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Recent Highlights in Hemicarcerand Chemistry

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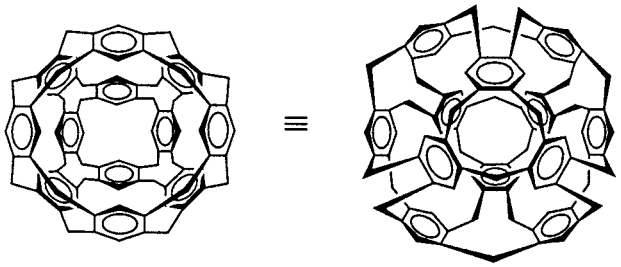
ABSTRACT
Since Donald J. Cram's first synthesis of a carcerand, which permanently entrapped a single guest molecule, many other carcerands and hemicarcerands have been synthesized and studied. Slowly, we begin to understand the role of the template in the formation of hemicarceplexes and carceplexes, why some hemicarceplexes are more stable than others, and how guests enter and exit the inner phases of molecular containers. In this Account we discuss our new insight in the chemistry of molecular containers, as well as recent highlights in through-shell chemistry and in the inner-phase stabilization of reactive intermediates.

Introduction

Over the past 15 years, a new research field has become one of the most exciting and challenging playgrounds of organic chemistry: the chemistry of and within molecular container compounds.[1] In 1983, Donald J. Cram introduced the concept of a closed-surface binding host that can imprison simple organic molecules.[2] He formulated the hypothetical structure **1** as a prototypical molecular



container compound. Though molecules have been trapped inside the cavities of polymeric matrixes, zeolites and clathrates, molecular containers that imprison single molecules were the first examples of a single molecule within a single molecule.[3,4] Immediately, many interesting questions come to mind. How would such a trapped molecule behave compared to its free twin? What would keep it inside and prevent its escape? What kinds of guests can be incarcerated? Does guest structure correlate with the shape and size of the container's cavity and doorways? Is chiral recognition in complexation possible? How could the guest be manipulated through the surrounding shell of the container? Is the generation and protection of highly reactive intermediates in a host's inner phase possible? From published idea to realization took two years. In 1985, Cram and co-workers[5] synthesized carcerand **2** by multiply binding cavitand **3** to **4** (Figure 1).

The name carcerand is derived from the Latin word *carcer*, meaning "prison". During its formation, **2** trapped almost every component present in the reaction flask. In each carcerand, the incarcerated guests did not leave their prison, even at high temperatures. Complexes with permanently imprisoned guests are called carceplexes.

Hemicarcerands, in contrast, incarcerate and liberate guests at elevated temperatures but form stable hemicarceplexes at ambient temperature. This paper gives the highlights of recent hemicarcerand research, providing the flavor of inner-phase chemistry and suggesting future

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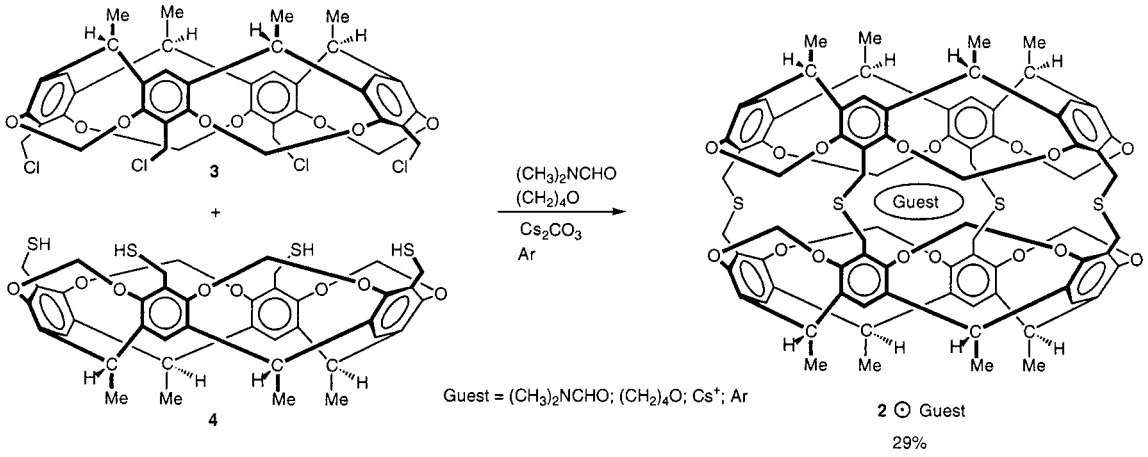


FIGURE 1. Synthesis of carceplex **2**.

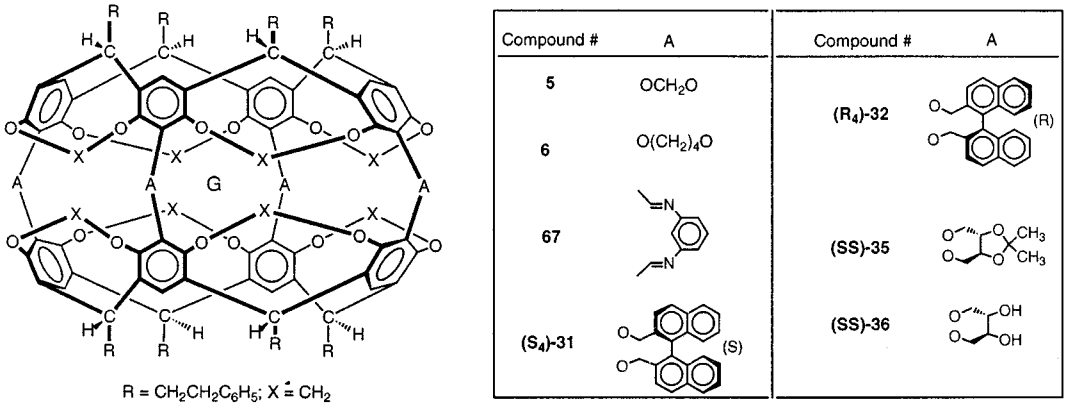


FIGURE 2. Structures of hemicarcerands.

