CHEMISTRY

THEORY PAPER: Theoretical organic chemistry-II

(as per Model CBSGS curriculum)

M.Sc. (Prog.) Semester IV

Supramolecular chemistry

VERSION: 2020

Teacher's e-Kit : Text material

TITLE:	**Supramolecular Chemistry**
Key words for Search:	Molecular recognition, catalysis, molecular, self-assembly, supramolecular Polymers, Gels and Fibres.

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Suggested Readings:

- Supramolecular Chemistry; Concepts and Perspectives, J. M. Lehn, VCH.
- Crown ethers and analogous compounds, M. Hiraoka, Elsevier, 1992. 30.
- Large ring compounds, J.A.Semlyen, Wiley-VCH, 1997. 31
- Bioorganic, Bioinorganic and Supramolecular chemistry, P.S. Kalsi and J.P. Kalsi. New Age International Publishers.

Web-links:

- http://ak-powell.chemie.uni-karlsruhe.de/teaching/Supramolecular%20Chemistry.pdf
- http://biointerface.org/nano/self-assembly/
- http://stanford.edu/dept/france-stanford/Conferences/Ethics/BensaudeVincent.pdf
- https://www.youtube.com/watch?v=4f_khh6paJI
- http://homepage.univie.ac.at/jeanluc.mieusset/Supramolecular%20Chemistry%206%20-%20Self-assembly.pdf
- http://www.saylor.org/site/wp-content/uploads/2011/05/Supramolecular-chemistry.pdf

Activities:

- Tell your students to find molecular recognition and self-assembly.

Table of Contents

SYLLABI OF THIS MODULE:

Supramolecular Chemistry

- 2.4 Molecular recognition and catalysis, molecular self-assembly. Supramolecular Polymers, Gels and Fibres.

Learning outcomes:

Upon completion of this course, student will be able to

1. Explain the Molecular recognition.
2. Explain the concept of recognition.
3. Describe the concept of self-assembly.

Introduction:

Analytical tools for chiral molecular recognition:

- Enantiomer separation via high performance liquid chromatography (HPLC)
- Nuclear magnetic resonance analysis
- UV-Vis Absorption
- Fluorescence
- Circular Dichroism
- Mass Spectrometry
- Electrochemical Methods

Concepts of Supramolecular Chemistry: Self- Assembly and Molecular Recognition:

- Supramolecular systems are often held together by weaker interactions than covalent systems.
- The weaker interactions allows host-guest binding to become a reversible process, so that a host and guest can associate and dissociate without either of the building blocks being damaged or altered.
- This can be useful for systems such as molecular switches and for catalysis, and is utilized frequently in natural enzymes.

Molecular Self-Assembly:

- Spontaneous construction of ordered structures from molecular building blocks.
- In other way, It is a process in which relatively small molecules undergo spontaneous association to give stable, large, and structurally well defined aggregates under equilibrium conditions.
- It is a basic feature of supramolecular chemistry and works on the principle of molecular recognition.
- Self-assembly also involves a reversible assembly process that is thermodynamically controlled.
- E.g. Very common in biological system, in particular spontaneous double helix formation of nucleic acids.
- The strategy for non biological self assembly is the same as that for the biological systems: noncovalent system works collectively over the large area within component molecules so that their combined effects.
- Self assembly often leads to nanostructures which have dimension in the range of 1 to 10^{2} nm and part of nanochemistry comes under this area as the emerging field of recent interest.
- There are different types of molecular self assembly and molecular recognition directed association of components working on different structural features.

(A) Molecular self assembly based on hydrogen bonds:

- Molecules capable of forming networks of hydrogen bonds are good candidates for self assembly.
- There are several examples reported for this phenomenon
- (1) Cyanuric acid (CA) and melamine (M) possess complementary hydrogen bonding sites.
- In aqueous solution, they form 1:1 complex to give a crystalline solid **70** which is stable up to temperature of 450^{0} C .

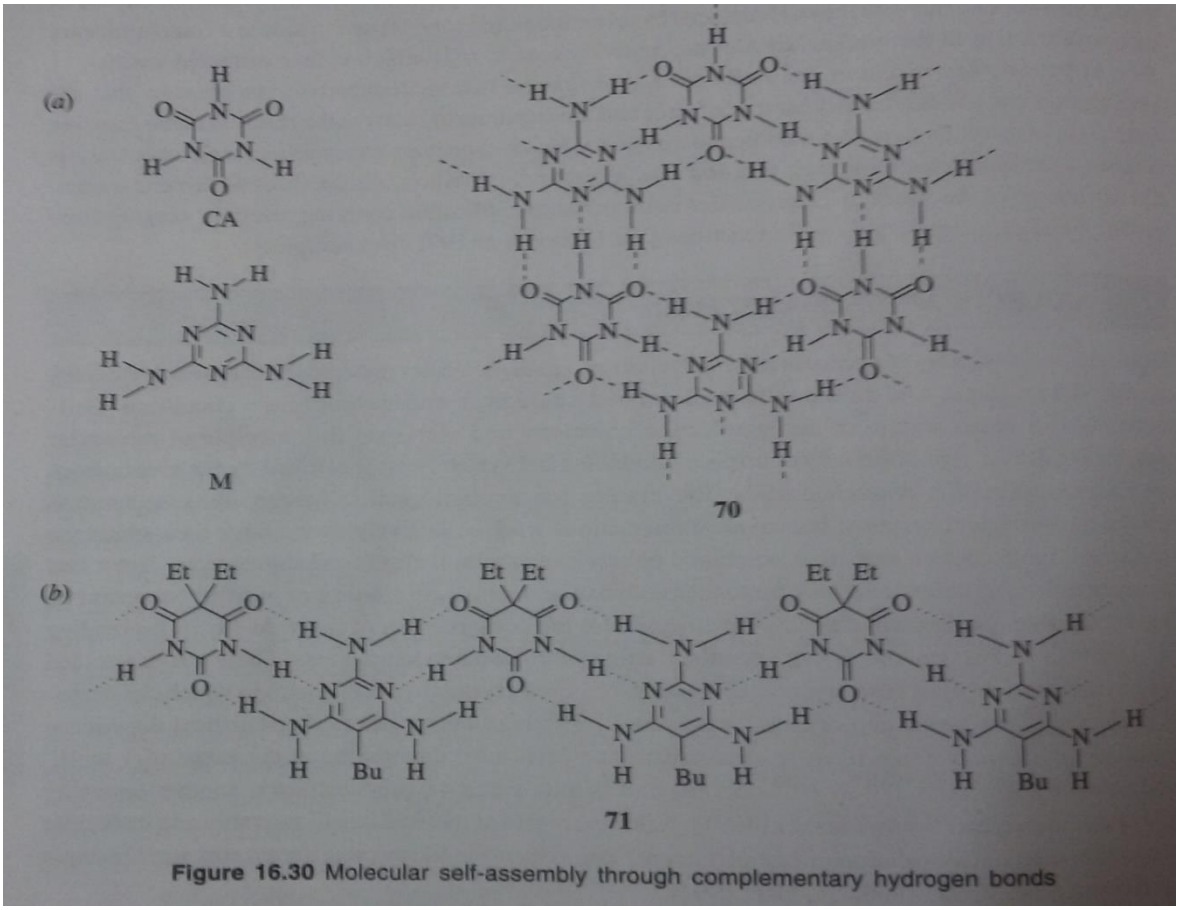


Figure 16.30 Molecular self-assembly through complementary hydrogen bonds

- The CA-M lattice has a planar structure containing hexagonal array of three CA and three M units.
- (2) 2,4,6-triaminopyrimidine (TAP) and barbituric acid derivatives (BA) form 1:1 cocrystals with structure 71.

