Model Studies in Molecular Recognition

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Recognition at the molecular level is a fundamental characteristic of biochemical systems. Recent models developed in bioorganic chemistry have revealed the importance of complementarity in size, shape, and functional groups in molecular recognition. Structures that feature a cleft are particularly effective in regard to complementarity since functional groups attached to the interior of the cleft converge on substrates held inside. The molecular clefts offer the advantage of efficient construction; their surfaces can be tailored for specific applications. This article describes their use for recognition of acids, bases, amino acids, metal ions, and neutral substrates. Their ability to provide microenvironments complementary to asymmetric molecules and their future promise are discussed.

ONE ASPECT OF BIOORGANIC CHEMISTRY IS THE DEVELOPment of models for biochemical systems. Catalysis, regulation, transport, and recognition are examples of phenomena that were recently assumed to require structures the size of biological macromolecules. New developments have led to a belief that such processes can occur in much smaller molecules that are synthetically accessible. This has inspired the activity in developing model systems (*1*). The difficulty has been in determining what structural features are responsible for a given process. Even without a unified picture of this relation between structure and function, a number of models have successfully shown how binding forces can increase rates for catalysis (*2*) and can generate allosteric effects for regulation (*3*). In this article I examine the use of model systems in exploring the principles of molecular recognition.

Molecular Shape, Size, and Surface

Large ring (macrocyclic) compounds are the dominant structures of bioorganic chemistry; trends in molecular recognition have also been much influenced by molecules of this type. Cyclodextrins, cyclophanes, and crown ethers are readily available, and they share the advantage that their interactions with smaller structures are easily conceptualized; recognition involves the filling of pockets or holes. Cyclodextrins **1** are particularly well suited for this purpose. These naturally occurring structures are rigid and bucket-shaped, and have hydrophobic interiors and hydrophilic exteriors that provide a place for organic molecules to "keep dry" in aqueous solution (*4*). The cyclodextrins recognize complementary surfaces (rather than functional groups) and a range of structures; molecules such as phenyls, adamantanes, and ferrocenes provide a complementary outer surface (*4*).

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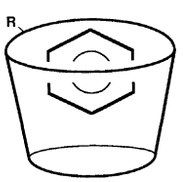
Cyclophanes **2** have similar overall shapes, but synthetic methods now make it possible to adjust the size and solubility of these molecules. In addition to hydrophobic binding, stacking interactions between aromatic subunits in the cyclophane and the substrate provide some directionality to the binding forces; the structures of the complexes are more rigid than those of cyclodextrins (*5*). Crown ethers **3** act almost exclusively on ionic substrates. Their selectivity



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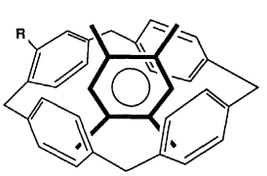
Cyclodextrin-benzene complex



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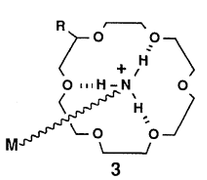
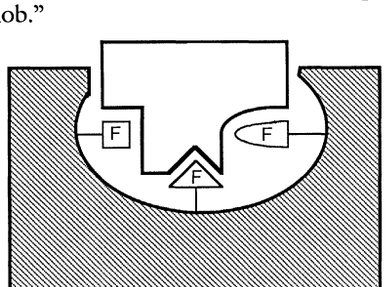
Cyclophane-durene complex



3

Crown ether ammonium complex

for spherical metal ions has been highly refined (*6*); at the molecular level, binding generally involves a primary ammonium function (*7*) so that recognition of molecules bears on the presence of this functional "knob."



Functional groups converge to create an active site.

4

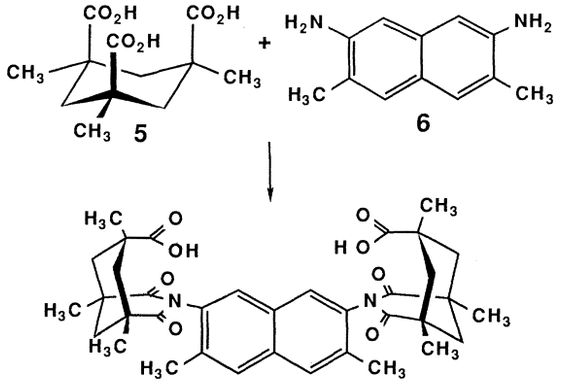
Functional Groups

The disadvantage common to macrocyclic molecules is that their structure causes problems in producing favorable interactions between functional groups on the substrate and the macrocycle once the complex is formed. Functional groups attached to macrocycles (R in **1**, **2**, and **3**) tend to diverge or become directed away from the cavity and from the substrates that are held inside (*8*). In contrast, functional groups on receptors such as enzymes or antibodies tend to converge (as in **4**) and act as an integral part of the active site.

This focusing of functional groups leads to the recognition of molecules that bear complementary functionality. The general shape of these naturally occurring receptors often features a molecular cleft. The characteristic of convergent functional groups has now been incorporated into synthetic structures. This aspect is the key to their success in molecular recognition; the principle involved is that effective identification requires surfaces of complementary size, shape, and functionality.

