Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 126–143
Bioorganic & Medicinal Chemistry

Review

Emerging trends in molecular recognition: Utility of weak aromatic interactions

Ashish Kumar Tewari* and Rashmi Dubey

Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221 005, India

Received 13 March 2007; revised 3 September 2007; accepted 12 September 2007
Available online 18 September 2007

Abstract—Aromatic interactions play a vital role in chemistry and biology. As about 20% are aromatic in nature, so the role of aromatic interactions become prominent in drug receptor interactions. Not only in drug receptor interactions but also in crystal engineering, protein folding, stacking interactions in DNA/RNA the role of the interactions is of utmost importance. With the emergence of supramolecular chemistry dendrimers, tweezers, rotaxanes, catenanes, and several supramolecular aggregates are associated with aromatic interactions. The mechanism of such interactions is still unknown by the replacement of a small substituent from the aromatic molecule may lead or destroy the interactions. In the present review several models are being discussed with arene interactions under selected heads.

Contents

Keywords: Aromatic interactions; Foldamers; Catenanes; Rotaxanes; Host–guest; Weak interactions.
* Corresponding author. Tel.: +91 5423208159; e-mail: tashish2002@yahoo.com

0968-0896/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2007.09.023

1. Introduction

1.1. Molecular recognition

Molecular recognition which is of central importance in chemistry and biology depends on non-covalent interactions such as H-bonding, stacking interaction, cation–π interaction, ionic interaction, hydrophobic interaction, etc. The role of non-covalent interaction in nature was fully recognized only in last two decades and is of key importance in biodisciplines.[1] Non-covalent interactions are poorly understood at present. Since the first synthesis of urea 150 years back, there had been a phenomenal growth in 'covalent synthesis'. According to Nobel Laureate Prof. J.M. Lehn time has come to do same for non-covalent chemistry.[2]

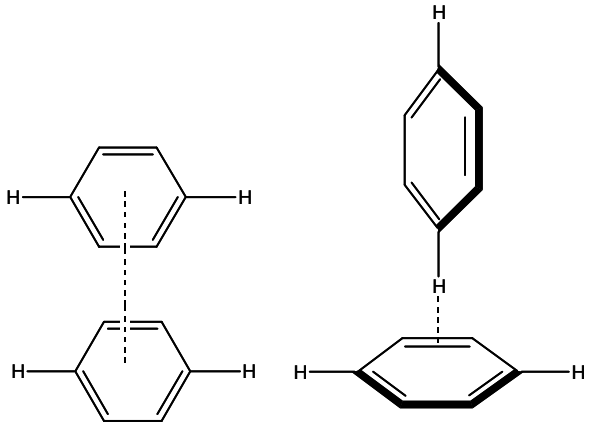
1.2. Non-covalent interaction

Modern chemistry is based on the understanding of the chemical bond. Atoms and molecules interact together leading to the formation of either a new molecule (reactive channels) or a molecular cluster (non-reactive channels). The former is covalent interaction while latter one is non-covalent or van der Waals interaction. Non-covalent interactions lead to the formation of a molecular cluster while covalent interactions lead to the formation of a classical molecule. The structure of liquids, solvation phenomena, molecular crystals, physisorption, and the structures of bio-macromolecules such as DNA (deoxyribonucleic acid) and proteins and molecular recognition are a few phenomena determined by non-covalent interactions.

Covalent interactions are of short range (<2 Å), whereas non-covalent interactions are known to act at distance of several angstroms. Unlike in covalent interaction (when occupied orbital of interacting atoms overlap and consists of a pair of electron shared by atoms), overlap in non-covalent interaction is unnecessary. In fact overlap between occupied orbital leads only to repulsion (exchange repulsion), that prevents the subsystems from approaching too closely.

2. Aromatic interaction

The interaction between molecules containing aromatic residues is referred to as aromatic (π–π) stacking or aryl stacks. These interactions are of utmost importance in drug chemistry as most of the drugs are aromatic and about 20% are aromatic. Benzene crystallizes as dimers, dimer-models in **1**, show aromatic interaction.[3] The nature of stacking interactions has been studied by using various spectroscopic tools and X-ray crystallography[4] is a foolproof method of understanding such interactions.

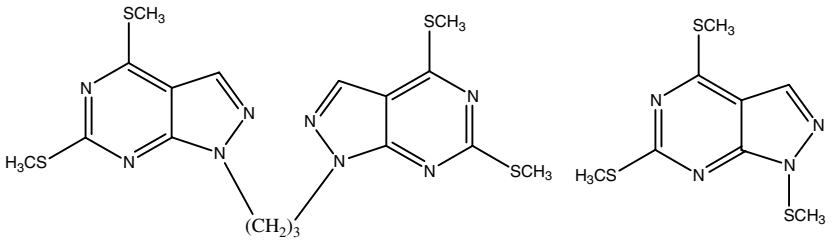


(1)

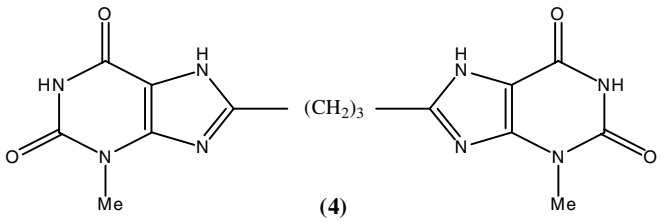
Generally aromatic interactions depend upon charge distribution and also the shape of molecule and require geometrical requisites.[5] Synthesis of 1,3-bis(4,6-dimethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl) propane **(2)** has been reported[6] which showed intramolecular stacking in both solution and solid state. Intramolecular stacking in compound **2** was deduced by comparison of its high-resolution proton NMR data with that of simpler monomeric compounds **3**.[7] X-ray crystallography of compound **2** not only confirmed intramolecular stacking but in addition also revealed intermolecular stacking.[8] It is important to mention here that compound **2** unlike compound **4** and **5** has no conventional H-bonding. On the other hand, synthesis, NMR, and X-ray crystallography of two more compounds **6** and **7** have been reported. Once again comparison of proton NMR data of these compounds (**6** and **7**)[9] with that of simpler monomeric compounds[10] suggested possibility of intramolecular stacking. X-ray crystallography of these two compounds (**6** and **7**) further confirmed intramolecular stacking, in addition intermolecular stacking was also revealed.[11] It is worth noting that pyrazolo[3,4-*d*]pyrimidine ring system is isomeric with biologically important purine ring system and was expected to show some physico-chemical properties of purine system.

2.1. Parallel aromatic interaction

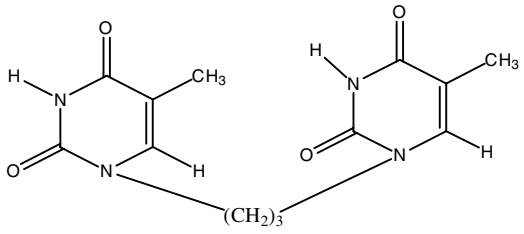
Organic compounds containing aromatic moieties tend to arrange themselves like a stack of coins. π–π interactions are caused by intermolecular overlapping of p-orbital in π conjugated systems, so they become stronger as the number of π electron increases. This



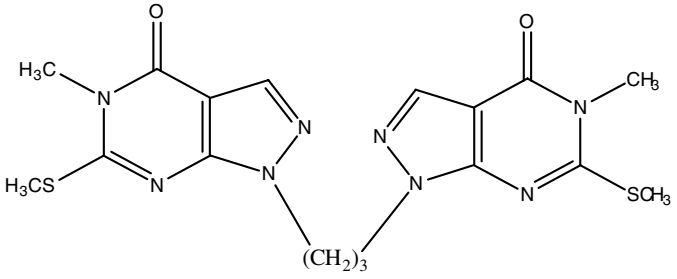
(2) (3)



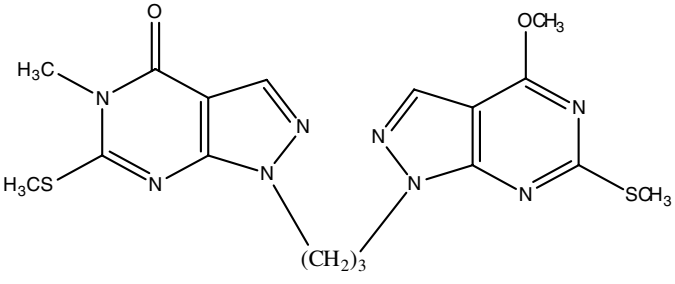
(4)



(5)

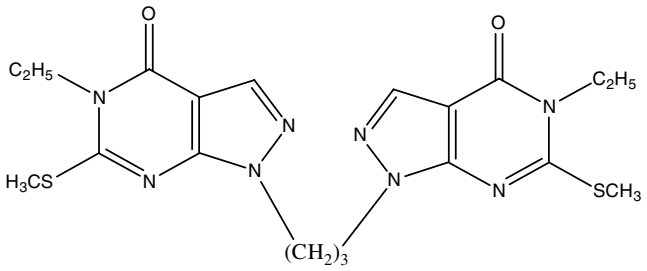


(6)



(7)

bonding behavior affects the properties of polymers as diverse as aramides, polystyrenes, DNA, RNA, proteins, and peptides. The effects can be explained in gas sensors to detect the presence of aromatic chemicals. π–π interactions act strongly on flat polycyclic aromatic hydrocarbons such as triphenylene, anthracene, and coronene because of the many delocalized π-electrons. This interaction is a bit stronger than other non-covalent interactions, and plays an important role in various part of supramolecular chemistry, for example, π–π interaction has a big influence on molecule-based crystal structure of aromatic compounds. X–ray crystal structure of **8**[12] has confirmed intramolecular stacking due to aromatic π–π interactions and in addition revealed intermolecular π–π interaction.

