HETEROCYCLES AND MOLECULAR RECOGNITION

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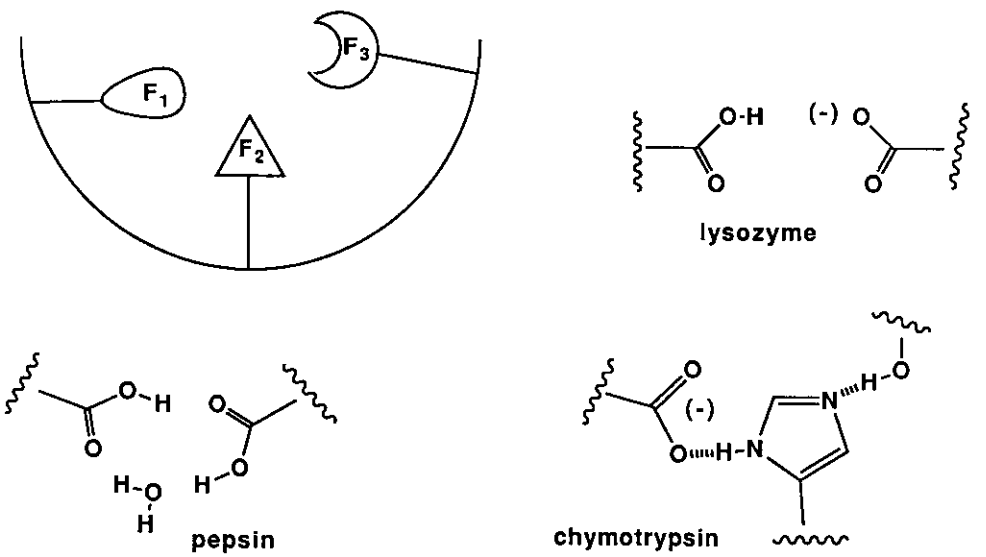
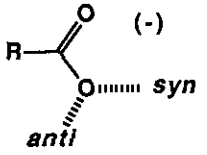
Abstract - The application of the heterocyclic compounds in the area of molecular recognition is explored with a number of examples. Hydrogen bonding, with its modestly directional characteristics, is shown to offer advantages in situations where recognition leads to subsequent chemical reactions.

It is indeed an honor for me to contribute to this special volume in memory of Professor Kametani. It is especially satisfying that heterocyclic compounds have been so useful in my research to explore the rules of molecular recognition. The heterocyclic compounds provide such a richness in hydrogen bonding donor and acceptor arrays that it is surprising that they have been used so little before the last few years. Perhaps it was because heteromacrocyclic compounds, such as crown ethers,[1] cryptands,[2] and spherands[3] were so popular. Any discussion of molecular recognition should begin with an acknowledgement of the debt it owes to macrocyclic chemistry. Cyclodextrins[4] had also been shown to be quite useful vehicles for complexation and even catalytic purposes, but the relatively non-directional nature of the hydrophobic binding forces involved made planning contacts between reactive centers in substrates and hosts quite difficult.[5] The use of hydrogen bonds, with their more directional characteristics, however, has been quite advantageous in this regard.



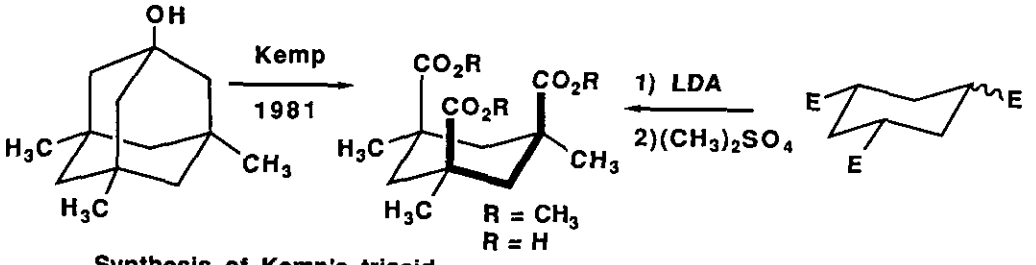
Functional groups, F, converge from a concave surface to create an active site