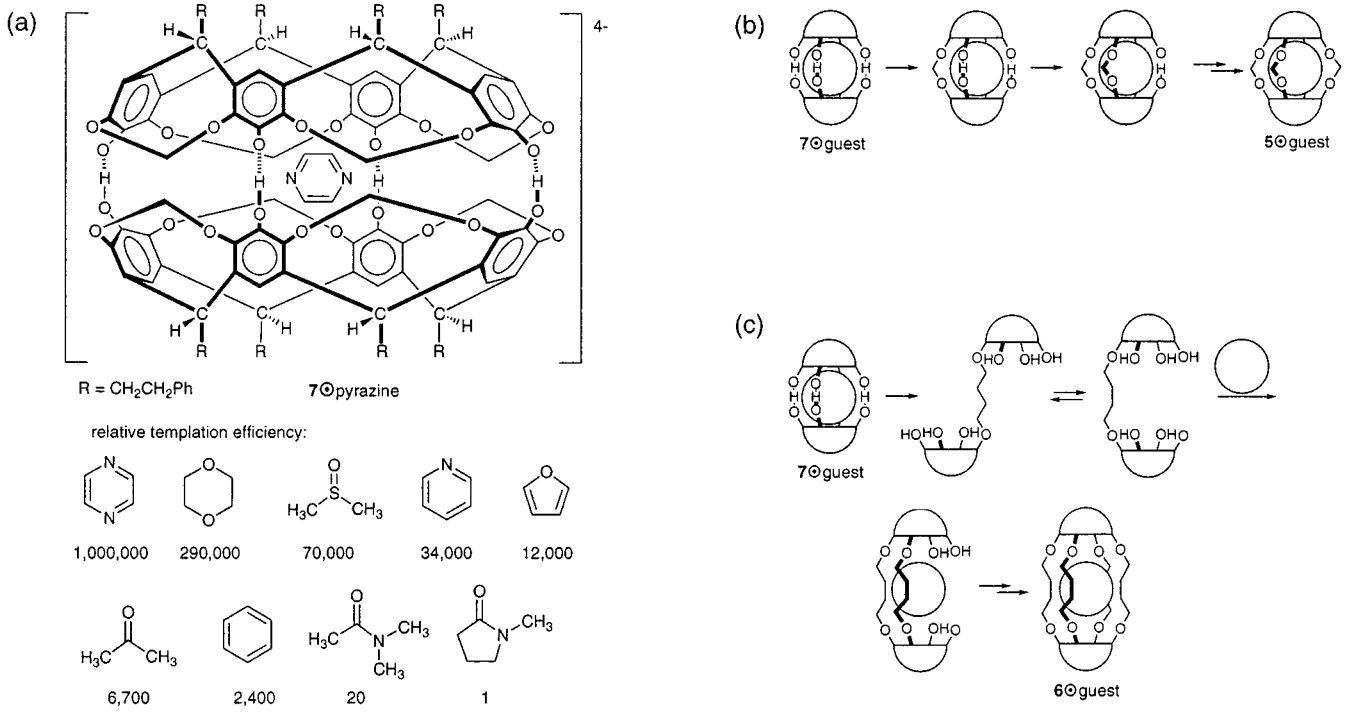
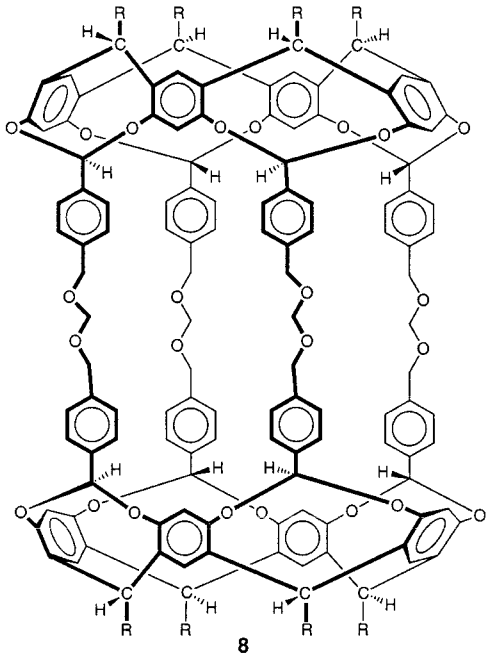


FIGURE 3. Transition-state model **7** for the guest-determining step and relative templation efficiency of molecules (a). Proposed mechanism for the formation of hemicarceplexes **5**·guest (b) and **6**·guest (c).

applications. The parent of this endeavor, Donald J. Cram, calls this work the most exciting research his group has ever done.

Hemicarcerands

A large variety of hemicarcerands has been synthesized by connecting two cavitands[2] with four appropriate linkers A (Figure 2).[1,5,6] Their cavities are suitable for the incarceration of guests (G) ranging in size and shape from gases such as Xe[6a] to solids such as C_{60}.[6c] The proper choice of the template molecule, which complements the inner phase of the target hemicarcerand, is vitally important.[6a]



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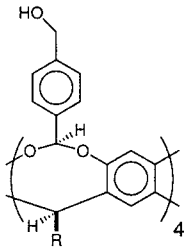


9

R = CH_2CH_2Ph

This was noted[6a] by Cram et al. and has been thoroughly investigated by the Sherman group.[7,8] They studied a library of small molecules as templates for the formation of **5**·guest and **6**·guest. For **5**·guest, yields, from zero to 87%, and template efficiency correlate nicely with the structural complementarity of the inner phase and the guest. The highest yield, for pyrazine, is impressive for a reaction that collects seven components by forming eight covalent bonds. Yields are maximized when the cavitand bowls and template guest can be preassembled in a trimeric hydrogen-bonded intermediate (Figure 3a,b).[9] NMR experiments and an X-ray structure demonstrate the formation of the trimeric complex **7**.[7b,c] However, complex **7** is not important for the formation of **6**·guest.[8] For this

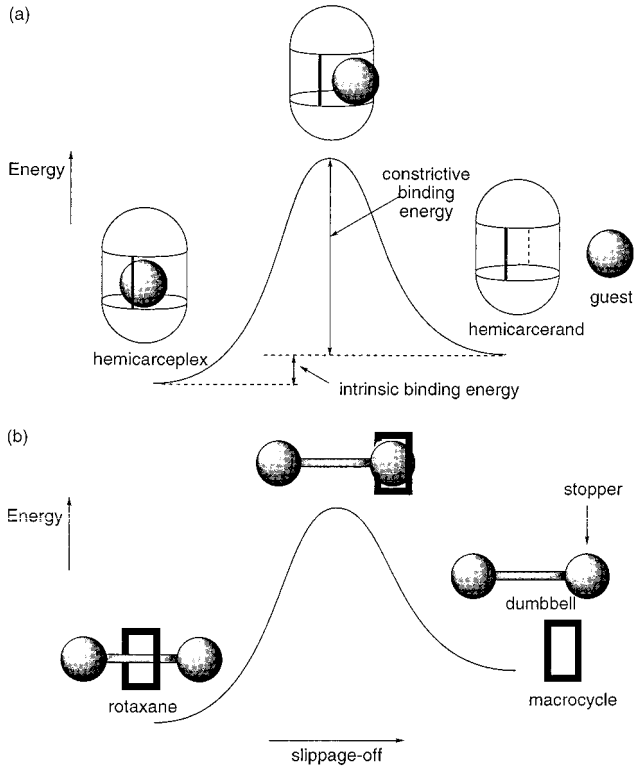


FIGURE 4. Energy profile of hemicarceplex dissociation (a) and rotaxane slipping-off (b).

larger host, yields are lower and correlate neither with the template effect nor with the template's ability to stabilize **7**. Likely, the formation of the first tetramethylene linkage disrupts **7**, allowing for subsequent intermolecular and intramolecular reactions. The template does not affect the course of the reaction until after formation of the second linker has determined the fate of the product (Figure 3c).

