CHEMISTRY

THEORY PAPER: Theoretical organic chemistry-II

(as per Model CBSGS curriculum)

M.Sc. (Prog.) Semester IV

Supramolecular chemistry

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TITLE:	**Supramolecular Chemistry**
Key words for Search:	Synthetic molecular receptors, molecular cleft, molecular tweezers and hydrogen sites.

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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.
- Supramolecular Chemistry Concepts and Perspectives by Jean–Marie Lehn
- Introduction to Supramolecular Chemistry by Helena Dodziuk
- Supramolecular chemistry by Jonathan W. Steed & Jerry L. Atwood

Web-links:

- http://ces.iisc.ernet.in/hpg/ragh/publication_list/Gadagkar_Publications/Gadagkar_19 8 8a.pdf
- http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1987/lehn-lecture.pdf
- http://www.ch.ic.ac.uk/local/organic/tutorial/steinke/SP-Nano-lecture6.pdf
- https://www-herz.physics.ox.ac.uk/publications/Schenning04a.pdf
- https://youtu.be/saeAIk61n1s

Activities:

- Tell your students to find about receptors, molecular cleft and molecular tweezers.

Table of Contents

SYLLABI OF THIS MODULE:

Supramolecular Chemistry

2.1 Supramolecular Chemistry

- 2.2 Synthetic molecular receptors: receptors with molecular cleft, molecular tweezers, receptors with multiple hydrogen sites.

Learning outcomes:

Upon completion of this course, student will be able to

Basics about the use of supramolecular entities as molecular devices.

Energy and electron transfer processes.

Introduction:

Synthetic Molecular receptor:

- Pedersen (1967) first introduced the concept of molecular recognition in abiotic chemistry then subsequently Lehn, Cram and others extended this area.
- They particularly involved in the synthesis of a large variety of macrocyclic polyethers, monocyclic and polycyclic and studied their complex forming ability.

- The stability of complex is expressed by the association constant Ka (M^{-1}) or ΔG (kJ/mol)
- The stability depends on two principles: Principle of preorganisation and principle of complementarity or structural recognition.
- According to the first, the more highly hosts and guests are organised for binding and for low solvation priror to their combination, the more stable are their complexes.
- If host and guest are not preorganised, they have to make so during complexes.
- The structural recognition requires that the guest must be accommodated in the cavity or cavities formed in the host nicely and binding sites must functions cooperatively.
- This field created the great interest in both academic and industrial world.

Molecular Tweezers:

- In the recent past, development of new chiral receptors capable of chiral discrimination processes has become an important and rapidly growing research area.
- Several structurally diverse synthetic receptors have been successfully prepared for asymmetric synthesis and recognition of neutral organic molecules, chiral molecules, and anions.
- Among the various artificial receptors synthesized so far, a special class of receptors, namely molecular tweezers[1] are currently attracting great interest.
- The term molecular tweezer was first time coined by Whitlock which are featured by two flat, generally aromatic pincers, separated by some kind of more or less rigid spacer. A rigid spacer enforces a syn-cofacial orientation of two aromatic rings creating a cleft that can bind an aromatic guest by π-stacking interactions.
- The design of molecular tweezers should account the three features, needed to enhance the binding of an aromatic guest molecule. These are (1) the presence of a spacer that prevents self-association, (2) a spacer that establishes a distance between the pincers of the tweezer of about 7 Å (plane to plane or centroid to centroid), ideal for the inclusion of a single aromatic guest, and (3) a spacer that holds the pincers rigidly in a syn conformation.
- Few examples on molecular tweezers have been discussed below to familiarise the reader with the background. Zimmerman and co-workers[2] have designed new molecular tweezers by considering these principles. In 21 tetrahydrodibenz [c, h] acridine is the spacer holding

two acridine ring systems with their planes parallel separated by a distance of nearly 0.72 nm, ideal for sandwiching an aromatic ring.

- The acridine units in 21 shwo remarkable cooperativity in complexation with 2, 4, 7-trinitrofluorenone.
- Incorporation of an annulated terpyridine in the spacer as in **22** which ligates with metal and the vacant coordination site of the metal can converge on the binding cleft increasing the affinity for coordinating an aromatic guset.
- Incorporation of a corboxyl, methyl carboxylate or nitrile group at the active site as in **23** provides, additionally, hydrogen-bonding interactions .
- These tweezers are found to be good binding agents for nucleotides ($Ka>10^{4}\ M^{-1}$), studied for 9-propyadenine (in **23**) π-sandwiching and hydrogen bonding to a single edge of an adenine thus result into exceptionally strong binding affinity.

