Design of Complexes between Synthetic Hosts and Organic Guests[1]

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The inspiration for the work described here comes from the hypothesis that highly selective molecular complexation between organic compounds must have played a central role in the molecular evolution of biological systems. The molecular basis for the natural selection of the species depends directly on selection of partners in molecular complexation based on structural recognition. Selective molecular complexation of ground states, transition states, and excited states depends on complementary placement of binding sites and steric barriers in the partners of a complex. One of the partners is usually an enzyme, a nucleic acid, or an antibody organized by covalent bonds into an array of binding and (or) catalytic sites that converge on a crevice or cavity. The second partner is a substrate, inhibitor, cofactor, or antigen whose binding sites are divergently arranged to fit that cavity. Inspired by the wonders of molecular evolution, the synthetic organic chemist has prepared many substrates and inhibitors having molecular weights of 150 to 400. These synthetic endeavors culminate in compounds that either pass or fail biological tests.

A newer field is emerging in which modifications of biological testing systems themselves are developed. Enzymes and coenzymes are being structurally changed and attached to solid supports to perform tasks set by the investigator.[2] Cyclodextrins are being modified so that they not only complex but also catalyze.[3] Gene synthesis[4] makes possible rational gene modification.

If selection in molecular complexation is a central feature of molecular evolution, the subject is worthy of extensive study by the organic chemist in completely synthetic systems. We call the synthesis and study of highly structured organic molecular complexes the field of host–guest chemistry.[5] A molecular complex is composed of at least one host and one guest component. The host is an organic molecule or ion whose *binding sites converge*. The guest is an organic molecule or ion, or a metal ion, whose *binding sites diverge*. In order to complex, a host and guest must possess a complementary stereoelectronic arrangement of binding sites and steric barriers. Since bonds, and thus binding sites, in guests diverge from central nuclei, location of the divergent binding sites presents little synthetic problem. Location of convergent binding sites, however, involves molecular organization of a support structure. Consequently, hosts tend to be larger and more complicated than guests, although either hosts or guests can be enlarged indefinitely by their covalent attachments to parts which are not involved in their binding. In general, guests are abundant, whereas hosts must be designed and synthesized. The biological counterpart of a host is an enzyme, a nucleic acid, or an antibody; that of a guest is a substrate, inhibitor, cofactor, or antigen.

The complexes of host–guest chemistry are held together in unique structural relationships by electrostatic forces other than those of full covalent bonds. The forces are of a pole–pole, pole–dipole, or dipole–dipole variety. More specifically, the components of a complex are bound together by hydrogen bonds, by ion pairs, by π-acid to π-base attractions, by metal-to-ligand associations, by van der Waals attractive forces, by surrounding solvent restructuring, or by partially made and broken covalent bonds (transition states). In ground-state complexation of organic compounds, high structural organization is usually produced only through multiple site binding. In the complexation of transition states, covalent bonds are being made and broken, and, therefore, the low geometric tolerances of covalency supplement the organizing features of the other types of binding. Host chemistry that involves crown ethers[6] or cryptands[7] that bind metal ions has already been reviewed.

Examples of Different Kinds of Complexes between Organic Hosts and Guests

Most naturally occurring host compounds are condensation polymers of α-amino acids, phosphoric acid, and nucleoside, or of glucose (e.g., the cyclodextrins).[3] The earliest synthetic host compounds investigated are the crown ethers of Pedersen,[8] which are formally

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(2) For example, G. M. Whitesides and A. Hirotoshi Nishikawa, "Affinity Chromatography", and K. Mosbach, "Immobilized Enzymes and Coenzymes", in "Applications of Biochemical Systems in Organic Chemistry", J. B. Jones, C. J. Sih and D. Perlman, Ed., Wiley-Interscience, 1976, Chapters VIII and IX, respectively.

(3) D. W. Griffiths and M. L. Bender, *Adv. Catal.*, 23, 209 (1973).

(4) R. Belegaje, E. L. Brown, H.-J. Fritz, M. J. Gait, R. G. Lees, K. E. Norris, T. Seikya, R. Contreras, H. Cupper, and H. G. Khorana, 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Sept 1976, Abstract CARB-12.

(5) D. J. Cram and J. M. Cram, *Science*, 183, 803 (1974).

(6) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, 11, 16 (1972).

(7) J.-M. Lehn, *Structure Bonding*, 16, 1 (1973).

(8) C. J. Pedersen, *J. Am. Chem. Soc.*, 89, 2495, 7017 (1967).