One might think that templation of a H-bonded complex, such as **7**, is required for an efficient hemicarceplex formation. However, an investigation by Gibb et al. contradicts this generalization.[10] They reported the synthesis of hemicarcerand **8** in a remarkable 80% yield via the covalent connection of two cavitands **9** in the absence of an apparent (single) molecular template. As a possible explanation, Gibb et al. suggested an efficient self-assembly of **9** through charged hydrogen bonds (CHBs) between the poorly acidic benzyl alcohol groups and their conjugated bases. Such CHBs are stronger than those in **7**.

Understanding *Constrictive* and *Intrinsic* Binding

Investigation of the properties of hemicarceplexes and the kinetics of complexation and decomplexation led to the discovery of *constrictive binding*.[6a,11] Hemicarceplexes are stabilized by intrinsic and constrictive binding (Figure 4a). Intrinsic binding, the free energy of complexation, depends on the magnitude of the noncovalent interactions between the guest and the host's inner surface. Constrictive binding, a physical barrier, is the activation energy required for a guest to enter the inner cavity of a hemicarcerand through a size-restricting portal in the

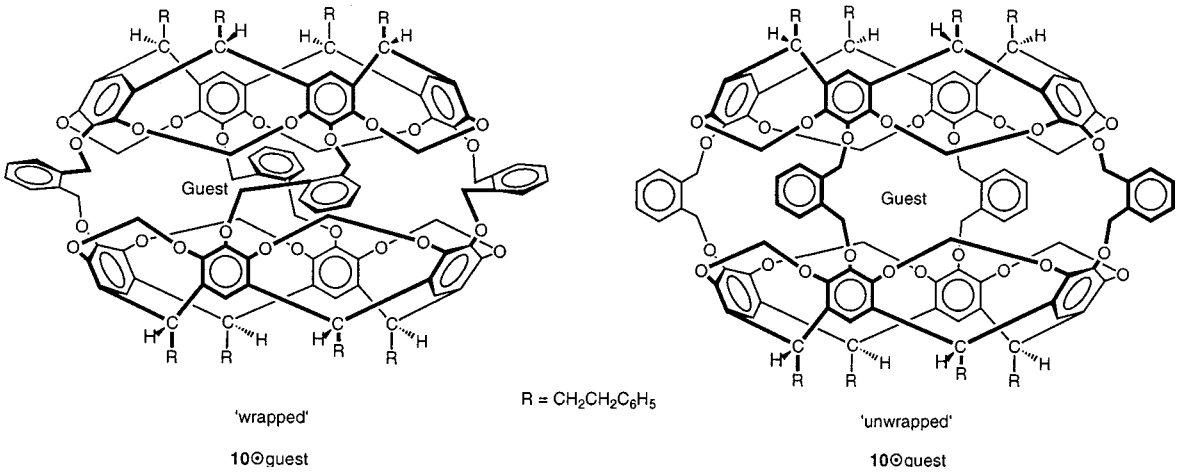


FIGURE 5. A wrapped and an unwrapped state of hemicarceplex **10**.

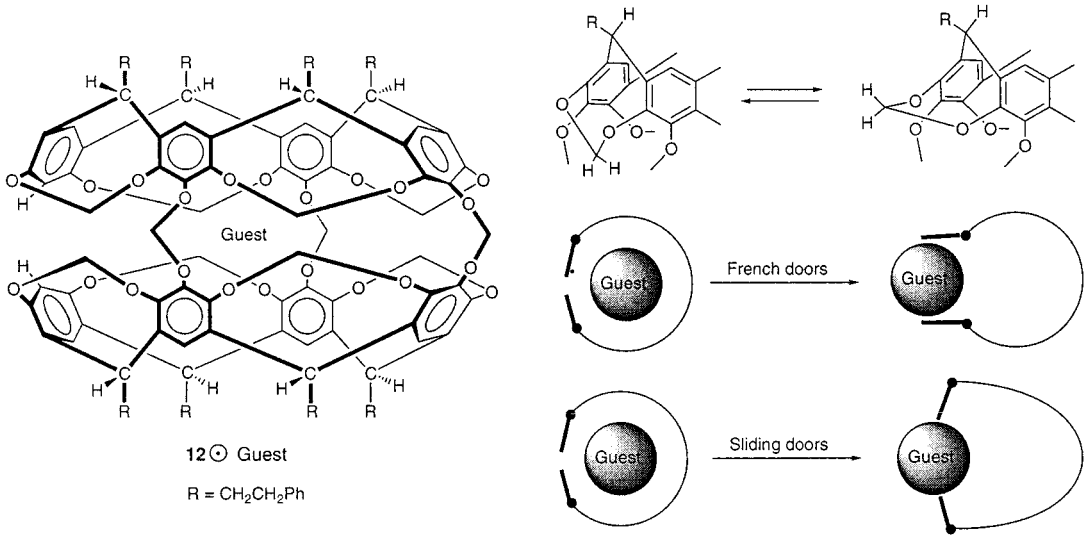


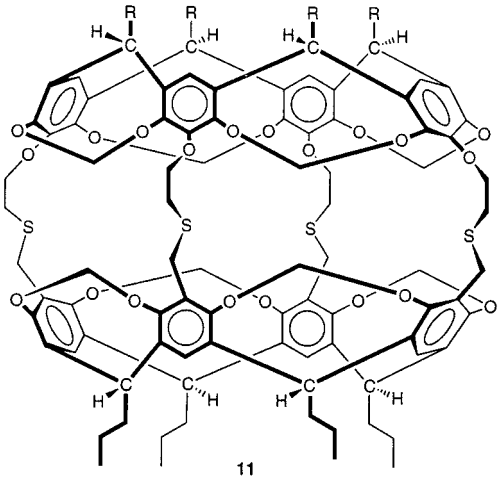
FIGURE 6. French door and sliding door mechanisms.

host's skin. In carceplexes, this barrier is so high that guest escape is impossible without host destruction. Related to constrictive binding are energies keeping rotaxanes assembled.[12] In rotaxanes, a macrocycle is slipped over a molecular dumbbell. The activation energy of rotaxane dissociation (slipping-off), which requires slipping of the macrocycle over a stopper, varies greatly and in some rotaxanes prevents slipping-off (Figure 4b).

Binding contributions for several hemicarceplexes **10**·guest were investigated experimentally.[13] Intrinsic binding for **10** varied inversely with guest size, while constrictive binding correlated with guest cross section. Calculations and a crystal study suggest that constrictive binding for **10**·guest involves the reorganization of host structure from a wrapped to an unwrapped state (Figure 5). Thus, **10**·guest and many other hemicarceplexes are stable at room temperature, yet slowly dissociate at temperatures above 100 °C.