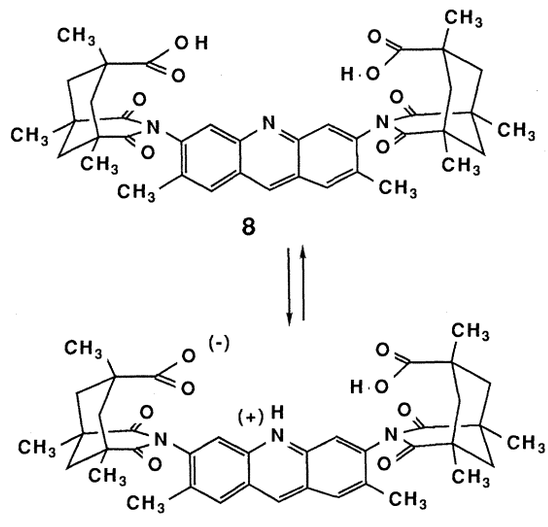
Construction of Molecular Clefts

The structural elements for the synthetic molecular clefts were provided by the triacid (*9*) **5** in which any two carboxyl groups connect to form a U-shaped structure and spacer units such as the substituted naphthalene **6**. Condensation of the two components yielded the molecular cleft **7**. The carboxyl groups are forced to converge because of interactions with the seemingly passive methyl groups. The aromatic methyl groups present a steric barrier to rotation about the C_{aryl}–N bond; the aliphatic methyls prevent epimerization of the carboxyl functions (*10*). The space between opposing carboxyl oxygens of **7** is 5.8 Å wide as determined from a crystallographic study of the monosodium salt.



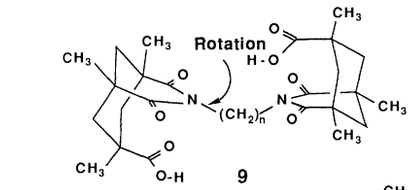
5 **6** **7**

A larger version of the cleft was quickly assembled from a similar condensation that involves acridine yellow, an inexpensive dye. The product **8** features an 8- to 9-Å distance between opposing oxygen atoms and includes an additional functional group, the lone pair of the acridine nitrogen, which emerges from the bottom of the cleft. In polar solvents the zwitterionic form **8a** is the dominant species; the cleft becomes a highly polar microenvironment. In contrast, the exterior of the molecule is a lipophilic domain that abounds with C–H bonds. The acridine spacer group presents a large, flat π-bonded surface. These domains give **8** unprecedented properties, such as the ability to transport amino acids in their zwitterionic forms (*11*).



8 ⇌ **8a**

The two structures derived from the naphthalene and acridine spacers illustrate a general problem encountered with small molecules: the opportunity for the model builder to fine-tune the structure is limited. For this case, the limit is represented by the width of a benzene ring (~2.5 Å). Spacer groups larger than naphthalene but smaller than acridine exist, but these require extensive synthetic efforts and such structures as biphenylene, for example, still lack the continuity that would be desired for increments on the order of 0.5 Å. The other extreme, which involves continuous changes in geometry, is available from freely rotating systems such as the diacids **9**, which are derived from α,ω diamines. These are also readily prepared from the condensation reactions that involve the triacid and the open-chained diamines of varying length (*12*). In such molecules, an entropic price is paid for this continuity in structure, since the probability of any one conformation is low.



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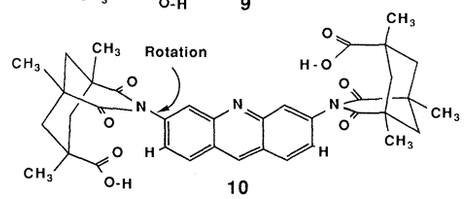

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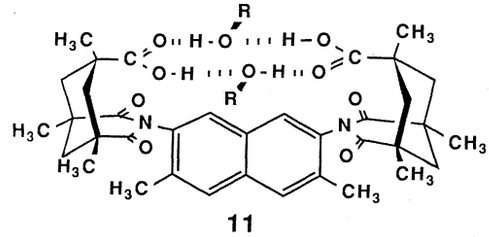
The optimal degree of rigidity for model receptors is not easily predicted. It is rare and fortunate when an exquisite fit is found between substrate and receptor. In those cases rigidity or preorganization is desirable for entropic reasons (*13*). More often, high rigidity presents an all-or-nothing situation; some flexibility is desirable, since it permits adjustment of conformation. The analogy in enzymology is a substrate-induced fit; catalytic turnover especially requires some flexibility, because complexation of substrate, binding to transition states and intermediates, and product release all must be accommodated. For natural receptors, some gross structural change is likely on complexation, because these changes economically transmit information. The high selectivity in antibodies suggests a fairly rigid binding site. Within the series of molecular clefts that have been prepared an intermediate degree of flexibility is represented by **10**. In this structure, rotation about the C_{aryl}–N_{imide} bond is rapid at ambient temperature. This permits a number of energetically reasonable conformations that are inaccessible to the locked version **8**.