(B) Metal-coordinated self assembly:

- The spontaneous association of substrates such as **72** containing two to five bipyridine (byp) groups, induced by Cu (II) ions.
- The two ligand strands coil around each other in a double helical fashion held together by tetrahedral binding site of Cu (I) ion which coordinates with four pyridine nitrogens.
- The di-, tri-, tetra-, and pentahelicates have been obtained using 72 with n = 0, 1, 2 and 3 respectively. Structure 73 represents trihelicate.
- The helicate formation occurred with positive cooperativity and self recognition due to ligands with different number of bpy units are used, only identical stands form the helix.

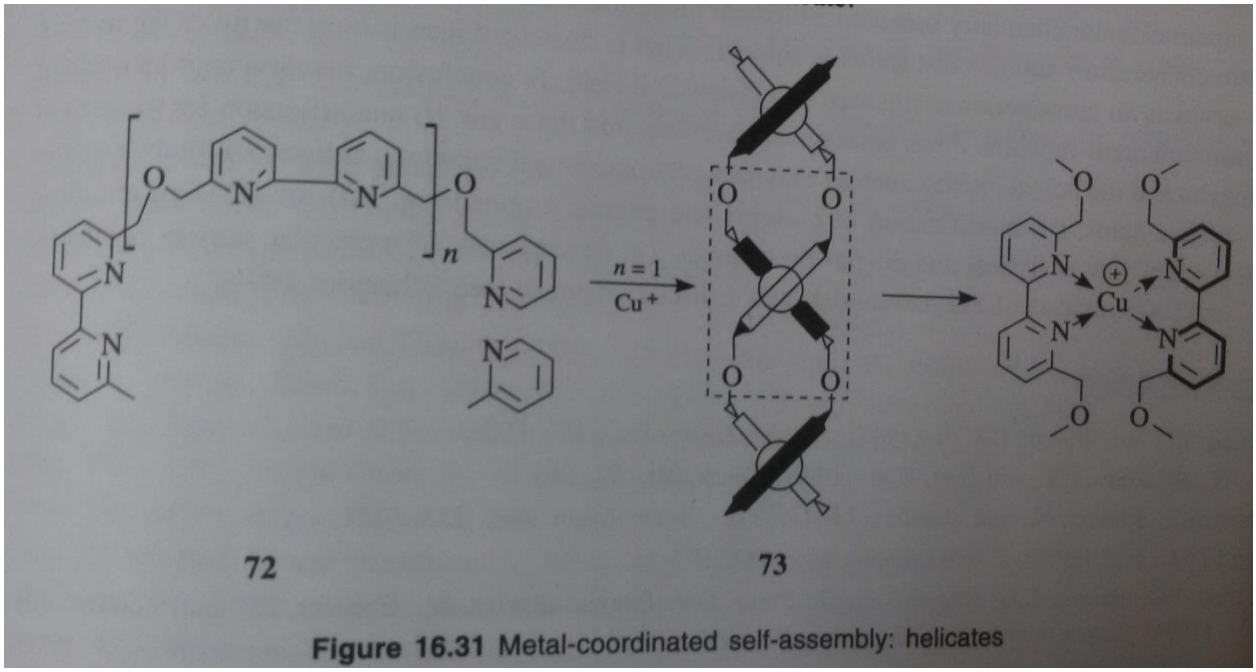
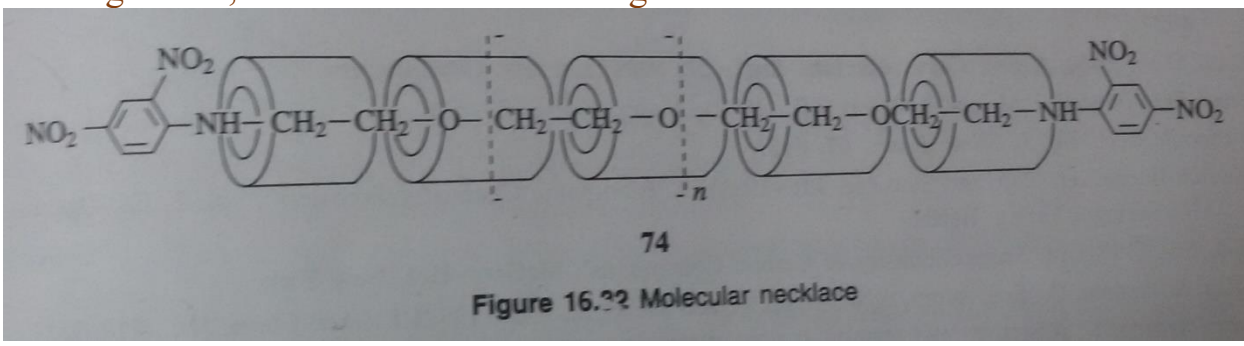


Figure 16.31 Metal-coordinated self-assembly: helicates

(C) Molecular Necklace:

- Karada et al. have shown the polyethylene glycol (PEG) penetrates the beaker like tunnel of alpha cyclodextrin (CD).
- Several CD molecules can be threaded on single PEG chain and the two terminals can be capped with bulky groups thus forming a molecular chain or molecular necklace.
- These researcher have obtained inclusion complexes of alpha CD with poly(ethylene glycol)bisamine and then capped the two ends by reacting with 2,4-dinitrofluorobenzene to give **74**.



74

Figure 16.32 Molecular necklace

Molecular recognition:

- Recognition is a phenomenon of identifying objects and ability to distinguish it from various other similar objects.
- Molecular recognition is a branch of supramolecular chemistry that deals with non-covalent interactions between the two or more molecules/ species, including cations, anions, neutral and chiral molecules or combination of them.

- One of the most important branches of molecular recognition is chiral recognition, because it is commonly achieved in biological systems.
- Receptors in our body easily distinguish between two molecules that have same chemical composition but different structures around a chiral carbon atom. e.g. we sense a sweet taste for D-glucose, but *L*-glucose tastes totally different.

- **Chiral Molecular Recognition:** Study of configuration, conformation, physical and chemical responses of a chiral molecule via diastereomeric interactions with other chiral entities.
- Interaction of chiral host with both the enantiomers of a guest through diastereomeric interaction.
- Optically active receptor can discriminate between two enantiomers of a chiral guest in complex formation.
- As the physical, chemical and biological activity of chiral compounds is mostly dependent on configuration and conformation of the molecules, study of the same becomes essential.
- Therefore, the area of chiral recognition of such molecules emerged to help industry and academia.
- The stereochemistry deals with three dimensional structures and recognition of chirality is mainly based on three point interactions between two suitable lock-key based two chiral entities (Host: Guest) resulting in diastereomeric interactions.
- The resulted two diasteromeric complexes exhibits different free energies and many of their physical properties such as membrane transport ability, solvent extraction properties, and chromagtographic behaviour.
- Methods of chiral resolution, determination of configuration, and enantiomeric purity, and asymmetric synthesis are all based on chiral recognition either in the ground state or in the transition state.