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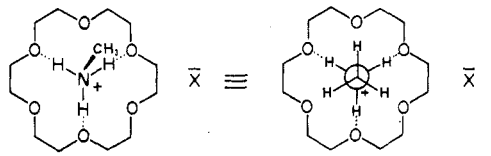
addition polymers of ethylene oxide[9] or copolymers of ethylene oxide and benzene oxides.[8]

The most studied organic-to-organic complexes are those between the macrocyclic polyethers as hosts and salts of primary amines as guests. **1** represents a Co-

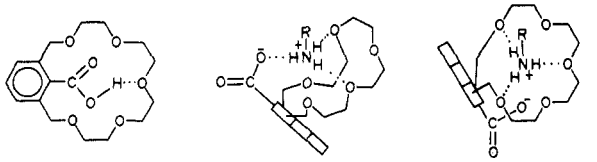


1 **2**

rey–Pauling–Koltun (CPK) molecular model of the complex between methylammonium ion and 18-crown-6 viewed with the methyl group protruding from the best plane of the oxygens (that of the page). **2** is a Newman projection formula of the same complex which depicts the three $NH^+\cdots O$ and three $N^+\cdots O$ binding sites. In these structures, the C–N bond is perpendicular to the best plane of the oxygens, and the tripod arrangement of the hydrogen bonds provides a reasonably rigid placement of guest relative to host. This basic structure is capable of wide variation by substitution of the ethylene by various other units (e.g., benzo) and by substitution of the methyl by other alkyl or aryl groups.

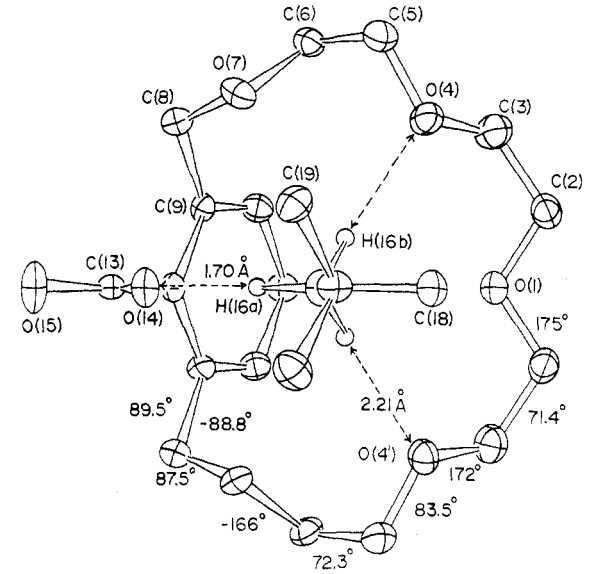
In the crystal structure of 18-crown-6,[10] the uncomplexed crown possesses inward-turning methylene groups that fill the hole. In the complexes,[10,11] the oxygens all turn inward, and the ethylene glycol units possess a gauche conformation as they do in solution.[12] The complexes described in this Account are held together by forces strong enough for the complexes to maintain their structures in solution without the benefit of lattice energies.

An example of a crystalline complex involves the carboxylate ion and two ether oxygens as hydrogen-bonding sites for the t-$BuNH_3^+$ ion. Molecular models (CPK) indicate that host[13,14] might complex in either



3 **4** perching structure **5** nesting structure

of two ways with the t-$BuNH_3^+$ ion to provide either a perching or a nesting position for the guest relative to the host (formulas **4** and **5**, respectively).[13,14] The x-ray structure (photographs taken at 120 K of the complex are shown in 6 and 7) indicates that it pos-



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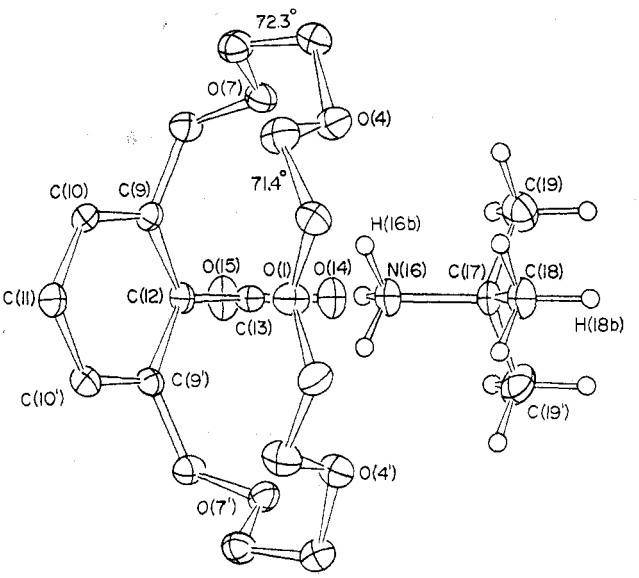


7

sesses the perching configuration **4**.[15] Noteworthy features of the crystal structures are that the three $NH^+\cdots O$ hydrogen bonds are arranged in a tripod, that the t-Bu–N bond is only ~3° from being perpendicular to the least-squares plane of the six binding oxygens, that these oxygens turn inward and somewhat upward toward the NH_3^+, and that the H–N^+–C–C dihedral angles are about 60°. The correspondence between what is observed in the x-ray structure and what is suggested by CPK molecular model examination for complex **4** is remarkably good.

Complex **8** in CPK models possesses a wreathlike host structure surrounding a guanidinium ion held in place by six hydrogen bonds. A crystalline 1:1 complex was formed which, unlike the guest alone, is soluble in chloroform.[16,17] Although hard evidence for **8** is lacking, the structure shown seems likely.

(9) (a) J. Dale and P. O. Christianson, *Acta Chem. Scand.*, **26**, 1471 (1972); (b) J. Dale and K. Daasvatn, *J. Chem. Soc., Chem. Commun.*, 295 (1976).