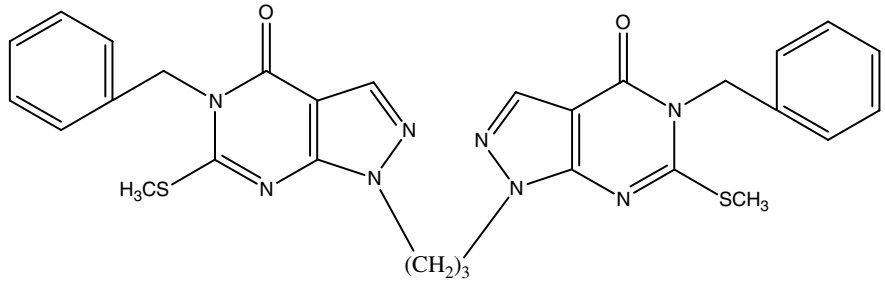


(8)

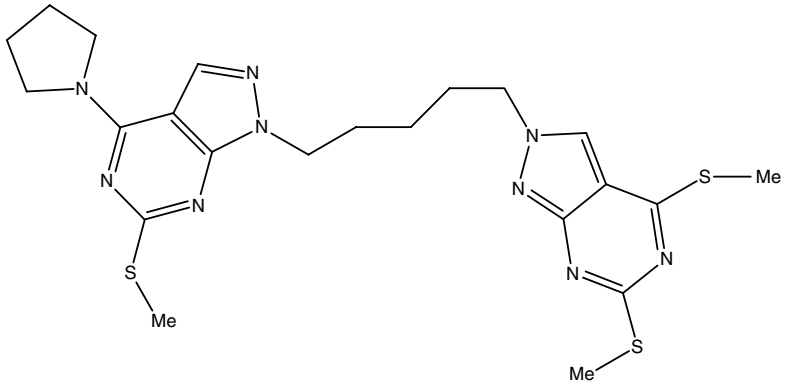
In the same sequence compound **9** with bulkier attachment benzyl group had been synthesized. X-ray crystal structure of compound has shown intramolecular aromatic π–π interaction.[13] Intramolecular interactions have been found retained in the compounds having substituent attached at oxygen.[14]

The crystal structures of 1-{5-[4,6-bis(methylsulfanyl)-2*H*-pyrazole[3,4-*d*]pyrimidin-2-yl]pentyl}-6-methylsulfanyl-4-(pyrrolidin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine **10** and 6-methylsulfanyl-1-{5-[6-methylsulfanyl-4-(pyrrolidin-1-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidin-2-yl]pentyl}-4-(pyrrolidin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**11**) which differ in having either a pyrrolidine substituent or a methylsulfanyl group show intermolecular stacking due to aromatic π–π interactions between the pyrazolo[3,4-*d*]pyrimidine rings.[15]

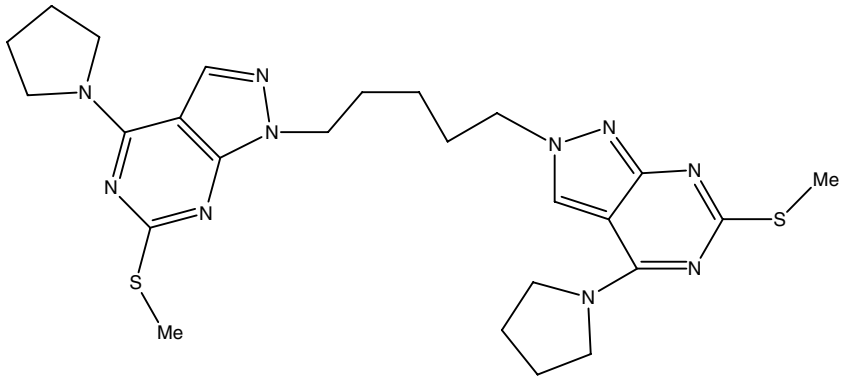
Proton NMR analyses of several newly synthesized dissymmetrical 'Leonard/trimethylene linker'[16] compounds 1/2/3-[(4,6-dimethylsulfanyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propyl]-5,7-dimethyl/ethyl-sulfanyl-1*H*/2*H*/3*H*-triazolo[4,5-*d*]pyrimidines (**12** and **13**) show intramolecularly stacked conformation in solution. X-ray crystallography of one dissymmetrical 'Leonard/trimethylene' linker



(9)

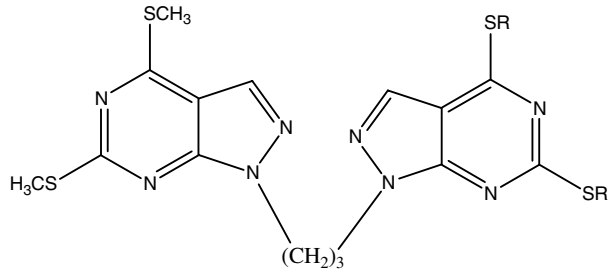


(10)

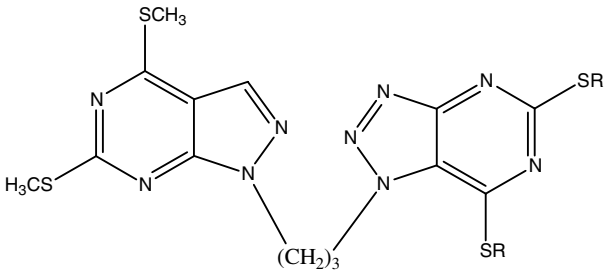


(11)

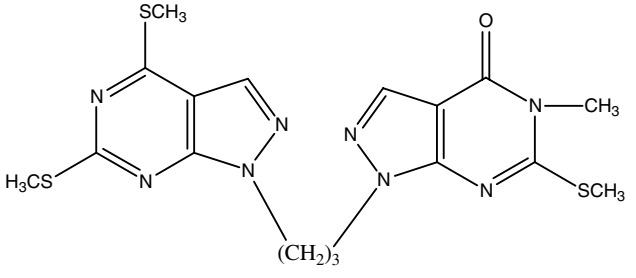
compound (**12b**) based on two different heterocycles, namely pyrazolo[3,4-*d*]pyrimidine core and triazolo-[4,5-*d*]pyrimidine, for the first time, shows unusual U-motif formed due to intramolecular π–π interactions, which is similar to earlier related pyrazolo[3,4-*d*]pyrimidine core based 10 symmetrical (**2** and **6**) and one dissymmetrical compound (**14**). Supramolecular structures of the new compound (**12b**) show unusual chain motif due to weak intermolecular CH...N and CH...S interactions. More importantly, the new compound (**12b**) shows S...arene interaction not shown by any earlier compounds (**2**, **6**, and **14**).[17]



12a: R = Me 12b: R = Et



13a: R = Me 13b: R = Et



(14)

2.2. Perpendicular aromatic interaction

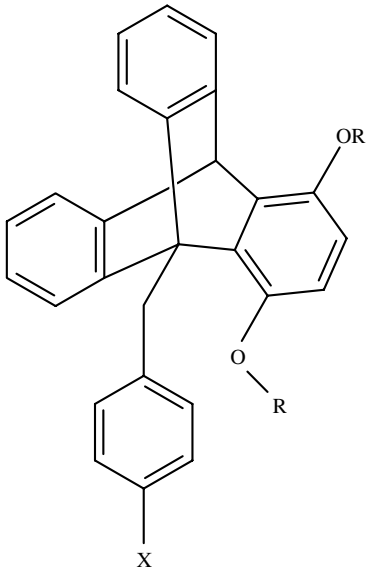
A related effect called T-stacking is often seen in proteins[18] where the partially positively charged hydrogen atom of one aromatic system points perpendicular to the center of the aromatic plane of the other aromatic system. In the recent years, there has been intense interest in the design of non-peptide oligomers that fold into well-defined secondary structures. Such type of materials forms new functional polymers with interesting catalytic and recognition properties. Simple anthranilamide derivatives can be combined to form oligomers having linear strand or single turn helical structures stabilized by intermolecular hydrogen bonding and π–π stacking interactions.

2.3. CH–π interaction

The interactions between arenes, alkenes, or alkynes with hydrocarbons are C–H...π interaction rather than interaction between aromatic rings and plays a significant tool in chemistry and biology.[19]

In proteins C–H...π interactions have been described which arise due to the formation of complexes of proteins with ligands or cofactors such as the heme group[18] and design of serine proteases inhibitors.[20] Previous studies have also shown that C–H...π interactions are even responsible for the stabilization of structural elements such as alpha or 3_{10} helices or non-proline cis peptide bonds.[21]

Parallel stacking is π–π interaction which occurs in DNA/RNA and T-shaped stacking is known as CH–π interaction which occurs in proteins. It is well known that distance between two nucleic acid bases (in DNA) is 3.4 Å. In order to understand such interactions use of 'trimethylene linkers' between two nucleic acid bases was pioneered by Prof. Leonard in 1968.[16] In case of some 1,9-disubstituted triptycene (**15**) there is arene–arene interaction and CH–π interaction due to presence of acetate groups. NMR spectroscopy shows that in the model system of triptycene at low temperature lone-pair–π interactions are dominant in *syn* conformers in 1, 9-disubstituted systems.[22]

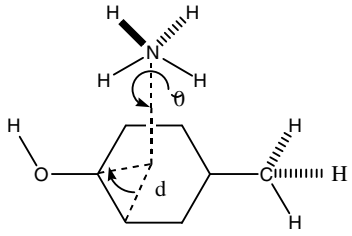


(15)

2.4. Cation–π interaction

It has been suggested that cation–π interaction constitutes a strong, specific driving force that plays a

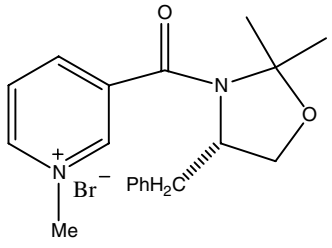
key role in molecular recognition. In biological systems, experimentally determined three-dimensional structures of proteins and theoretical calculations at different level of complexity in (**16**) provide information into this type of interaction.[23] Interaction of cationic species with π electron of aromatic rings has been theoretically observed earlier.[24] Cation–π interaction involve short distance interaction, large number of gas phase studies have established the cation–π interaction to be among the strongest of non-covalent binding forces.[25]



(**16**)

Many types of cation–π, lone pair–π, π–π stacking, and non-covalent interactions are involved in biological and chemical recognition processes. Now some lone pair–π interactions are provided by ab initio studies and these interactions are revealed with electron deficient π-systems.