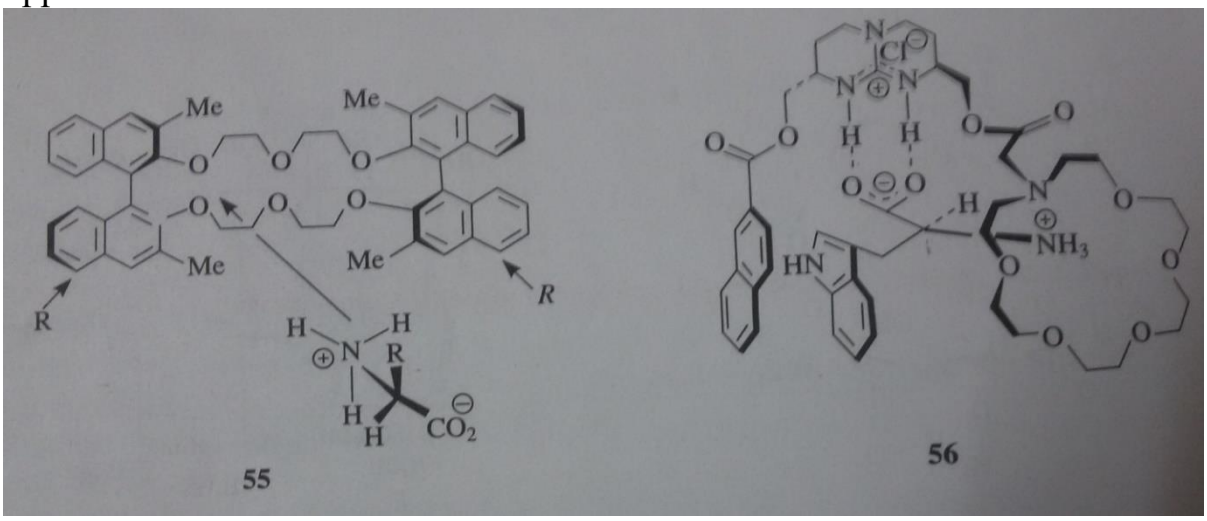
(a) Crown ethers and chiral framework:

- Cram, Lehn and others have demonstrated that enantiopure crown ethers and cryptands are capable of enantioselective recognition of chiral ammonium salts.
- Crams group synthesized the C2 symmetric crown ether **55** in enantiomerically pure R,R-form.

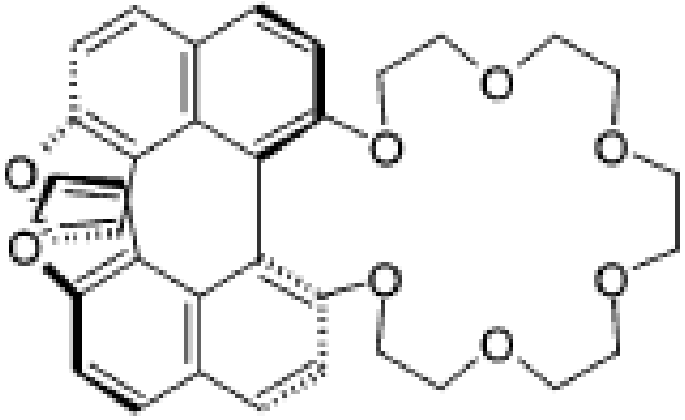
The R,R receptor **55** preferentially binds salts of D-α-amino acids and esters and the complexes can be extracted by CDCl3 from aqueous solution.

- Chiral recognition factors ranges from a high value of 31 for PhCH(CO2Me)NH3PF6 to a low value of 2.3 for MeCH(CO2H)NH3ClO4, corresponding to free energy difference between diastereomeric complexes of 8kJ mol-1 to 1.5 kJ mol-1.

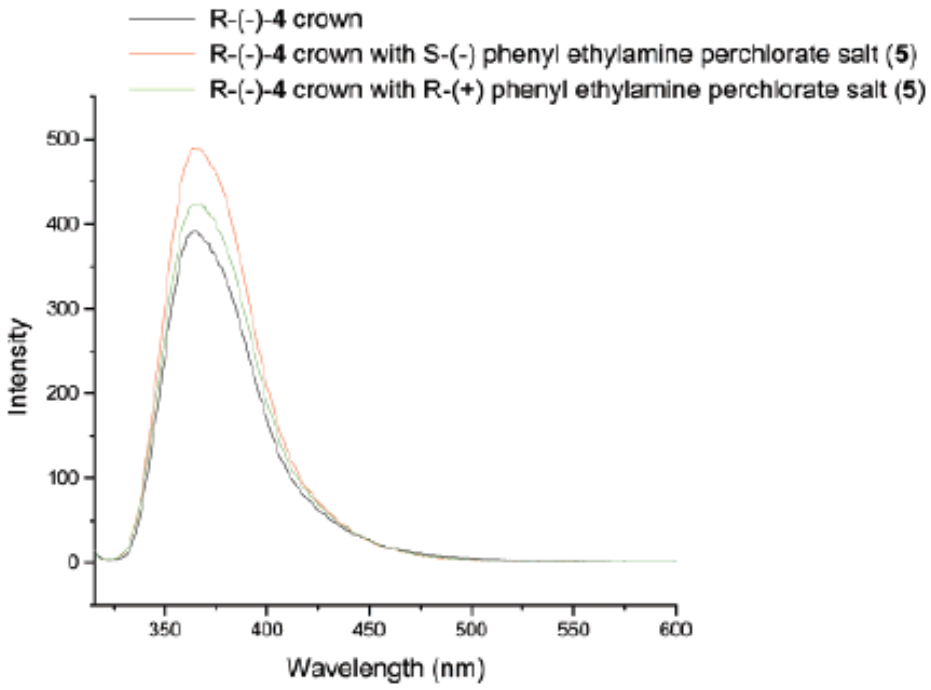
- The D-amino acid salts fit better in the circular cavity than their opposite enantiomer.

