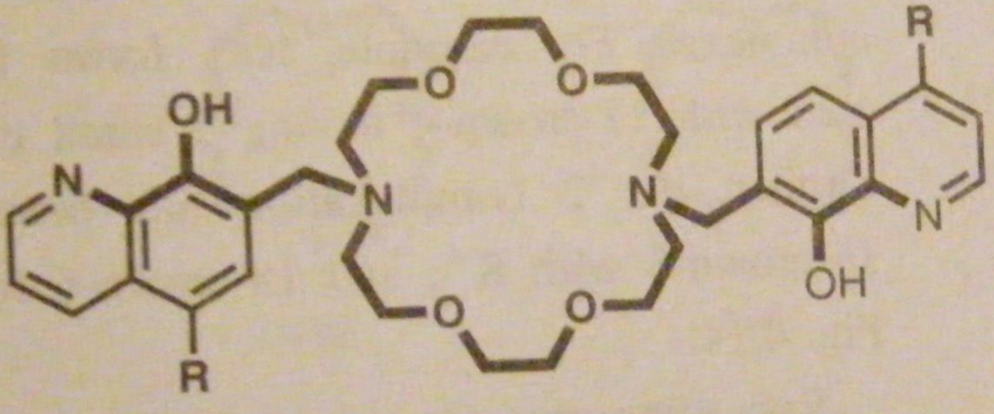


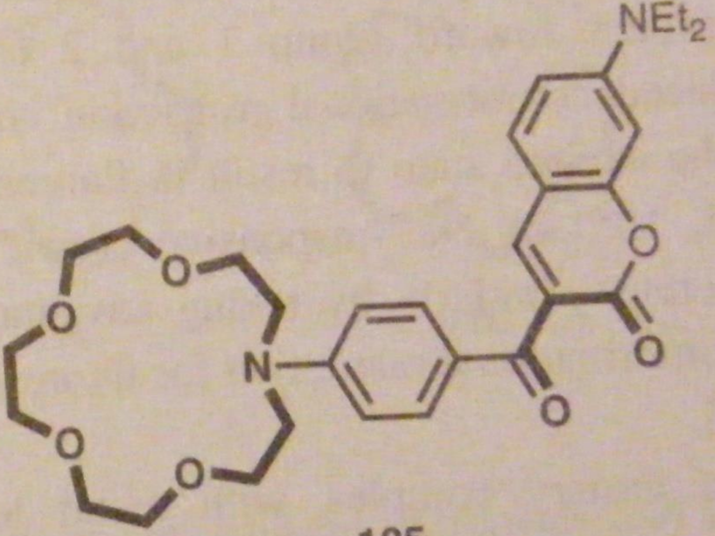
103

Macrocyclic ligands: lariat ethers

Lariat aza-crowns (Hg(II), Mg(II), Pb(II) chelators



104a (R = NO_2)
104b (R = H)
104c (R = Cl)