(10) (a) J. D. Dunitz and P. Seiler, *Acta Crystallogr., Sect. B*, **29**, 589 (1973); (b) J. D. Dunitz, M. Dobler, M. Seiler, and R. P. Phizackerly, *ibid.*, **30**, 2733 (1974); (c) H. B. Bürgi, J. D. Dunitz, and E. Schefter, *ibid.*, **30**, 1517 (1974).

(11) I. Goldberg, *Acta Crystallogr., Sect. B*, **31**, 754 (1975).

(12) D. Live and S. I. Chan, *J. Am. Chem. Soc.*, **98**, 3769 (1976).

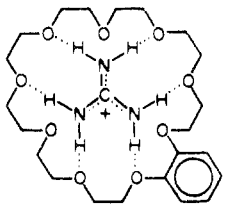
(13) M. Newcomb and D. J. Cram. *J. Am. Chem. Soc.*, **97**, 1257 (1975).

(14) M. Newcomb, S. S. Moore, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 6405 (1977).

(15) I. Goldberg, *Acta Crystallogr., Sect. B*, **31**, 2592 (1975).

(16) K. Madan and D. J. Cram. *J. Chem. Soc., Chem. Commun.*, 427 (1975).

(17) E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore, and D. J. Cram. *J. Am. Chem. Soc.*, **99**, 2564 (1977).



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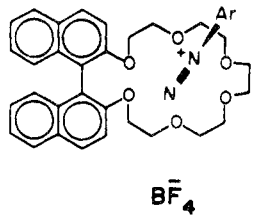

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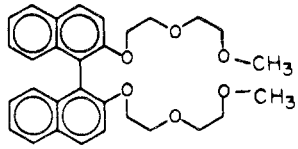

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Structure **9**, of a complex between an aryldiazonium ion and a binaphthyl macrocyclic ether, provides an explanation for the following facts.[18,17]

(1) In CPK molecular models, the $N^+{\equiv}N$ group of $ArN^+{\equiv}N$ snugly fits into the cavity of 18-crown-6 and the host of **9** with all electron pairs of the O's turned inward. A solution of 18-crown-6 in $CDCl_3$ solubilized otherwise insoluble solid *p*-toluenediazonium tetrafluoroborate to give a guest-to-host molar ratio of 0.8. A $CDCl_3$ solution of the host of **9** solubilized 0.9 mol of the same guest, and the dissolution produced a marked ^1H NMR change for the host's $ArOCH_2$ protons. The analogue of the host of **9**, containing one less OCH_2CH_2 group, failed to solubilize the salt because the hole was too small to embrace the $N^+{\equiv}N$ group. The open-chain compound **10** also failed to solubilize the salt. Thus, preorganization of the host prior to complexation is a prerequisite for strong binding.

(2) The host of **9** in $CDCl_3$ solubilized 1 mol of 3,4-dimethylbenzenediazonium tetrafluoroborate, but both the host of **9** and 18-crown-6 failed to solubilize the salt of 2,6-dimethylbenzenediazonium tetraphenylborate. Models indicate that the 2,6-dimethyl groups occupy the space needed to place a cyclic ether collar around the $N^+{\equiv}N$ group.

(3) Solutions of complexes **9** having various *p*-aryl substituents gave colors that varied from yellow to red (unlike the complexes of 18-crown-6). Molecular models of **9** indicate the Ar and naphthalene rings can occupy parallel planes within van der Waals contact distances when the $N^+{\equiv}N$ group is inserted in the hole. The colors appear to be due to charge-transfer electronic transitions between host and guest.

(4) Complexation of the aryldiazonium salts stabilized them toward reagents with which they ordinarily react very rapidly.[18,17]

These studies provide the important conclusion that scale molecular models of potential complexes can be used in a limited way in advance of experiment to screen for potentially complementary host–guest relationships. Models are probably more valuable in predicting what *will not* rather than in predicting what *will* work. They provide a compass in an uncharted sea of molecular possibilities of complementary host–guest relationships.

(18) G. W. Gokel and D. J. Cram. *J. Chem. Soc., Chem. Commun.*, 481 (1973).

Effect of Structure on Binding Potential of Hosts for Standard Guests

Although molecular models of possible complexes tell the investigator what hosts might be interesting to synthesize, some scale of binding potential is needed so hosts can be evaluated once available. The x-ray structures of enzyme–inhibitor complexes indicate that selective complexation combines complementary placements of multiple binding sites and steric barriers.[19] This section describes a semiquantitative scale for the binding of synthetic hosts to guests which allows an evaluation of the electronic effects involved. The range of structures of the hosts used hints at the variety of units that can now be assembled by rational synthesis.