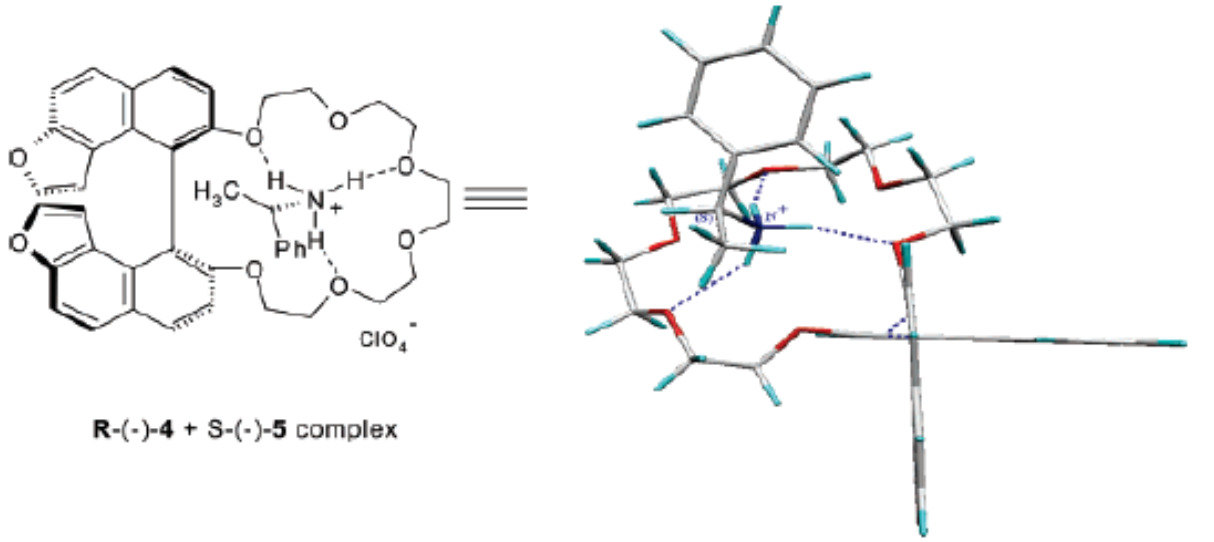


- Mendoza and coworkers synthesized an enantiopure receptor S,S-**56** containing a chiral guanidinium functionality, a crown ether moiety, and a naphthalene ring.
- It shows higher enantioselective ability towards aromatic amino acids such as L-tryptophane and L-phenylalanine which is possibly due to formation of several hydrogen bonds simultaneously in the flexible and folded receptor with L-tryptophane.
- The naphthalene ring provides additional π-stacking interactions.
- Liquid-liquid extraction technique has been used for resolution.
- In recent past our group has successfully synthesized chiral furo fused BINOL and its macrocycle derivatives.
- Among the all the derivatives one of the macrocycle showed the application in chiral molecular recognition of the Phenyl ethyl amine and Ethyl ester of valine.

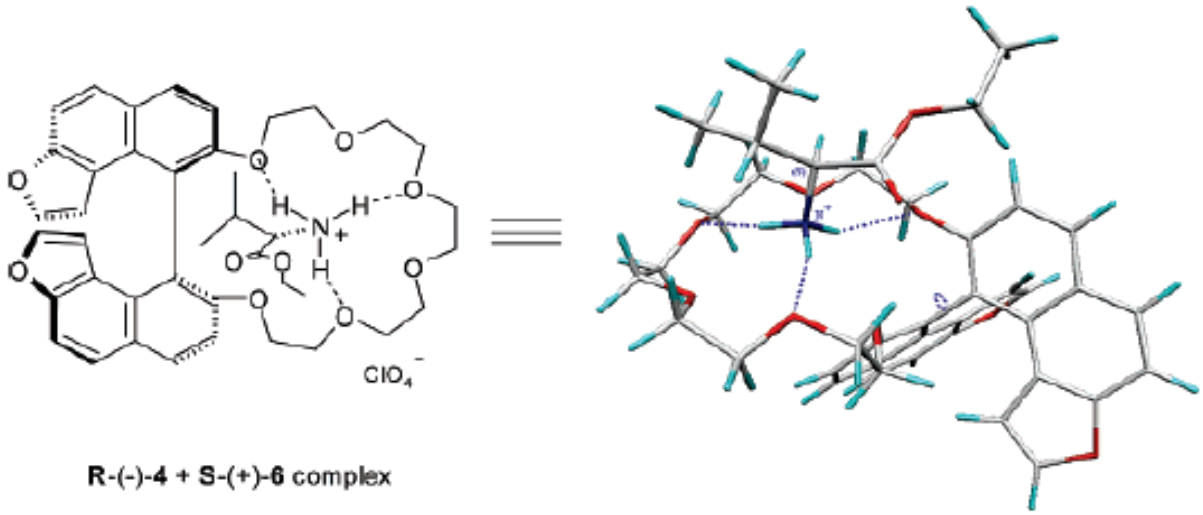


R-(-)-4


R-(-)-4 crown
R-(-)-4 crown with S-(-) phenyl ethylamine perchlorate salt (5)
R-(-)-4 crown with R-(+) phenyl ethylamine perchlorate salt (5)
Intensity
0
100
200
300
400
500
350
400
450
500
550
600
Wavelength (nm)

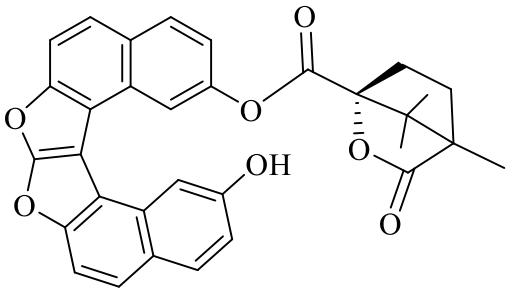


R-(-)-4 + S-(-)-5 complex

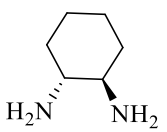


R-(-)-4 + S-(+)-6 complex

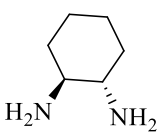
- A novel dioxa[6]helicene-based supramolecular chirogenic system (1) as a specific chiral recognition host for enantiopure trans-1,2-cyclohexanediamine (2) is reported.
- Host 1 with an inherent free phenolic group and a (1S)-camphanate chiral handle on the opposite terminal rings of the helicene chromophore acted as an efficient turn on fluorescent sensor for S,S-2 with an excellent enantioselective factor, α = KSS/KRR = 6.3 in benzene.