Hemicarceplexes are chiral in their wrapped state due to the twisting of the host's cavitands. Chapman and Sherman introduced the term *twistomers* for the two twisted enantiomers. Recently, they observed the wrapping (twisting) and unwrapping (untwisting) of hemicarceplex **5**·guest by variable-temperature NMR spectroscopy and measured the energy barrier for this process.[14] In hemicarceplex **5**·(*R*)-(−)-2-butanol, the twistomers are diastereomers which interconvert with an activation barrier of $\Delta G^{\ddagger} = 12.6$ kcal/mol, based on the coalescence temperature of the guest and host NMR signals. The activation barriers of *twistomerism* and hence its detectability strongly depend on the nature of the bridges. Thus, only a *half-twistomerism* was observed for hemicarceplexes **11**·guest with guest = NMP, DMF, and DMA due to largely different rates of twistomer isomerization in both hemispheres of **11**·guest.[15]

Molecular mechanics calculations by Houk and coworkers suggest that "gates" control constrictive binding in some hemicarceplexes.[16] Two gating mechanisms were proposed (Figure 6). In the *French door* mechanism, the methylene spanners (X in Figure 2) open the portals by a chair-to-boat transition, which requires an activation energy of 17.5 kcal/mol. Calculations for **10**·ethyl acetate predict that both *French door* and *sliding door* mechanisms lower the constrictive binding energy from 26 to 20 kcal/mol, close to the experimentally measured activation barrier of 22.2 kcal/mol.[13] For hemicarceplexes of **12**



11

R = $(CH_2)_4CH_3$

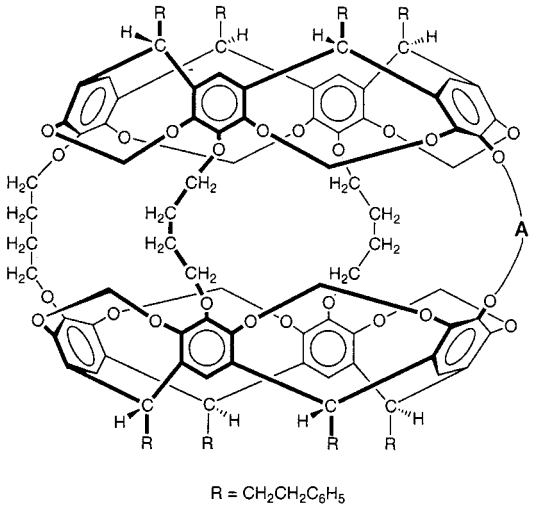
with $(CH_3)_2NCHO$ or $(CH_3)_2NCOCH_3$, a double French door mechanism is predicted to lower the barrier to guest escape by approximately 28 kcal/mol.[16a]

Less Symmetrical Hemicarcerands

In addition to gating, the lengths of the bridges and the sizes of the guests control complex formation and stability in solution. In 1995, diol **13**, containing only three $(CH_2)_4$ bridging groups, and new host systems **14**−**24** synthesized from **13**, in which the fourth bridge differs from the other three (Figure 7), were reported.[17−20] These unsymmetric hosts allowed the investigation of the dependence of complexation properties on the portal size and shape. The decomplexation rate constants for the 1,4-dimethoxybenzene complexes increase as the lengths of the fourth bridges increase (**6** ≪ **19** < **20** < **22**).[20] For **19**·1,4-dimethoxybenzene and **22**·1,4-dimethoxybenzene, the increase in portal size by one CH_2 group corresponds to an increase in the rate constant by a factor of 177. However in **22**, **23**, and **24**, the largest portals are nominally the same size (28-membered rings). Increasing the *blocking power* as in **23** by substitution of 1,4-$(OCH_2)_2C_6H_4$ for the $O(CH_2)_6O$ bridge of **22** decreases the rate constant by a factor of 9.5.[20] This is consistent with the orientation of the 1,4-$(OCH_2)_2C_6H_4$ bridge in the crystal structure of **23**·$PhNO_2$.[19] When the 9,10-$(CH_2)_2$-anthracenyl bridge (**24**) is substituted for the $(CH_2)_6$ bridge of **22**, the rate constant decreases by a factor of at least 600.[20] The strong dependence of decomplexation rates on the nature of the unique bridges and the sizes and shapes of the guests is encouraging for a hemicarcerands approach to specificity of binding of important organic compounds.

Modulation of portal size and inner-phase shape is also achieved through varying the intrahemispheric spanners as in **25** (**MM**), **26** (**EE**), **27** (**PP**), **28** (**EM**), **29** (**PM**), and **30** (**PE**) (Figure 8).[21]

Corey−Pauling−Koltun (CPK) model examination suggests that **P** bowls are conformationally mobile. However, if bonded rim-to-rim with relatively rigid **E** or **M** bowls as in **27** or **28**, the **P** bowls assume a **bo**−**su** conformation,



R = $CH_2CH_2C_6H_5$

13, A = H H; **14**, A = $CH_2CH_2(OCH_2CH_2)_3OCH_2CH_2$;

15, A = CH_2; **16**, A = $(CH_2)_2$; **17**, A = $(CH_2)_3$; **6**, A = $(CH_2)_4$;

18, A =  ; **19**, A = $(CH_2)_5$; **20**, A =  ;

21, A =  ;**22**, A = $(CH_2)_6$; **23**, A =  ;

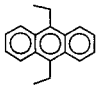
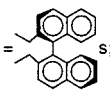
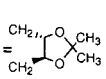
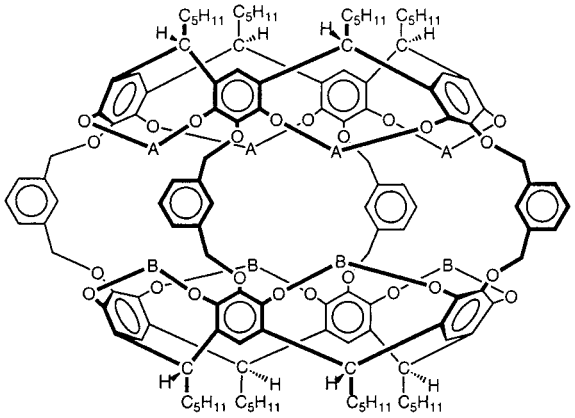
24, A =  ; **33**, A =  s; **34**, A = 

FIGURE 7. Hemicarcerands with a unique fourth bridge.



25, A = CH_2, B = CH_2; **26**, A = $(CH_2)_2$, B = $(CH_2)_2$;
27, A = $(CH_2)_3$, B = $(CH_2)_3$; **28**, A = $(CH_2)_2$, B = CH_2;
29, A = $(CH_2)_3$, B = CH_2; **30**, A = $(CH_2)_3$, B = $(CH_2)_2$

FIGURE 8. Hemicarcerands with different spanner groups A and B in the upper (A) and lower bowls (B). A and B are ethylene (**E**), methylene (**M**), or propylene (**P**).

with the four *b*ridges *o*utward (**bo**) and the four *s*panners *u*pward (**su**). Models of hemicarcerands **25**−**30** provide the order **PP** > **PM** > **MM** > **PE** > **EM** > **EE** in maximum portal size. Because **P** bowls are flexible, the order of portal adaptability to guest shape is **PP** > **PM** > **PE** > **MM** > **EM** > **EE**. These hosts show high structural recognition in complexation. For example, 1,2-disubstituted benzene guests are preferred to 1,3- and 1,4-disubstituted isomers,

and **EE** complexes PhCH(Me)CH_2Me ~25 times faster than its isomer Me_3CPh.