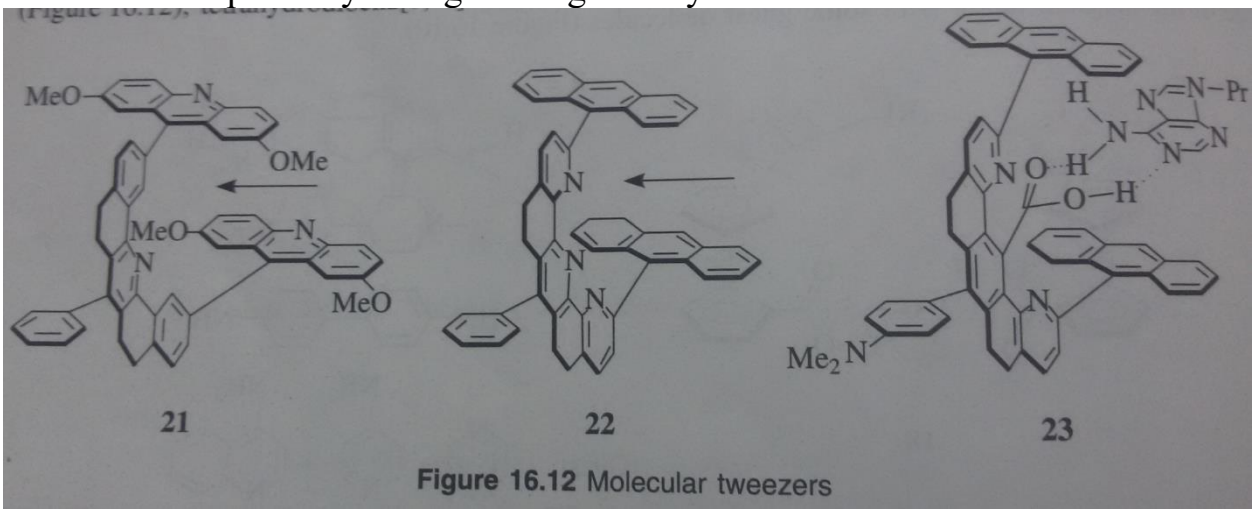


Figure 16.12 Molecular tweezers

Previous work by our group: Tetrahedron asymmetry **2016**, *27*, 130-135

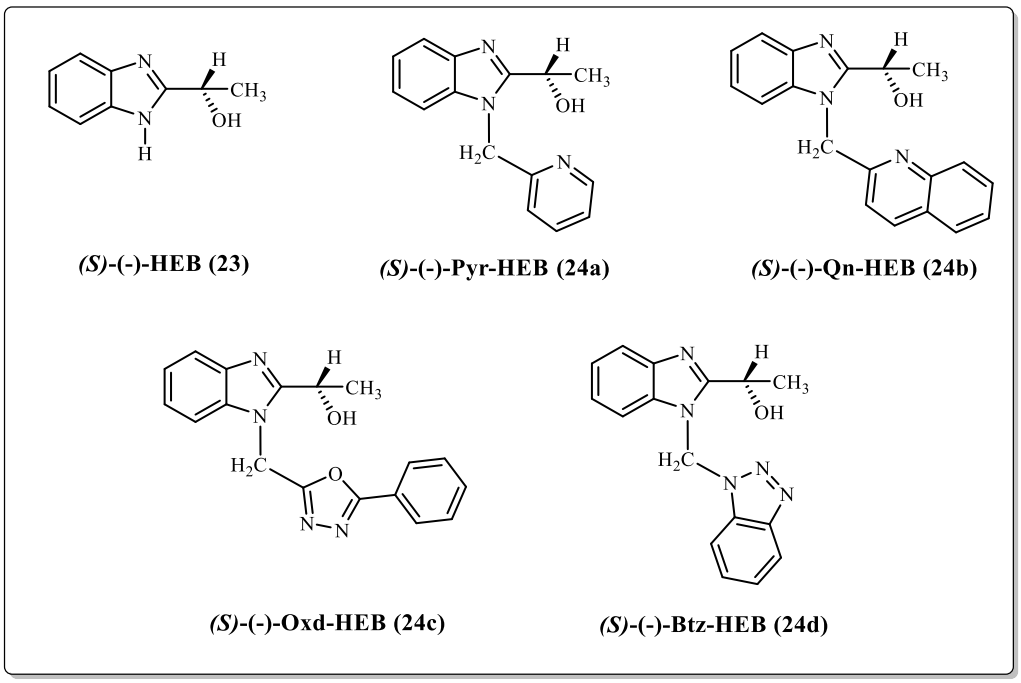
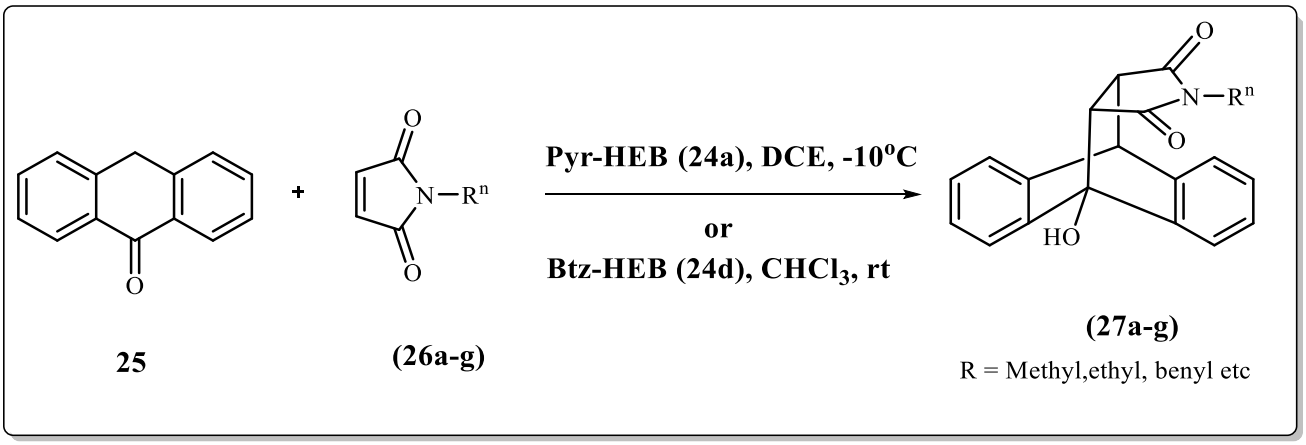


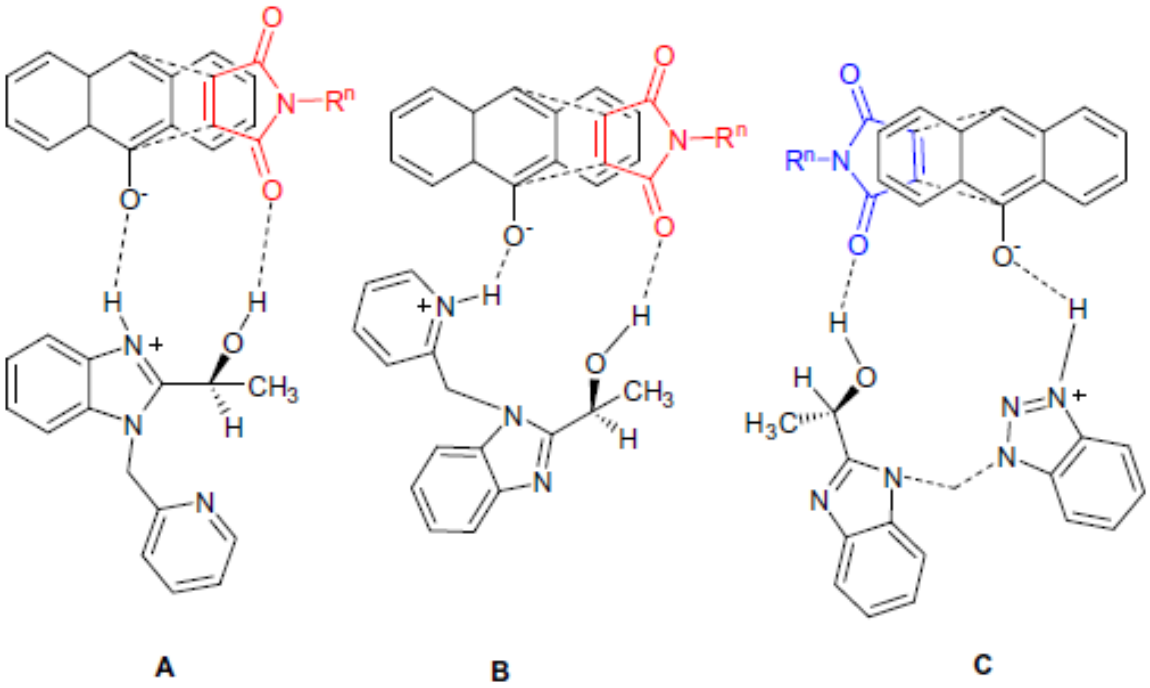
Figure. Synthesized chiral tweezers (**23**, **24a-d**).



Scheme . Benzimidazole derived chiral molecular tweezers **24**(a-d) catalysed asymmetric Diels-Alder reaction between anthrone, **25** and maleimide, **26a-g**.

- Synthesized chiral benzimidazole based tweezers by attaching achiral part of heterocycle as the pincers such as **pyridine, quinoline, oxadiazole, benzotriazole**, **found utility** as the organocatalyst for the Diels Alder reaction of **antrone** and malei..
- Tweezers exhibit the organocatalytic activity for the Diels Alder reaction with ee upto 88%. Interestingly reversal of enantioslectivity was observed.