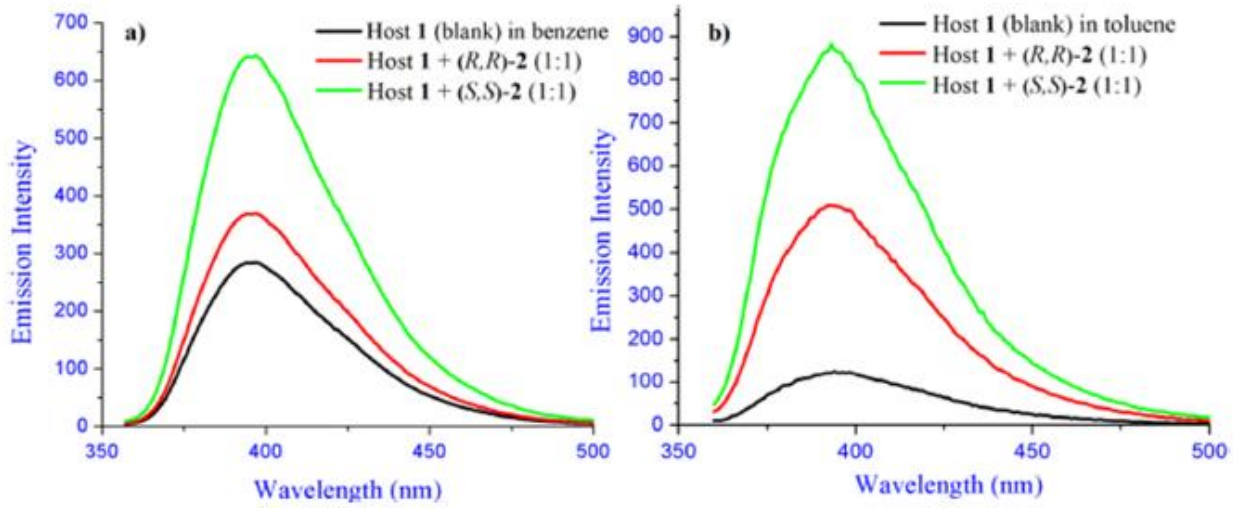
Helicene camphanate



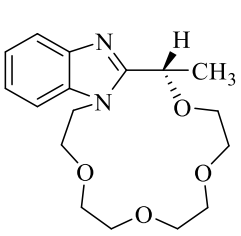
(*R*,*R*)-CHD



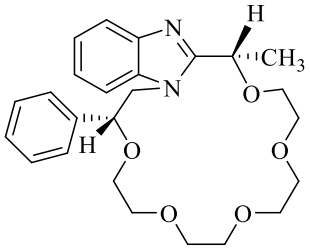
(*S*,*S*)-CHD



- Recently, our group has synthesized the chiral benzimidazole based receptors, mono aza-15-crown-5 **181**,monoaza-[18]crown-6 (*S,R*)-**182,** (*S,S*)-**183**, and [18]crown-6-sized azacrown **184.**
- Supramolecular interactions between the aza-crown host,**181** and enantiomerically pure amine guests in the ionic and neutral forms displayed the enantio-discrimination ability for phenylethyl amine and naphthylethyl amine. However, the reversed enantioselective binding was observed for [18] crown-6, aza-crowns (*S,R*)-**182**, (*S,S*)-**183**, and (*S*)-**184**.

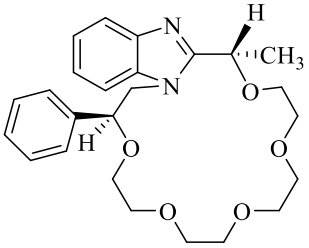


(*S*)-**181**

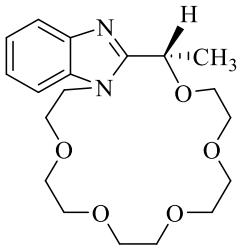


(*S,R*)-**182**

2



(*S,S*)-**183**

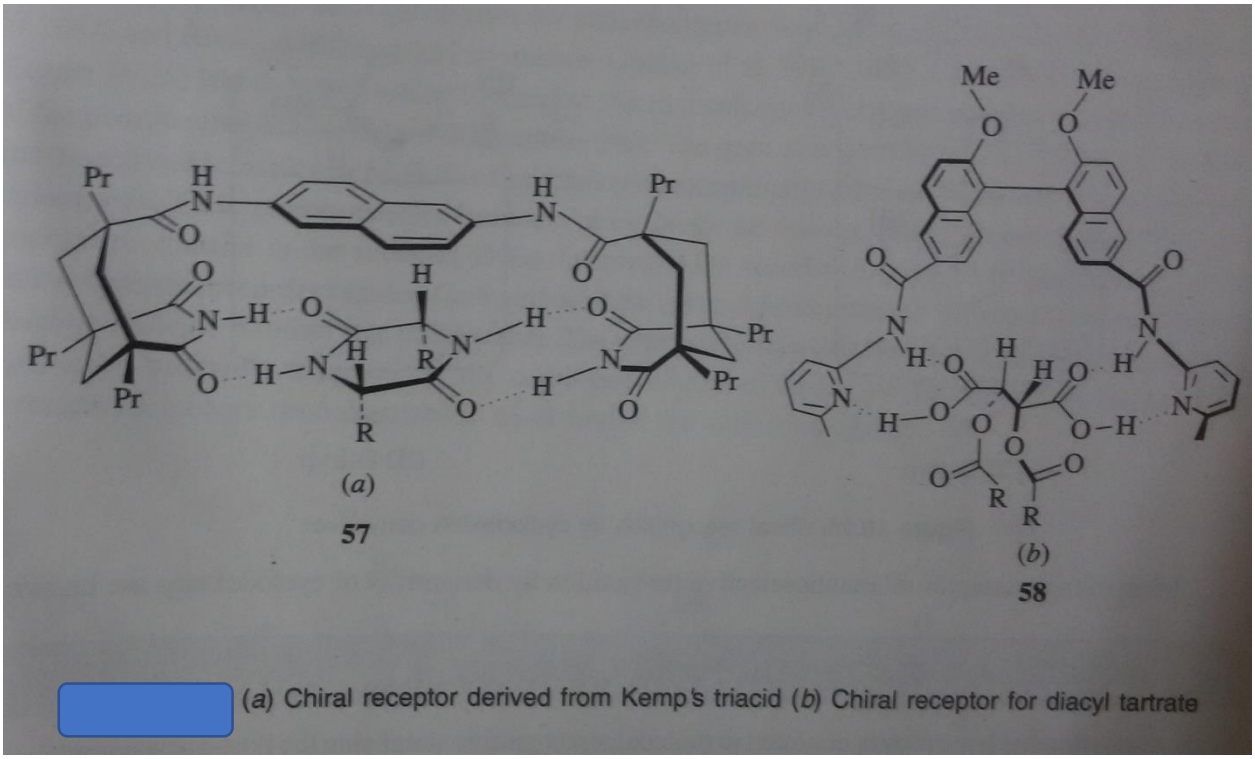


(*S*)-**184**

(b) Chiral receptor from Kemps triacid:

- Rebek's group have synthesized a enantiopure receptor **57**, derived from Kemps triacid in which amide and lactam functions like cleft like cavity.
- It shows a very high enantioselective recognition in its complexes with diketopiperazines such as cyclo-Leucine-L-leucine.
- In the preferred complex **57**, four hydrogen bonds are formed without incurring any unfavourable steric interaction (with the R groups

pointing outwards). For a mismatched fit, at best three hydrogen bonds can be formed.



(a) Chiral receptor derived from Kemp's triacid (b) Chiral receptor for diacyl tartrate

(c) Chiral receptor for tartaric acid:

- Hamilton and co-workers have synthesized the C2 symmetric receptor R-(-)-**58**, for chiral recognition of diacylated racemic tartaric acid also with C2 symmetry.
- It has two acylaminopyridine units linked through the chiral 1,1'-binaphtyl spacer.
- It has two anti carboxyl groups, apparently bound to two opposite faces of the binding cavity with the two acyloxy groups hanging outwards as the complex **58** with L-(+)-derivative, is slightly favoured over the one with D-(-)-derivative in which the acyloxy groups are pushed upwards.

(d) Cyclodextrins and derivatives:

- α-Cyclodextrin (natural) has been used for enantioselective binding of trytophan formimng inclusion complex.
- R-enantiomer formed the strong binding over the opposite enantiomer.
- Rizzarelli and co-workers have used 6-deoxy-6-N-histamino-β-cyclodextrin Cu (II) complex as an enantioselective receptor for aromatic amino acids.
- E.g. D-tryptophane binds strongly to it with the aromatic ring trapped inside the CD hydrophobic cavity while L-tryptophane leaves the ring system the ring system outside as shown in the two structures **59** and **60**.

