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Model studies in recognition using new molecular shapes

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Abstract - The challenges presented by the selective complexation of small, biologically significant molecules are being faced through the use of new molecular shapes in which stereoelectronic considerations are incorporated. Molecular clefts, in which hydrogen bond donors and acceptors are arranged in a convergent sense, are particularly advantageous for this purpose. They are readily assembled and their linings can be altered to provide microenvironments complementary to a range of target structures. Amines, metal ions, nucleic acid components, and amino acids have all been bound within such structures. In addition, applications in biomimetic catalysis and asymmetric recognition are being developed.

INTRODUCTION

Given the many successes of macrocyclic compounds in bioorganic chemistry and the devotion of entire conferences to the discussion of structures of that shape, what follows below might be regarded as apostasy. Abandoning macrocylic compounds for alternative shapes followed our realization that most macrocyclic compounds involve the convergence of Lewis bases. They are nearly ideal complements to spherical cations, but for other guest species they have limitations. If the target guest species is a base, then structures featuring complementary arrays of acids are required. Stereoelectronic effects, however, make it difficult to arrange the convergence of acids in general and carboxylic acids (ref.1) in specific (Fig. 1). Attachment of carboxylic acids to macrocycles is easily accomplished, (ref. 2) but the acidity tends to diverge from the binding site; our intent to control the microenvironment near the hydrogen of the carboxylic acid led to the use of a molecular cleft (Fig. 2).

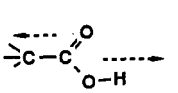


Fig. 1
Acidity is directed away from the rest of the structure

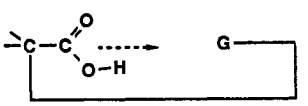
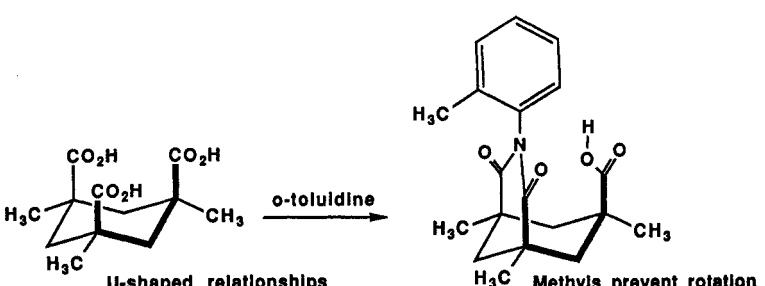


Fig. 2
Acidity is directed toward specific groups of the structure

This required that a U-turn be engineered into the structure because the first bond leading from the carboxyl group is pointing in exactly the wrong direction. Fortunately, Kemp's (ref. 3) description of an unusual tricarboxylic acid (Fig. 3) provided the scaffold on which this U-turn could be negotiated. Specifically, the triaxial arrangement of the carboxyl functions insures that a U-shaped relationship exists between any two of them. This triacid can be used as a module for "reversing" the sense of molecules that it contains. For example, condensation with simple anilines leads to imides, and with ortho substituted anilines further conformational restriction is achieved. The region of space near the carboxylic acid hydrogen becomes subject to some control.



U-shaped relationships in Kemp's triacid

Fig. 3

Methyls prevent rotation or epimerizations

MOLECULAR CLEFTS

By merely combining two of the triacid molecules with a suitably substituted phenylene diamine we were able to generate the first of our synthetic molecular clefts. This architectural motif could be repeated with other aromatic spacers, specifically with acridine yellow and a naphthalene diamine (Fig. 4). Crystallographic studies showed that only the carboxylic acids separated by a benzene spacer exist as hydrogen bonded dimers, i.e. ~2.6Å between opposing carboxyl oxygens. The acridine spacer presents ~8.5Å and the mid-size naphthalene version provides ~5.5Å for this distance. The stacking interactions offered by these aromatic spacers, particularly the acridine are also available for binding certain amino acids (ref. 4).