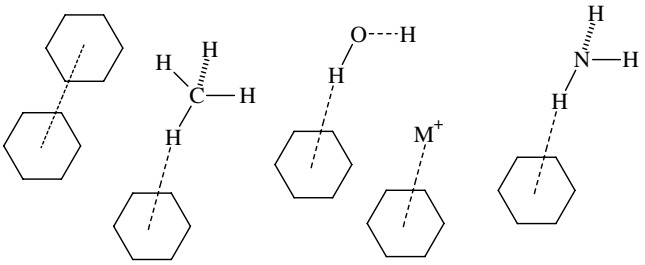
Intramolecular py^{+}–π interactions have been postulated in some reaction intermediates.[26] The cation–π complex in (**17**) is that the pyridinium and the phenyl ring lie parallel to each other and the two rings are arranged face to face, the distance between which is about 3.4 Å.[27]



(**17**)

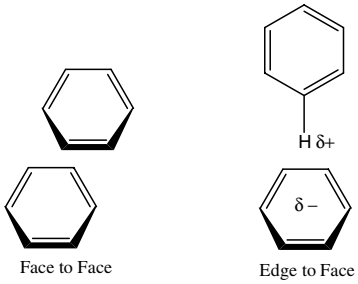
2.5. Intermolecular aromatic weak interactions

Intermolecular interactions of aromatic molecules like π/π, OH/π, NH/π, and cation/π interactions are important in the fields of chemistry and biology. These interactions control the crystal structure of aromatic molecules, the stability of biological systems and their molecular recognition processes. For understanding the structure and properties of molecular assemblies and improving materials, drug design strategy, physical origin, and magnitude of the interactions are known essentially. Only experimental details are not sufficient to study aromatic weak interactions; therefore, ab initio calculation methods have been applied in order to investigate aromatic interactions. X-ray crystal structure of 4,4′-(ethylenedioxy) dibenzaldehyde showing intermolecular aromatic interactions, two phenyl rings of different molecules are 3.58 Å distance apart.[28]



(**18**)

Interactions between aromatic rings play an important role in stabilizing proteins structure as shown in (**18**). For recognition of proteins, nucleotide bases either possess a number of inter-ring geometries ranging from a parallel face to face stacking to a perpendicular edge to face (**19** and **20**) or the positively charged hydrogen atom on one ring interacts with negatively charged region on the second ring.[29]



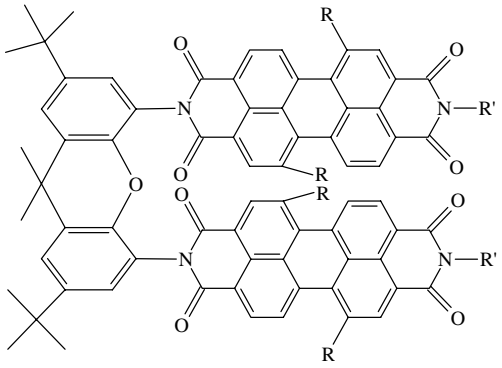
19 20

Aromatic ring interaction also influences stereochemistry of many organic reactions; several evidences had been observed.[30] Interactions between benzene dimers are different when water, chloroform or liquid benzene is used as a solvent or in case of gas phase. In case of liquid benzene, chloroform, and water benzene dimers having ring center–ring center separation of ca. 5.5 Å, are energetically favored.[31]

Corey in 1972 postulated the first synthetic application of a π-stacking interaction in the synthesis of prostaglandins,[32] π-stacking effect influenced asymmetric bond formation reaction under both stoichiometric (chiral auxiliaries) and catalytic conditions.[33]

2.6. Change in ring size influences weak interactions

In the gas phase, stacked structure having larger arene ring size is favored over smaller ring size,[31] Charge delocalization or rapid hopping of charges is a requirement of organic electronics. Several dimers may be formed by π–π interactions through radical cation and neutral aromatic molecules, of perylene-3,4, 9,10-bis (dicarboximide) (PDI) (**21**) having electron hopping is self-assembled π-stacked molecule by ENDOR (electron-nuclear double resonance) studies.[34]



(21)

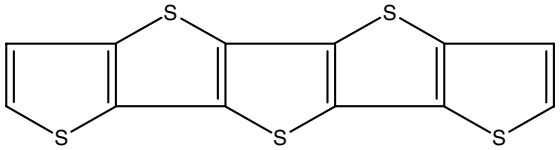
Using solid phase micro-extraction method and fluorescence quenching approach interaction of phenanthrene and 9-amino phenanthrene with natural organic matter (NOM) of different origin was found to be influenced by concentration of polycyclic aromatic compound (PAC) as well as NOM on the binding constant. Experimental evidences have shown that there is an aromatic interaction between NOM and the amino group.[35]

Many π radical cations having π conjugated system and hetero atoms stabilize themselves to form π and/or σ dimers. In case of conducting polymers the π-dimerization is a very natural phenomena. π-Dimerization is also found in radical anions. UV–vis, NIR, ESR, NMR, and X-ray crystallography had shown that these radical cations self-associated to form σ and/or π dimers.[36]

In 9,10-di(9,9-dioctyl fluorine)anthracene, X-ray data show that the aromatic rings of adjacent molecules are separated by a distance for any significant π–π interaction and fluorine rings are oriented such that the *n*-octal groups face array from each other.[37]

2.7. Hydrogen bonded aggregates

Cyclodextrin forms well-defined supramolecular aggregates used in chemistry and material sciences. β Cyclodextrins form aggregate with 4-hydroxyazobenzene and 4-amino azobenzene by extensively hydrogen bonded and π–π interactions that interaction was proved by X-ray, UV–vis, and NMR spectroscopy.[38]



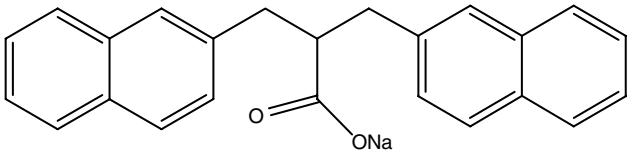
(22)

Organic semiconductors are also used in the field of material chemistry like in pentacene, where π–π system plays an important role. Small semiconductor materials, thiophene-based molecules, having intra and intermolecular interactions, van der Waals interaction, weak hydrogen bonding, π–π stacking, sulfur–sulfur interactions[39] are caused by high polarizability of sulfur electron in thiophene (**22**) rings.[40]

2.8. Study of effect of electrostatics

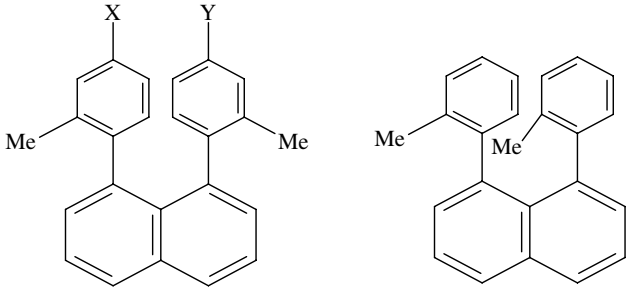
In life sciences, π-stacking interaction plays a crucial role and they usually show face to face π-stacking interaction and dipole–dipole interactions. In case of naphthalene, aryl or heteroaryl groups present in periposition having π stacking are used to develop new materials. 1,8-Diacridyl naphthalene when investigated by crystallographic and spectroscopic methods shows intramolecular interaction having cofacial aryl groups that undergo face to face but not face to edge interaction in solid as well as in solution.[41]

Crystallographic data in aqueous solution of dinaphthyl carboxylates show that the linkers in (**23**) allow intramolecular edge to face interaction.[42]



(23)

Cozzi et al.[43,44] have come up with a very simple and elegant way of doing this. Naphthalene has been used as a covalent scaffold to hold two interacting aromatic rings in a face to face stacked geometry, **24** and **25**.



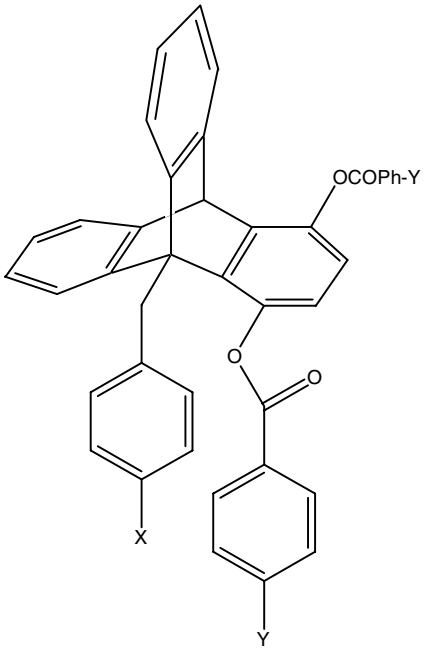
X, Y = H, OMe, COOMe, NO_2

(24) (25)

The methyl group acts as markers so that the restricted rotation can be monitored by NMR spectroscopy. The authors claim that these differences are a direct measure of the relative magnitudes of the π–π interactions and it was concluded that the concept of CT or EDA interactions was highly misleading and π–π interactions were dominated by electrostatics.[45]

In triptycene-derived compound (**26**) showing arene–arene interactions, parallel displaced orientation have been found, in the case of arene bearing electron-with-

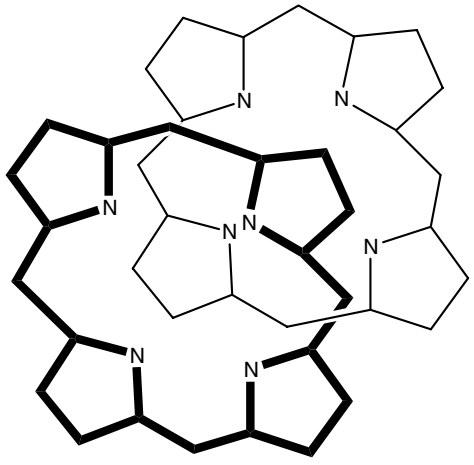
drawing groups interactions are attractive. The polar/π forces are responsible for aromatic stacking interaction.[22] In case of 1,8-diarylnaphthalene, the aryls occupy parallel stacked geometry, due to steric congestion and barriers to rotation were used to find strength and to investigate the nature of interaction between arenes. The groups present on arene moieties indicate that polar/π electrostatic effects are dominant over charge-transfer effect in determining the arene–arene interaction.[46]



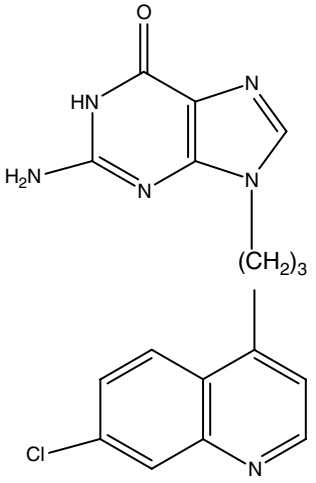
(26)

Interaction between aromatic rings via π-stacking form the origin of many phenomena in organic material science and biological chemistry, including the electron transport in DNA through stacked π-bases.