- The ternary complexes shows an enatioselective factor of 1.41 in favour of the D-enantiomer providing method for resolution of D, L-tryptophane by HPLC.
- This is the first example of mixed inclusion-ligand exchange chromatogarphy for chiral resolution of amino acid.
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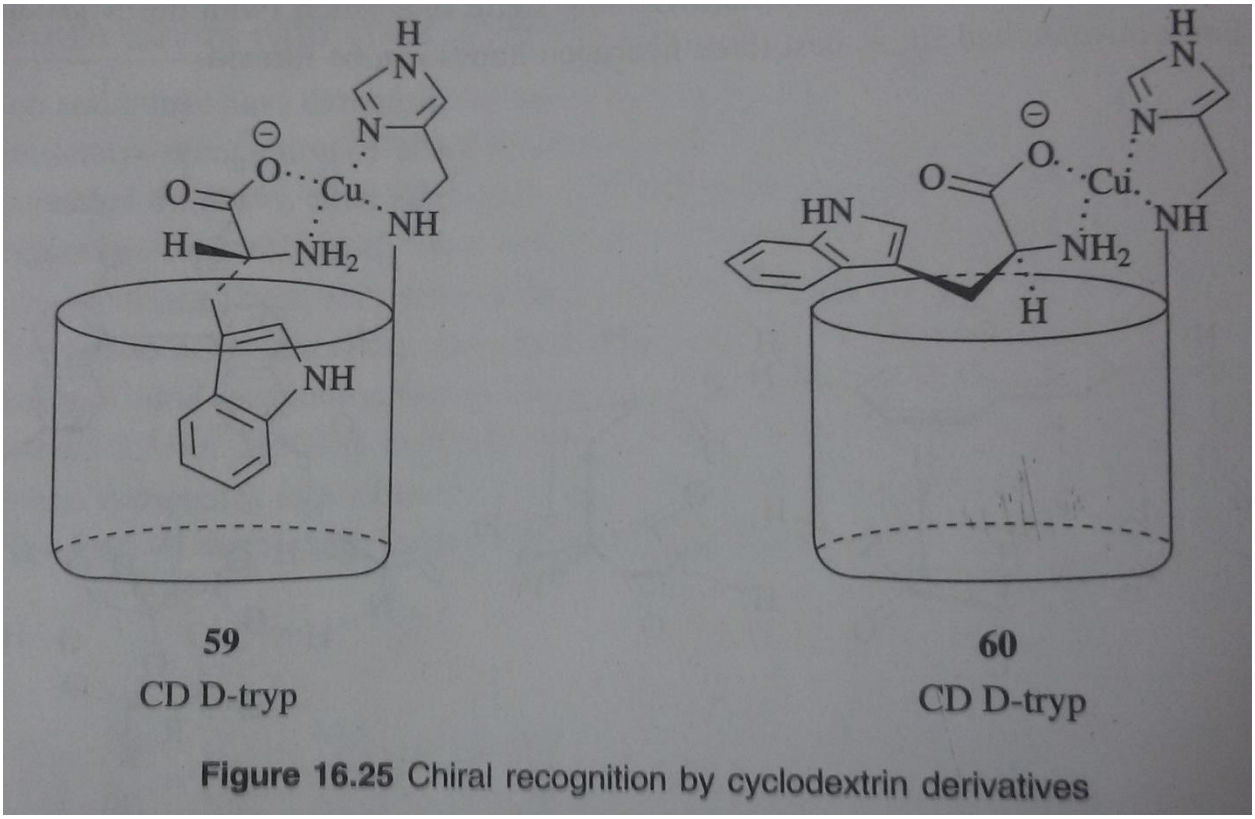

Figure 16.25 Chiral recognition by cyclodextrin derivatives

Molecular Recognition and Catalysis

- Previously we have discussed molecular recognition stabilising the host guest complexes in the ground state.
- Major objective is to merge molecular recognition and catalysis in a bid to produce enzyme mimics or artificial enzymes.
- Similar to molecular recognition, catalysis also based on the noncovalent interactions.

(a) **Phosphadiester cleavage:**

- To design artificial catalyst for phosphadiester clevage (important for partial hydrolysis of DNA and RNA), Hamilton and co-workers have synthesized the receptor **61** which is well suited to stabilise the trigonalbipyramidal intermediate B in the cleavage of the phosphodiester A to C by nucleophile (Nu).
- The ground state complex represented by 61-A and the activated complex by 61B.

- The isophthaloyl spacer provides the steric fit and the two guanidinium moieties facilitate proton transfer from the receptor to the leaving group in the second step.
- The phosphoryl transfer in the substrate D (an intramolecular reaction to give E) in the presence of **61** follows pseudo first order kinetics.
- Comparison of the first order rate constant with that of uncatalysed reaction shows a 700 fold rate acceleration.
- The reaction follows Michaelis-Menten kinetics showing saturation behaviour.
- The combined effects of hydrogen bondings and electrostatic interactions (charge neutralisation) in 61B lower the activation energy.

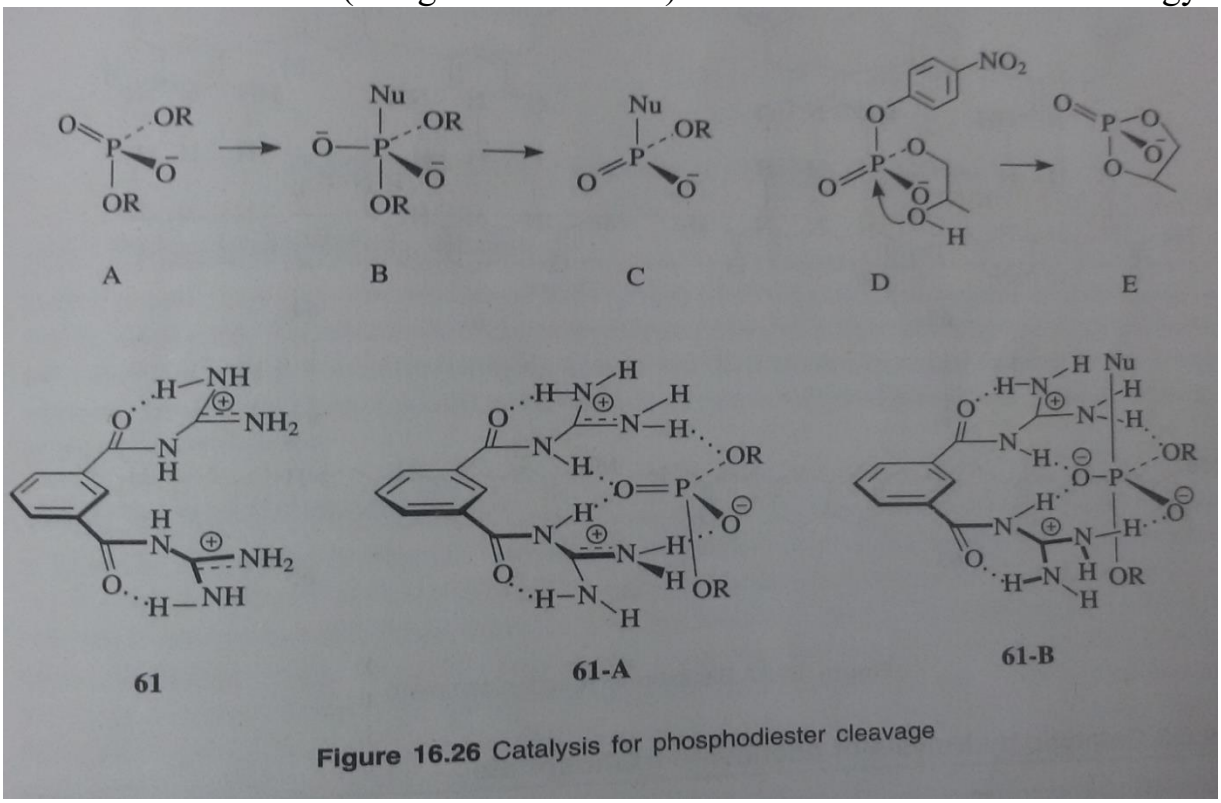

Figure 16.26 Catalysis for phosphodiester cleavage

(b) Bisubstrate reaction template:

- Kelley and co-workers have made a different approach for achieving catalytic effect in receptor-mediated bond forming reactions.
- The receptor molecule has two sites to bind two substrates which are capable of reacting with each other in **62** to form the product **63**.
- The complex **62** is a ternary one and because of the appropriate steric fit of the two reacting functionalities and of the intramolecularity of the reaction, it gives the product **63** rather easily with a 6 fold rate acceleration.
- Because of the identical binding sites, some non-productive ternary complex's are also formed.