Binding Forces and Selectivity

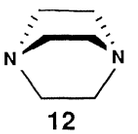
In **7** or **8**, the two acidic groups are unable to form intramolecular hydrogen bonds. Steric effects hinder the formation of the dimers and chain structures that characterize intermolecular hydrogen bonding of carboxylic acids. Yet these functions are available to other hydrogen-bond donor-acceptor pairs; smaller molecules that are able to bridge the gap are bound tenaciously (*14*). For example, two molecules of isopropanol were bound by **7** in the solid state. Each alcohol molecule could provide a set of complementary



11

hydrogen bonds, as shown in **11**. With amines, a 2:1 stoichiometry was also observed in binding; with 1,2 diamines, β-aminoalcohols, or vicinal diols such as dimethyl tartrate, 1:1 complexation occurred. The carboxyl groups of this system present an ideal microenvironment for the formation of "cooperative" hydrogen bonds (*15*), a situation that is a specific consequence of the convergence of functional groups in the molecule.

The larger cleft of the acridine **8** offered sufficient space for a number of substrates. With diamines of complementary size and shape, molecular chelation resulted. Heterocyclic diamines could be used as substrates; equilibrium association constants (K_a) revealed a number of binding modes within the cleft (*16*). With relatively strong bases such as diazabicyclooctane **12**, proton transfer occurred and ionic forces contributed to binding as in **13**. Association constants K_a were $\sim 10^5\ M^{-1}$ and activation barriers $\Delta G_c\ddagger$ for exchange were about 11 kcal/mol. The monocyclic **14** was much less



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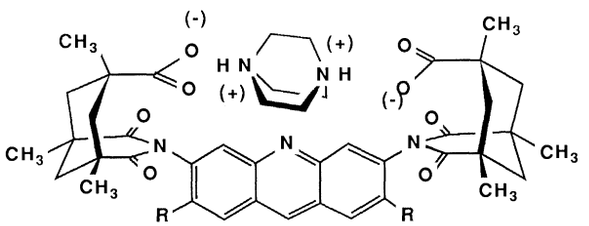

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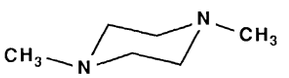
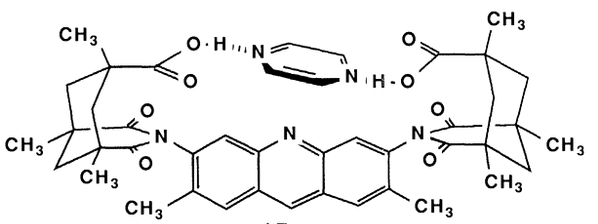


14

efficiently bound because the *N*-methyl groups could not be accommodated within the cleft. Weak bases such as pyrazine were bound less tightly ($K_a = 10^3$), but mere basicity is not the only consideration. Pyrazine formed a complex **15** about ten times as strong as the one formed by the stronger base pyridine.



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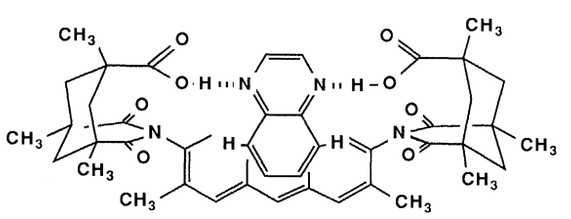
Additional binding could be observed when stacking interactions were possible. For example, quinoxaline, a structure of comparable basicity to pyrazine, was bound about 20 times as tightly. The overlap of aromatic surfaces is indicated in complex **16**. Such

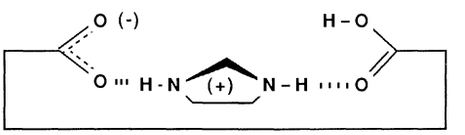


16

stacking interactions can be observed in organic solutions ($CDCl_3$) and are independent of the hydrophobic binding that is frequently involved when such stacking occurs in water (*17*).

Cooperative hydrogen bonding can also occur in the interaction of imidazole to **8**. This base accepts a proton to form an initial 1:1 complex **17** ($K_{a1} = 10^6$), in which the carboxylate becomes a better lone pair donor and the carboxylic acid that remains becomes a better hydrogen donor. A second imidazole can be bound, despite the formation of unfavorable charge-charge interactions in **18**.

Imidazole complexes



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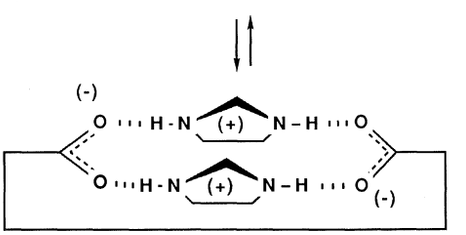
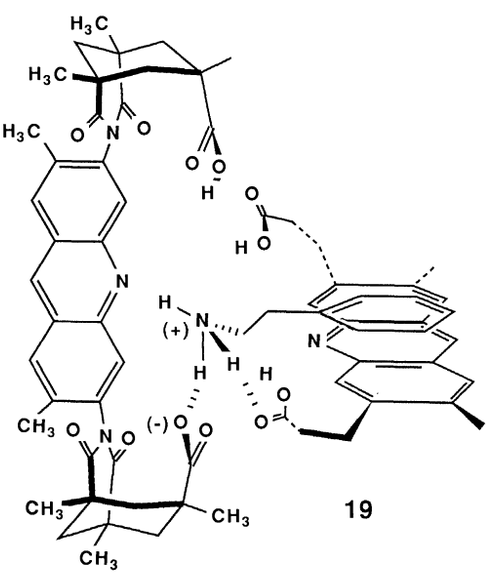