Useful information was observed with π–π stacked porphyrin model of C.A. Hunter, who studied cofacially linked porphyrin dimers and observed that strong π–π interactions between the two porphyrins forced the cavity to collapse and inhibited substrate binding.[47]

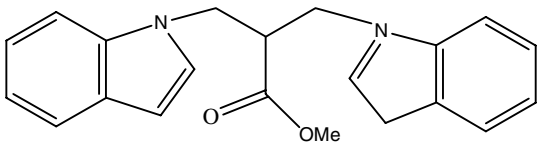


The choice of linker to connect arene moieties might be important to regulate folding. Several aromatic foldamers were constructed by connecting arene with urea, guanidine, or amide also trimethylene linkers, also polyfluorene spacers had been introduced to construct a variety of wire like properties to examine the electron-transport phenomenon.[48] One illustration is the use of polymethylene bridges (**28**) in particular the trimethylene bridge—$(CH_2)_3$—as synthetic spacers for examining repulsive and attractive intramolecular interactions.[49]



(28)

Computational and experimental studies of stacking interaction of sodium (2,2)-bis(indol-1-yl-methyl) acetate (**29**) in water and DMSO investigate the role of the hydrophobic effect on aromatic stacking interactions. Tilted T-shaped stacked, off-center stacked, face to face stacked, and non-stacked conformation were observed in vacuum where as in water tilted T-shaped stacked and non-stacked conformer existed. Larger population of the stacked conformations in DMSO-d_6 was expected if the electrostatic interaction was the only driving force of the aromatic stacking interactions.[50]



(29)

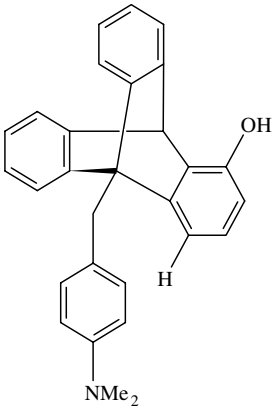
3. Supramolecular aggregates

The use of non-covalent interactions to organize monomer into larger supramolecular polymeric aggregates has seen a dramatic growth. Polymer-like properties can be obtained with supramolecular materials that employ weak hydrogen bond interaction in conjugation with phase segregation. The degree of polymerization (DP) mainly depends on the strength of the supramolec-

ular interaction between the monomers as well as the monomer concentration.[51]

In case of gel used in soft organic materials, template synthesis, drug delivery derived from carbohydrates,[52,53] amino acids,[54,55] urea,[56,57] cholesterols,[58,59] etc, the binary systems of these gels have groups to obtain organogelators which interact with each other by electrostatic action,[60] hydrogen bonding, donor–acceptor interactions[61] further self-assemble via hydrogen bonding, π–π interactions, van der Waals forces, etc. They show strongly enhanced fluorescence emission.[62]

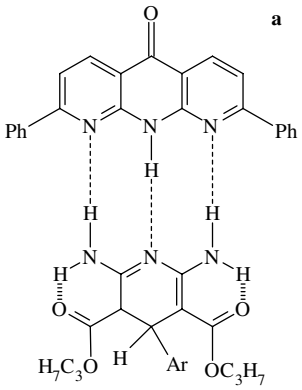
In case of triptycene 1,9-disubstitution (**30**), charge transfer effect has been observed when perfluorophenyl group and dimethyl amino-substituted phenyl groups are present.[63]



(30)

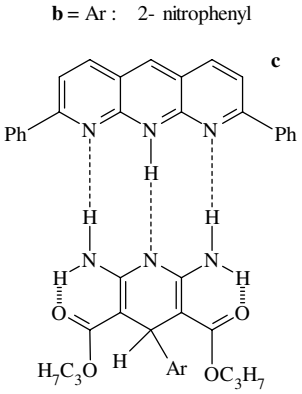
Heterocycles capable of forming robust hydrogen-bonded complexes in solution, the use of hydrogen bonds to confer binding strength and selectivity has become a dominant issue in host–guest complexation studies. Both conventional and non-conventional H bonds play important role in biological structures.[64]

The difference in stability between complexes (**31a** and **31b**) and (**32c** and **32d**) is striking. Despite their structural similarity and identical number of hydrogen bonds, the latter complex is more stable by over 4 kcal/mol.[65] These results are consistent with Jorgensen's proposal that the variable stability of triply hydrogen bonded complexes originate in the arrangement of the hydrogen bonding sites. Efforts are underway to incorporate some of these new complexes into supramolecular assemblies. These results are consistent with Jorgensen's proposal that the variable stability of triply hydrogen bonded complexes (**33**) originate in the arrangement of the hydrogen bonding sites. The use of heterocycles in this manner can, however, be complicated by prototropy (the most common type of tautomerism, involves a proton shift).

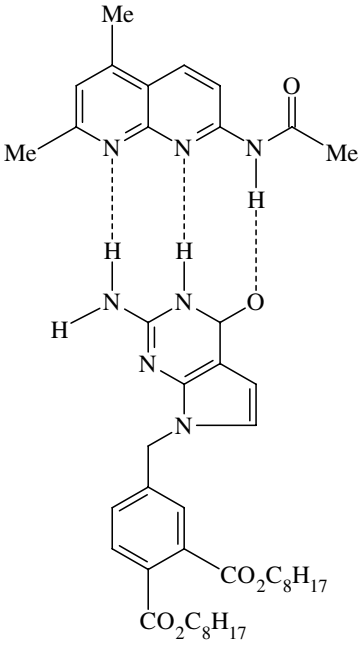


d = Ar : 3-nitrophenyl

(31)



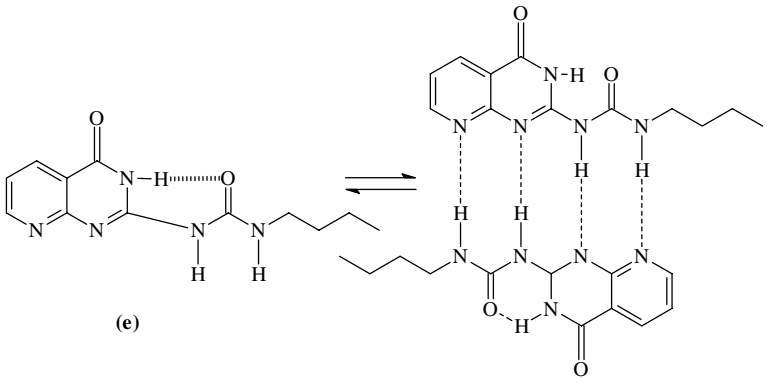
(32)



(33)

Interestingly, prototropy does not compromise the ability of all heterocycles to self-associate. A new heterocycle (**34e** and **34f**) designed to contain a self-complementary AADD (A, D = hydrogen bond acceptor and donor) hydrogen bonding array, which was soluble in non-polar organic solvents, which suggested that the polar hydrogen bonding groups were protected by dimerization.[66] ^{1}H NMR spectra in toluene-d_8 were consistent with the formation of (*f*). All NH signals were down field and in the region expected for hydrogen-bonded dimers.

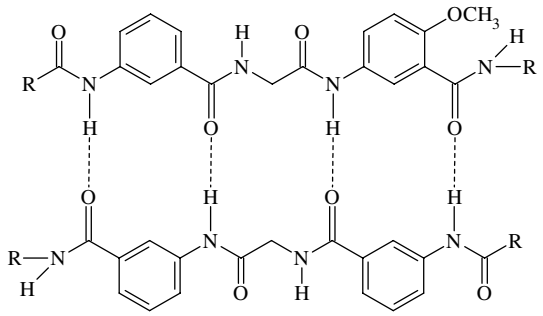
The construction of supramolecular architectures will be greatly facilitated if a diverse set of structural motifs leading to highly specific intermolecular interactions becomes available, and from above point of view hydrogen bonds have attracted the attention in mediating the self-assembly of supramolecular structures. Furthermore to increase the strength, directionality, and specificity of



(34)

hydrogen-bonding interactions, there is currently intense interest in designing array (sequences) of hydrogen bond donor (D) and acceptor (A) sites described above.

Introducing such functionalities, hydrogen-bonded duplexes with unnatural backbones (**35**) have been reported with hydrogen-bonded dimers based on heterocycles.[67]

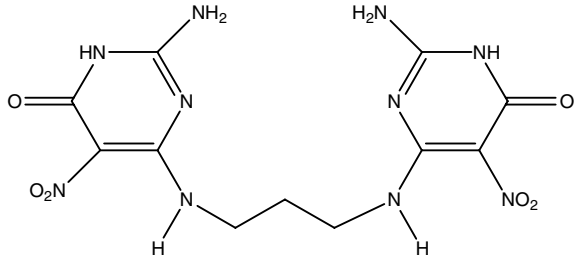


(35)

In various biologically important reactions and molecular recognition, hydrogen bonding plays an important role. Some hydrogen-bonded donors are now used as acid catalysts in organic chemistry. Thiourea and urea derivatives are commonly known general acid catalysts.[68]

4. Recognition processes in proteins

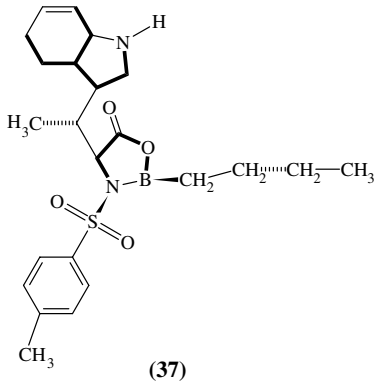
Recognition of carbohydrates by protein also plays an important tool in broad range of biological activities like fertilization, embryogenesis, and many pathological processes. Hydrogen bonding interaction are common in hydroxyl groups within polypeptide chains of amino acids but depending on the stereochemistry of the monomer, constituting oligosaccharides chain, the presence of rather apolar C–H groups indeed constitute patches that provide van der Waals, CH–π, and hydrophobic interactions. The use of fluorescence and NMR spectroscopy with tectins in solution prove the role of aromatic residues in the binding site of lectins for stacking.[69] In water solution, interactions are observable between nucleic acid bases connected by polymethylene chains, particularly a trimethylene chain, B-$(CH_2)_3$-B′, where B and B′ are 9-substituted adenine or guanine or 1-substituted cytosine, thymine, or uracil residues (**36**).[16]



(36)

5. Other weak interactions

For development of some catalyst C–H–O interaction and π-stacking interaction are important. In that field *N*-tosyl-(*S*)-tryptophan-derived B-butyl-1,3,2-oxazaborolidin-5-one (NTOB) catalyst **(37)** commonly used in Diels-Alder cycloaddition is a useful complex formed between 2-bromoacrolein and NTOB shown C–H–O hydrogen bond and π-stacking interaction is supported by ^{1}H NMR and UV-spectroscopy. Acrolein–NTOB complexes are stabilized by attractive π–π interaction and molecular recognition of the NTOB catalyst also involves binding of Lewis acid via B–O donor–acceptor interaction.[70]



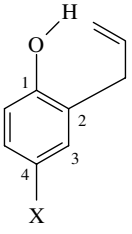
(37)