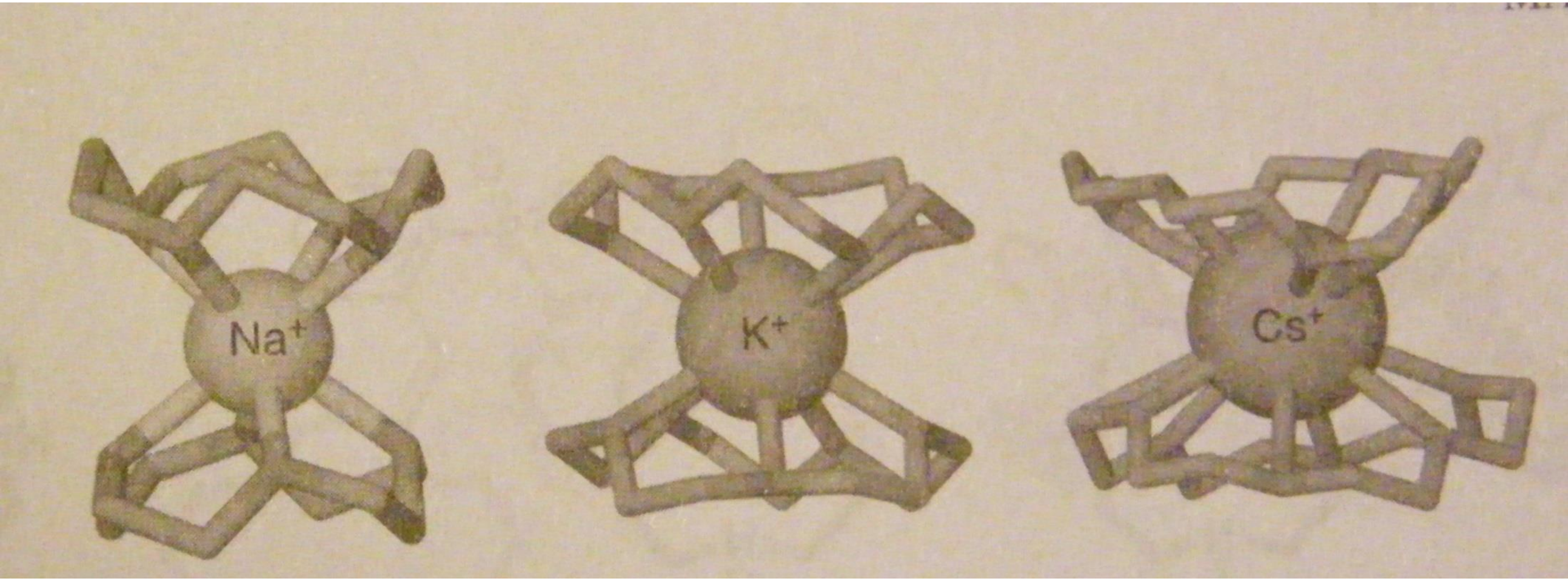


105

Macrocyclic ligands: (aza)crown ethers

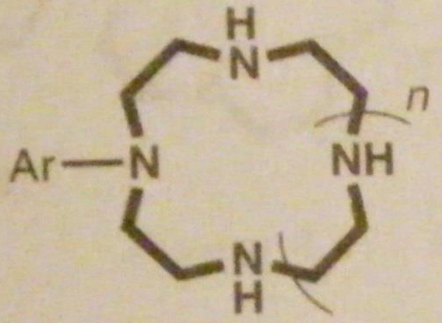
Stoichiometry vs. Cavity size

1:2 with 12-crown-4 1:2 with15-crown- 5 1:2 with18-crown- 6

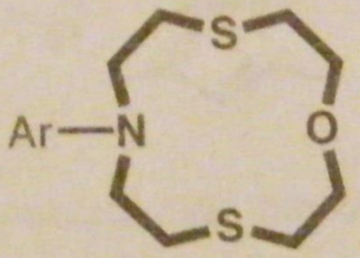


Macrocyclic ligands: (aza)crown ethers

Changing donor atoms



112



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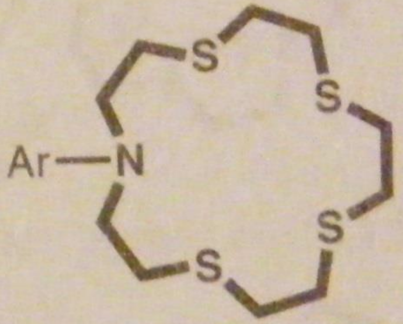
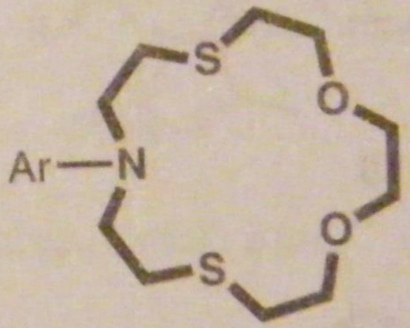