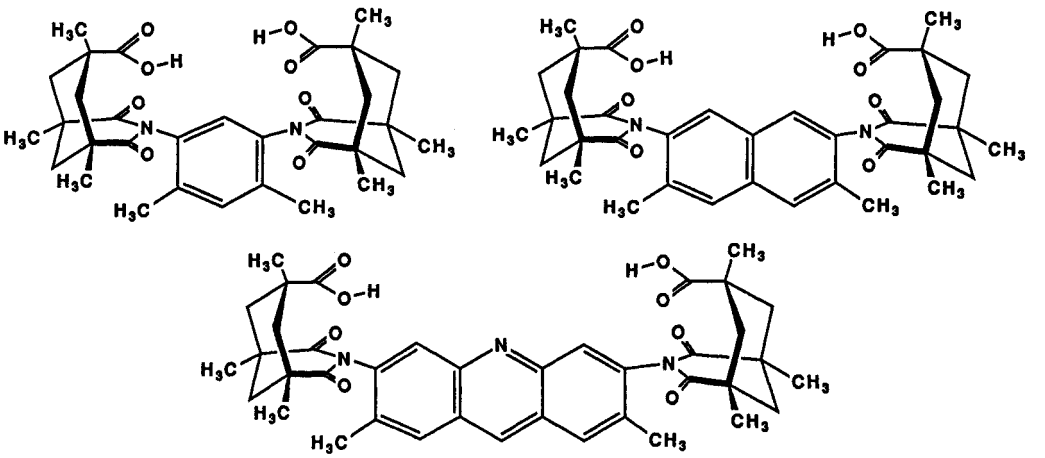


Fig. 4 Convergent diacids with aromatic spacers

The close contact of the two carboxylic acids with the benzene spacer led to some very unusual acidities (ref. 5). The second pKa is > 11, and the ΔpKa (6 units) becomes a measure of the price that is paid to force two negative charges into a small volume of space, particularly if the more basic (ref. 1) syn lone pairs are forced to converge. The instability of the dianion can be used to great advantage because its affinity for alkaline earth ions is large. For example, calcium or magnesium ions are extracted from aqueous solution into chloroform with these diacids, and they can be transported across simple liquid membranes as chelate complexes (ref. 6) (Fig. 5).

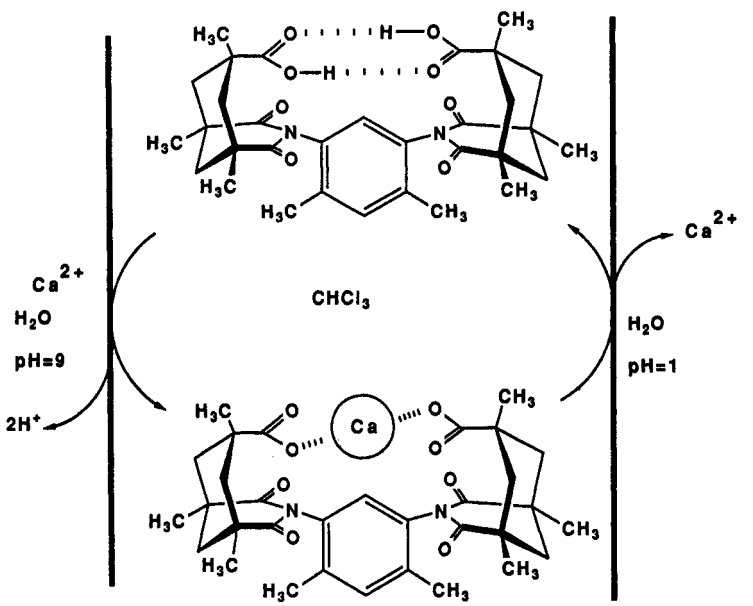
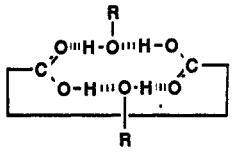


Fig. 5
Calcium transport across liquid membranes

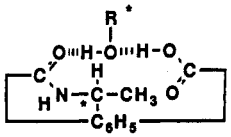
Relative rates:

A-23187 = 1.0
Diacid = 0.7

The mid-size version involving the naphthalene spacer binds tenaciously to small molecules that can transmit the acid/base information of two dicarboxylic acids across the cleft. Both alcohols and amines form 2:1 complexes, whereas diamines and diols form 1:1 complexes (Fig. 6). They have proven quite useful as chiral solvating agents or shift reagents for NMR. The mono functionalized derivative with α-phenyl-ethylamine places an asymmetric center very near the site where a racemic alcohol is bound, and a large effect on the nmr spectra is the result (ref. 7). With conventional chiral acids, the asymmetric center (at the α carbon) would be at some distance from the guest and therefore less effective in creating an anisotropic environment.