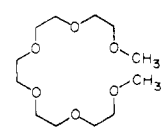
The scales developed[20] involved distributing *t*-$BuNH_3^+X^-$ salts between D_2O and $CDCl_3$ and measuring spectrometrically, in the absence and presence of host, the amounts of guest in the $CDCl_3$ layer. From the results, association constants (K_a) between host and guest in $CDCl_3$ were calculated, along with free energies of association ($\Delta G°$). The association constant is defined by eq 1, and the free energy of association by eq 2.

$$\text{host} + t\text{-BuNH}_3^+X^- \underset{CDCl_3}{\overset{K_a}{\rightleftharpoons}} t\text{-BuNH}_3^+\cdot\text{host}\cdot X^- \quad (1)$$

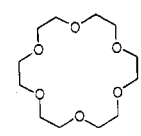
$$\Delta G° = -RT \ln K_a \quad (2)$$

Because $\Delta G°$ values changed so radically with changes in host structure, X^- was varied so that measurements could be made on a wide range of compounds. The most used X^- was SCN^-, but pic^- (pic = picrate), ClO_4^-, and Cl^- were also employed. The scales were normalized to the SCN^- scale at 24° by adding the following empirically obtained increments to the $\Delta G°$ values observed for the other salts: for pic^-, 0.0 kcal/mol;[21] for ClO_4^-, + 2.5 kcal/mol;[21] for Cl^-, −2.05 kcal/mol.[22] The finer comparisons in the following discussion always involved the same counterion. Below each formula in this section appears the estimated $\Delta G°$ value at 24° normalized to the SCN^- scale.

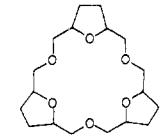
Open-chain model compound **11** and 18-crown-6 (**12**)



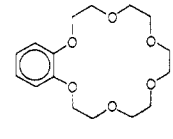
11
−2.9



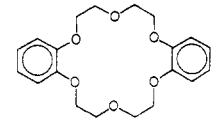
12
−8.9



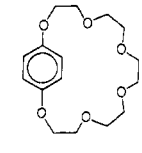
13
−9.0



14
−7.9 (−7.8)



15
−6.7



16
−2.9

(19) R. E. Dickerson and I. Geis, "The Structure and Action of Proteins", Harper and Row, New York, N.Y., 1969, pp 67–97.

(20) (a) J. M. Timko, S. S. Moore, D. M. Walba, P. Hiberty, and D. J. Cram. *J. Am. Chem. Soc.*, **99**, 4207 (1977); (b) J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel, and D. J. Cram. *ibid.*, **96**, 7097 (1974). The scales developed in (a) depend on more reliably determined distribution constants than those of (b).

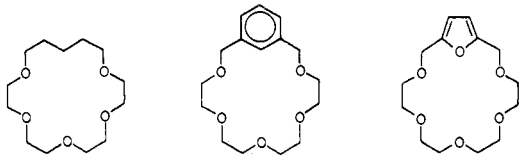
(21) S. S. Moore, M. Newcomb, T. L. Tarnowski, and D. J. Cram. *J. Am. Chem. Soc.*, **99**, 6398 (1977).

(22) M. Newcomb, J. M. Timko, D. M. Walba, and D. J. Cram. *J. Am. Chem. Soc.*, **99**, 6392 (1977).

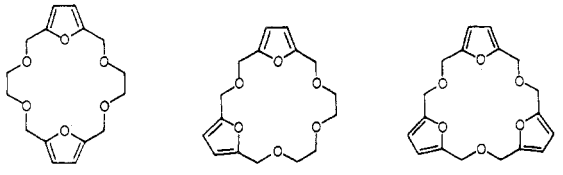
differ in molecular composition by only two hydrogen atoms, yet **12** is the better host by ~6 kcal/mol. Thus organization of binding sites prior to, rather than during, complexation is a necessary requirement for strong binding. In the perhydrotrisfuranocycle **13** (mixture of the two all-cis isomers), the six oxygens possess an enforced, inward-turning conformation. However, this further refinement in molecular preorganization provides an additional binding energy of only ~0.1 kcal/mol. Apparently the all-gauche preference for the $O-CH_2-CH_2-O$ conformation of **12**[12] in solution provides close to an ideal geometry for binding RNH_3^+. An interesting fact about **13** is that it was synthesized by two methods in which sucrose was the *only organic starting material or reagent used.*[20a,23]

Introduction of one benzo group into 18-crown-6 (as in **14**[8]) decreases the binding energy by 1.0 kcal/mol;[20a] two benzo groups (as in **15**[8]) decrease the binding energy by 2.2 kcal/mol.[20a] The aryl groups probably make their attached oxygens less basic. Compounds **14** and **16** are isomeric and differ only in the placement of their O's. Whereas **14** can provide three $NH^+\cdots O$ and three $N^+\cdots O$ binding sites, **16** is restricted to two of each type of site, at the most (CPK models). This mislocation of sites in **16** results in a 5-kcal/mol decrease in binding potential.

Cycles **17**, **18**, and **19** contain oxygens arranged ideally



17 −4.4 **18** −4.8 **19** −7.2 (−7.2)

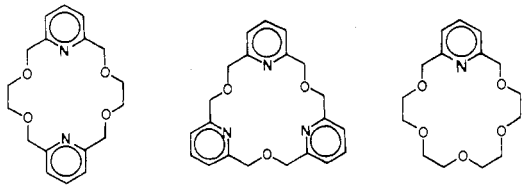


20 −3.3 **21** −5.6 (−5.7) **22** −4.1

to form three $NH^+\cdots O(CH_2)_2$ and two $N^+\cdots O(CH_2)_2$ interactions, but the third interaction to N^+ involves a CH_2, a π-aryl, or a furanyl O group.[20a] The respective decreases in binding power from that of **12** as a standard host are 4.5, 4.1, and 1.7 kcal/mol. These decreases indicate the sixth site interaction in each case is repelling rather than attracting.