- By using non-identical binding sites as in **64** which permits the formation of the productive complex only, the acceleration rate has been increased by a factor of 12.

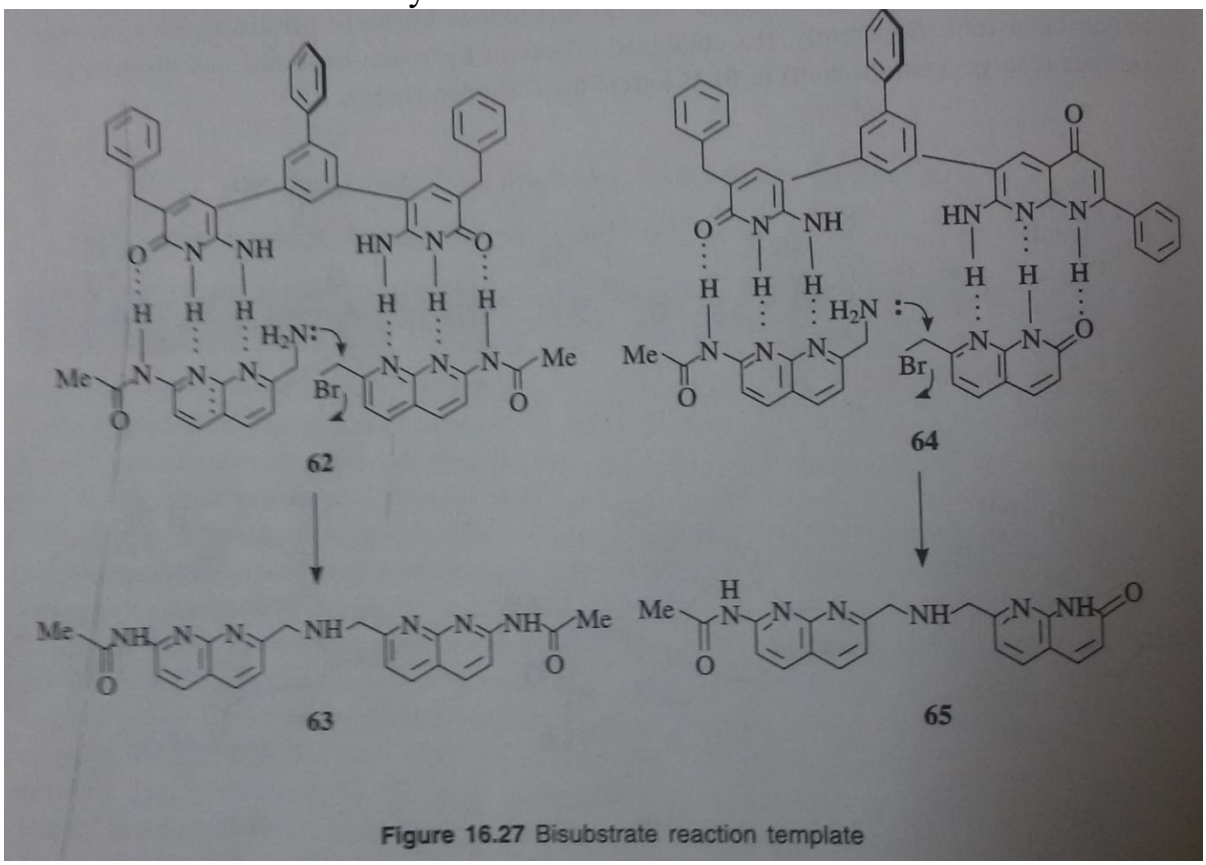

Figure 16.27 Bisubstrate reaction template

- The syntheses are rare examples in which a bond-forming reaction rather than a bond cleavage reaction is catalysed (the products **63** and **65** have each a new C-N bond).
- The binding sites of the receptors, however, do not resemble the active sites of any enzyme. The receptors, therefore, cannot be properly called enzyme models but are artificial enzymes.

(c) **Catalytic hydrolysis of adenosine triphosphate:**

- Lehn and coworkers have shown that protonated macrocyclic polyamine can catalyse the hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP).
- Thus the 24 membered cyclic hexaammonium **66** binds ATP strongly (five of the six ammonium ions are hydrogen bonded to four oxygens of the triphosphate).
- This is followed by an intramolecular transfer of the terminal phosphate to the sixth nitrogen giving an intermediate which then loses phosphate ion by reaction with water.

- The probable mechanism given here resembles that of hydrolysis by the serine proteases. A transient intermediate identified as phosphoramides **67**.
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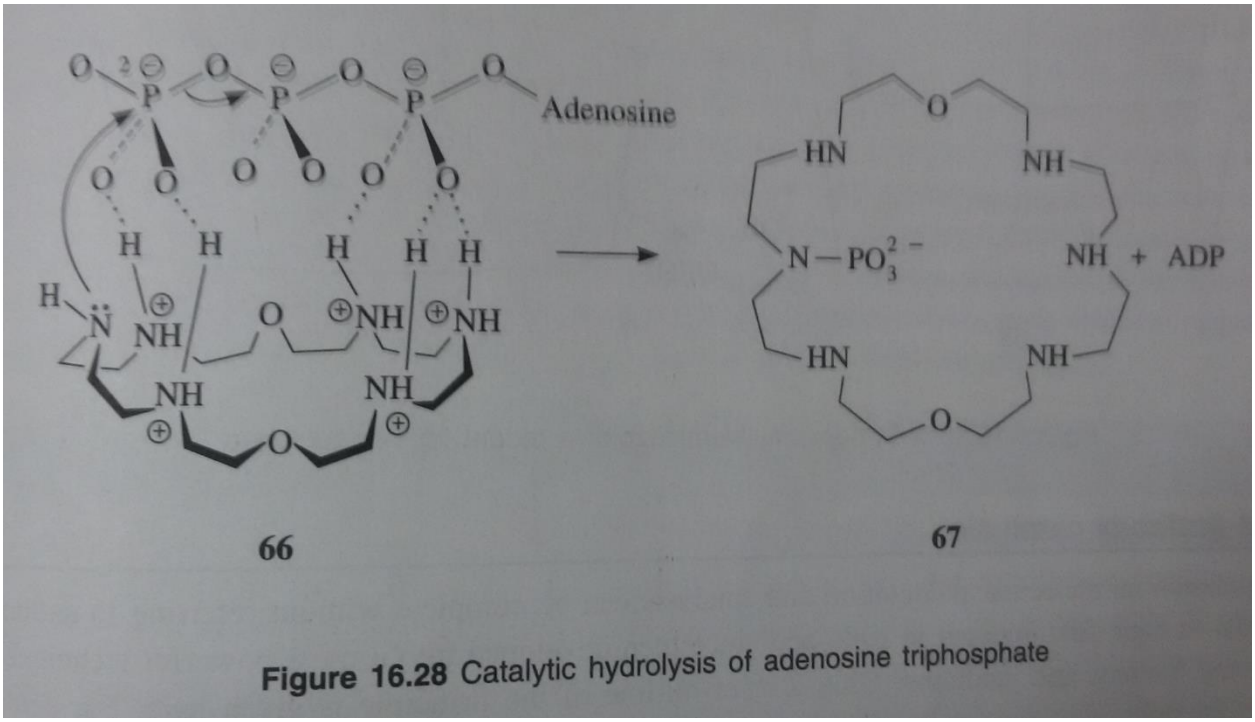