Chiral Recognition in Hemicarcerands

Portal adaptability to guest shape is very important for the chiral recognition in complexation−decomplexation of hemicarcerand−hemicarceplex systems, which was reported in 1991 for (S_4)-**31** and (R_4)-**32** (Figure 2).[22]

More recently, (*S*)-**33**·$CHCl_3$ and (*SS*)-**34**·Me_2NCOMe (Figure 7) were prepared from **13**.[23] The preparation of (*S*)-**33**·guest in solutions of large excesses of suitable racemic guests in $(Me_2N)_3PO$ (a solvent too large to enter **13**) produced diastereomeric ratios of 1:1 to 1:5. Heating (*S*)-**33**·$CHCl_3$ in the presence of eight different racemic guests gave diastereomeric ratios for (*S*)-**33**·guest ranging from 1:1 to 1:2.7. On the other hand, (*SS*)-**34** showed chiral recognition with only one guest, suggesting that, for (*SS*)-**34**, the guest preferentially enters through the more flexible nonchiral portals instead of the two chiral portals.

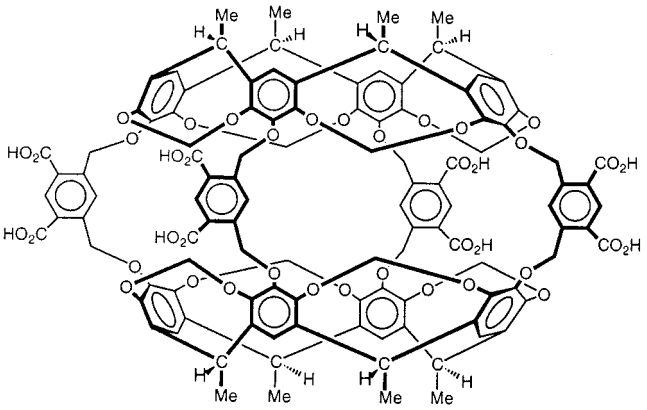
Most dramatically, (*S*)-**33**, in the presence of excess racemic 4-$MeC_6H_4S(O)Me$, formed exclusively (*S*)-**33**·(*R*)-4-$MeC_6H_4S(O)Me$. The diastereomeric ratio must be >20, since no complexed guest was detected by ^{1}H NMR when the experiment was repeated with only (*S*)-guest and (*S*)-**33**. The fast decomplexation rate of (*S*)-**33**·(*R*)-4-$MeC_6H_4S(O)Me$ indicates that chiral recognition involves an equilibration between diastereomers rather than a kinetic resolution. A ratio >20 provides a value of $\Delta G > 2.4$ kcal/mol difference in free energy for the two diastereomeric complexes. When the 4-Me group of the guest was omitted as in racemic $C_6H_5S(O)Me$, the diastereomeric ratio was 1.6, or $\Delta G = 0.37$ kcal/mol in favor of the (*R*)-guest.[23]

Can chiral hemicarceplexes, differing only in the configuration of the guest, be separated by chromatography? Experimentally, hemicarceplex (*S*)-**33**·(*R*)-PhS(O)Me was easily separated from (*S*)-**33**·(*S*)-PhS(O)Me ($R_f = 0.41$ and 0.27, respectively), whereas (*SS*)-**34**·(*R*)-PhS(O)Me and (*SS*)-**34**·(*S*)-PhS(O)Me gave the same retention times. The acetonide bridge of (*SS*)-**34** is relatively rigid, adapting very little to the configuration of the guest, while the bismethylene−binaphthyl bridge of (*S*)-**33** can change its naphthyl-to-naphthyl dihedral angle to complement its guest.

Hemicarcerands with four threonide bridges, (SS_4)-**35** and (SS_4)-**36** (Figure 2), were synthesized, and the crystal structures of their complexes were determined.[24] The ^{1}H NMR spectrum of (SS_4)-**35**·Me_2SO in $CDCl_3$ gave two CH_3 singlets at δ −0.91 and −1.03. Neither splitting nor coalescence of these signals occurred for (SS_4)-**35**·Me_2SO between −80 and 180 °C, showing the enantiotopic character of the guest methyls in the asymmetric environment of the chiral host. In 4:1 2-butanol (racemic)−Ph_2O, (SS_4)-**35** formed a 2:1 ratio of diastereomeric complexes, with widely differing R_f values ($R_f = 0.8$ and 0.5) on thin-layer chromatographic plates. Thus, (SS_4)-**35**·2-butanol shows a surprisingly large sensitivity of surface-absorption properties, as does (*S*)-**33**·PhS(O)Me. The fact that (SS_4)-**36** is soluble in EtOH suggests that if the eight $PhCH_2CH_2$ groups of (SS_4)-**36** were replaced by Me groups, the host might be water soluble.

Water-Soluble Hemicarcerands

Water solubility is particularly desirable if hemicarcerands are candidates for drug delivery systems. Recently, the synthesis, spectra, and binding properties of the first water-soluble hemicarcerand **37** were reported.[25]



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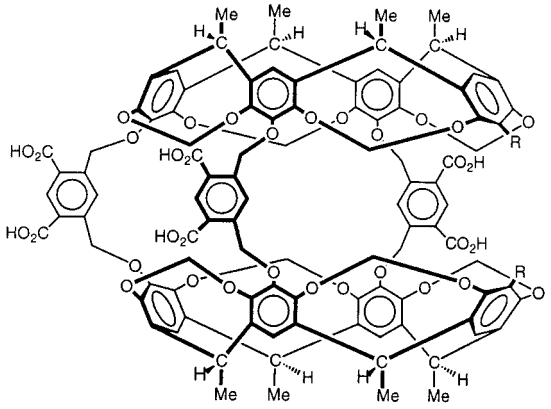
Octaacid **37** formed one-to-one stable hemicarceplexes with 14 guests in D_2O at pH 9 whose ^{1}H NMR spectra were recorded. Slow exchange between free and incarcerated guests made spectral differentiation possible. Complexation was complete in a few minutes at room temperature except for naphthalene, whose dissolution in D_2O was the rate-limiting step. Very likely, other guests that form stable hemicarceplexes with **25** (Figure 14) also form stable complexes with **37** in D_2O, since the hosts' interiors are nearly identical. Complexes of **37** and **25** with the common guests 1,4-$Me_2C_6H_4$ and 1,4-$(MeO)_2C_6H_4$ have been studied. Unlike the complexes of **37**, those of **25** decomplex rapidly at 25 °C in $CDCl_3$, preventing the recording of their ^{1}H NMR spectra. Since the guests are lipophilic, hydrophobic binding should contribute more to the stability of **37**·Guest in D_2O than does solvophobic binding in $CDCl_3$ to **25**·Guest.[25]

Surprisingly, **37** failed to complex lipophilic salts $Me_4N^+Br^-$, $PhMe_3N^+Br^-$, $PhCH_2Me_3N^+Br^-$, and 3-$MeC_6H_4CO_2^-Na^+$. Probably, D_2O solvates their charges better than does the interior of **37**. It appears that the enthalpic solvation energies of the ions by water inhibit complexation, though the release of many inner-phase- and guest-solvating water molecules would provide an entropic driving force for complexation.