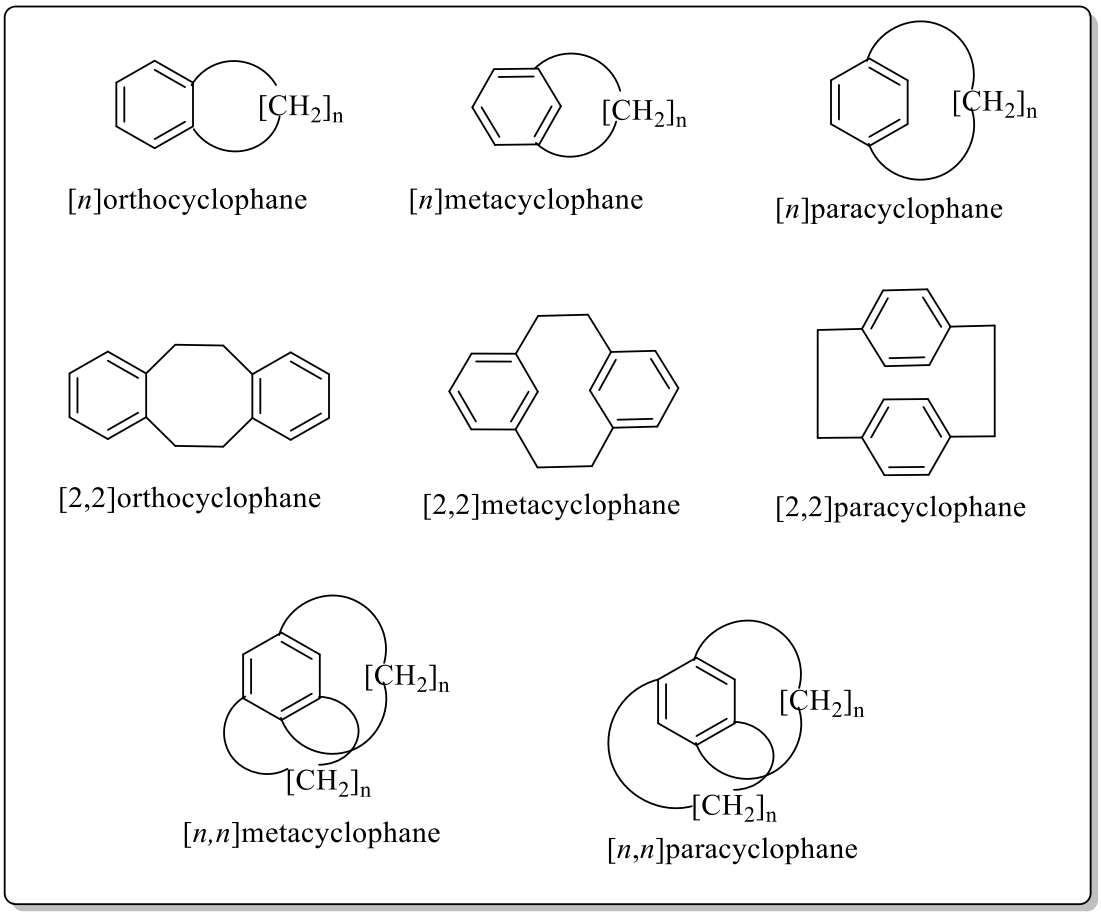
- Organocatalysts with pyridine, quinoline, and 1,3,4-oxadiazole achiral heterocyclic subunits gave DA adducts with an (*S*,*S*)-configuration, the organocatalyst with a benzotriazole subunit caused formation of the (*R*,*R*)-configuration for the DA adducts



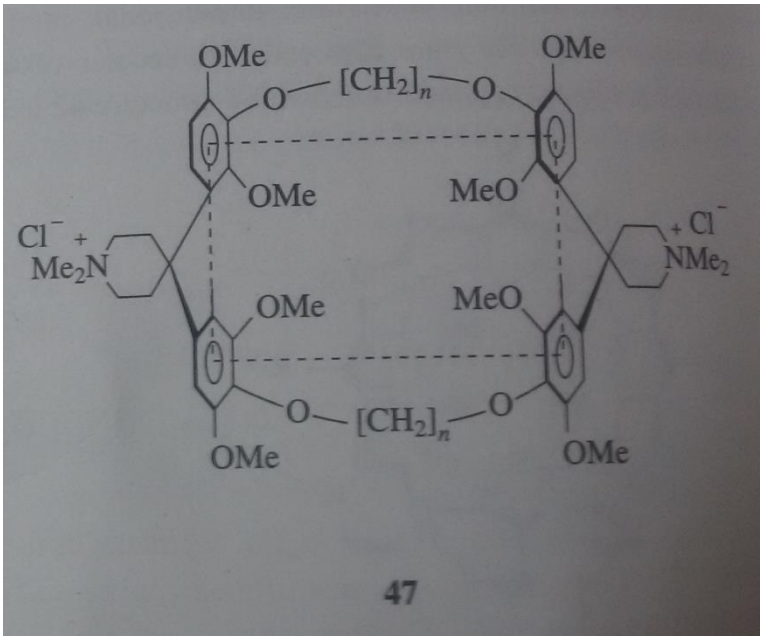
A B C

Cyclophanes:

- Cyclophanes are strained organic molecules which contain aromatic rings as well as aliphatic units. The aromatic rings provide rigidity to their structure, whereas the aliphatic units form bridges between the aromatic rings and also provide flexibility to the overall structure.
- A general classification of cyclophanes is as follows: [*n*]orthocyclophane, [*n*]metacyclophane, and [*n*]paracyclophane.
- The prefixes represent the position of the attachment to an aromatic system while [*n*] represents the number of methylene groups present in the aliphatic bridge.