Cooperative hydrogen bonding



Asymmetric centers in close contact

Fig. 6

MOLECULAR CHELATION

The acridine spacer offers both rapid accessibility and a larger cleft. As a result, it has occupied most of our attention in this series. Complementary functionality and size was provided by a number of heterocyclic compounds. Diamines express their basicity (lone pairs) in divergent directions and we have worked through the selectivity of such processes with a number of examples (ref. 8) (Fig. 7). Moreover, the strong dipole of the acridine portion provides stacking opportunities for aromatic derivatives and an additional point of binding is provided. Neutral heterocycles are also bound within the cleft. Either the dicarboxylic acid or the corresponding diamide finds suitable hydrogen bonding surfaces with diketopiperazine derivatives. We have explored the promiscuity of this cleft using heterocycles which present a series of different hydrogen bonding patterns.

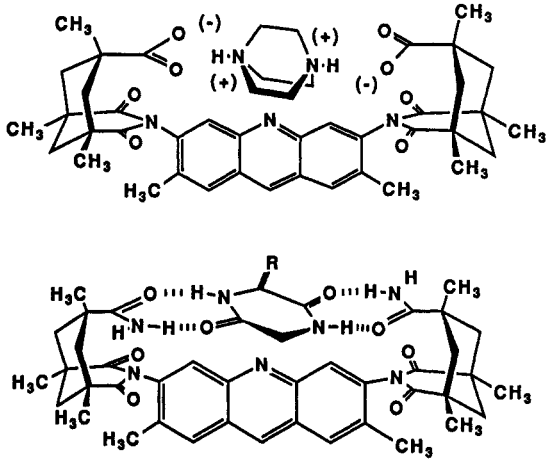


Fig. 7
Molecular chelation of heterocycles using ionic forces and hydrogen bonds

In altering the lining of the cleft for heterocyclic substances, it became apparent that slight modifications could be engineered into the structure that could provide surfaces complementary to nucleotide bases (ref. 9). Accordingly, an imide (Fig. 8) was prepared. It presents hydrogen bonding edges and an aromatic stacking surface which converge from perpendicular directions to create a microenvironment ideal for adenine derivatives. With suitable control systems it is possible to dissect the relative contributions of base-pairing and aromatic stacking in solvents such as $CDCl_3$. By appending two of the units to a single aromatic surface, a molecular chelating agent results. It can interact with adenine in both Watson-Crick and Hoogsteen senses; in addition, it can muster aryl stacking forces. This material provides such a complementary array of hydrogen bonds that is capable of extracting adenine and its derivatives such as adenosine from aqueous solution into an organic solvent! (ref. 10).

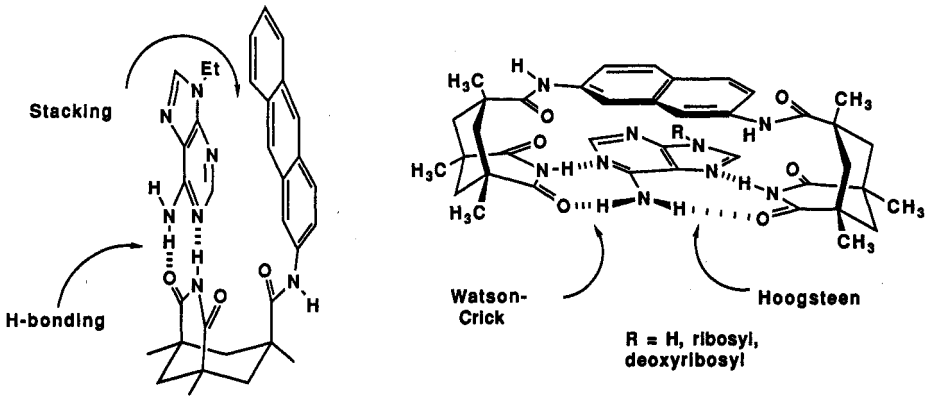


Fig. 8

SIZES AND SHAPES

The number of different shapes available is limited only by the access to spacer elements. For example, tren gives a trisimide. It can act as a molecular "tool chuck" involving three convergent imides. It finds a complement in melamine, for example; slow exchange is observed at room temperature in the nmr spectra and up to 9 hydrogen bonds could be involved (Fig. 9). A tetra aryl porphyrin spacer is also available, due to the highly efficient synthesis of the nucleus described by Lindsey (ref. 11). Here the distance is complementary to 4,4'-bipyridyl and indeed a 2:1 complex is formed with this heterocycle (ref. 12).