18

A combination of ionic and stacking interactions resulted in the highly selective binding of **8** to the physiologically important β-arylethylamines. In such binding a number of stoichiometries were observed, such as 2:1, 1:1, and 1:2. The ternary complexes **19** showed large association constants ($K_a \sim 10^7\ M^{-2}$ liter^{-2}). Specific recognition was observed of dopamine, tryptamine, and other structures that bear the β-arylethylamine functions, for example, **20**. In contrast, neither the γ-phenyl-propylamine **21a** nor the δ-phenyl-butylamine **21b** formed stacks or ternary complexes with **8**. The distance between the carboxyl functions of **8** and its stacking surface is similar to that in a recent model proposed for central nervous system receptors for these amines (*18*).



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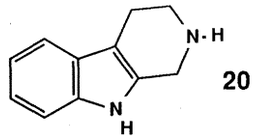
The construction of receptors for certain amines is particularly simple, since some amines can act as templates for themselves. For example, the triamine **22** condensed with the triacid to form a new



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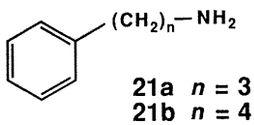
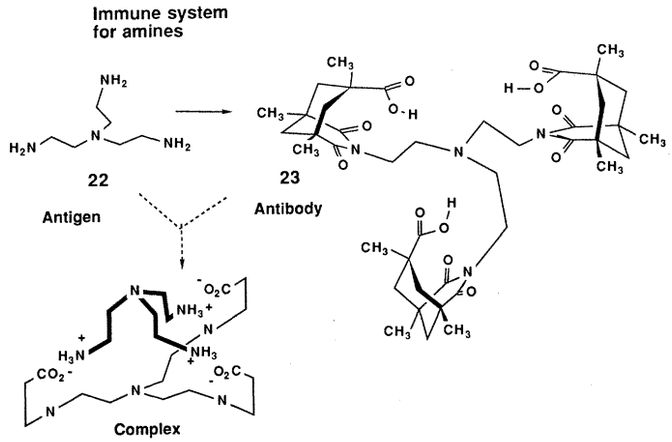
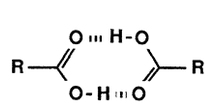


21a $n = 3$
21b $n = 4$

triacid **23**. In a single step **22** was converted into a molecule that was complementary in shape, size, and functionality to the original molecule. A stoichiometric complex was in fact formed between **22** and **23**. In biochemical terms, the amine acted as an antigen and provided the parent skeleton for the construction of its own antibody. This sequence is similar to that in an actual immune system.



Carboxylic acids are also known to recognize themselves, but in the form of cyclic hydrogen-bonded dimers **24** (the ideal complement for a carboxylate is an amidinium or guanidinium ion as in **25**). In the molecular clefts the formation of intramolecular hydro-



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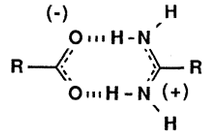

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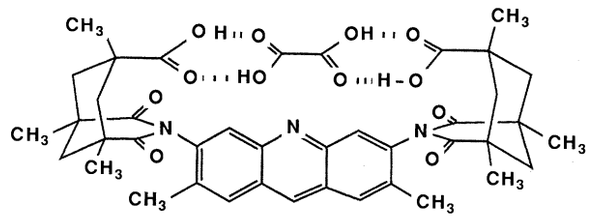
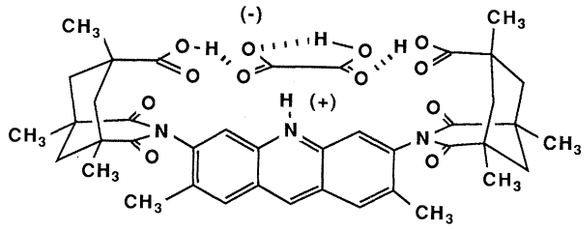
gen bonds between acids is prevented by the rigid aromatic spacers, yet these functions are poised for intermolecular bonding to appropriate dicarboxylic acids. Stoichiometric complexes were formed by **8** with diacids of complementary size, shape, and pK_a. Spectroscopic evidence favored structures such as **26a** or **26b** for the complex with oxalic acid (*19*). Binding measurements revealed another feature of the unusually polar microenvironment within the cleft. Malonic and oxalic acids appeared to be stronger acids than picric acid when in contact with **8** in a $CDCl_3$ solution. This represented a reversal of the usual order of acidity and probably arose from the specific stabilization provided by the receptor to the conjugate base of malonic or oxalic acid. Such changes in apparent pK_a values were observed in the interaction of carboxylic acids with macrocyclic polyamine ligands (*20*) and may also have been a factor in the low pK_a value of acids found at the active sites of enzymes, such as the serine and aspartic proteinases.