A second advantage is provided by an alternative shape to macrocyclic compounds. Specifically, these molecules are in the shape of a cleft, with concave surfaces lined with functional groups. Such structures are inspired by natural receptors: antibodies, enzymes, even the grooves of nucleic acids, and they show the feature of convergence of functionality. To be sure, the ethereal oxygens of crown ethers also are convergent functionalities, but these have such low reactivities that they are not useful in catalytic settings. The carboxyl group, however, finds its way into many enzyme active sites; lysozyme, aspartic proteases, and serine proteases are just a few examples. A rather remarkable observation made by Gandour[6] concerns the orientation of carboxyl groups at such active sites. He pointed out that invariably the more basic syn lone pairs are directed toward the substrate. That is, carboxylates will be most effective as bases or nucleophiles when their more basic lone pairs are properly oriented.



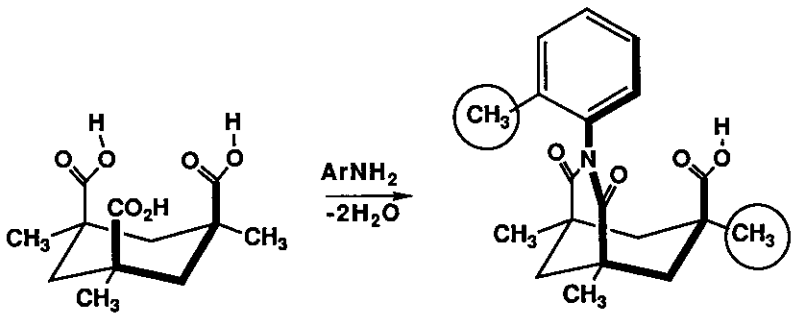
Stereoelectronic effects at carboxyl oxygen

In order to place a carboxylate in the appropriate orientation, we desired a concave scaffold, and that was provided by a unique carboxylic acid described by Kemp.[7] In this structure three carboxyl functions are forced into a triaxial conformation, a result which insures that a U-shaped relationship exists between any two of them. This relationship becomes the source of the concave shapes that we discuss in this review. This material can now be made on a large scale by an alkylation reaction as shown and it has even become commercially available.[8]



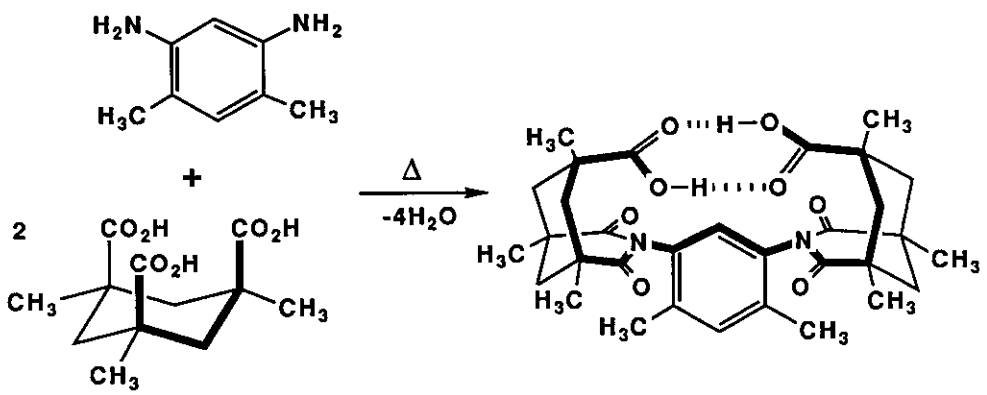
Synthesis of Kemp's triacid

Condensation of the Kemp triacid with amines leads to imides, and with aromatic amines leads to structures that have an aspect of being folded back upon themselves. Thus the remaining carboxyl group of the triacid is now directed back at other parts of the structure. Indeed, it is possible to use remote steric effects to further reduce the rotational freedom of such structures. Thus, an ortho methyl group prevents rotation about the C-aryl N-imide bond, and insures that groups meta to the nitrogen will be suspended in space near the acidic proton of the carboxylic acid.