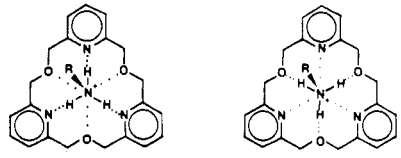
The arrangements of oxygens in hosts **12**, **14**, **15**, and **17–22** are very similar. We examined the possibility that the six interaction sites contribute additively to the total free energy of binding independent of their relative locations and numbers in these and other cycles of the same size containing only these units.[20a] With the measured $\Delta G°$ values for **12**, **15**, **20**, and **21** and this hypothesis, the $\Delta G°$ values for **14**, **19**, and **21** were calculated. They appear in parentheses beside the observed values listed under the formulas. The agreement between calculated and observed values is surprisingly good. This hypothesis of *additivity of contact site free energies* leads to the prediction that the interesting compound $(o\text{-}CH_2OC_6H_4OCH_2)_3$ might have $\Delta G°$ = −5.7 kcal/mol and that $\Delta G°$ of cyclohexa-2,5-furanyl should be +7.8 kcal/mol (a nonhost) at 24 °C. The partial positive charge on the furanyl O accounts for its nonbinding character. From an ab initio calculation of the energies of binding of NH_4^+ and $HOCH_2CH_2OH$ in various conformations, it was concluded that a $NH^+\cdots O$ interaction is about three times more binding than a $N^+\cdots O$ interaction.[20a]

Application[22] of the hypothesis of additivity of contact site free energies to complexation between t-$BuNH_3^+$ and hosts **12**, **23**, and **24**[24] ($CDCl_3$ at 24 °C)



23 −8.4 **24** −8.8 **25** −8.9 (−8.8)

gave a calculated $\Delta G°$ of binding for pyridocycle **25** very close to that which was measured (compare the two values underneath the formulas). The values listed underneath the host structures have been corrected from X = Cl^- to X = SCN^-.[22] These calculations are independent of whether structures of type **26** or of type



26 **27**

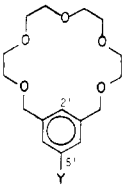
27 are assumed for the complexes. The former with $NH\cdots N^+$ hydrogen bonds are probably the more stable.

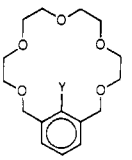
There are nine other pyridocycles as yet unsynthesized which combine, in various ways, pyridine or pyridine and CH_2OCH_2 groups to give 18-membered central rings containing six binding sites. Their free energies of association with t-$BuNH_3^+SCN^-$ have been predicted using these principles.[22] For example, that for cyclohexa-2,6-pyridyl is estimated to be −8.0 kcal/mol.

The association free energies for t-$BuNH_3^+SCN^-$ complexing hosts such as **18** (in $CDCl_3$ at 24 °C) were found to be sensitive to substituents in both the 2′ and 5′ positions. The ^1H NMR spectra of the complexes of **18** and **28–32** indicated they possessed the nesting conformation (the t-Bu protons were in the magnetic field of the aryl and thus moved upfield).[21] In this conformation, the N^+ is close to the π electrons in the 2′ position (CPK models). When Y occupies the remote 5′ position, the binding energies change between extremes of 5.1 kcal/mol (Y = $C(CH_3)_3$) and 2.7 kcal/mol (Y = CN), a difference of 2.4 kcal/mol. Thus, the electron density of the π system seriously affects the stability of the complex in the expected direction. The responses to changes in Y (seven different substituents) of the stabilities of complexes between hosts such as **28–30** and t-$BuNH_3^+$, NH_4^+, Rb^+, and Cs^+ were correlated by Hammett-type linear free energy relationships.[21]

(23) J. M. Timko and D. J. Cram, *J. Am. Chem. Soc.*, **96**, 7159 (1974).

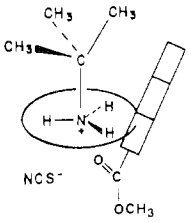
(24) M. Newcomb, G. W. Gokel, and D. J. Cram. *J. Am. Chem. Soc.*, **96**, 6810 (1974).





18, Y = H, −4.8
28, Y = $C(CH_3)_3$, −5.1
29, Y = CN, −2.7
30, Y = $CO_2C_2H_5$, −3.8

31, Y = CO_2CH_3, −6.5
32, Y = CN, −4.2



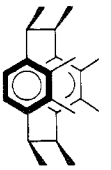
33

The magnitudes of the binding powers of hosts such as **18** are comparably sensitive to substituents in the 2′ position. However, in some cases the *direction* of the effect is inverted. Thus, substitution of the CO_2CH_3 group in the convergent 2′ position of **18** (as in **31**) *increases* its free energy of binding by 1.7 kcal/mol, whereas substitution of the $CO_2C_2H_5$ group in the divergent 5′ position (as in **30**) decreases the binding energy by 1.0 kcal/mol. These comparisons indicate that, in the complex of **31**, the CO_2CH_3 group provides an additional binding site and that the complex possesses structure **33**. This structure was envisioned prior to these experiments through examination of CPK molecular models. The linear cyano group substituted in place of the forked carbomethoxy group of **31** (as in **32**) decreased the binding capacity by 2.3 kcal/mol. The linear cyano group places the electron pair of the N: out of contact with N^+ or NH^+ of the guest, and therefore it does not act as an additional binding site.[14]