Figure 16.28 Catalytic hydrolysis of adenosine triphosphate

(d) A model for ribonuclease:

- Breslow and co-workers have prepared β-cyclodextrinylbisimidazole **68** which catalyses the hydrolysis of cyclic phosphates (such as 4-t-butylcatecol cyclic monophosphate) in a selective manner with bifunctional catalysis, a neutral imidazole and an imidazolium cation serving as the two functional groups.
- With the t-butylphenyl group hydrophobically bound inside the CD cavity, the cyclic phosphate group is placed between two imidazole moieties: one acting as general base and the other (N-protected) acting as the proton donor selectively to P-01 of the cyclic phosphate.
- With the two imidazole groups hydrogen bonded to (nucleophilic) water molecule and the leaving oxygen at the apical position of the trigonal bipyramid, the in line mechanism can give only 4-t-butyl-2-monophosphate regioselectively through the intermediate 69.
- Although 68 resembles ribonuclease in its active site and the mechanism of reaction, catalysis is slow compared to typical ribonucleases.
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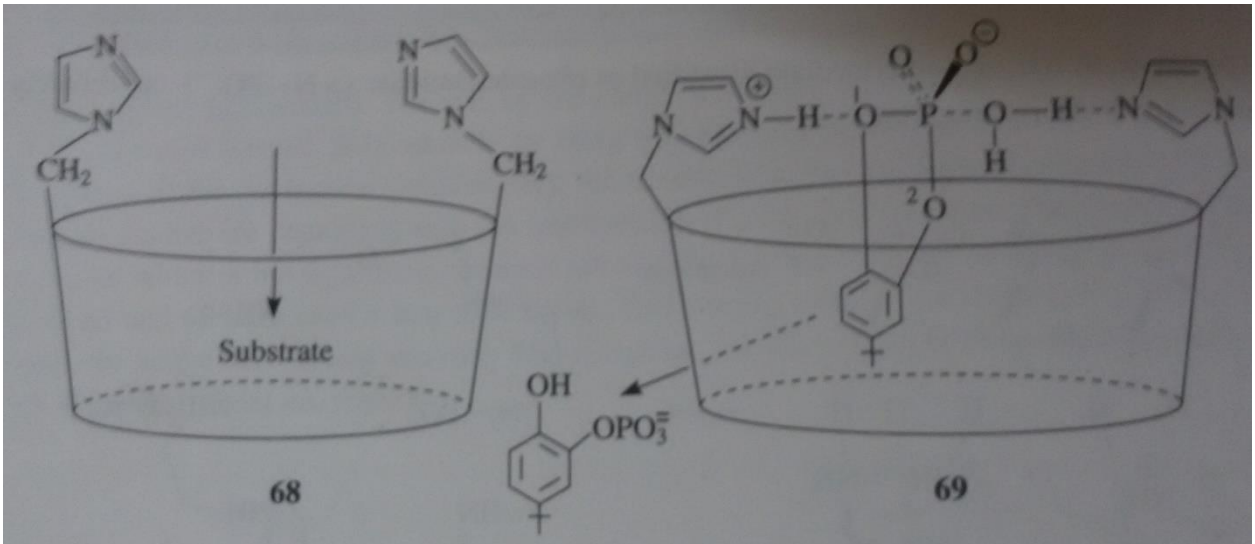

Figure 16.29 β-Cylodextrinylbismidazole: a model for ribonuclease

(e) Antibody catalysis:

- It is most powerful technique in chemistry, biology and medicine.
- Antibodies are large protein molecules (immunoglobulins) consisting of four polypeptide chains, produced by specific lymphocytes or immunocytes in response to foreign macromolecules, known as antigen introduced in the body.
- Antigen and antibody are highly complementary to each other and form strong complex.
- Different strategies have been followed for antibody catalysis.
- (1) By using haptens (small molecules) which resemble (structurally and stereoelectronically) the rate determining transition state of the considered reaction, the binding sites of an antibody are so designed that they selectively stabilise the transition state through molecular recognition and thus bring down the activation energy.
- E.g. antibodies raised against tetrahedral and negatively charged phosphate and phosphonate which are transition state analogues of carbonate and ester hydrolysis respectively, catalyse these reaction with accelerated rates.

(2) The antibody binding sites are so modified by specific haptens that the reacting partners are brought into close proximity as required in a highly ordered transition state.

- Here the antibody sites behave as entropic traps and help to overcome the entropy disadvantage.
- E.g. A hapten with a cyclohexane ring locked into a conformation resembling the highly ordered Diels-Alder transition state with the help of an ethano bridge generates an antibody which would catalyse the cycloaddition.

(3) Specific catalytic groups e.g., of general acid-base type may be introduced into the binding sites.

- Thus E2 elimination of β-fluoroketone (or β-hydroxyketone), a hapten of analogous structure but with α-H replaced by an ammonium group is used to induced a complementary carboxylate anion in the binding sites of antibody next to α-H which is thus extracted easily.

(4) An antibody may be raised to a multisubstrate analogue so that the binding sites can simultaneously bind the cofactor and substrate to catalyse the reaction in the enzymic fashion.

- Most importantly, there is no fundamental difference between enzyme catalysis and antibody catalysis both showing high selectivity, high reaction rate, saturation, inhibition, and Michaelis-Menten kinetics.
- The advantage of the antibody catalysis lies in its versitile application covering reactions ranging from peptide bond cleavage to pericyclic reactions.

Summary:

- Self-assembly is the spontaneous and reversible association of molecules or ions (tectons) to form larger, more complex supramolecular entities according to the intrinsic information contained in the molecules themselves.
- Fundamentally self-assembly is a convergent process in which a number of components assemble into, ideally, a single fi nal, stable structure. Self-assembly is thus very distinct from chemical emergence which is a divergent process in which complexity evolves over time.
- Self-assembly broadly divided into two classes 1. Self-assembly of inorganic structures and 2. Self-assembly of organic structures.
- Inorganic self-assembly and self-organization involve the spontaneous generation of well-defined metallo-supramolecular architectures from organic ligands and metal ions.
- The self-assembly of organic supramolecular species makes use of interactions other than metal ion coordination, such as electrostatic, hydrogen bonding, van der Waals, stacking or donor-acceptor effects as found in proteins, nucleic acids, liquid crystals and molecular complexes.