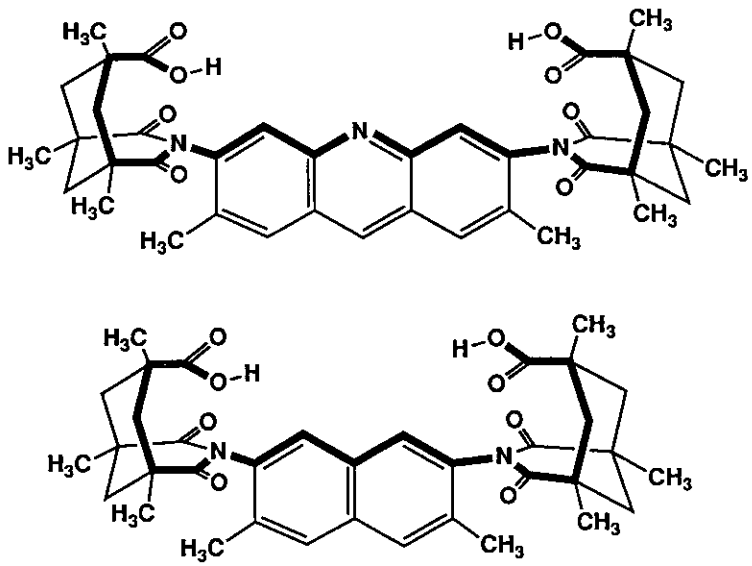
Methyls prevent rotation and epimerization

Molecules of a complete concave shape were then available by merely condensing an appropriate diamine with two equivalents of the Kemp triacid. The experimental protocol is quite simple: one merely performs a mixed melting point between the two components and high yields of dicarboxylic acids are obtained. For the case at hand, extensive intramolecular hydrogen bonding is observed because the two carboxyl groups are fixed with respect to one another. They show unusual acid-base properties and can be used as peracids to give epoxidation of olefins with some selectivity.[9] The cleft of such molecules, however, is quite small. They can accommodate metal ions and they show extraordinary affinity for magnesium and calcium.[10] This affinity is likely due to the orientation of the more basic syn lone pairs in a trans fashion on the metal ion center.



Synthesis of convergent carboxyl functions

Molecules with larger clefts were also available from bigger aromatic spacers. For example, acridine yellow, an inexpensive dye, condenses quite nicely to give a dicarboxylic acid with more than 8 Å between opposing carboxyl oxygens. This leads to a structure with an additional functional group, the heterocyclic nitrogen, featuring a lone pair directed into in the area between the two carboxylic acids.