Nowhere has the combination of chemical environments of **8** been more influential than in its interaction with amino acids. The



26a



26b

polar cleft, the aromatic surface, and the lipophilic coating were uniquely complementary to those amino acids that bear aromatic side chains. As with other β-arylethylamines, ternary complexes were formed, but the solubility characteristics permitted **8** to extract these amino acids in their zwitterionic forms from water into chloroform (*12*). Although the structure of the complex awaits crystallographic determination, spectroscopic studies again indicated extensive aryl-aryl stacking within these complexes. This interaction allowed the selective transport of aromatic amino acids across a liquid membrane. The flux of amino acids through $CHCl_3$ with **8** as the carrier between neutral water phases is reported in Table 1 (*21*). Specific recognition of the aromatic nucleus and its position in the side chain can be inferred from these data.

For comparison, transport with the cationic detergent Aliquat 366 (methyl tricapryl ammonium hydroxide) at $pH = 13$ is also shown. With such carriers only the anionic forms of the amino acids were transported; the intrinsic lipophilicity of the amino acid side chains largely determined the relative rates (*22*). Similar trends were observed with crown ethers as carriers; these operated at low pH and transported the protonated forms of amino acids or their esters (*23*).

Neutral Substrates

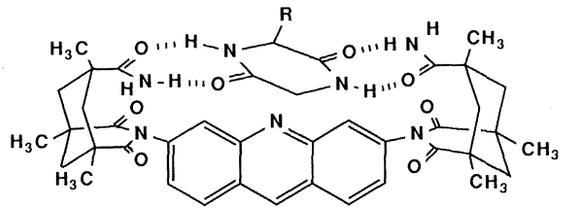
Unlike the situation with acid or basic substrates, where proton transfer contributes to recognition by the model receptor, binding to lactams involves hydrogen bonding exclusively. Recent discussions (*24*) have emphasized that hydrogen bonds are not so much created as they are merely exchanged in aqueous solution; accordingly, overall enthalpic changes are modest. For binding to **8**, complementary amide components were limited to primary amides or lactams, which are functional groups that exhibit high affinity for water, particularly at their oxygen atoms (*25*).

Not surprisingly, the diacid **8** and its diamide were "waterlogged"

Table 1. Transport of amino acids. Transport rates are in millimoles transported per hour per square centimeter per mole of carrier.

Carrier	Amino acid				
	Phenyl-alanine	Trypto-phane	Leucine	Tyrosine–methyl ether	γ-Phenyl-butyrine
8	8.5	42	<0.1	18	0.2
Aliquat 366	7	6.7	3.5		

with two to four molecules of water that were difficult to liberate. Binding experiments in $CHCl_3$, a noncompeting solvent, revealed that stoichiometric complexes were formed with diketopiperazines **27** ($K_a \sim 10^4$) and amides such as malonamide. With structures of inadequate hydrogen bonding capacity, for example, sarcosine anhydride, complexation did not occur (*14*).



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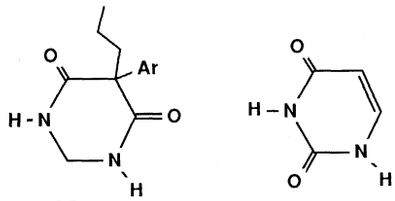
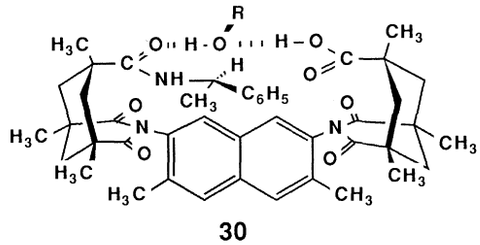


28 **29**

Slight changes of geometry in the substrate were also accommodated by **8**. For example, primidone **28** formed 1:1 complexes, but only traces of uracil **29** were bound within the cleft. These results provide a measure of the selectivity of these receptors. The carboxyls of **8** have sufficient in-plane flexibility to "stagger," as required for diketopiperazines, or to bend, as required for primidone. Such motions are only necessary for idealized linear hydrogen bonds. The failure of uracil to bind may be due to the closer distance needed between the carboxyl groups and the increased bending that this geometry required for hydrogen bonding.

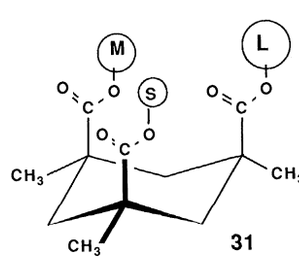
Asymmetric Microenvironments

The advantages offered by hydrogen bonds and their modest directional characteristics are apparent in the recognition of asymmetric centers within these clefts. The optically active monoamide **30** presents an asymmetric microenvironment between the hydrogen bond donor and acceptor. In the presence of racemic amines or alcohols, **30** acts as a chiral solvating agent (*26*), and its efficacy can be attributed to the optimal placement of the asymmetric center near the site of hydrogen bonding (*14*).