The Use of Steric Barriers to Impart Structural Recognition Properties to Hosts

Biological hosts for organic guests tend to have molecular weights of 10 000 or more. Most of the mass is associated with the supporting framework for those molecular parts that shape the complexing cavity. In the design of possible synthetic hosts, the most difficult problem is the conciliation of interesting guest structures with host structures whose syntheses are feasible. Several imperatives provide useful guidance. (1) Design hosts that combine maximum stability with minimum molecular weight. (2) Use repeating structural units wherever possible. (3) Design hosts that provide the maximum amount of symmetry compatible with desired properties. (4) Make maximum use of conformationally unambiguous molecular units. (5) Incorporate units that rigidly extend in three dimensions. (6) Maximally use molecular units that serve several purposes. (7) Use units with rigidly convergent and substitutable sites for binding and shaping. (8) Use units with rigidly divergent and substitutable sites for manipulation of gross physical properties (e.g., solubility), or for attachment to solid supports. (9) Avoid intramolecular complexation in hosts which competes with desired host–guest complexation. (10) Avoid hosts whose cavities can collapse by conformational reorganization. (11) Design series of hosts that can be synthesized from common intermediates. (12) Incorporate units that provide spectral probes for structures of the anticipated complexes. (13) Employ the maximum number of binding sites compatible with high rates of complexation–decomplexation. (14) Design hosts to avoid ambiguity as to which sites in the host will contact which sites in the guest. (15) Design hosts that will avoid complexing unwelcome guests, and thus are able to differentiate between guests. (16) Remember that in host design strong entropic driving forces oppose selective complexation, and that the host will use all structural degrees of freedom available to avoid differentiating between guests. (17) In catalytic hosts, design to stabilize the rate-limiting transition states. (18) Where covalent bonds are being made and broken between host and guest, treat the locus of the transition state as a binding site of low geometric tolerance. Some of these principles were used in the design of the hosts discussed in the following paragraphs.

Several rigid three-dimensional units have proved particularly useful in host design. The layered structure of [2.2]paracyclophane has 16 substitutable sites, eight of which are semiconvergent in one direction and the other eight of which are semiconvergent in the opposite direction (see **34**). Parent hosts **35**, **36**, and **37** were



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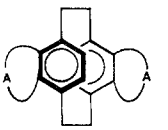
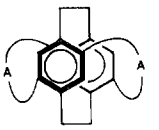
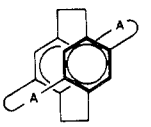


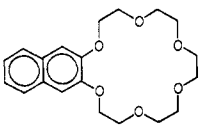
35, A = $O(CH_2CH_2O)_5$
achiral, sided
NH_4^+, −9.04
t-$BuNH_3^+$, −3.80



36, A = $O(CH_2CH_2O)_5$
chiral, nonsided
NH_4^+, −7.8
t-$BuNH_3^+$, −3.1



37, A = $O(CH_2CH_2O)_5$
achiral, sided
NH_4^+, −7.1
t-$BuNH_3^+$, −3.1



38
NH_4^+, −9.64
t-$BuNH_3^+$, −7.66

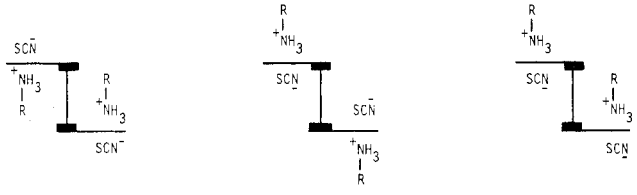
synthesized[25] to determine if their binding characteristics justified pursuit of more sophisticated structures based on the [2.2]paracyclophane unit.

The extraction–spectroscopic technique[20] for determining free energies of association was applied to hosts **35**–**38** complexing with ammonium and *tert*-butylammonium picrates in $CDCl_3$ at 24 °C. The values obtained are listed beneath the formulas.[25b] Compound **38** serves as a two-dimensional model host in whose complexes with *t*-$BuNH_3^+$ steric interactions between

(25) (a) R. C. Helgeson, J. M. Timko, and D. J. Cram. *J. Am. Chem. Soc.*, **96**, 7380 (1974); (b) R. C. Helgeson, T. L. Tarnowski, J. M. Timko, and D. J. Cram, *ibid.*, **99**, 6411 (1977).

the *t*-Bu and the aryl groups are absent (CPK models). For model host **38**, $(\Delta G_{NH_4^+}) - (\Delta G_{t\text{-}BuNH_3^+}) = -2.0$ kcal/mol, a Δ value that measures the intrinsic difference between the binding abilities of the two guests in the absence of steric effects. The Δ value for **35** is −5.2 kcal/mol, for **36** is −4.7 kcal/mol, and for **37** is −4.0 kcal/mol. The larger this Δ value, the greater is the *structural recognition* in complexation of the guest by the host. All three of the cyclophane hosts that extend in three dimensions show greater structural recognition than the two-dimensional host, **38**: host **35** by −3.2 kcal/mol, **36** by −2.7 kcal/mol, and **37** by −2.0 kcal/mol. These values provide a crude measure of repulsions between the *t*-Bu group and the steric barriers in the hosts.