5.1. Hydrophobic interaction

Many crucially important processes take place in water. Understanding of the role water plays remains poorly understood. If we want to understand the influence of water on processes at the molecular level, we need to be able to study structures at that level. For crystals, this is relatively straightforward: the fact that we can arrange molecules—however complex—in a regular repeating arrangement in a crystal means we can exploit the power of crystallography in solving structures from simple crystals to proteins and viruses, whereas in a liquid we have no crystalline order, we have to use other techniques. Hydrophobic interactions along with hydrophilic interactions help to determine the three-dimensional shape of biologically important molecules and structures such as proteins and cell membranes. If hydrophobic substances are dissolved in aqueous medium, they tend to occupy minimum area. A role for apolar (hydrophobic) interactions in the formation and stabilization of protein structure is generally well accepted.[71]

5.2. Hydrogen bonding

We seek the knowledge of hydrogen bonding in many fields like biochemistry, pharmaceutical chemistry, and supramolecular chemistry as well as in molecular recognition and self-organization. OH–π hydrogen bond was detected by IR spectroscopy in 2-phenylphenol in CCl_4 solution. 4-Substituted 2-allyl phenols (**38**) was identified to form intramolecular OH–π hydrogen bonds and strength and IR frequency depends on substituents present at 4-position.[72]



(38)

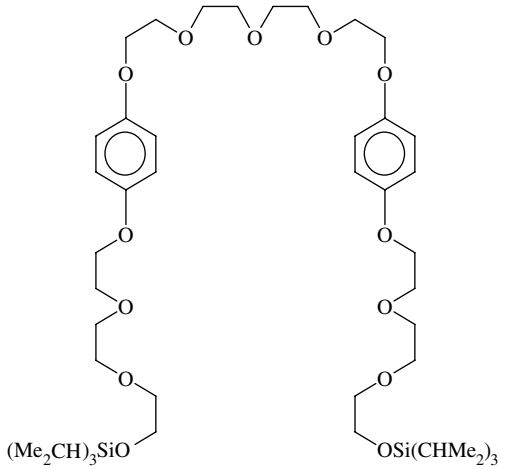
Hetero association of an antibiotic and dye in aqueous solution is stabilized mainly by dispersion van der Waals interactions.

Hydrogen bonding promoted the rate of hetero Diels-Alder reaction, forming C–H…O bond between nonpolar solvent (chloroform) and carbonyl oxygen of unactivated ketones.[73]

Hydrogen bonding also mediated selectivity in many organic reactions. It provides general background of self-assembly in synthesis.[74]

6. Catenanes and rotaxanes

Catenanes and rotaxanes are self-assembled from molecular components containing π-electron-rich and deficient aromatic units. When non-covalent bonding interactions are the stabilizing feature between the components of [2] catenane and [2] rotaxanes, then they retain their interlocked molecular structures. [2] rotaxane would function as molecular shuttle i.e., a molecular assembly in which a tetra cationic 'bead' moves back and forth like a shuttle, between two identical 'stations' in the form of hydroquinol units grafted symmetrically into a polyether 'thread' terminated at the ends by large triisopropylsilyl groups (**39**) that act as stoppers. By this technological method 'molecular machines' will emerge.[75]



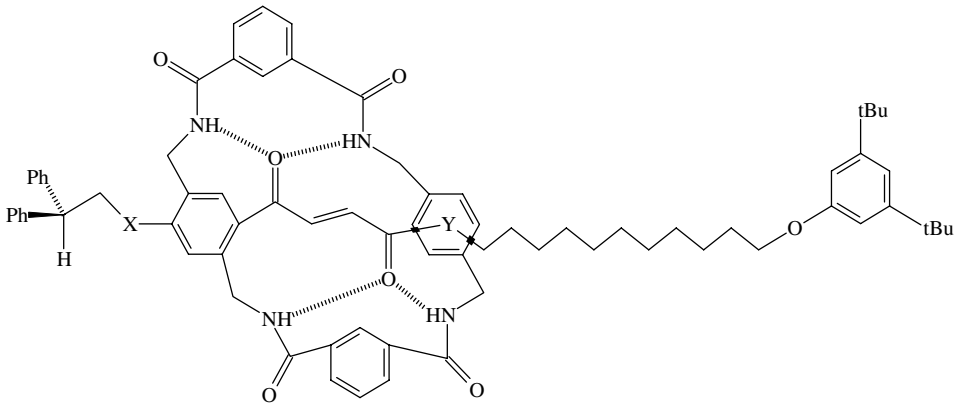
(39)

The components are designed to receive, store, transfer, and transmit information in a highly controllable manner following their spontaneous self-assembly at the supramolecular level.

For synthesis of hydrogen bond assembled rotaxane, structural rigidity and the pre-organization of thread binding sites are shown to have a major influence on template efficiency. Pre-organization is so effective that with good hydrogen bond acceptors (amides), a 'world record' yield of 97% for a [2]rotaxane is obtained. The structures of the rotaxane (**40**) are established unambiguously in solution by X-ray crystallography.[76]

It is interesting to note that cooperative interactions, organizations, and structural rigidity are key elements in the mode of action of the 'super-bug' antibiotic that binds weakly to the ester-terminated D-Ala-D-Lac sequence on the cell surfaces of vancomycin-resistant enterococci.[77]

Rotaxane systems comprises of aromatic crown ether loop components, that encircles pyridyl-substituted naphthalene diimide thread components with bulky metalloporphyrin stopper components, which are held together by a series of secondary interactions. Attachment of rotaxane thread component to the loop component to yield the daisy chain or hermaphrodite type compound was expected to either self-complex or form



(40)

complex oligomeric structures through intermolecular interactions. In the field of mechanoelectrical and photoelectrical communication systems and devices capable of storing and processing information number of [2]catenanes and [2]rotaxanes are synthesized. The non-covalent bonding interactions are used to self-assemble and X-ray crystallographic studies show that solid state complexes are formed between π-electron-rich and π-electron-deficient units having slightly large separation for a π-stacking interactions, a key feature of both solution and solid state complexes.[78]

Molecular folding that leads to compact conformation in flexible molecule is a type of intramolecular recognition, which has specific non-covalent interactions.

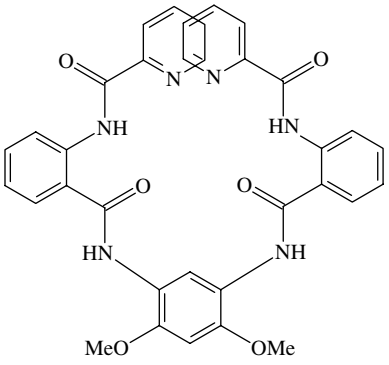
7. Foldamers

Oligomers and polymers that adopt a specific compact conformation by folding are named foldamers. The well-defined three-dimensional structures produced by folding, which furnish the appropriate location of active sites in molecules, are responsible for their sophisticated chemical functions. In case of β-peptides (β-amino acids) folding property is observed due to the presence of H-bonding in back bones of oligomers.[79] Aromatic π–π stacking is efficient for the creation of aromatic foldamers. These multilayered structures show unique optical properties due to aromatic interaction in vertical direction.[80]

In case of foldamers with a specific sequence of alternating rigid perylene chromophores and flexible ethylene glycol chain existing as free π-stacked folded nanostructure, the range of spectra observed is an indicator of the range of π–π interaction between adjacent chromophores.[81]

The folded structure of a phenyleneethylene oligomer is stabilized by intramolecular cation–π interaction between a methyl pyridinium ion and a phenyl ring.[82]

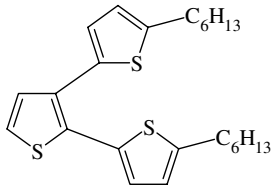
Some non-peptide oligomers that fold to a well defined secondary structure possess interesting catalytic or recognition properties. Simple molecular components based on anthranilamide (**41**) can be used to form oligomers with novel folding properties.[83]



(41)

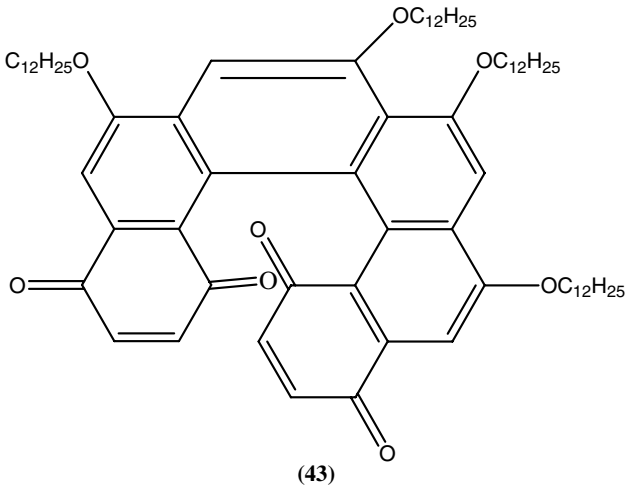
8. Dendrimers

In phenylene dendrimers π–π stacking interaction is responsible for self-assembly into nanowires. Thiophene dendrimers (**42**) exhibit nanostructures through the influence of π–π stacking and van der Waals forces derived from the packing of the alkyl chains.[84]



(42)

Two extraordinary properties show self-aggregation by the materials consisting of molecules of nanoracemic helicene. First is an enormous ability to rotate the plane of polarization of plane polarized light, much greater than that of dilute solutions, of the comprising molecules. The second property is spontaneous organization of the molecules into macroscopic fibrous structures. Molecule of (**43**) do aggregate which is evident from the properties of their solutions.[85] X-ray and electron diffraction demonstrate that the molecules are organized in hexagonally packed columns.