30

A chiral cavity that could recognize single asymmetric centers in general would be quite useful. In modern organic synthesis a number of reagents that feature C_2 symmetry have been developed (*27*). These shapes are very successful in distinguishing between the two sides of a π system. They offer no obvious advantages for the interaction with a chiral center. For this purpose, three domains appear better suited for recognition than the two inherent in structures with C_2 axes. Accordingly, we used the three carboxyls of the triacid to partition one face of the structure into large, medium, and small spaces, as in **31**. The acid ester amide **32** acted as a spectroscopic probe for racemic amines (*28*). A number of amino acid derivatives of the triacid can be envisioned for multiple-site recognition of target structures.



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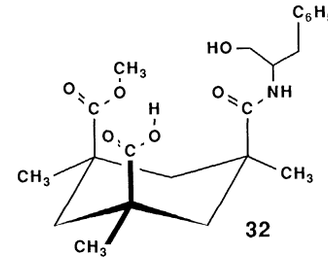

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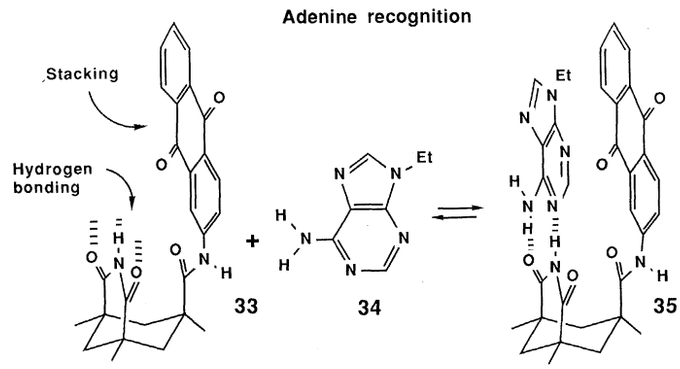
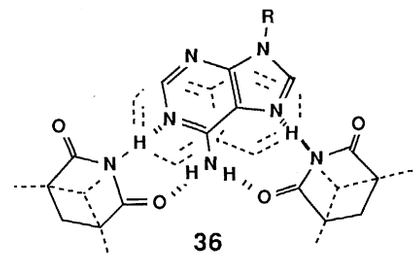
Edges and Planes

The classical form of molecular recognition is the base-pairing of purines and pyrimidines in nucleic acids. In addition to the hydrogen bonding (*29*) that characterizes the Watson-Crick pairs, stacking interactions (*30*) also stabilize the double helix (*31*). Receptors have been modified to provide a molecular surface on which both forces can be simultaneously evaluated (*32*). Structures such as **33** provide an edge for hydrogen bonding and an aromatic plane for stacking interactions. These binding forces converge from perpendicular directions and present a surface complementary to bases such as adenine.



33 **34** **35**

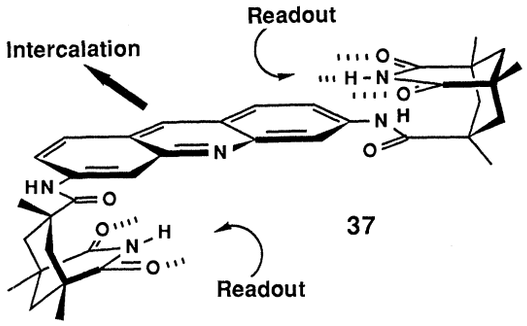
Adenine derivatives such as the 9-ethyl compound **34** were bound in $CDCl_3$ by hydrogen bonding to the imide function and by stacking on the aromatic surface. A second generation of these structures is now available and shows binding to the adenine derivative in a chelating sense that involves both Watson-Crick and Hoogsteen geometries (*30*), as sketched in **36**. The goal is to create



36

reagents that permit predictable, sequence-specific binding to intact double-stranded nucleic acids (*33*). One approach involves the development of layered systems such as **37**. The ability of acridines to intercalate can provide the driving force for association to the nucleic acid; the hydrogen bonding edges are poised to "read out" information above and below the intercalation plane. To do so with

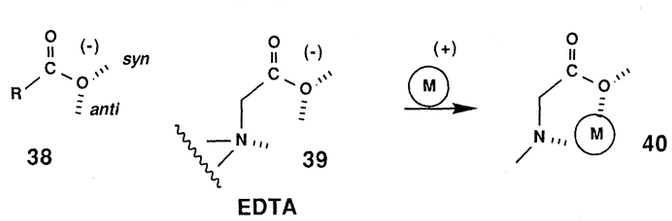
some specificity, the imide function must be tailored to provide hydrogen bond donors and acceptors complementary to the functions exposed by intact base pairs in the major or minor grooves.