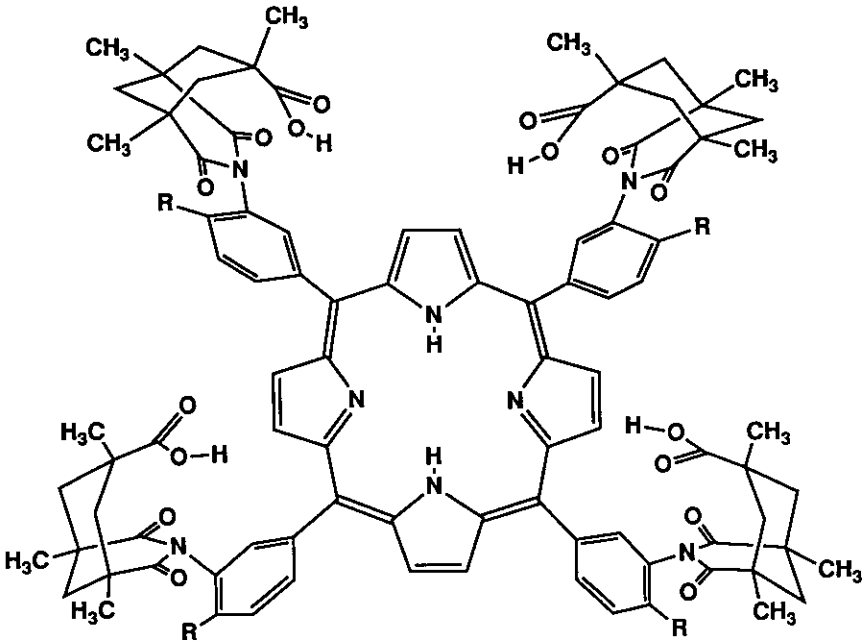


Molecular clefts derived from aromatic spacers

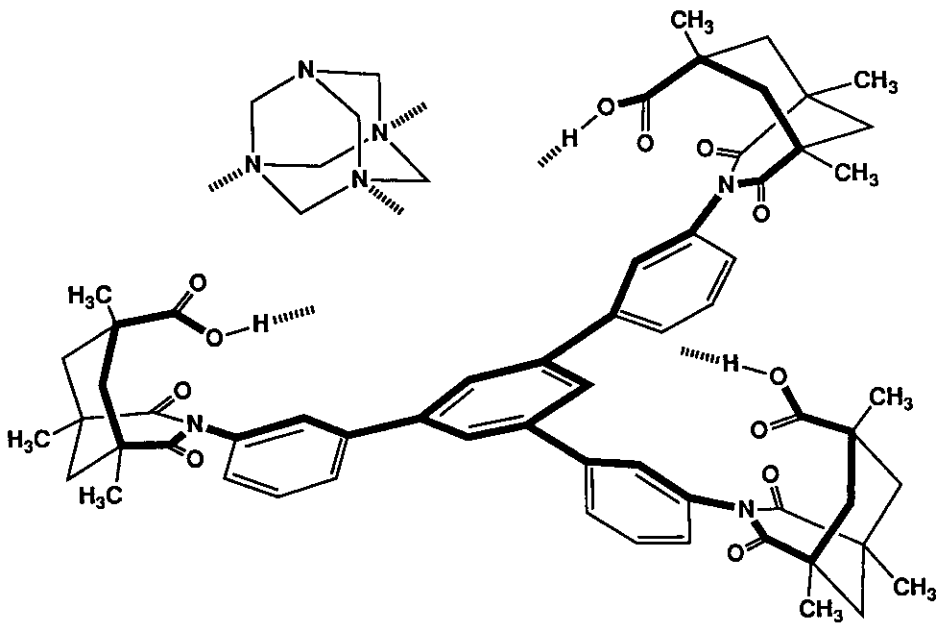
A number of other diamines are available, including flexible α,ω–diaminoalkanes, and some quite exotic aromatic spacers can also be obtained. The acridine derived diacid expresses acidity in a convergent sense and it is not surprising that it binds tenaciously to heterocyclic bases that express basicity in a divergent sense.[11] Molecules such as pyrazine and DABCO are chelated tightly within the cleft and recent calculations[12] make quite useful predictions about the matching of sizes in host and guest species in this series. A tetracarboxylic acid is readily assembled[13] on the porphyrin skeleton, thanks to an improved tetraarylporphyrin synthesis.[14] This molecule has spacer groups suitable for binding 4:4 bipyridine and indeed 2:1 complexes are made with that substrate.

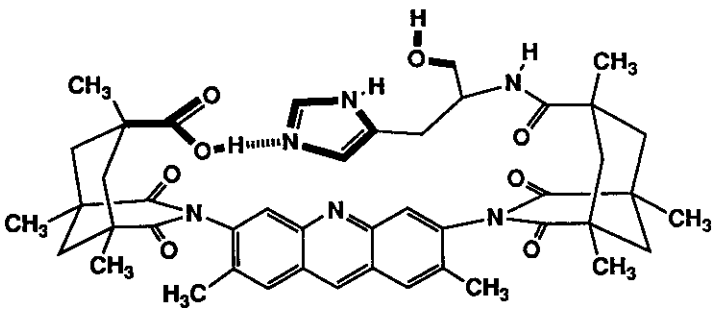
Rigid systems with three arms are also available. For example the triarylbenzene derivative has been prepared, with both the meta and para isomers being available. The former binds nicely to triazene or hexamethylenetetramine while the latter (para) isomer binds tren.[15]

Alternate functionality may be introduced to these clefts. For example, acylation of histidinol by the acridine derived diacid leads to a unique model for the active site of the serine proteases. The carboxyl group and imidazole converge in an arrangement resembling the active site.[16] It is our growing conviction that multifunctional catalysts, be they synthetic or enzymic in nature, owe a good deal of their activity to the rigid spacers that keep them from collapsing upon one another. That is, the active site provides a constellation of functionality poised for reaction, but kept from direct contact by the scaffolding of the peptide backbone.