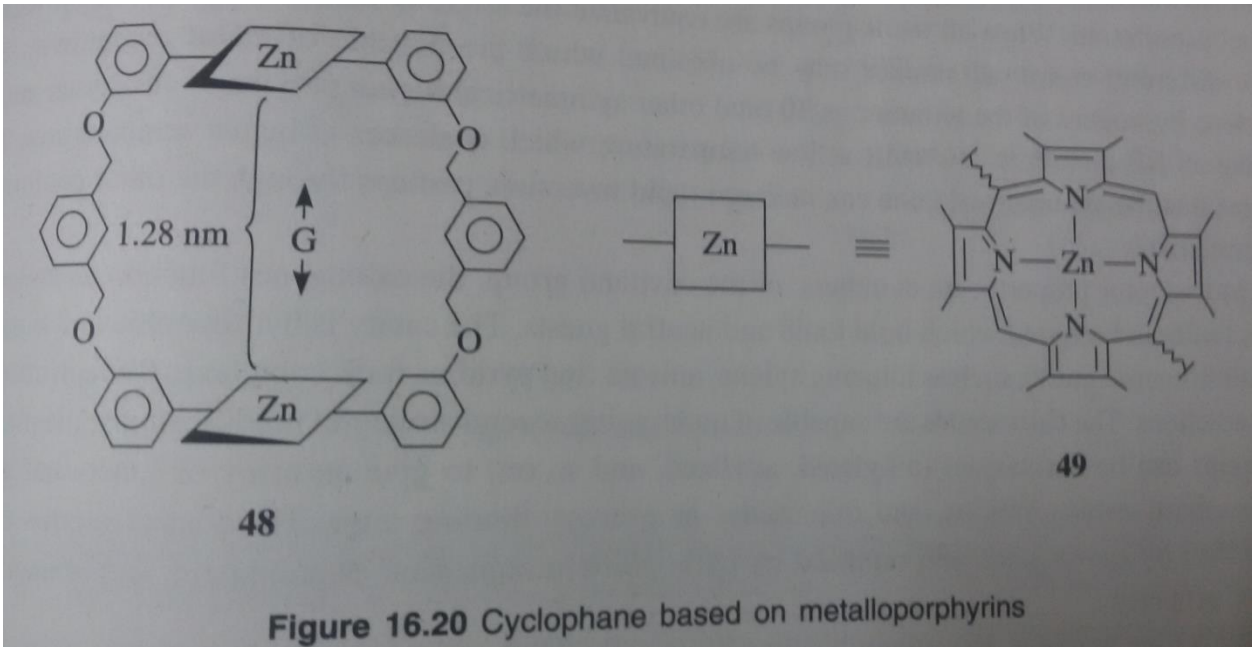
- Two general types of cyalophanes
- (a) Cyclophane diphenylmethane units: Two diphenylemthane units are joined from both sides by dioxaalkane chain as in **47** forming rectangular boxlike cavity shaped by four aromatic rings.
- The aromatic rings impart a high degree of rigidity, the dioxaalkene chains regulate the size of cavity, and binding forces are provided by π-stacking interactions.
- The quaternary ammonium cations situated far from the lipophilic cavity make the receptors water soluble. P-Xylene, p-dicyanobenzene, p-diaminobenzene, and p- dinitrobenzene are some of the guest molecules.



47

(b) Cyclophanes based on metalloporphyrins:

- In these receptors, two metalloporphyrins such as **49** are incorporated in macrocyclic rings with their planes parallel and separated by appropriate spacers as in **48**.
- The receptors have two binding sites, the vacant orbitals of metals, e.g. Zn on two opposite faces pointing towards the centre and are called ditopic.
- A guest molecule like 4,4'-dipyridyl which fits nicely in the cavity forms strong complex with its two basic nitrogen atoms coordinating with the metal atoms.
-



48 49

Figure 16.20 Cyclophane based on metalloporphyrins

Receptors with molecular cleft:

A large number of receptors have been designed which are provided with molecular clefts having convergent functionalities such as CO2H, OH, NH, or metal ion empty orbitals around the clefts.

(a) **Receptors were derived from Kemps triacid:**

- Rebek and co-workers have used Kemps triacid **4** to synthesise a number of receptors such as **6** in which two carboxyl groups are constrained in a convergent conformation follows as a model of active sites of enzymes, lycozyme and aspartic proteinases.
- Some characteristics of these receptors are: The equatorial Me groups in Kemps triacid K1 make the system near anancomeric (only one conformation preferred) and also prevent any possible epimerisation. The diaminoacridine moiety acts as a rigid spacer regulating the width of the cleft. The methyl substituents in the acridine ring **5** prevent free rotation around aryl N-bond and hold the two Kemps acid residues in stable conversent conformation.
- The carboxyl groups in **6** are fully preorganised for complexation with diazabicyclooctane (DABCO) 7, quinoxaline 8, and similar molecules can fit in nicely giving very stable due to intermolecular hydrogen bondings.