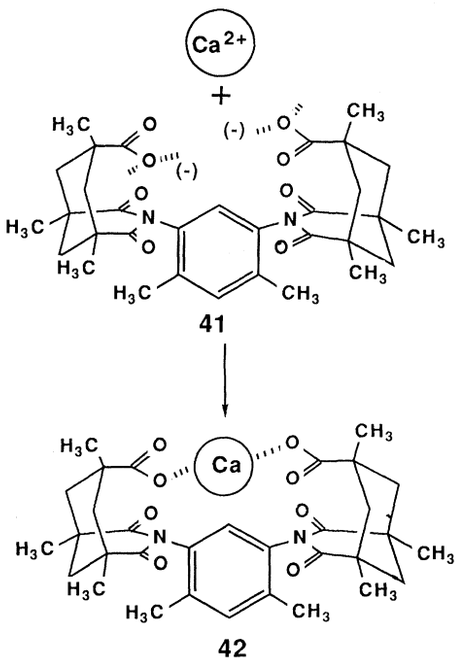
37

Metal Chelation

The development of selective sequestering agents for metal ions has been a long-standing pursuit of inorganic coordination chemists. Many of the successful chelating agents such as EDTA involve carboxylate functions as ligands. Recent discussions (*34*) of stereoelectronic effects at the carboxyl oxygen emphasized the difference in the basicity of the in-plane lone pairs **38**; evidence suggests that the *syn* lone pair is the stronger base. The classic carboxyl chelates, however, are constrained by their molecular shapes to have the less basic *anti* lone pairs in contact with the metal ion (39 →40).



The structures that have convergent carboxyls are not subject to these limitations. For example, dianions such as **41** present an ideal



41

42

microenvironment for divalent metal ions. Titrations of the corresponding diacids showed large ΔpK_a values (about 6) (*35*). Such structures had extremely high affinity for alkaline earth ions such as Ca^{2+} and Mg^{2+}. Again, the lipophilic skeletons of these molecules permitted the facile extraction and transport of Ca^{2+} from aqueous solution through organic liquid membranes (*36*). It appears that even spherical ions respond to the viselike shape of these molecular clefts.

Conclusions

This article has emphasized the importance of complementary size, shape, and functionality in molecular recognition. The advantages of convergent functional groups in the design of model receptors has been highlighted. It seems reasonable that clefts could now be designed and efficiently assembled to recognize almost any small molecule or ion. Larger substrates such as carbohydrates, peptides, and nucleotides are likely future targets for recognition. The construction of complementary functionality has been inspired by the recent development of stereoelectronic effects in organic chemistry. Even so, these notions were anticipated nearly 40 years ago by Pauling (*37*), who suggested that the active sites of enzymes involved structures that are complementary to transition states.

REFERENCES AND NOTES

1. R. Breslow, *Science* **218**, 532 (1982); R. C. Hayward, *Chem. Soc. Rev.* **1983**, 285 (1983); F. Vogtle, H.-G. Lohr, J. Franke, D. Worsch, *Angew. Chem. Int. Ed. Engl.* **24**, 727 (1985); D. J. Cram, *Science* **219**, 1177 (1983); J. P. Collman *et al.*, *J. Am. Chem. Soc.* **107**, 2000 (1985); J.-M. Lehn, *Science* **227**, 849 (1985); J. Rebek, Jr., *Acc. Chem. Res.* **17**, 258 (1984).
2. R. Breslow, M. F. Czarniecki, J. Emert, H. Hamaguchi, *J. Am. Chem. Soc.* **102**, 762 (1980); D. J. Cram and H. E. Katz, *ibid.* **105**, 135 (1983); J. Rebek, Jr., T. Costello, R. Wattley, *ibid.* **107**, 487 (1985).
3. J. Rebek, Jr., *et al.*, *ibid.* **107**, 7481 (1985); I. Tabushi, S. Kugimiya, M. Kinnaird, T. Sasaki, *ibid.*, p. 4192.
4. M. L. Bender and M. Komiyama, *Cyclodextrin Chemistry* (Springer-Verlag, New York, 1978); G. Trainor and R. Breslow, *J. Am. Chem. Soc.* **103**, 154 (1981).
5. H. Setter and E.-E. Ross, *Chem. Ber.* **88**, 1390 (1955); *ibid.*, p. 1395; K. Odashima, A. Itai, Y. Iitaka, K. Koga, *J. Am. Chem. Soc.* **102**, 2504 (1980); S. P. Miller and H. W. Whitlock, Jr., *ibid.* **106**, 1492 (1984); J. Winkler, E. Coutouli-Argyropopoulou, R. Leppkes, R. Breslow, *ibid.* **105**, 7198 (1983); F. Diederich and D. Griebel, *ibid.* **106**, 8037 (1984); C. D. Gutsche, *Acc. Chem. Res.* **16**, 161 (1983).
6. For leading references see: R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, J. Christensen, *Chem. Rev.* **85**, 271 (1985); D. J. Cram and S. P. Ho, *J. Am. Chem. Soc.* **108**, 2998 (1986). For recognition of anions, see F. P. Schmidtchen and G. Muller, *Chem. Commun.* **1984**, 1115 (1984).
7. J.-P. Behr, J.-M. Lehn, P. Vierling, *Helv. Chim. Acta* **182**, 1853 (1982).
8. See, for example, D. J. Cram, P. Y.-S. Lam, S. P. Ho, *J. Am. Chem. Soc.* **108**, 839 (1986).
9. D. S. Kemp and K. S. Petrakis, *J. Org. Chem.* **46**, 514 (1981).
10. J. Rebek, Jr., *et al.*, *J. Am. Chem. Soc.* **107**, 7476 (1985).
11. J. Rebek, Jr., and D. Nemeth, *ibid.*, p. 6738.
12. B. Askew, G. Russo, K. Williams, T. Tjivikua, unpublished results.
13. S. P. Artz and D. J. Cram, *J. Am. Chem. Soc.* **106**, 2160 (1984); D. J. Cram *et al.*, *ibid.* **107**, 3645 (1985); R. Breslow, *Isr. J. Chem.* **18**, 187 (1979); W. L. Mock and N.-Y. Shih, *J. Org. Chem.* **51**, 4440 (1986).
14. J. Rebek, Jr., *et al.*, *J. Am. Chem. Soc.* **107**, 6736 (1985).
15. G. A. Jeffrey and S. Takasi, *Acc. Chem. Res.* **11**, 264 (1978).
16. J. Rebek, Jr., and D. Nemeth, *J. Am. Chem. Soc.* **108**, 5637 (1986).
17. For a recent study in organic solvents, see F. Diederich, K. Dick, D. Griebel, *ibid.*, p. 2273.
18. E. J. Lloyd and P. J. Andrews, *J. Med. Chem.* **29**, 453 (1986) and references therein.
19. J. Rebek, Jr., D. Nemeth, F.-T. Lin, *J. Am. Chem. Soc.*, in press.
20. E. Kimura and A. Sakonaka, *ibid.* **104**, 4984 (1982). For other studies of selective binding of carboxylic acids, see R. Breslow, R. Rajagopalan, J. Schwartz, *ibid.* **103**, 2905 (1981); M. W. Hosseini and J. M. Lehn, *ibid.* **104**, 3525 (1982).
21. J. Rebek, Jr., B. Askew, D. Nemeth, K. Parris, *ibid.*, in press.
22. J.-P. Behr and J. M. Lehn, *ibid.* **95**, 6108 (1973); H. Tsakube, *Tetrahedron Lett.* **22**, 3981 (1981).
23. M. Newcomb, J. L. Toner, C. Helgeson, D. J. Cram, *J. Am. Chem. Soc.* **101**, 4441 (1979).
24. For a discussion, see A. R. Fersht *et al.*, *Nature (London)* **314**, 235 (1985); N. Stahl and W. P. Jencks, *J. Am. Chem. Soc.* **108**, 4196 (1986).
25. R. Wolfenden, P. M. Anderson, P. M. Cullis, C. C. B. Southgate, *Biochemistry* **20**, 849 (1981).
26. G. R. Weisman in *Asymmetric Synthesis*, J. D. Morrison, Ed. (Academic Press, New York, 1983), vol. 1, chap. 8.