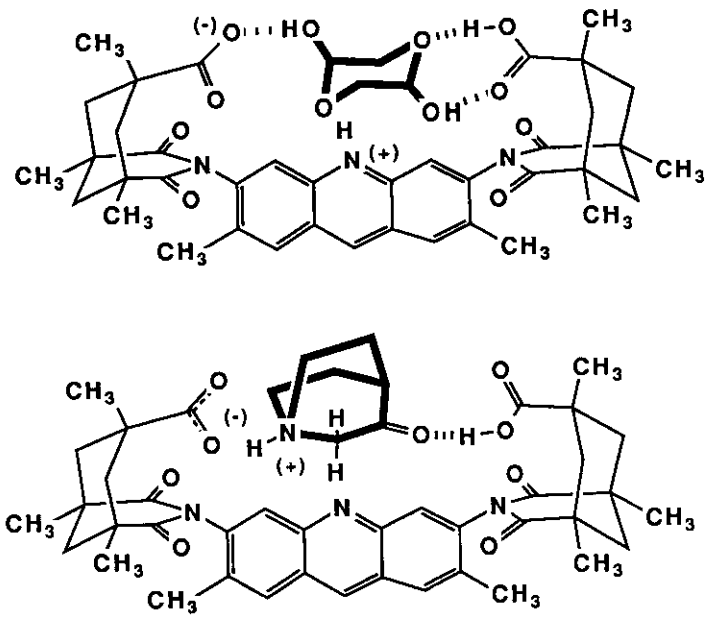
Synthetic receptor for 4,4' bipyridine





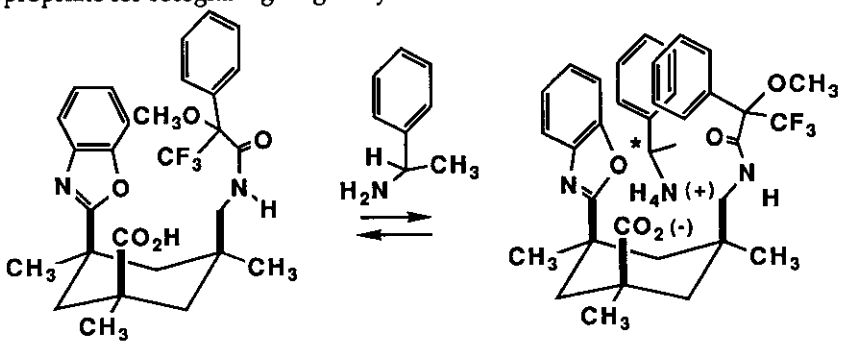
Model for the catalytic triad of the serine proteases

One very pertinent expression of this has been seen in the use of the acridine diacid as an enolization catalyst.[17] Since the acid and base components here converge from perpendicular directions these stereoelectronics are ideal for an enolization catalyst.[18] Indeed, molecules that fit within the cleft, such as quinuclidinone, are enolized by this material through functional groups acting in a concerted manner. In hemiacetal cleavage reactions this material is again extraordinarily effective.[19] The molecule can grasp the substrate and present acids and bases in a fashion ideal for cleavage of the endocyclic C-O bond.



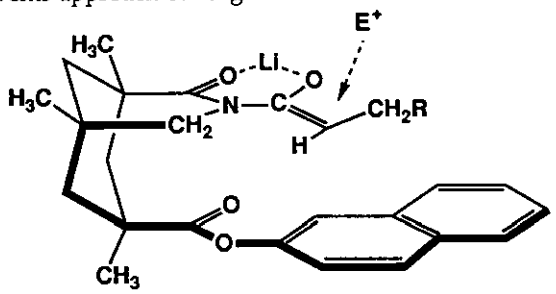
Concerted catalysis of hemiacetal cleavage and enolization processes

The concave shape provided by the U-turn in the Kemp triacid may also be used to an advantage in asymmetric recognition. For example, the cyclohexane skeleton can provide large, medium, and small functional groups, all protruding from a single face of the structure, and such structures are quite appropriate for recognizing single asymmetric centers.[20]



Small,medium and large groups protrude to create an asymmetric microenvironment

Asymmetric synthesis can also be achieved by using these derivatives as chiral auxiliaries. For example, the enolate shown reacts with high facial selectivity toward electrophiles because the large aromatic shelf prevents approach of reagents from beneath.[21]