Piatniski et al. drew the same conclusions from a calorimetric study of the binding properties of the tris-bridged hosts **38** and **39**.[26] Binding of charged guests in water was not observed unless complexation does not require desolvation of the charged guest portion. Binding constants for noncharged organic guests ranged from 10^3 up to 10^{-7} M^{-1}. An enthalpy−entropy plot showed that guest binding requires a larger degree of desolvation than observed for other open hosts, e.g., cyclodextrins or



38 (R = H)

39 (R = OH)

cyclophanes. The order of affinity for the isomeric xylenes and dimethoxybenzenes is meta > para ≫ ortho. The observed preference for meta-substitution underlines the importance of CH−π interactions for molecular recognition by hemicarcerands: for the meta-disubstituted guests, the number of CH−π interactions between the guest and the host's aryl units is maximized (Figure 9).

Reactive Intermediates and Inner Phase Chemistry

One ingenious application is the stabilization of short-lived reaction intermediates as guests, protected from destruction by the constrictive binding of the surrounding hemicarcerand. The beauty of the container approach is its simplicity, compared to other techniques for studying reaction intermediates. Cram et al. first stabilized the highly reactive cyclobutadiene **40**, the "Mona Lisa of organic chemistry" (Figure 10).[27] They generated **40** photochemically from α-pyrone **41** inside hemicarcerand **12** (Figure 6). The structure of cyclobutadiene is critical to the theory of aromaticity,[28] yet prior to its inner-phase isolation, the molecule had been made and studied only in cryogenic matrixes below 8 K.[29]

In the absence of oxygen, **12·40** was stable up to 60 °C! When a solution of **12·40** was oxygenated, inner-phase maleic aldehyde **42** was produced. Prolonged photolysis split incarcerated **40** into two acetylene molecules, which escaped into the bulk phase. A reaction cycle of reactive intermediates was completed inside the inner phase: photolysis at 300 nm converted **12·41** into photopyrone **12·43**, which rearranged at 90 °C to **12·44**. Upon heating, **12·44** reverted quantitatively to **12·41**.

These transformations were essentially quantitative. They all took place in the inner phase. Cram predicted the inner-phase stabilization of other highly reactive species, and indeed, almost half a century after G. Wittig postulated didehydrobenzene **45**,[30] and J. D. Roberts proved its existence via ^{14}C-labeling studies,[31] this reactive intermediate was stabilized by incarceration (Figure 10).[32]

o-Benzyne **45** was generated photochemically from benzocyclobutenedione **46** inside **6** (Figure 2). Photolysis above 400 nm gave incarcerated benzocyclopropenone **47**, previously studied in bulk solution only below −78 °C.[33] Now, protected from hydrolysis by the surrounding host shell, **47** was stable at room temperature, and the crystal structure of **6·47** was determined.[34] Further photolysis extruded CO and generated **6·45**. Because ^{13}C NMR signals are less strongly shifted, fully ^{13}C-labeled *o*-benzyne was generated inside **6** and its ^{13}C NMR spectrum recorded. Comparison of the guest ^{13}C−^{13}C coupling constants with coupling constants of model compounds suggests that incarcerated *o*-benzyne is a cumulene.[32] However, the most recent ab initio calculations[35] do not support the pronounced bond length alternation expected for a cumulene, and the electronic structure of *o*-benzyne is still in question.

Above −98 °C, incarcerated *o*-benzyne undergoes an innermolecular Diels−Alder reaction with an aryl unit of **6**.[36] Though an innermolecular reaction may be unwanted, reactions at a concave surface are unusual,[37] and their study might be useful for probing topochemical effects in solids or rigid matrixes.[38] Only one product is formed in the reaction of **45** with **6**.[36] The activation enthalpy $\Delta H^{\ddagger}$ = 11.6 kcal/mol for the innermolecular reaction is 0.9 kcal/mol higher than that calculated for the Diels−Alder reaction between benzene and **45**, suggesting a poor fit of host and guest in the transition state due to the concave surface of the hemicarcerand reactant.[39]

Recently, the highly strained cycloheptatetraene **48** was stabilized by incarceration in the inner phase of **6** (Figure 11).[40,41] This important intermediate in the phenylcarbene rearrangement has been subject of numerous experimental and theoretical studies.[42−44] Photolysis of **6·**phenyldiazirine led to **6·48** (30% yield) via a photochemical phenylcarbene rearrangement after undesired innermolecular phenylcarbene insertion reactions were partially suppressed by deuterating **6** (X = CD_2 in Figure 2). Like that of cyclobutadiene, the inner-phase stability of **48** is remarkable. Although free **48** has fleeting existence in solution, **6·48** is stable at 60 °C in the absence of oxygen. Very unexpected is the quantitative formation of **6·**benzene if **6·48** is exposed to oxygen. Low-temperature NMR studies uncovered the intermediate formation of dioxirane **49**, which decarboxylates after a cycloheptatriene−norcaradiene shift. Surprisingly, incarcerated **48** does not react with bulk-phase water or methanol, despite their ability to enter the inner phase through a portal in the host shell. Free **48** reacts instantaneously with both reactants via the planar cycloheptatriene **50**, which is the transition-state structure for the enantiomerization of **48**.[45] In an effort to measure the enantiomerization barrier of **48**, phenyldiazirine was photolyzed inside chiral (*S*)-**34**, yielding a 2:3 mixture of diastereomeric hemicarceplexes (*S*)-**34·**(+)-**48** and (*S*)-**34·**(+)-**48**.[41] The absence of dynamic broadening of guest protons in the ^{1}H NMR spectrum of both diastereomeric hemicarceplexes at 100 °C suggests a barrier height greater than 19.6 kcal/mol, consistent with theoretical predictions.[44] From this study it is clear that the reaction phase has a tremendous effect on the rate of interconversion between **48** and **50**.