114



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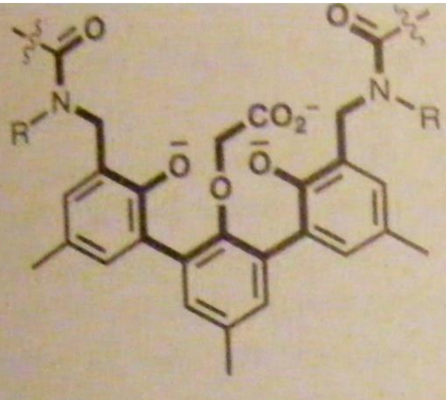
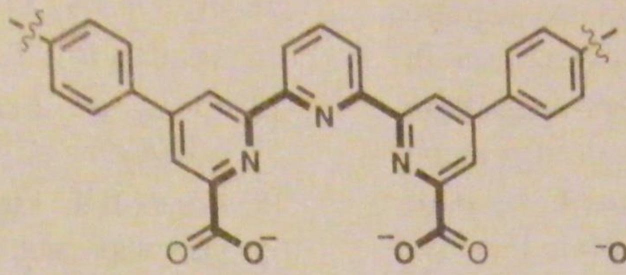
Macrocyclic ligands: (aza)crown ethers

Lanthanide (III) binders



129



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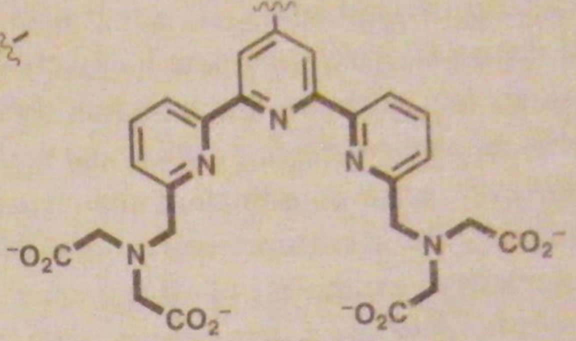

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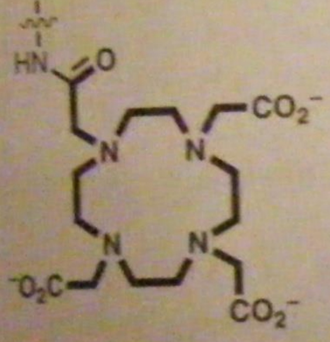

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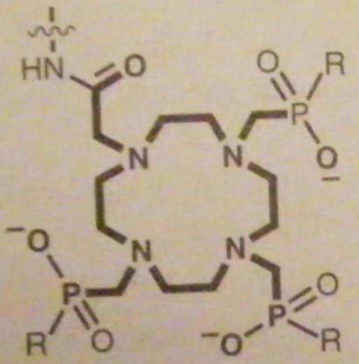

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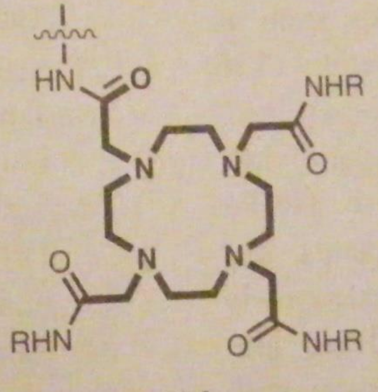

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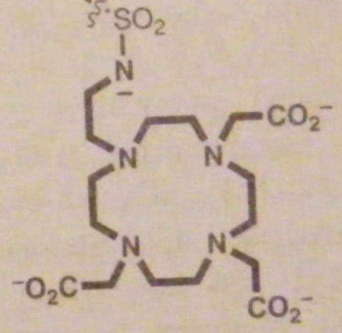

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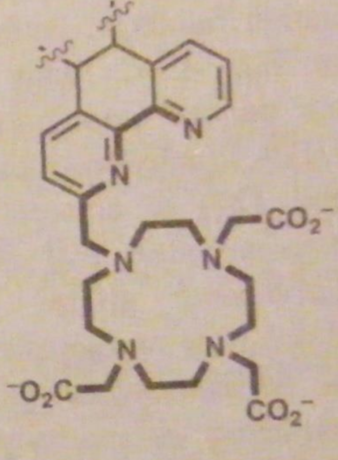

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ligands binding lanthanide(III) ions.