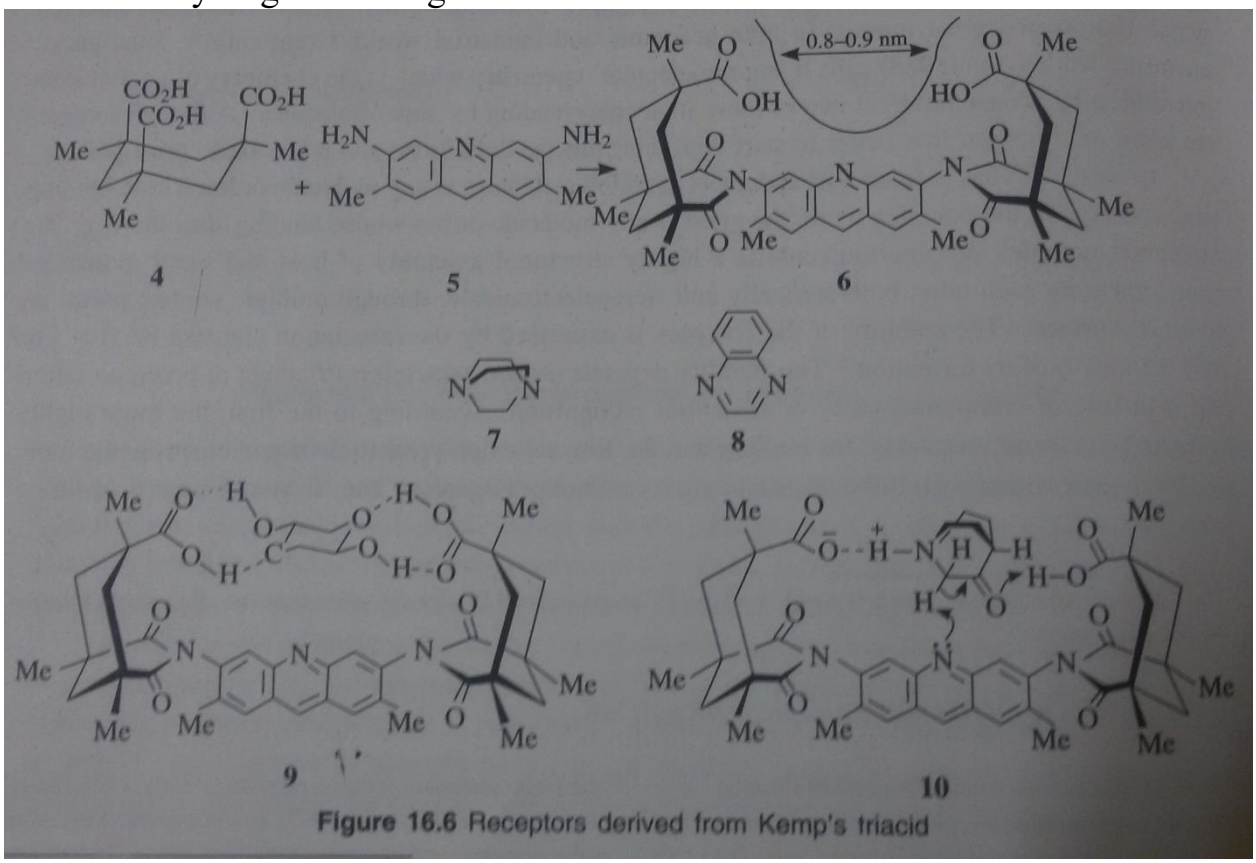


Figure 16.6 Receptors derived from Kemp's triacid

- The preorganisation increases the complex stability is demonstrated by ratio of Ka is 12:1 corresponding to an enthalpy difference of 6 KJ/mol.
- These receptors are also capable of binding small biological targets such as amino acids, heterocyclic amines, and diketopiperazines.
- Due to cleftlike receptors the glycoaldehyde dimer which fits in the cleft giving the complex **9**.
- The acid base catalytic behaviour of the converging CO2H groups and the acridine nitrogen lone pair in 6 accelarate α-hydrogen exchange (through enolisation) in quiniclidinone which also fits in the cleft giving the complex **10**.
- The ideal arrangement for acid-base components in a concerted enolisation involves their approach from perpendicular directions (stereoelectronic factors) which is maintained in the complex **10** and exchange rate in CDCl3 saturated with D2O is extremely fast.
- Addition of DABCO forms a very stable complex with **6** effectively inhibits the exchange. Thus the system behaves as an artificial enzyme: it shows saturation, turnover, and competative inhibition which are characteristics of an enzyme reaction.
- Rebek group (1990) developed another series of receptors from Kemps triacid which stimulate interactions present in the nucleic acid components and also demonstrate that base-pairing can enhance acyl transfer.
- Two of the carboxylic groups of Kemps acid are engaged in an imide ring and the third is aminidified to give a new receptor as shown in **11**.
- In addition to hydrogen bonding's which amount approximately to 9.0 kJ/mol, there are also aryl aryl stacking (Π-stacking) interactions of approximately 5kJ/mol of energy.
- The stacking interaction are reduced as the aryl group is changed from anthracyl to naphthyl, naphthyl to phenyl, and phenyl to methyl by approximately 1.5kJ/mol in each successive step.
- Geometric consideration indicate that the stacking interactions are face to face rather than edge to face type.
- This base pairing effect has been utilised in an acyl transfer reaction for **12** to **13**.
- This base pairing assists the acyl transfer (in catalytic manner) is demonstrated by replacing H of the imide N by Me which prevents base pairing and the rate of the coupling drops by factor of six.

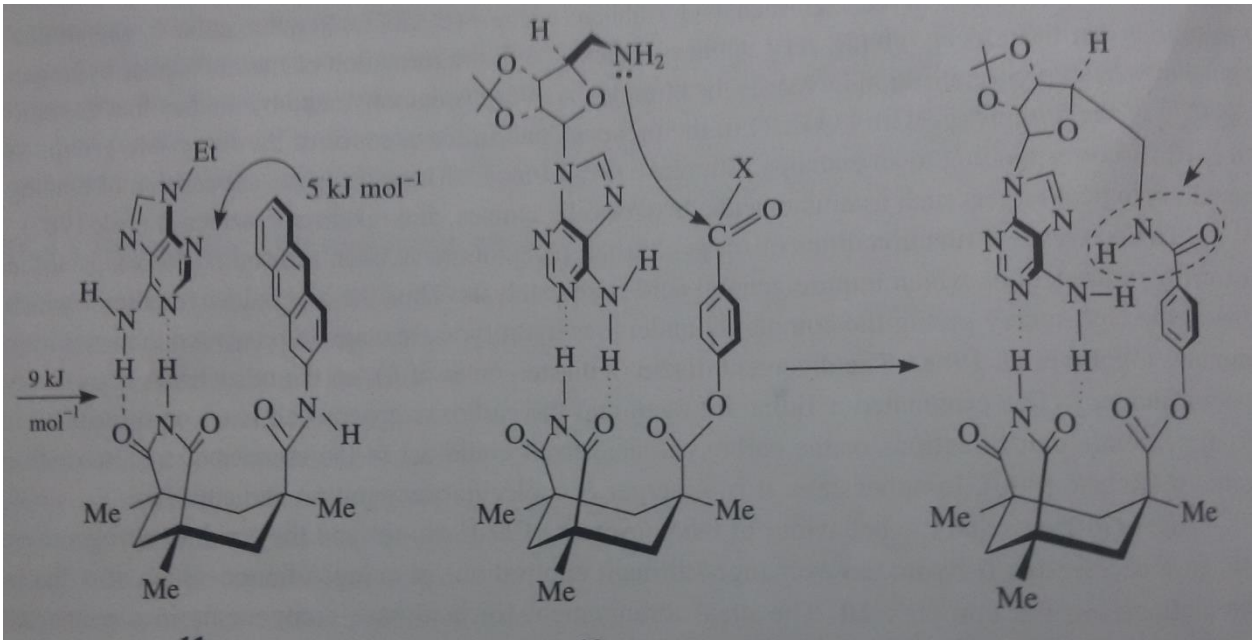


Figure 16.7 Base-pairing and acyl transfer in synthetic receptor

- By replacing the phenyl ring in **12** by naphthyl (a longer spacer), the same template behaviour through base-paring is observed but now instead of a trans amide, a cis amide is formed.
- The cis amide can relax to trans amide by a motion straightening the folded structure and exposing the hydrogen-bonding surface once again.
- This restarts the base-pairing and dimerization occurs with self-replication.

- Cleft like receptors **14** is derived from Kemps triacid imide with naphthyl diamine spacer and other **15** is derived from 5, 11-imethano [b,f]-[1,5] dibenzodiazocine.
- In the latter, the convergent angular disposition of the carboxyl groups is maintained by Trogers base structure.
- They form strong complexes with adenine, adenosine, and biotin.

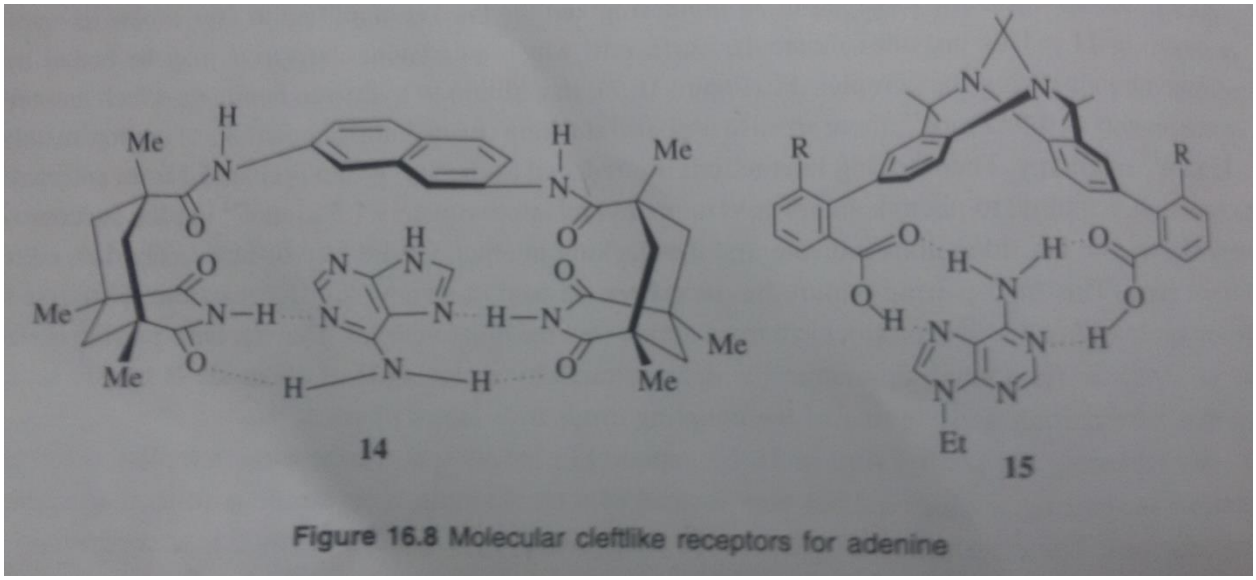


Figure 16.8 Molecular cleftlike receptors for adenine

Two dimensional molecular clefts:

- A few two dimensional molecular clefts have been designed which form stable complexes with flat substrates.
- They have convergent functionalities on both sides.
- In the receptor **16** the slight curvature in the arrangement of the rings is maintained by the central cyclopentadiene unit.
- It is very good receptor for uric acid type of molecules which are held inside the curvature by four hydrogen bonds.
- Second one **17** represents a twisted polyaza cleft which has preorganized and convergent hydrogen-bond donors complementary to diversent 1,3 diketoenolates in complexation with 1,3-cyclohexadionate.

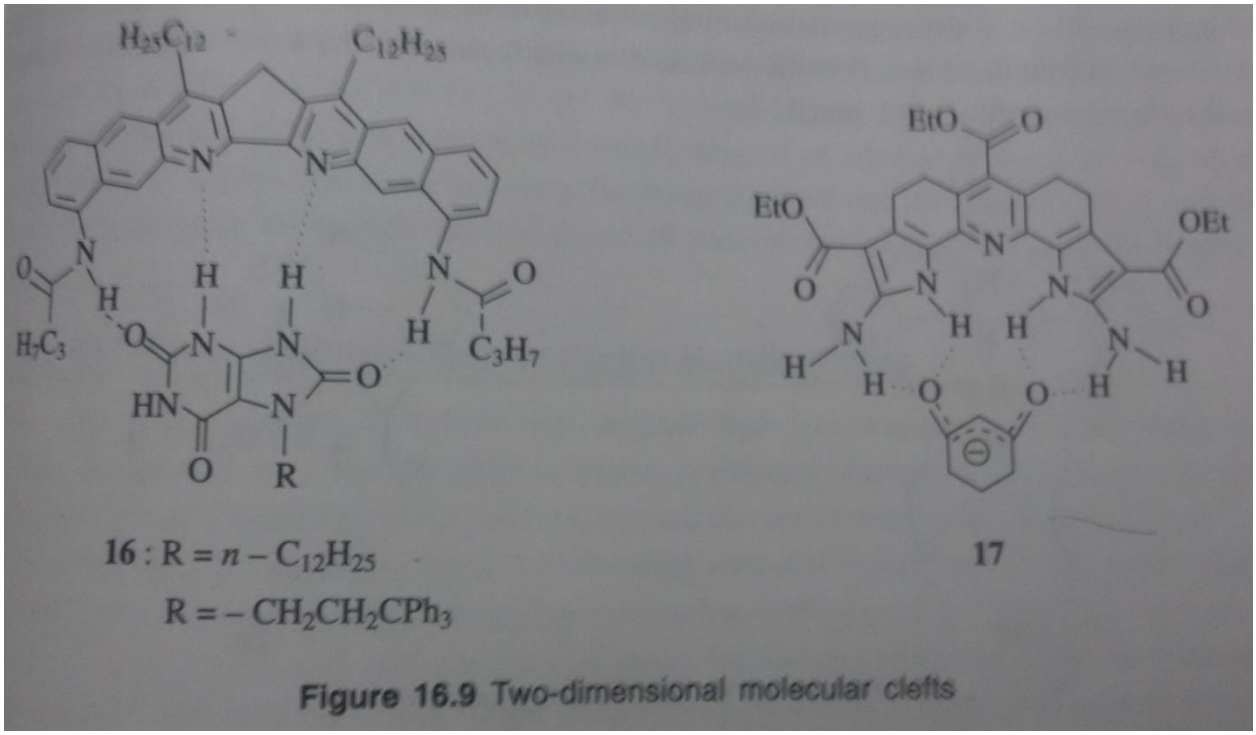


Figure 16.9 Two-dimensional molecular clefts

(c) Molecular clefts based on ferrocenes:

- A gropu of cleftlike receptor have been designed in which two ferrocene moieties with appropriate functionalities form the cleft by means of organic spacers.
- They serve as complexing agents for small molecules and appears to have high potentiality.
- The rotational barrier in ferrocene is quite low so that preorganisation of functional group by rotating the bottom rings by an atomic ball bearing mechanism is easy.
- Structure **18** represents a general type in which R is spacer with different backbone for complexation of guest.

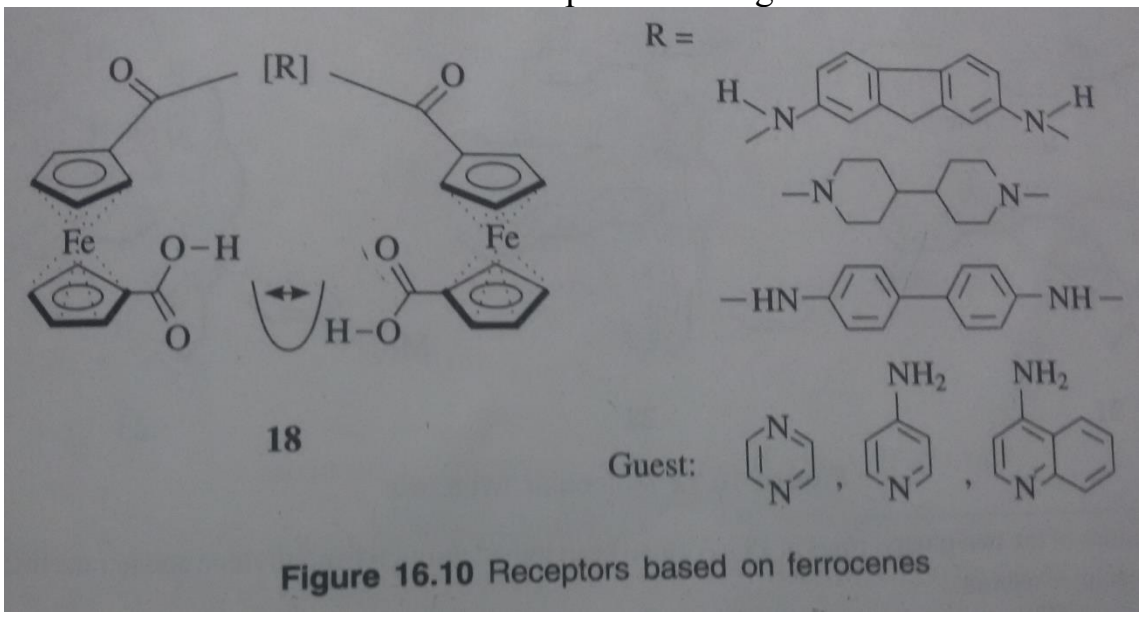


Figure 16.10 Receptors based on ferrocenes

(d) Metalloclefts:

- Metalloclefts with a Lewis acidic uranyl cation capable of coordinating with a basic site have also been designed.
- Two typical metalloclefts are **19** and **20**.
- The distance between the two nearly parallel aromatic cleft walls is approximately 0.6-0.8nm which is optimal for an aromatic ring of a guest molecule to get in.
- The uranyl cation prefers a pentagonal bipyramidal coordination with the two oxygens at the apical positions and with the four coordination site (two phenolated oxygens and two salophene nitrogens) and a neutral molecule (H2O) at the equatorial positions.
- Benzylamine, pyridine, and 4-t-butylpyridine form strong complexes with these metalloclefts with their aromatic ring held by π-stacking interactions and the basic nitrogen coordinated to uranyl.