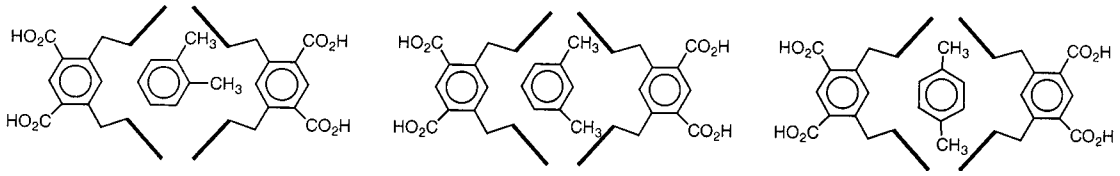


FIGURE 9. Preferred orientations of the isomeric xylenes in the inner phases of **39** and **40**, illustrating the different number of host−guest CH−π interactions.

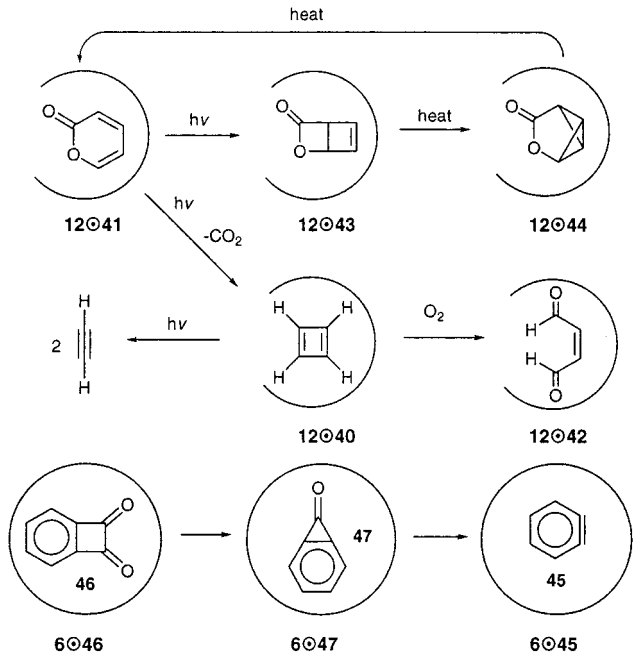


FIGURE 10. Photochemical generation of cyclobutadiene and *o*-benzyne inside hemicarcerands **12** and **6**, respectively.

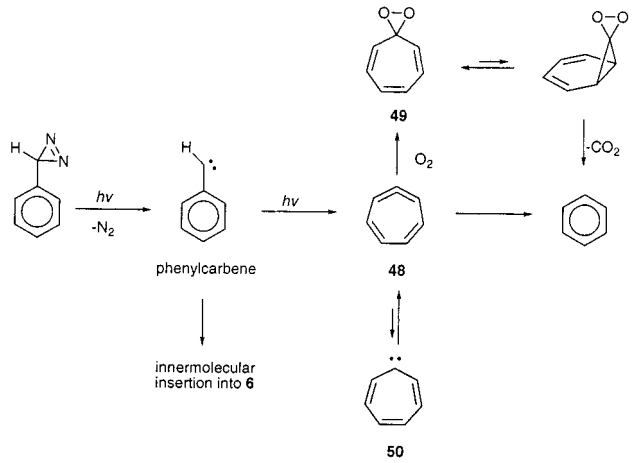


FIGURE 11. Inner-phase phenylcarbene rearrangement inside hemicarcerand **6**.

Through-Shell Reactions

Other through-shell reactions between incarcerated guests and bulk phase reactants have sometimes been unexpected, too. The alkylation studies of Kurdistani et al.[17] suggest relationships between guest reactivity, guest orientation, and bulk-phase reagent size for through-shell reactions. Several phenols were alkylated in the inner phase of **6** (Figure 2). Two factors, the portal size and the guest orientation in the inner phase, determined the observed reactivity. Methylation of the phenolic OH groups with MeI can be correlated with guest orientation in the inner phase relative to an equatorially located portal. Methylation of *p*-cresol or *p*-hydroquinone was impossible, while *o*-cresol, *m*-cresol, and resorcinol were quantitatively methylated, and catechol gave a mixture of mono- and dimethylated guests. Examination of crystal structures of hemicarceplexes of **6** with 1,4-disubstituted benzene guests[6b] suggests that the OH group of *p*-cresol is located in a protected polar cap of the host. On the other hand, ortho- or meta-disubstituted benzene guests have one substituent in a shielding polar cap, whereas the second substituent is close to an equatorial entryway. A linear transition state, with a "pseudo solvent cage" of limited conformational flexibility in the host's portal, is consistent with these results (Figure 12a).

The ability to travel long distances through space makes electrons ideal reactants for through-shell reactions. An oxidation−reduction cycle involving the four incarcerated hydroquinones **51**−**54** and the parent quinones **55**−**58** (Figure 12b) was carried out in the inner phase of **6** (Figure 2).[46] The normally unstable quinones were stable at 100 °C when protected by the surrounding host and were quantitatively reduced back to the hydroquinones. Surprisingly, incarcerated nitrobenzene **59** was reduced to *N*-hydroxylaniline **60** rather than aniline, the product in the bulk liquid phase. These results suggest that electrons and protons are transferred through the host portals in to and out of the inner phase. They also imply the possibility of electron transfers between two or more incarcerated guests whose hosts are placed at controllable distances from one another. This was one motivation to synthesize the first dimeric hemicarcerand systems, in which either identical or different cavities with equal or different guests can be held apart at designed distances.[47]

Dimers **61**·2NMP and **61**·2DMA were prepared by the reaction of 1,2,4,5-$(BrCH_2)_4C_6H_2$ **62** with 2 mol of **13** (eqs 1 and 2, Scheme 1). Although *m*-xylyl or *o*-xylyl dimers presumably could be formed, no *m*-xylyl product **63** was found. The product-determining steps involve the formation of the second ether linkage, to give a 26-membered ring (*o*-xylyl reaction) or a 27-membered ring (*m*-xylyl reaction). Apparently, the *o*-xylyl linkage is kinetically favored.

A second system was synthesized from two hemicarceplexes, **64**·$CHCl_3$ and **65**·$CHCl_3$ (eq 3, Scheme 1). During product isolation, the $CHCl_3$ guests exchanged with water to give **66**·$6H_2O$, suggesting that it is possible to prepare dimers with different guests in the two cavities.