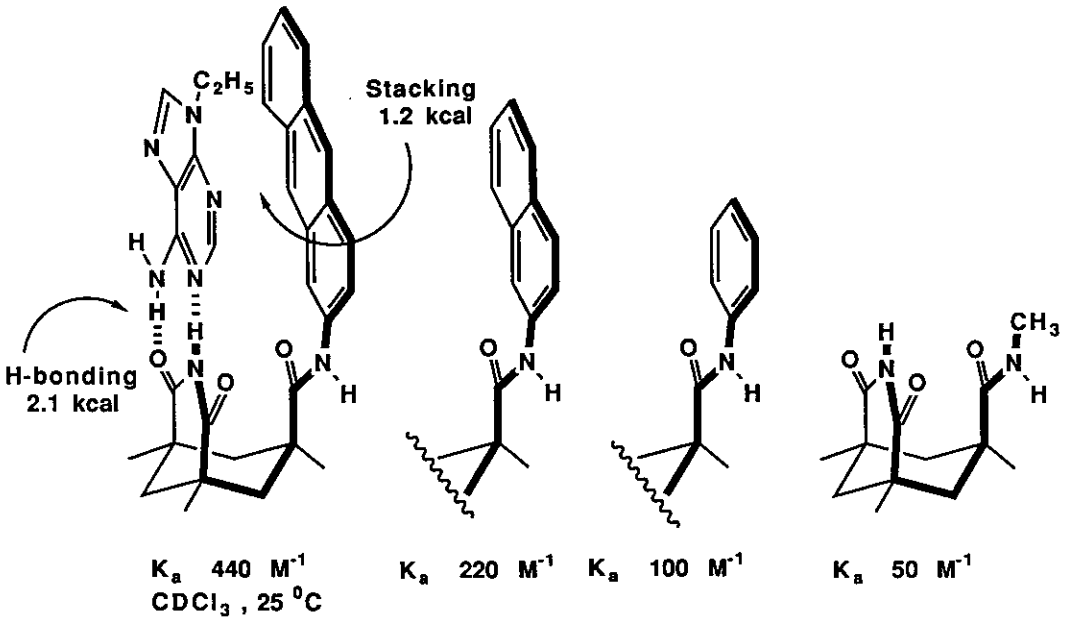


Asymmetric alkylation of enolates

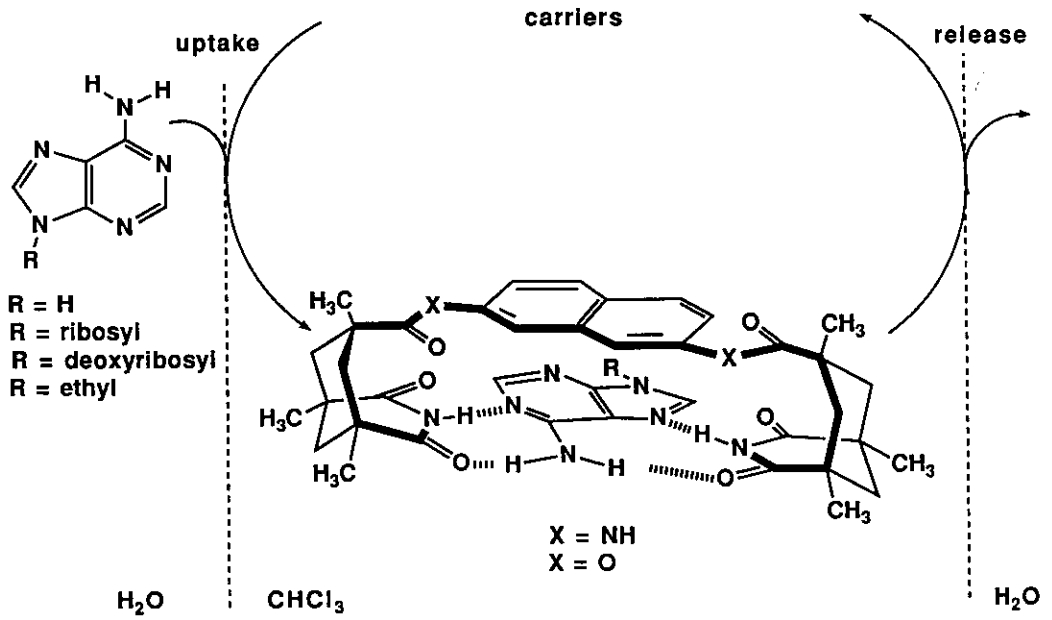
Molecules of this general shape have also proved quite effective in the recognition of nucleic acid components. For example, the imides shown provide hydrogen bonding surfaces similar to that of thymine, while the aromatic surface provides a polarizable entity for π-stacking interactions. We have separated these two variables by studying a series of aromatic surfaces and find that about one kilocalorie is available with the largest anthracyl surface.[22]