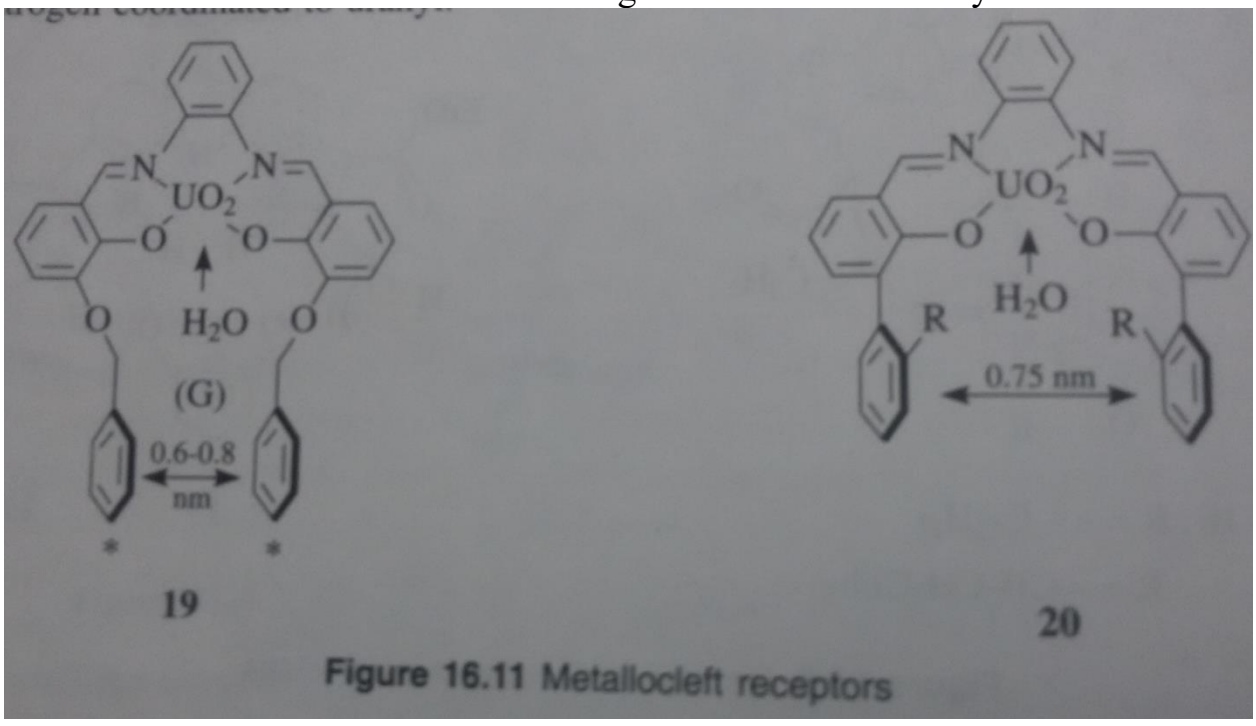


Figure 16.11 Metallocleft receptors

Receptors with multiple hydrogen bonding sites:

- Very few molecular receptors work with multiple hydrogen bonding sites as the prime recognition element.
- In addition to cleft like receptors previously discussed, some macrocyclic receptors, particularly those designed by Hamiltons groups are discussed.
- They have circular cavity provided with a number of hydrogen bonding sites.

- Guest having multiple complementary hydrogen-bonding sites such as barbiturates **24**, urea derivatives, uric acid and nucleic acid bases form strong complexes with these receptors.
- They have aromatic and heteroaromatic rings joined through amide or ether linkages in a circularly array which is not exactly preorganised but the aromatic rings confer some degree of rigidity.
- Barbiturates are clinical drugs while urea and uric acid are excretable metabolites.
- Availability of selective binders for these molecules may hopefully help to develop chemical sensors based on membrane-bound receptors.