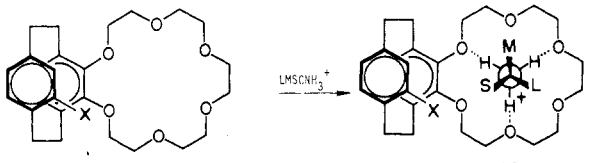
These results indicate that, of the three cyclophanes, systems such as **35** are worthy of the most study on several grounds. (1) In the absence of steric effects, **35** is the best binder, and the higher the binding energy, the more structured the complex. (2) Host **35** shows the highest structural recognition, since about half of the binding energy can be canceled by steric effects. (3) Host **35** is the easiest to prepare and structurally modify. (4) Formally, the macrocyclic rings of **35** have two different sides from which bound alkylammonium groups might extend, and thus the molecule is said to be "sided". Although fully complexed **35** might have three isomeric structures, A, B, and C, ^{1}H NMR spectral



A *syn,syn* B *anti,anti* C *anti,syn*

studies of the complex between **35** and *t*-$BuNH_3^+SCN^-$ indicated it to be of the syn, syn configuration (A). In models (CPK) of **35**, the electron pairs of the two aryl oxygens are rigidly oriented syn to the transannularly located benzene ring. This conformation is enforced by the attached methylene groups which are wedged between the ortho oxygen and the ethylene bridge of the [2.2]paracyclophane system.

The high *structural recognition* exhibited by **35** suggests that chiral host **39** should exhibit *high chiral*

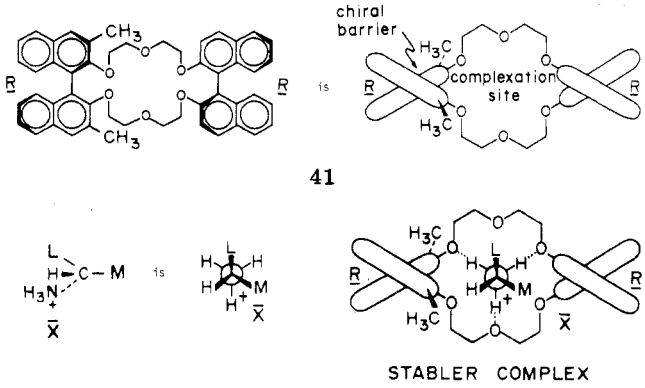


39 **40**

recognition of the enantiomers of racemates of the general structure $LMSC^*NH_3^+X^-$, where L, M, and S are *large*, *medium*, and *small* substituents. In CPK models of the diastereomeric complex envisioned as being the more stable (**40**), S is against the larger steric barrier (ArX), M is against the smaller steric barrier (ArH), and L has no steric restriction. Compounds such as **39** are currently being prepared for testing of their chiral recognition capacity.[26]

(26) H. Nakamura and D. J. Cram, work in progress.

High chiral recognition by optically active hosts such as **41**, which contains the binaphthyl unit, has been



observed in complexation of salts of primary amine racemates.[27] Substances such as α-phenylethylamine, amino esters, and amino acids have been studied as guests in distribution experiments between an aqueous layer of $LiPF_6$ (or $LiClO_4$) and a chloroform layer containing optically pure host. The hosts are insoluble in the aqueous layer and the guest salts are insoluble in the organic layer in the absence of the hosts. When present, the hosts selectively complex, lipophilize, and draw into the organic layer one guest enantiomer more than the other. The guests vary in their hydrophilicity–lipophilicity balance, and both hosts and guests vary in their binding potentials, which grow out of the stereoelectronics of their binding sites. Usually, the amount of guest transferred to the organic layer can be adjusted by using differing amounts of Li salt in the aqueous layer and of acetonitrile in the organic layer. After equilibration, the layers are separated, the guest is isolated from each layer, and its optical purity is determined. From the values obtained, the enantiomer distribution constant (EDC) is calculated; it is defined as the ratio D_A/D_B, where D_A is the distribution constant between two layers for the more complexed and D_B is that for the less complexed enantiomer. The difference in free energies between the diastereomeric complexes in the organic layer, where complexation occurs, is $\Delta(\Delta G^\circ) = -RT \ln (EDC)$.[27c]

In this rational approach to optical resolution, compound **41** is the most generally successful host developed thus far. The compound possesses a C_2 axis, and, therefore, complexation from either face produces the same complex. Host **41** is such a poor binder that its association constants occupy the lower end of the ammonium or *tert*-butylammonium picrate or thiocyanate scales. However, under the proper conditions, the following EDC values have been obtained: 2.4 ($\Delta\Delta G^\circ$ = −0.48 kcal/mol) for α-phenylethylammonium hexafluorophosphate,[28] 38 ($\Delta\Delta G^\circ$ = −2.0 kcal/mol) for methyl *p*-hydroxyphenylglycinate hexafluorophosphate, 36 ($\Delta\Delta G^\circ$ = −1.95 kcal/mol) for tryptophan perchlorate, and 52 ($\Delta\Delta G^\circ$ = −2.15 kcal/mol) for phenylglycine perchlorate.[27c] Chemical shifts in the ^{1}H NMR of the protons in both hosts and guests of the diastereomeric complexes have provided considerable information

(27) (a) E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 2692 (1973); (b) R. C. Helgeson, J. M. Timko, P. Moreau, S. C. Peacock, J. M. Mayer and D. J. Cram, *ibid.*, **96**, 6762 (1974); (c) S. C. Peacock and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 282 (1976).