In binding to adenine derivatives, both Watson-Crick and Hoogsteen base-pairing may be achieved simultaneously by a diimide spaced with a suitable aromatic surface. The naphthalene derivatives shown, for example, are capable of extracting adenine or its derivatives from aqueous solutions and transporting them across simple liquid membranes.[23]

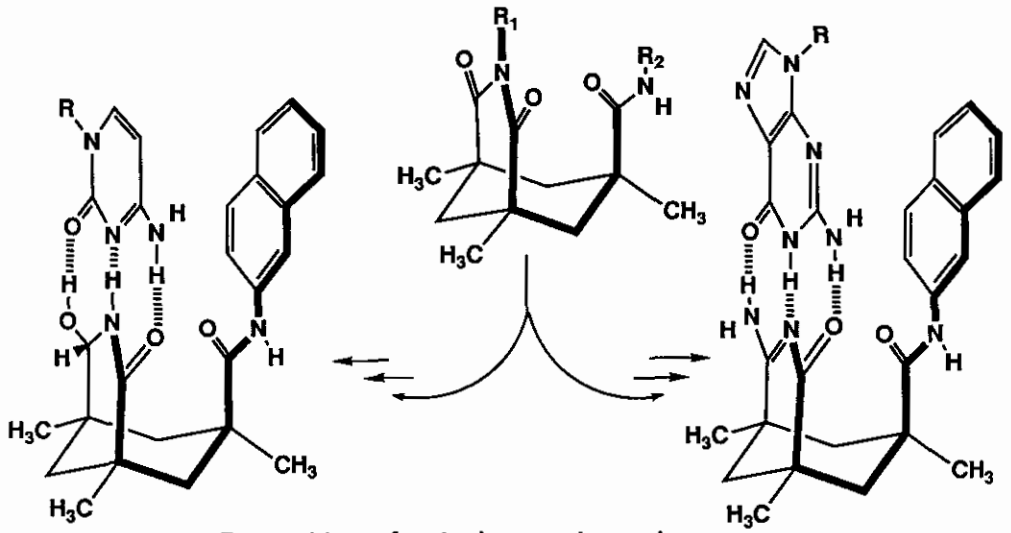
Again, the hydrogen bonding edges may be tailored to accommodate other nucleotide components with high selectivity. Two examples involving guanine recognition and cytosine recognition are shown.[24]