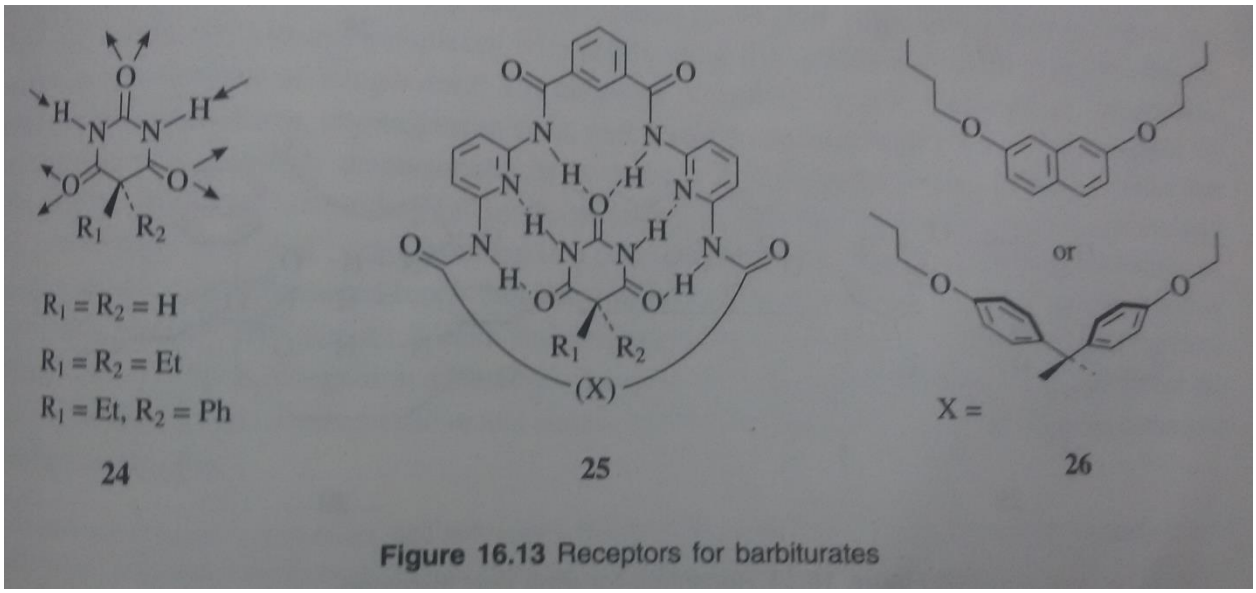


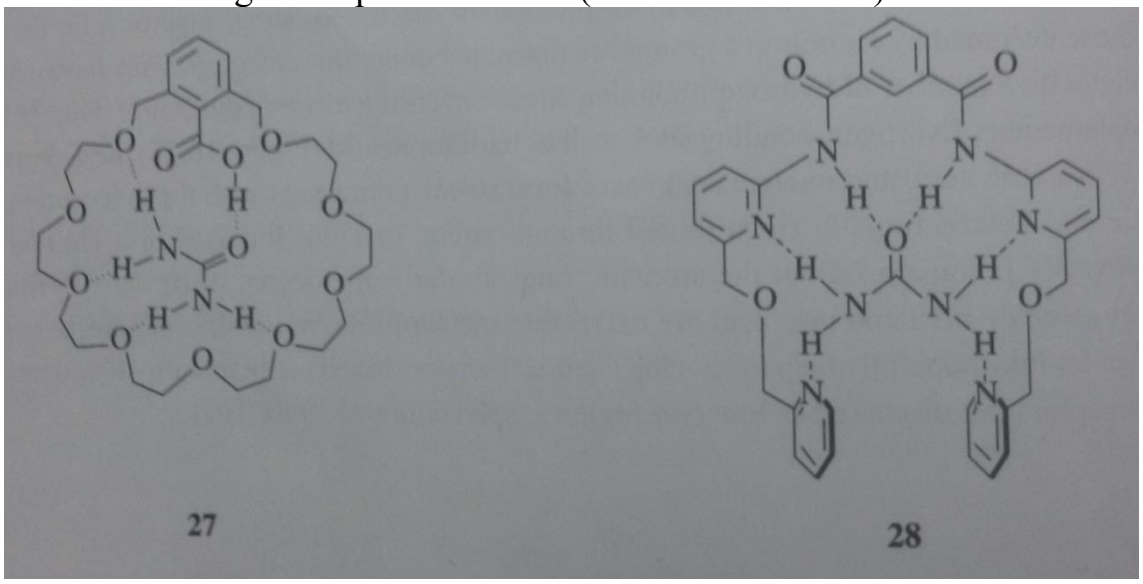
Figure 16.13 Receptors for barbiturates

(a) **Receptors for barbiturates:**

- Barbiturates **24** have as many as eight potential sites for hydrogen bond formation: six lone pair on C=O and a pair of N-H groups.
- Suitable receptors containing 2,6-diaminopyridine units joined by an isophtaloyl spacer at the top and second spacer X (as in **26**) at the bottom have been designed as shown in 25 which possess a constrained macrocyclic framework with a cavity.
- The cavity has six hydrogen bonding sites as seen in the complex with barbiturates.
- The function of the spacers in twofold: to prevent collapsing the structures by intramolecular hydrogen bonds and to regulate the size of the cavity.
- The spacer X may even serve a third purpose by providing additional interactions with 5,5-substituents in barbiturates.
- These receptors form strong complexes with barbiturates with Ka vakue ranging from 10^{2} to 10^{5} M^{-1}

(a) Receptors for Urea:

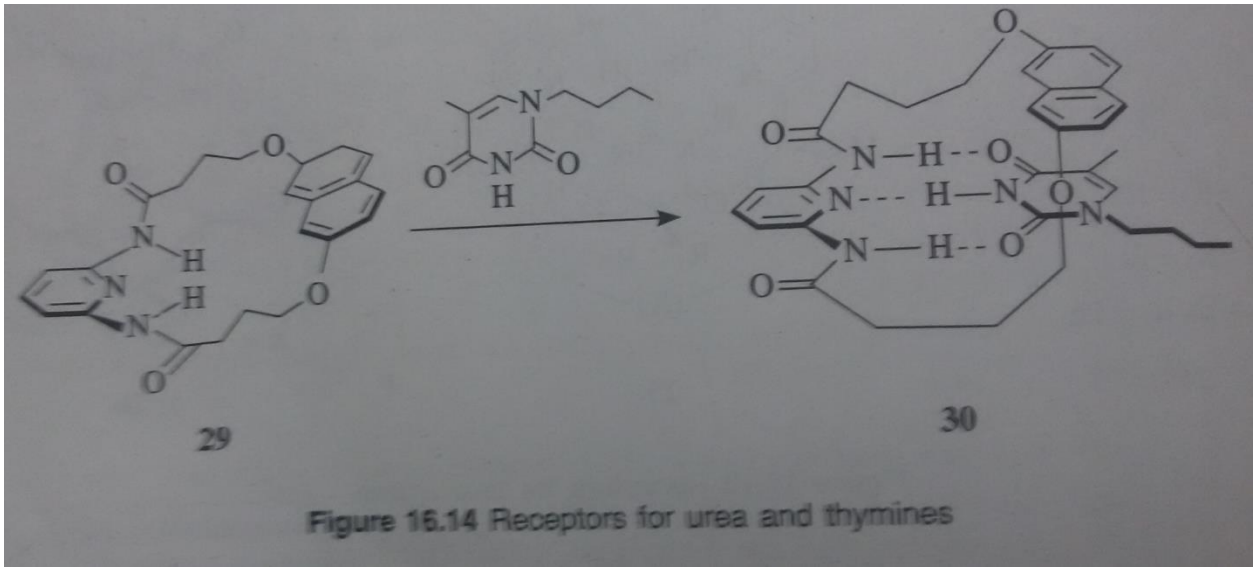
- Crown ethers do not bind urea strongly.
- Reinhoudt and coworkers have developed macrocyclic crown ethers containing an acidic function such as CO2H for increasing the binding strength through the formation of additional hydrogen bonds as seen in the urea complex **27**.
- The receptor here is 2-carboxyl-1,3-xylyl -30-crown-9 and the complex has Ka value of $2.3\times10^{3}\ M^{-1}$ in CDCl3.
- The open ended receptor **28**, a modification of 25 forms a still stronger complex with urea ($Ka = 1.6 \times 10^{4}\ M^{-1}$)



27 28

(c) Receptors for thymines:

- Hamilton and van Engen have introduced, in addition to multiple hydrogen-bonding sites in receptors, π-stacking interactions to provider better recognition of planar heterocyclic nucleotide bases such as thymine and derivatives.
- One such receptor is **29** which binds 1-butylthymine giving the complex **30** having three hydrogen bonds and one set of π-stacking interactions.



29 30

Figure 16.14 Receptors for urea and thymines

Summary

- Molecular receptors are host molecules that contain a binding site or a cavity for a smaller guest molecule or an ion.
- Molecular clefts were then described by Rebek in 1985 as rigid receptors exhibiting convergent functional groups directed toward each other and separated by a spacer.
- Molecular tweezers, and molecular clips, are host molecules with open cavities capable of binding guest molecule.
- The open cavity of the molecular tweezers may bind guests using non-covalent bonding which includes hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, π-π interactions, and/or electrostatic effects. These complexes are a subset of macrocyclic molecular receptors and their structure is that the two "arms" that bind the guest molecule between them are only connected at one end leading to a certain flexibility of these receptor molecules.