(28) S. C. Peacock and D. J. Cram, unpublished results.

about the structures of the complexes, particularly with phenylglycine methyl ester salts as guests. The naphthalene rings in CPK molecular models of **41** are perpendicular to the best plane of the oxygens. The ring currents of the naphthyl groups provide magnetic probes for the placements of the methyls, the methines, and the ortho protons of the amino ester guests. Likewise, the phenyl group of the phenylglycine ester provides a probe for the placement of the methyls and of the central methylene protons of **41**. The structure of each diastereomeric complex turned out to be approximately what was expected from CPK molecular model examination.[27b]

Hopefully, better binding hosts such as **39** will provide higher chiral recognition, which must derive from a complementary arrangement of steric barriers for one diastereomeric complex and of high steric inhibition of complexation for the other. High binding free energies of hosts for small guests such as NH_4^+ are probably a prerequisite for high chiral recognition. The high free-energy cost of the organization required for chiral recognition must be paid for by a high intrinsic binding potential of the host. However, if binding energies become very high, the advantages of very rapid rates of complexation–decomplexation are lost, and the uses to which complexation can be put are limited.

These studies demonstrate that, with the inspiration of biological systems and the help of scale molecular models, organic-to-organic complexes can be designed which, when synthesized, show the anticipated molecular organization. If complexation is a central feature in the operation of biological systems, then hosts which are designed and synthesized by organic chemists could become the theme of much research in the future.

Conformational Studies of Hexahydropyridazine Derivatives

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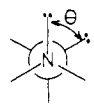
The preference of many compounds with adjacent heteroatoms for adopting conformations in which the lone-pair orbitals on the heteroatoms are nearly perpendicular has been discussed as the "gauche effect".[1] There are two principal factors which have been used to rationalize this preference: repulsion between the lone-pair orbitals[2] and attractive lone-pair–adjacent-bonding-pair interaction.[3] Although the relative importance of these two factors is not yet known, it is clear that there is a significant torsional barrier to rotation about a heteroatom–heteroatom bond and that this barrier, which is not steric in origin, involves the lone-pair electrons. Hydrazines provide attractive systems for quantitative study of the influence of lone-pair–lone-pair dihedral angle (θ in I) on conformational equilibrium and rate constants. The identical energies of the lone-pair orbitals in the (hypothetical) absence of interaction and the relatively large orbital–orbital overlaps expected because of the relatively short N–N bond length should make the torsional effect larger than in most other cases.[4] For derivatives of 1,2-dimethylhexahydropyridazine (**1**), the well-known

1 **1ee** **1ae** **1aa**

steric requirements of the six-membered ring will limit the available conformations to chair forms with equatorial and/or axial disposition of the substituents (**1ee**, **1ae**, and **1aa**), isolated from each other by reasonably substantial kinetic barriers.

It may be noted that **1ee** is required to have θ near 180°, and thus is electronically destabilized by a large lone-pair–lone-pair repulsion and the lack of an adjacent bonding orbital anti to either lone pair. **1ae** and **1aa**, on the other hand, have the electronically preferred gauche lone-pair orientation (θ near 60°) but are clearly sterically destabilized by the presence of axial substituents on the six-membered rings. Because of the conflicting steric and electronic effects, conformational study of six-ring hydrazine derivatives would be expected to reveal the relative sizes of these effects. We describe here work which has led to the measurement of equilibrium and rate constants for conformational



I

Stephen F. Nelsen was born in Chicago and received his undergraduate training at the University of Michigan, where his interest in organic chemistry was stimulated principally by Martin Stiles. After earning his Ph.D. degree at Harvard University with P. D. Bartlett in 1965, he joined the faculty at the University of Wisconsin, where he is professor of chemistry. His research involves the study of reaction mechanisms, largely in free radical and radical ion reactions, and emphasizes the importance of the influence of conformational geometry upon reaction rate.

(1) S. Wolfe, *Acc. Chem. Res.*, **5**, 102 (1972).

(2) M. J. S. Dewar and W. B. Jennings, *J. Am. Chem. Soc.*, **95**, 1562 (1973).

(3) (a) L. Radom, W. J. Hehre, and J. A. Pople, *J. Am. Chem. Soc.*, **94**, 2371 (1972); (b) N. D. Epiotis, *ibid.*, **95**, 3087 (1973); (c) R. C. Bingham, *ibid.*, **97**, 6743 (1975); (d) T. Brunck and F. Weinhold, *ibid.*, **99**, in press. We thank Professor Weinhold for discussion of this work prior to publication.

(4) Both large overlap and small ΔE are required to maximize orbital–orbital interactions: R. Hoffmann, *Acc. Chem. Res.*, **4**, 1 (1971).

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