Evaluation of aromatic stacking in molecular recognition

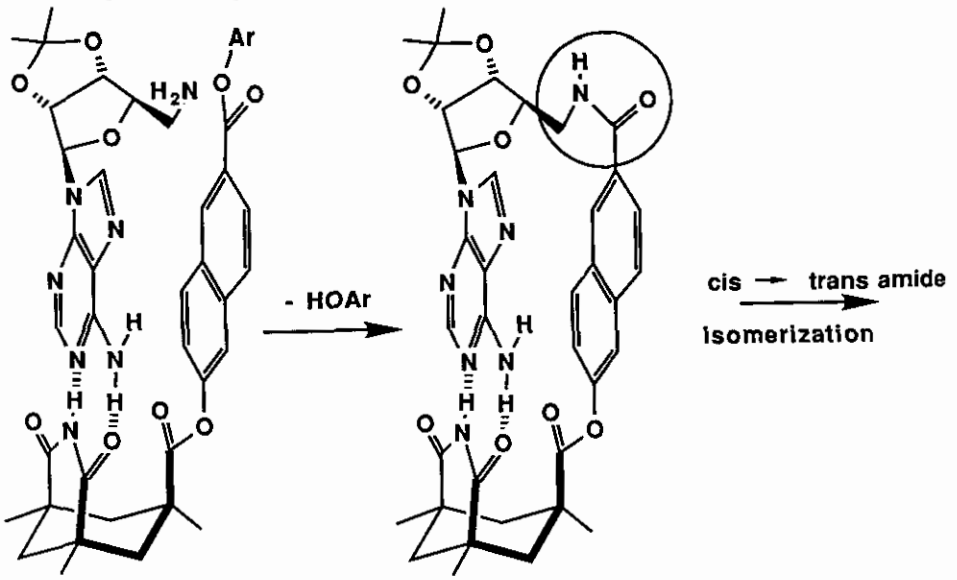


Transport of adenine across liquid membranes

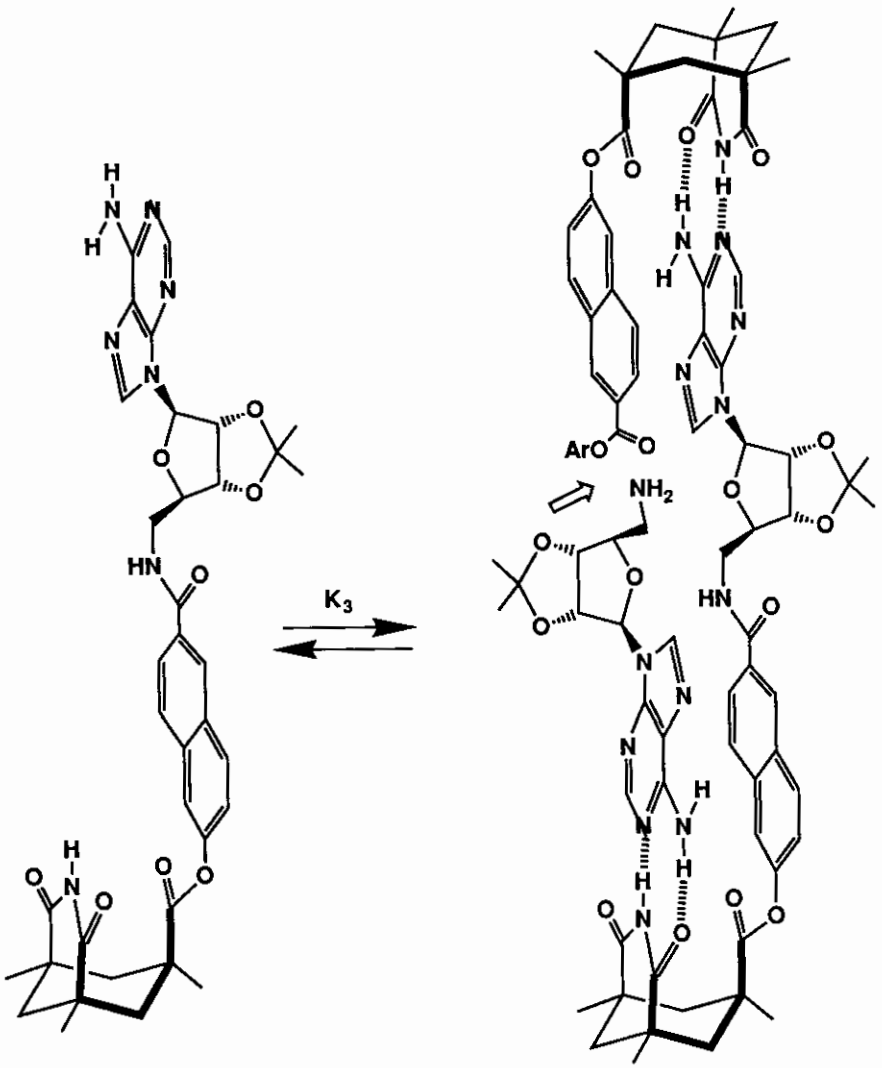


Recognition of cytosines and guanines

The high degree of recognition available with these substances led us to explore their usefulness in template synthesis. By placing a nucleophilic component in the adenine piece and an electrophilic component on the aromatic surface, it could be shown that acyl transfer was enhanced by prior base-pairing. Moreover, the resulting amide product is capable of catalyzing its own formation; that is, it acts as a template by gathering both reacting components in a termolecular complex.[25] In this complex, acyl transfer can proceed as shown and it is possible to use this autocatalytic system, which shows a primitive sign of life, to explore self-replication.



Intramolecular acyl transfer through base - pairing



Autocatalysis in a self - replicating system

One of the many goals of such research is to try to bring the recognition and catalytic events closer together in space and in time. In this manner, recognition merges with catalysis, and maximum binding to the transition state[26] would be achieved. We are working toward these goals and will report on them in due course.

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