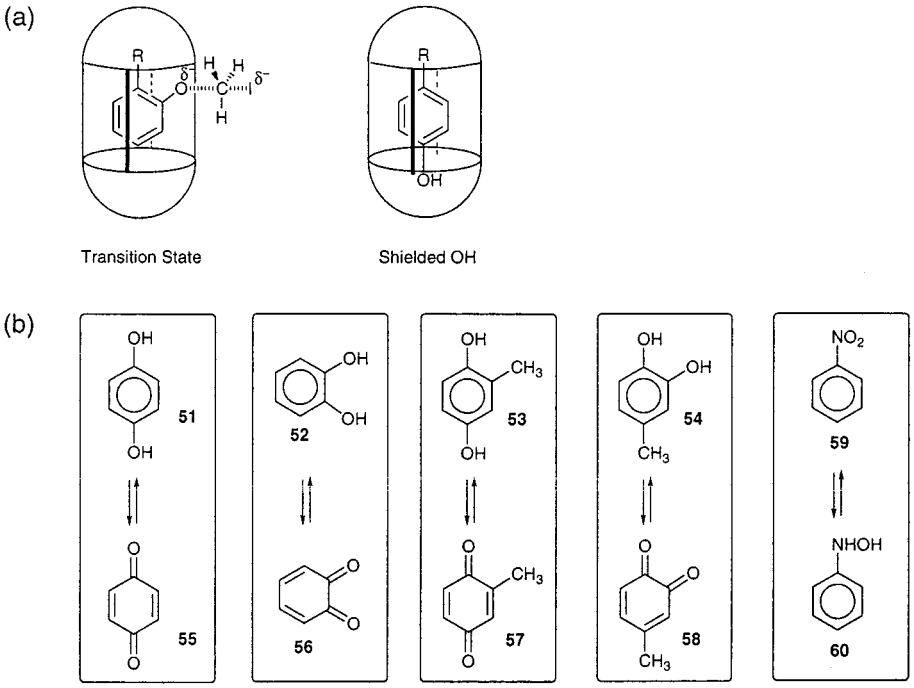
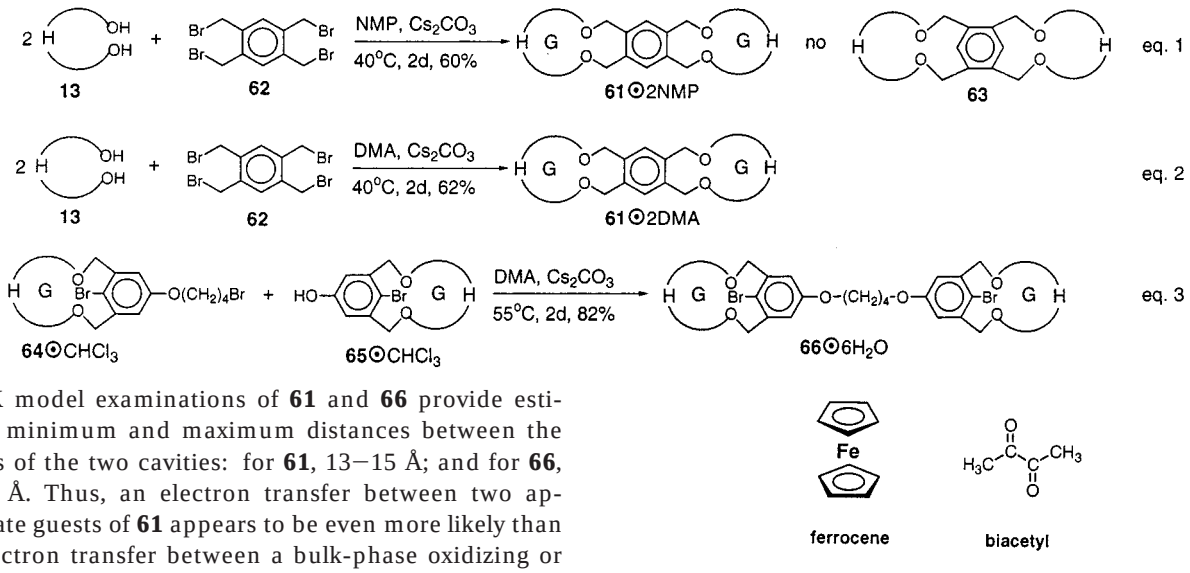


FIGURE 12. Schematic representation of transition state for exposed O^- and protected OH (a) and oxidations and reductions in the inner phase of **6** (b).

Scheme 1



CPK model examinations of **61** and **66** provide estimated minimum and maximum distances between the centers of the two cavities: for **61**, 13−15 Å; and for **66**, 13−26 Å. Thus, an electron transfer between two appropriate guests of **61** appears to be even more likely than the electron transfer between a bulk-phase oxidizing or reducing agent and an incarcerated guest, as observed for the quinones.[46]

In a further investigation of redox reactions involving hemicarceplexes, Kaifer et al. compared the electrochemistry of free ferrocene and of ferrocene incarcerated in host **67** (Figure 2).[48] Reversible heterogeneous electron transfer, kinetically and thermodynamically hindered in the inner phase, was successfully demonstrated. A more positive half-wave potential for oxidation due to the hydrophobic nature of the inner phase and a 10-fold rate retardation were measured. Kaifer et al. suggested that rate retardation might result partly from the higher mass of **67**·ferrocene compared to that of ferrocene and partly from a change in electronic coupling between the ferrocene center and the electrode surface, due to the increase in minimum electrode-to-ferrocene center distance from 3.5 Å for free ferrocene to about 9 Å for **67**·ferrocene.

Whether the hemicarcerand's aromatic structure mediates the electronic coupling is not clear. Deshayes and coworkers[49,50] investigated this important aspect of electron and triplet energy-transfer processes through a disordered intervening medium which is difficult to study in solution with freely diffusing acceptors and donors. In a detailed investigation of the temperature dependency of through-shell triplet energy transfer between incarcerated biacetyl (**10**·biacetyl; Figure 5) and various bulk phase acceptors,[50] they demonstrated that the intervening host shell affects the triplet energy-transfer rates very little. By far most important are the internal reorganization energies of the reactants. The choice of biacetyl as triplet energy donor

was fortunate. Its small internal reorganization energy allowed probing the correlation between the internal reorganization energy of the bulk-phase acceptor and the triplet energy-transfer rates. Since the measured rates were far below the diffusion-controlled limit, typical inverted region behavior as predicted by the classical Marcus relationship for nonadiabatic energy transfer was observed. Due to the importance of the internal reorganization energy of the reactants, two different donor/acceptor pairs with identical driving force can have triplet energy-transfer rates that differ by as much as 3 orders of magnitude.[50] These remarkable results and those discussed in the previous section show that hemicarcerands allow one to address long-standing questions important to physical organic chemistry in a novel and elegant fashion.

Future Aspects

The exploration of the chemistry of hemicarcerands from conception to the present involved their design and synthesis, determination of their guest-binding properties, and their use to address scientific questions. Designability of molecular structures of hosts and guests for specific uses is an exciting feature of hemicarcerand research. We anticipate future uses of hemicarceplexes in the following fields: catalysis, drug and radiation delivery and release systems, separation science, guest−indicator systems, light-electrical switches, super- and semiconducting polymers, memory storage devices, and scavenging impurities for water purification. These unique hosts will continue to be useful in the elucidation of reaction mechanisms, in the stabilization of important reaction intermediates, and in providing inner phases as media for unusual organic reactions.

Personally attractive aspects of hemicarcerand research are its combinations of mystique with revelation, design with correlation, novelty with utility, and basic with applied research. It exercises in equivalent portions the imaginative and the analytical aspects of the intellect. Research results speak to the receptive investigator dictating the next experiments and suggesting distant new goals.

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