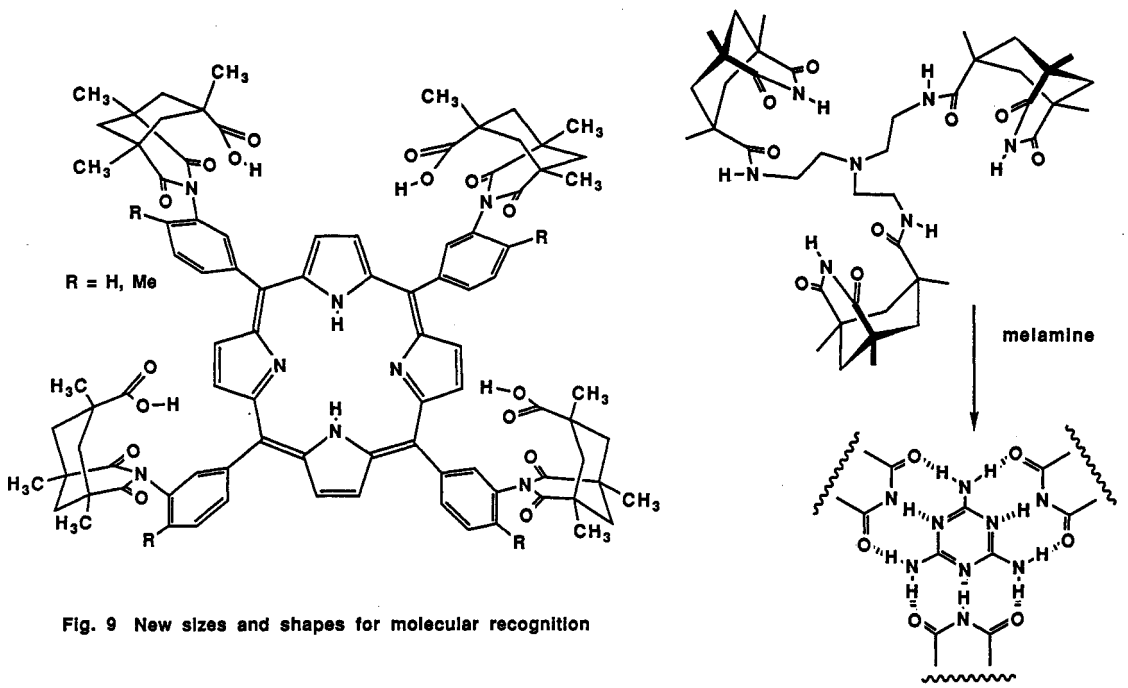


Fig. 9 New sizes and shapes for molecular recognition

Nature's use of weak intermolecular forces, which act only at short distances, leads to high selectivity. This behavior can be profitably imitated in model studies of molecular recognition. For example, by merely reducing the imide function of the adenine receptor with $NaBH_4$, the effective acid-base pattern of hydrogen bonds is altered. Now cytosine derivatives are bound more effectively than adenine derivatives (ref. 13) (Fig. 10).

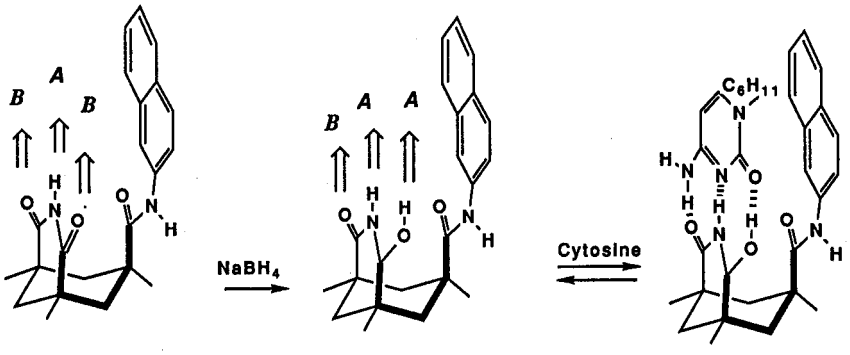


Fig. 10 Binding selectivity is determined by patterns of acids (*A*) and bases (*B*).

Recently, we have brought our experience on adenine recognition to bear on the problem of self-replicating systems, and some progress has been made in this regard. In connecting an adenine to a receptor for adenine, a system that is capable of dimerizing (or polymerizing) is created because it is self-complementary. The monomer, however, is capable of acting as a template for its own construction (Fig 11). Base pairing at both ends brings the reactive centers together and such a system can self-replicate through autocatalysis. Sorting out the kinetic parameters (ref. 14) in systems is not an easy task, but model compounds could be of considerable general use for testing notions in prebiotic chemistry.