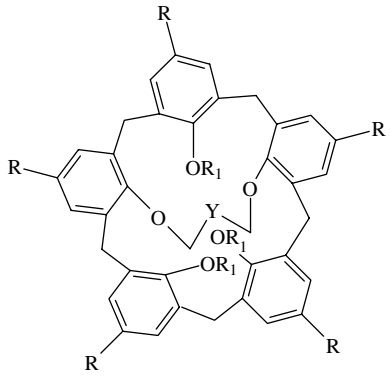
(43)

9. Calixarenes

Calixarenes systems also play an important tool in supramolecular chemistry, because of their easy preparation. Carlixarenes can also be used in the molecular receptors as the fundamental building block having host-guest like properties. The *N*-phenylcarboxamide substituents prefer a coplanar arrangement with substantial π–π overlapping in non-polar solvent $CDCl_3$.[86]

In case of calixarenes, larger macrocycles like oxacalix [4] arene and oxacalix [12] arene were detected by MALDI-TOF and that formation is favored by macrocyclic π–π interaction. In place of acetone, DMSO is likely to increase π–π interaction and that type of multiporphyrin arrangement plays an important role in biological area.[87]

When two phenolic oxygen (**44**) of the calixarene substructure are linked together by a polyether moiety, they form macrobicyclic molecule calixcrowns, and the backbone of calix [4] arene is provided with host–guest type properties to help for crown ether moieties of different length to be assembled to create converging binding sites. In this type of moieties CH–π and cation–π type interactions with lot of non-covalent interaction are found.[88]

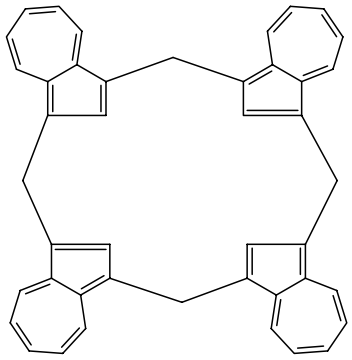


Y = $(CH_2OCH_2)_4$

(44)

In some cases the calixarene having carboxyl groups is associated with the calixarene having the pyridine rings even in the absence of guest molecules. The supramolecular heteropolymers were constructed by different cyclodextrin linked by non-covalent interaction with host molecules.[89]

In the field of molecular recognition and binding studies, calixarene shows important role and has properties like porphyrines including anion binding interactions. Now a new macrocyclic structure has been developed, also that azulene (**45**) forms quatyrin macrocycle type calixarene.[90]



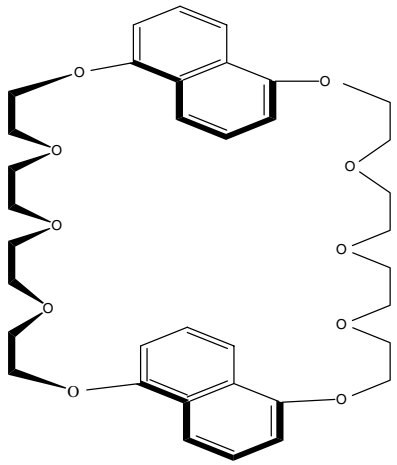
(45)

10. Electronic devices

In recent years organic materials are used in material chemistry basis for the assembly of artificial muscles, molecular switches, and other nanodevices.[91–94] In this field mainly polypyrole, polyaniline, polythiophenes are used as a conducting polymers. Thiophene oligomers among them are most important and promising organic conductive materials, and due to their ability to form π-stacked oligomers they have become significant in recent years. Carlix[4]arene and bithiophene forms, oligomers, and ab initio method were actually used to study π-stacking in oligothiophene dimers.[95]

The recent interest and potentially huge technological opportunities associated with the miniaturization of components for electronic device have driven supramolecular chemistry to embrace the challenge of designing molecular scale machines. Rotaxane and catenanes are two promising supramolecular topologies that have been extensively explored as useable molecular scale machines.

The design and chemical synthesis of flexible supramolecular structures (**46**) are based on host–guest chemistry and resulting compounds are probed using a variety of techniques, including diffusion ordered NMR, spectroscopy (DOSY), and cold-spray ionization mass spectrometry (CSI-MS).[96]



46

11. Host and guest devices

The self-association behavior exhibited in both solution and the solid state suggested that the imine bond is compatible with the *m*-phenylene ethynylene system and does not significantly interfere with π–π stacking interactions.[97] In case of Cucurbit [6] Uril analog, molecular recognition properties are characterized by fluorescence spectroscopy. Host (Cucurbit [6] Uril) has capability to form strong complex with the guest containing aromatic ring. Other non-covalent interactions like ion–dipole, hydrophobic effect, and hydrogen bonding are preferred to form strong host–guest type of relation between Cucurbit [6] Uril analog with nitro aromatics, amino acids, dyes, neurotransmitters, and even nucleobases. These analogs (**47**) are widely used as fluorescence sensor in many chemical and biological field.[98]

In host–guest complexation of aromatic compounds, double helical structure of DNA[99] and proteins, three-dimensional structure of protein,[100] self-assembly and molecular recognition phenomena show important role having π–π interactions and non-covalent interactions. Phenylene ethynelene macrocyclic compound show self-aggregation and π–π interaction in organic solvents.[101–104] In that compound substituents present also play important role in aggregation. ^{1}H NMR, CD, and VPO techniques examined their aggregation in $CHCl_3$, THF, and acetone and it shows that [3 + 3] cycloalkynes with stronger electron-withdrawing substituents exhibit stronger aggregation.[105]

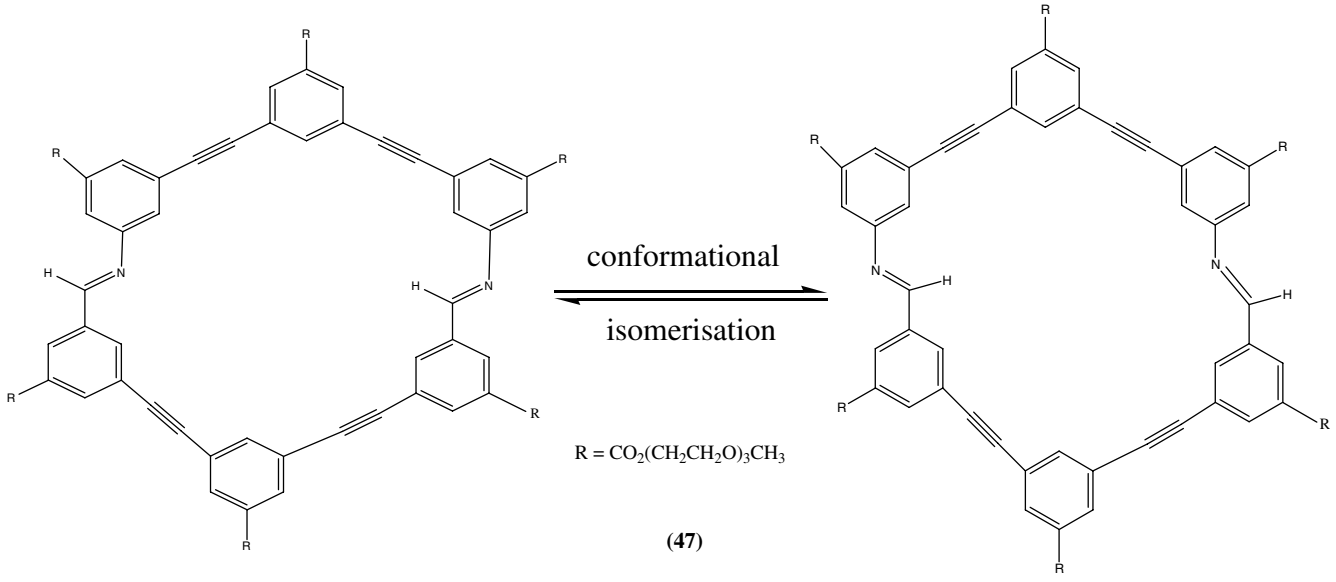
1,3-bis(bromo methyl)benzene and bis(4-hydroxyphenyl) ether forms hexaoxacyclophane and the 1:1 complex forms between hexaoxacyclophene and benzene shown by X-ray crystal structure intermolecular and intercomplex aromatic ring interaction of an edge to face type.[106]

Cyclophanes have deep enforced cavity systems for the hydrophobic binding sites where enzymes and antibodies bind aromatic substrates, apolar host–guest complexation strengths determined by solvation effects shows that binding is strongest in case of solvents having low molecular polarizability and having high cohesive interactions.[107]

12. Synthetic receptors

Developments of synthetic receptors have made use of hydrogen bonding interaction and single π-stacking surface. In this area a macro cyclic receptor (molecular tweezers) is used having a binding site of two aromatic surfaces and a carboxylic acid.

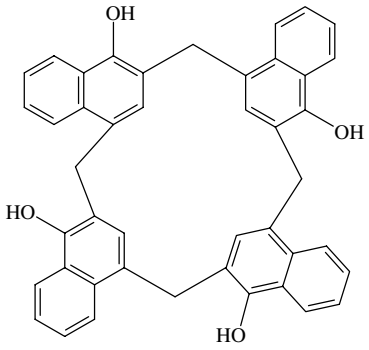
It has been shown also that 'π-sandwiching' and hydrogen bonding to a single edge of adenine can result in exceptional bonding affinity.[108]



(47)

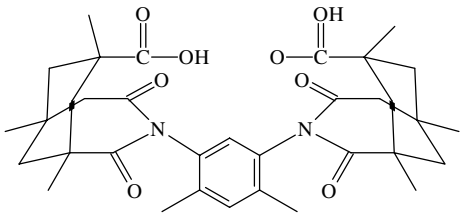
Some 2,3-disubstituted naphthalene ring–base macro cycles (**48**) also have a calixarene like structure and act as molecular receptors, for binding in their cavity to C_{60} or C_{70} type electron deficient guest molecules. With TMACI showing larger stability constant, cation–π interaction may be more effective than π–π interaction in that type of host–fullerene complexations.[109]

X-ray crystal structure demonstrates the conclusion having octa-*O* ethoxy derivative with two acetonitrile guest molecules.



(48)

Rebek and coworkers developed a variety of molecular clefts for recognition of small H-bonding molecules. In that field they developed a Rebek imide receptor (**49**) having π stacking platform attached by ester or amide linkers to the imide scaffold.[110]



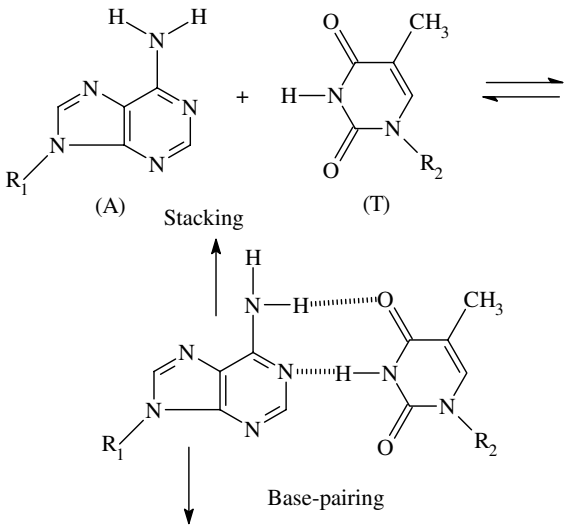
(49)

In case of biopolymers protein forms thermophilic and hyperthermophilic microorganisms have shown extraordinary thermal stability by properly optimizing the delicate balance of weak molecular attraction.[111]

In nucleic acids, adenine, and thymine having base pairing and stacking interaction between adjacent base pair provide additional stability for the helical structure (**50**).[112]

In series of thymine receptors the geometry of aromatic-aromatic interactions in molecular recognition can be controlled by modifying the electronic characteristics of one component.