27. H. B. Kagan, *ibid.*, vol. 5, chap. 1; M. G. Finn and K. B. Sharpless, *ibid.*, chap. 8; H. B. Kagan and T. P. Dang, *J. Am. Chem. Soc.* **94**, 6429 (1972); S. Masamune, B. M. Kim, J. S. Petersen, T. Sato, S. Veenstra, *ibid.* **107**, 4549 (1985); R. Noyori *et al.*, *ibid.* **102**, 7932 (1980); R. Noyori, *Pure Appl. Chem.* **53**, 2315 (1980). For asymmetric recognition in chromatography and its origins in multisite binding, see W. H. Pirkle and J. C. Pochapsky, *J. Am. Chem. Soc.* **108**, 5627 (1986).
28. B. Askew, unpublished results.
29. Y. Kyogoku, R. G. Lord, A. Rich, *Proc. Natl. Acad. Sci. U.S.A.* **57**, 250 (1967).
30. S. I. Chan, M. P. Schweitzer, P. O. P. Tso, G. K. Helmkamp, *J. Am. Chem. Soc.* **86**, 4182 (1964); M. P. Schweitzer, S. I. Chan, P. O. P. Tso, *ibid.* **87**, 5241 (1965).
31. W. Saenger, *Principles of Nucleic Acid Structure* (Springer-Verlag, New York, 1984), chap. 6.
32. C. Buhr, D. Nemeth, S. Jones, unpublished results.
33. For a recent review, see P. B. Dervan, *Science* **232**, 464 (1986).
34. R. Gandour, *Bioorg. Chem.* **10**, 169 (1981).
35. J. Rebek, Jr., R. J. Duff, W. E. Gordon, K. Parris, *J. Am. Chem. Soc.* **108**, 6068 (1986).
36. L. Marshall and S. Luis, unpublished results.
37. L. Pauling, *Nature (London)* **161**, 707 (1948).
38. I thank my co-workers for their contributions: B. Askew, P. Ballester, C. Buhr, T. Costello, A. Costero, M. Doa, R. Duff, P. Gil, W. Gordon, N. Islam, S. Jones, M. Killoran, S. Luis, L. Marshall, J. McManis, D. Nemeth, K. Parris, G. Russo, Tj. Tjivikua, K. Williams, R. Wolak. The National Institutes of Health and the National Science Foundation provided funds for the synthesis and studies of molecular recognition; Year Laboratories supported the metal chelation studies. The J. S. Guggenheim Foundation provided a fellowship to me. I thank W. C. Still for the color photograph of the calculated molecular structure which appears on the cover of this issue.