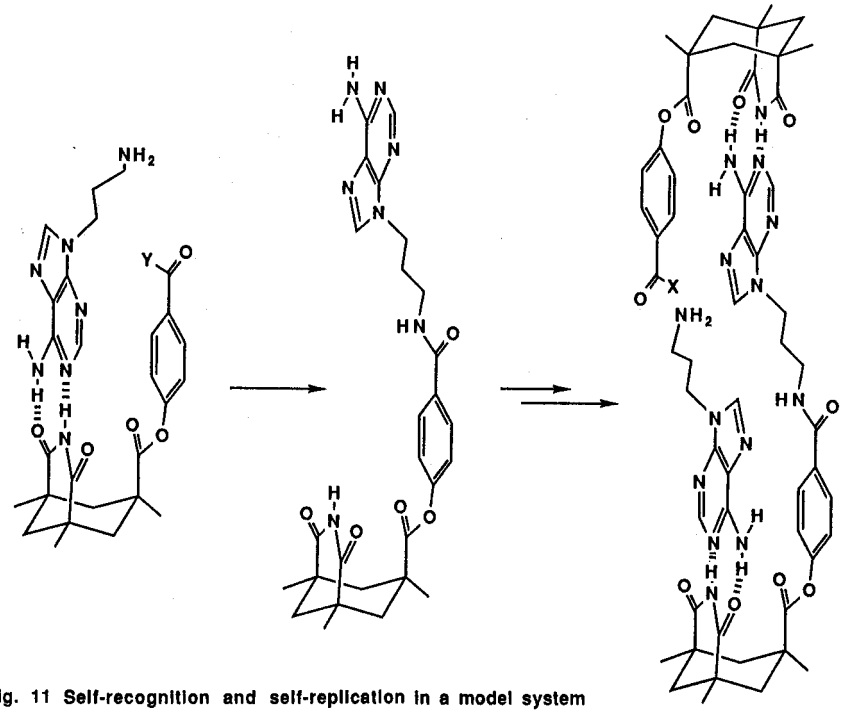


Fig. 11 Self-recognition and self-replication in a model system

CATALYSIS

The moderate directional characteristics of hydrogen bonds can also be used in catalytic settings. The ability to "direct" carboxylic acids and orient them toward other parts of a given structure has now provided cases of intramolecular enolizations (ref. 15) (Fig. 12). The cooperative effects of the imidazole/carboxylate pair, (a system that resembles the active sites of the serine proteases) can also be observed (ref. 16). Both these cases depart from existing models in that the more basic syn lone pairs of the carboxylate are directed toward the reaction partner.

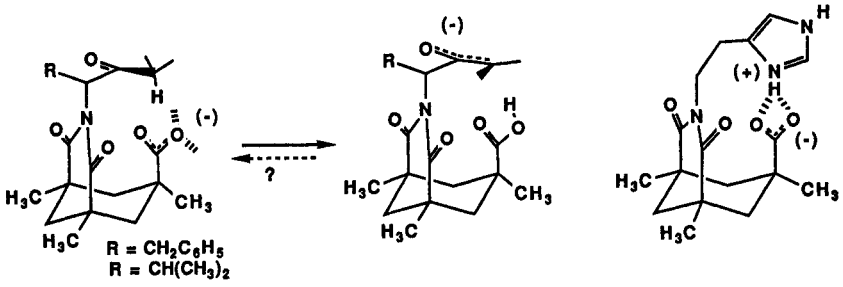


Fig. 12 Intramolecular general base catalysis by carboxylate *Z* lone pairs

A more ambitious undertaking involves the generation of synthetic catalysts. In this context the rigid spacer elements provide the advantage of separating acid base pairs to explore the possibilities of concerted catalysis. With less rigid structures or those that involve divergent functionality, such an arrangement is difficult to achieve. The convergent dicarboxylic acid derived from acridine resembles the active site of lysozyme in structure. It shows an unusual activity for cleavage of certain hemiacetals (ref. 17). Presumably, its functionalities can grasp the substrate yet present acid and base groups poised for what is likely to be concerted catalysis (Fig. 13).

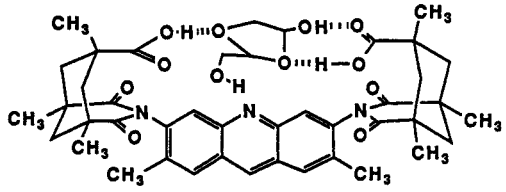


Fig. 13
Catalysis of hemiacetal cleavage by convergent functional groups

With suitable modifications it should be possible to generate stereoelectronically relevant models for other enzyme active sites. The ultimate goal here is the convergence of recognition with catalysis; these events must occur closely together in space and time to model the Pauling principle for enzyme action (ref. 18). We are pursuing this goal and we will report on our progress in due course.

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