In molecular biology protein and nucleotides interact with each other in many signal transduction and energy transfer processes. In case of ATP having binding sites



(50)

of aromatic, aliphatic, cationic, and hydrogen bonding residues, the NMR analysis demonstrates that aromatic interactions with the trp side-chain and CH–π interactions between ribose protons and the trp residue have contribution to binding, and that aromatic stacking interactions provides a energetic contribution to recognition of ATP.[113]

In proteins having aromatic interiors, aromatic interactions stabilized the globular structures. In closely packed flat aromatic rings these interactions are found to be more important. Benzene dimers are favored both in T-shaped and parallel displaced clusters. X-ray diffraction shows that interhelix association in the crystals of peptides is promoted by phe-phe interaction and in tetra peptide phe-gly-phe-gly the absence of buckling of peptide chain may have its origin in the observed network of aromatic interaction in the crystals.[114]

In peptides the folded structure is stabilized by many cooperative interactions. This type of cooperativity could play an important role in the formation and propagation of amyloid and progression of a variety of pathological disorder related to β-strands. To the strand direction folding of a multistranded β-sheet structure propagate perpendicular as well as parallel. In case of β-hairpin (2β) and three stranded antiparallel β-sheet (3β), NMR shows that 3β consistent with edge to face π–π interaction involves stabilizing aromatic residues of rational design in the case enthalpy driven.[115] NMR data shows that phe-phe cross strand pairs have edge to face interactions and due to aromatic and aliphatic interaction in water the self-association in peptide contains phe-phe cross strands.[116]

13. The weak interactions in ligand proteins complexes

Non-covalent weak interactions play important role in biological systems. Metal-coordinated histidine imidazoles and aromatic amino acid side-chains show π–π

interaction which influences the reactivity of blue copper protein.[117] Using quantum mechanical calculations the protein-ligand interaction energy between CDK2 (cyclin-dependent kinase 2) and five inhibitors with the N^2-substituted 6-cyclohexylmethoxypurine scaffold has been carried out.[118] Several examples of protein- ligand interaction that make use of cation–π interactions such as trimethylated lysine and neurotransmitter acetylcholine have been described earlier.[119] The opioid receptor binding affinities of certain organic molecules were compared with the affinities of four new ligands bearing an ortho- or *para*-hydroxyl substituent. The data indicated that either the electronic state of the phenolic ring is critical for the ligand's interaction with an opioid receptor, or that there must be a specific distance and angle for a hydrogen bond between the phenolic moiety and an amino acid in the binding domain that cannot be altered.[120] The docking of a series of arylpiperazine derivatives with structurally different aryl part to the binding site of a model of human 5-HT_{1A} receptor has also been reported.[121] NMR spectra revealed the cation–π interaction in nicotinic acetylcholine receptor's site of action.[122]

14. Conclusions

Several number of forces are responsible for binding of xenobiotics in biology, study of individual is not easy so the forces must be studied separately. As aromatic interactions are responsible for so many important phenomena in chemistry and biology, study of such interactions some times becomes beneficial. In medicinal chemistry a better understanding of aromatic π–π interactions will enhance the discovery of new drug. Crystal engineering, protein folding, and other materialistic properties can also be investigated through the knowledge of such interactions.Utility of non-covalent interactions also seems to be involved in protein stabilization and forming synthetic receptors.

References and notes

1. Muller, K. D.; Hobza, P. *Chem. Rev.* **2000**, *100*, 143.
2. Lehn, J. M. *Perspective in Supramolecular Chemistry*; VCH: Weinheim, 1995.
3. Jennings, W. B.; Farrell, B. M.; Malone, J. F. *Acc. Chem. Res* **2001**, *34*, 885.
4. Dahl, T. *Acta Chem. Scand.* **1994**, *48*, 95.
5. Hunter, C. A. The role of Aromatic interactions in Molecular Recognition, *Chem. Soc. Rev.* **1994**, *23* 101.
6. Avasthi, K.; Chandra, T.; Bhakuni, D. S. *Ind. J. Chem.* **1995**, *B34*, 944.
7. Garg, N.; Avasthi, K.; Bhakuni, D. S. *Synthesis* **1989**, 876.
8. Biswas, G.; Chandra, T.; Avasthi, K.; Maulik, P. R. *Acta Crystallogr.* **1995**, *C51*, 2453.
9. Avasthi, K.; Rawat, D. S.; Chandra, T.; Bhakuni, D. S. *Ind. J. Chem.* **1998**, *37B*, 754.
10. Avasthi, K.; Chandra, T.; Rawat, D. S.; Bhakuni, D. S. *Ind. J. Chem.* **1998**, *37B*, 1228.
11. Maulik, P. R.; Avasthi, K.; Biswas, G.; Biswas, S.; Rawat, D. S.; Sarkhel, S.; Chandra, T.; Bhakuni, D. S. *Acta Crystallogr.* **1998**, *C54*, 275.
12. Avasthi, K.; Aswal, S.; Maulik, P. R. *Acta Crystallogr.* **2001**, *C57*, 1324.
13. Avasthi, K.; Tewari, A.; Rawat, D. S.; Sharon, A.; Maulik, P. R. *Acta Crystallogr.* **2002**, *C58*, 494.
14. Avasthi, K.; Aswal, S.; Kumar, R.; Yadav, V.; Rawat, D. S.; Maulik, P. R. *J. Mol. Struct.* **2005**, *750*, 179.
15. Avasthi, K.; Farooq, S. M.; Tewari, A. K.; Sharon, A.; Maulik, P. R. *Acta Crystallogr.* **2003**, *C59*, o42.
16. Browne, D. T.; Eisinger, J.; Leonard, N. J. *J. Am. Chem. Soc.* **1968**, *90*, 7302.
17. Avasthi, K.; Farooq, S. M.; Bal, C.; Kumar, R.; Tewari, A. K.; Maulik, P. R. *J. Mol. Struct*., in press, Available online 12 January 2007.
18. Castellano, R. K.; Diederich, F.; Meyer, E. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210.
19. (a) Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/p Interaction. Evidence, Nature and Consequences*; Wiley-VCH: New York, 1998; (b) Nishio, M. *Cryst. Eng. Commun.* **2004**, *6*, 130.
20. Shimohigashi, Y.; Maeda, I.; Nose, T.; Ikesue, K.; Sakamoto, H.; Ogawa, T.; Ide, Y.; Kawahara, M. *J. Chem. Soc., Perkin Trans.* **1996**, *1*, 2479.
21. Brandl, M.; Weiss, M. S.; Jabs, A.; Sühnel, J.; Hilgenfeld, R. *J. Mol. Biol.* **2001**, *307*, 357.
22. Gung, B. W.; Xue, X.; Reich, H. J. *J. Org. Chem.* **2005**, *70*, 7232.
23. Minoux, H.; Chipot, C. J. *Am. Chem. Soc.* **1999**, *121*, 10366.
24. Staley, R. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 5920.
25. Ma, J. C.; Dougherly, D. A. *Chem. Rev.* **1997**, *97*, 1303.
26. (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719; (b) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169.
27. Yamada, S.; Morita, C. *J. Am. Chem. Soc* **2002**, *124*, 8184.
28. Tewari, A. K.; Singh, V. P.; Puerta, C.; Valerga, P. *Acta Crystallogr.* **2007**, *E63*, 1930.
29. Muchldorf, A. V.; Engen, D. V.; Warner, J. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6561.
30. Evans, D. A.; Engen, D. V.; Warner, J. C.; Hamilton, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184.
31. Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768.
32. Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616.
33. Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475.
34. Tauber, M. J.; Kelley, R. F.; Giaimo, J. M.; Rybtchinski, B.; Wassielewski, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 1782.
35. Blanco, M.; Coello, J.; Iturriaga, H.; Maspoch, S.; Serrano, D. Springer Berlin/Heidelberg, *J. Anal. Chem.* **1999** *4*, 364.
36. Nishinaga, T.; Komatsu, K. *Org. Biomol. Chem.* **2005**, *3*, 561.
37. Brownnstein, S. K.; Ding, J.; Robertson, G.; Roovers, J. *J. Org. Chem.* **2002**, *67*, 663.
38. Liu, Y.; Zhao, Y-L.; Chen, Y.; Guo, D. S. *Org. Biomol. Chem.* **2005**, *3*, 584.
39. (a) Marseglia, E. A.; Grepioni, F.; Tedesco, E.; Braga, D. *Mol. Cryst. Liqcryst.* **2000**, *137*, 348; (b) Barbareka, G.; Zambianchi, M.; Bongini, A.; Antolini, L. *Adv. Mater.* **1993**, *5*, 834.
40. Xiao, K.; Liu, Y.; Qi, T.; Zhang, W.; Wang, F.; Gao, J.; Qiu, W.; Ma, Y.; Cui, G.; Chen, S.; Zhan, Z.; Yu, G.; Qin, J.; Hu, W.; Thu, D. *J. Am. Chem. Soc.* **2005**, *127*, 13281.
41. Mei, X.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 5487.
42. Newcomb, L. F.; Haque, T. S.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 6509.
43. Cozzi, F.; Cinquini, M.; Annuziata, R.; Dwyer, T.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 5729.

44. Cozzi, F.; Cinquini, M.; Annuziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330.
45. Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1584.
46. Cozzi, F.; Siegel, J. S. *Pure Appl. Chem.* **1995**, *67*, 683.
47. Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525.
48. Rathore, R.; Abdelwahed, S. H.; Guzei, I. A. *J. Am. Chem. Soc.* **2003**, *125*, 8712.
49. Leonard, N. J. *Acc. Chem. Res.* **1979**, *12*, 423.
50. Pang, Y. P.; Miller, J. L.; Kollman, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 1717.
51. Sivakova, S.; Bohnsack, D. A.; Mackay, M. E.; Suwanmala, P.; Rowan, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 18202.
52. (a) Bao, C. Y.; Lu, R.; Jin, M.; Xue, P. C.; Tan, C. H.; Zhao, Y. Y.; Liu, G. F. *Carbohydr. Res.* **2004**, *339*, 1311; (b) Rao, C. Y.; Lu, R.; Jin, M.; Xue, P. C.; Tan, C. H.; Zhao, Y. Y.; Liu, G. F.; Nano, J. *Sci. Nanotechnol.* **2004**, *4*, 1045; (c) John, G.; Jung, J. H.; Minamikawa, H.; Yoshida, K.; Shimizu, T. *Chem. Eur. J.* **2002**, *8*, 5494; (d) Friggeri, A.; Gronwald, O.; van Bommel, J. C.; Shinkai, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 10754.
53. Jung, J. H.; Amaike, M.; Nakashima, K.; Shinkai, S. *J. Chem. Soc. Perkin Trans.* **2001**, *2*, 1938.
54. Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Chem. Eur. J.* **2003**, *9*, 348.
55. Suzuki, M.; Nigawara, T.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Tetrahedron Lett.* **2003**, *44*, 6841.
56. Yabuuchi, K.; Marfo-Owusu, E.; Kato, T. *Org. Biomol. Chem.* **2003**, *1*, 3464.
57. Estroff, L. A.; de Hamiton, A. *Angew Chem., Int. Ed.* **2000**, *39*, 3447.
58. Sugiyasu, K.; Fujita, N.; Takeuchi, M.; Yamada, S.; Shinkai, S. *Org. Biomol. Chem.* **2003**, *1*, 895.
59. Jung, J. H.; Ono, Y.; Shinkai, S. *Angew. Chem., Int. Ed* **2000**, *39*, 1862.
60. Ayabe, M.; Kishida, T.; Fujita, N.; Sada, K.; Shinkai, S. *Org. Biomol. Chem.* **2003**, *1*, 2744.
61. Babu, P.; Sangeetha, N. M.; Vijay Kumar, P.; Maitra, U.; Rissanen, K.; Raju, A. R. *Chem. Eur. J.* **2003**, *9*, 1922.
62. Bao, C.; Lu, R.; Jin, M.; Xue, P. C.; Tan, C.; Liu, G.; Zhao, Y. *Org. Biomol. Chem.* **2005**, *3*, 2508.
63. Gung, B. W.; Patel, M.; Xue, X. *J. Org. Chem. Soc.* **2005**, *70*, 10532.
64. Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: U.K., 1999.
65. Murray, T. J.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 4010.
66. Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710.
67. Gong, B.; Yan, Y.; Zeng, H.; Jankunn, E. S.; Kim, Y. W.; Jin, Zhu; Ickes, H. *J. Am. Chem. Soc.* **1999**, *121*, 5607.
68. Yoshiji, Takemoto *Org. Biomol. Chem.* **2005**, *3*, 4299.
69. Aboitiz, N.; Cañada, F. J.; Ušáková, L. H.; Kuzma, M.; Kren, V.; Barbero, J. J. *Org. Biomol. Chem.* **2004**, *2*, 1987.
70. Wahwong, M. *J. Org. Chem.* **2005**, *70*, 5487.
71. (a) Kauzmann, W. *Adv. Protein Chem.* **1959**, *14*, 1; (b) Tanford, C. *J. Am. Chem. Soc.* **1962**, *84*, 4240.
72. Rademacher, P.; Khelashvili, L.; Kowski, K. *Org. Biomol. Chem.* **2003**, *3*, 2620.
73. Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662.
74. Archer, E. A.; Gong, H.; Krische, M. J. *Tetrahedron* **2001**, *57*, 1139.
75. Anelli, P. L. *J. Am. Chem. Soc* **1991**, *113*, 5131.
76. Gatti, F. G.; Leigh, D. A.; Nepogodiev, S. A.; Slawin, A. M. Z.; Teat, S. J.; Wong, J. K. Y. *J. Am. Chem. Soc.* **2001**, *123*, 5983.
77. Williams, D. H.; Bardsley, B. *Angew. Chem Int., Ed. Engl.* **1999**, *38*, 1172.
78. Anelli, P. L.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Delgado, M.; Gandolfi, M. T.; Goodnow, T. T.; Kaifer, A. E.; Philp, D.; Pietraszkiewicz, M.; Prodi, L.; Reddington, M. V.; Slawin, A. M. Z.; Speneer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 193.
79. Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180.
80. Masu, H.; Sakai, M.; Kishikawa, K.; Yamamoto, M.; Yamaguchi, K.; Kohmoto, S. *J. Org. Chem.* **2005**, *70*, 1423.
81. Han, J. J.; Wang Alexander, W.; Li, D. Q. *J. Am. Chem. Soc.* **2006**, *128*, 672.
82. Heemstra, J. M.; Moore, J. S. *Chem. Commun.* **2004**, 1480.
83. Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587.
84. Xia, Ci.; Fan, X.; Locklin, J.; Advincula, R. C.; Gies, A.; William, Nonidez *J. Am. Chem. Soc.* **2004**, *126*, 8735.
85. Lovinger, A. J.; Nuckolls, C.; Katz, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 264.
86. Krebs, F. C.; Larsen, M.; Jorgensen, M.; Jensen, P. R.; Bielecki, M.; Schaumburg, K. *J. Org. Chem.* **1998**, *63*, 9872.
87. Hao, E.; Fronczek, F. R.; Vicente, M. G. H. *J. Org. Chem.* **2006**, *71*, 1233.
88. Salvo, G. D.; Gattuso, G.; Notti, A.; Parisi, M. F.; Pappalardo, S. *J. Org. Chem.* **2002**, *67*, 684.
89. Kuwabara, T.; Aoyagi, T.; Takamura, M.; Matsushita, A.; Nakamura, A.; Veno, A. *J. Org. Chem.* **2002**, *67*, 720.
90. Colby, D. A.; Lash, T. D. *J. Org. Chem.* **2002**, *67*, 1031.
91. (a) Lu, W.; Fadeev, A. G.; Qi, B.; Smela, E.; Matters, B. R.; Qing, J.; Spinks, G. M.; Mazurkiewicz, J.; Zhou, D.; Wallace, G. G.; Macfarlane, O. R.; Forsyth, M. *Science* **2002**, *297*, 983; (b) Jager, E. W. H.; Inganäs, O.; Lundström, I. *Science* **2000**, *288*, 2335.
92. Baughman, R. H.; Cui, C.; Zakhidov, A. A.; Iqbal, Z.; Barisci, J. N.; Spinks, G. M.; Wallace, G. C.; Mazzoldi, A.; Rossi, D. De.; Rinzler, A. G.; Jaschinski, O.; Roth, S.; Kertez, M. *Science* **1999**, *284*, 1340.
93. Landi, B. J.; Raffaelle, R. P.; Heben, M. J.; Alleman, J. L.; van Derver, W.; Gennett, T. *NanoLett* **2002**, *2*, 1329.
94. (a) Smella, E. *Adv. Mater.* **2003**, *15*, 481; (b) Bay, L.; West, K.; Sommerlarsen, P.; Skaarup, S.; Bensliman, M. *Adv. Mater.* **2003**, *15*, 310; (c) Balzani, V.; Gómez-López, M.; Stoddart, J. F. *Acc. Chem. Res.* **1998**, *31*, 405.
95. Scherlis Damain, A.; Marzari, N. *J. Am. Chem. Soc.* **2005**, *127*, 3207.
96. Johnstone, Ken D; Yamaguchi, Kentaro; Gunter, Maxwell J *Org. Biomol. Chem.* **2005**, *3*, 3008.
97. Zhao, D.; Moore, J. S. *J. Org. Chem.* **2002**, *67*, 35.
98. Lagona, J.; Wagner, B. D.; Isaacs, L. *J. Org. Chem.* **2006**, *71*, 1181.
99. Hunter, C. A. *J. Mol. Biol.* **1993**, *230*, 1025.
100. Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23.
101. (a) Zhang, J.; Moore, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 9701; (b) Shetty, A. S.; Zhang, J.; Moore, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 1019.
102. (a) Tobe, Y.; Utsumi, N.; Kawabata, K.; Naemura, K. *Tetrahedron Lett.* **1996**, *37*, 9325; (b) Tobe, Y.; Utsumi, N.; Nagano, A.; Naemura, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1285.

103. Höger, S.; Bonrad, K.; Mourran, A.; Beginn, V.; Möller, M. *J. Am. Chem. Soc.* **2001**, *123*, 5651.
104. Lin, C. H.; Tour, J. *J. Org. Chem.* **2002**, *67*, 7761.
105. Sugiura, H.; Takahira, Y.; Yamaguchi, M. *J. Org. Chem.* **2005**, *70*, 5698.
106. Brown, G. R.; Chana, S. S.; Stoddart, J. F.; Slawin, A. N. Z.; Williams, D. J. *J. Chem. Soc. Perkin Trans.* **1989**, *1*, 211.
107. Smithrud David, B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 339.
108. Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054.
109. Tran, A. H.; Miller, D. O.; Georghion, P. E. *J. Org. Chem.* **2005**, *70*, 1115.
110. (a) Rebek, J., Jr. *J.Recognit.* **1988**, *1*, 1; (b) Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1990**, *3*, 245; (c) Jeffrey, G. S.; Curran, D. P.; Geib, S. V.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *144*, 7007; (d) Jeong, K. S.; Parris, K.; Ballester, P.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1990**, *5*, 555.
111. Wang, W.; Wan, W.; Zhou, H. H.; Niu, S.; Li Alexander, D. Q. *J. Am. Chem. Soc.* **2003**, *125*, 5248.
112. Rebek, J.; Askew, B., Jr.; Ballester, P.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K. *J. Am. Chem. Soc.* **1988**, *110*, 6561.
113. Butterfield, S. M.; Sweeney, M. M.; Waters, M. L. *J. Org. Chem.* **2005**, *70*, 1105.
114. Aravinda, S.; Shamala, N.; Das, C.; Srivarzjini, A.; Karle, I. L.; Balaram, P. *J. Am. Chem. Soc.* **2003**, *125*, 5308.
115. Griffiths-Jones, S. R.; Searle, M. S. *J. Am. Chem. Soc.* **2000**, *122*, 8350.
116. Talko, C. D.; Waters, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 9372.
117. Rehab, A.; Yuji, O.; Yoshiko, U.; Takamitsu, K.; David, D.; Doreen, B.; Hiroshi, H. *J. Bioinorg. Chem.* **2007**, *12*, 165.
118. Alzate-Morales, J. H.; Contreras, R.; Soriano, A.; Tuñon, I.; Silla, E. *Biophys. J.* **2007**, *92*, 430.
119. Dougherty, D. A. *J. Nutr.* **2007**, *137*, 1504S.
120. Kima, I. J.; Derschb, C. M.; Rothmanb, R. B.; Jacobsona, A. E.; Rice, K. C. *Bioorg. Med. Chem.* **2004**, *12*, 4543.
121. Zlatovića, M. V.; Šukalovićb, V. V.; Schneiderc, C.; Roglića, G. M. *Bioorg. Med. Chem.* **2006**, *14*, 2994.
122. Watts, A. *Mol. Mem. Bio.* **2002**, *19*, 267.