# Building on Cram's Legacy: Stimulated Gating in Hemicarcerands

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CONSPECTUS: Donald Cram's pioneering Nobel Prize-winning work on host—guest molecules led eventually to his creation of the field of container molecules. Cram defined two types of container molecules: carcerands and hemicarcerands. Host—guest complexes of carcerands, called carceplexes, are formed during their synthesis; once a carceplex is formed, the trapped guest cannot exit without breaking covalent bonds. Cram defined a quantity called constrictive binding, arising from the mechanical force that prevents guest escape. The constrictive binding in carceplexes is high. In contrast, hemicarcerands have low constrictive binding and are able to release the incarcerated guests at elevated temperatures without breaking covalent bonds. We have designed molecules that can switch from carcerand to hemicarcerand through a change in structure that we call gating. The original discovery of gating in container molecules involved our computational studies of a Cram hemicarceplex that was observed to release a guest upon heating. We found that the side portals of this hemicarceplex have multiple thermally accessible conformations. An eight-membered ring that is part of a portal changes from a "chair" to a "boat" structure, leading to the enlargement of the side portal and the release of the guest. This type of gating is analogous to phenomena often observed with peptide loops in enzymes. We refer to this phenomenon as thermally controlled gating.

We have also designed and synthesized redox and photochemically controlled gated hemicarceplexes. Gates are built onto host molecules so that the opening or closing of such gates is stimulated by reducing or oxidizing conditions, or by ultraviolet irradiation. In both cases, the appropriate stimuli can produce a carceplex (closed gates) or hemicarceplex (open gates). A hemicarceplex with closed gates behaves like a carceplex, due to its very high constrictive binding energy. When the gates are opened, constrictive binding is dramatically lowered, and guest entrance and exit become facile. This stimulated switching between open and closed states controls access of the guest to the binding site. The experimental and computational investigations of gated hemicarcerands and several potential applications of gated hemicarceplexes are described in this Account.
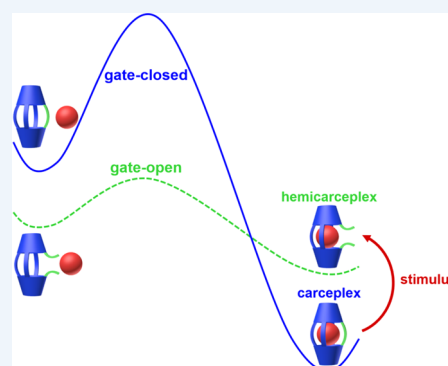
INTRODUCTION

Evolution has led to selective protein and nucleic acid receptors that specifically bind small molecules and catalyze chemical reactions. Inspired by Nature's ability to create biological entities that bind specific organic compounds, scientists have synthesized host molecules to mimic the host—guest binding processes in Nature. Numerous synthetic host systems have been designed and developed, pioneered by the discoveries of crown ethers by Pedersen,[1] spherands by Cram,[2] and cryptands by Lehn.[3] These hosts are all molecules bearing concave surfaces that provide convergent binding sites for another molecule or ion with compatible divergent binding sites. Synthetic receptors often exhibit good selectivity in binding metal cations. Chiral recognition and enantiomer separation were also achieved in hosts with one or more chiral elements.[4] These achievements in host—guest complexes have laid a solid foundation for the development of more sophisticated systems.

Many natural enzymes control access of substrates to the active sites by the conformational changes of peptide loops; this phenomenon has been referred to as "gating".[5] Pancreatic lipase, an enzyme that hydrolyzes dietary fat in the digestive system, has a lid over its active site when not activated (Figure 1a). The lid opens when the protein is activated upon contact with a lipid surface. This conformational change was probed by

EPR spectroscopy in a recent publication by Carrière and co-workers.[6] HIV-1 protease undergoes a sliding door mechanism (see later discussion), as revealed from both crystal structure analysis and molecular dynamics simulations.[7] Figure 1b shows the overlap of HIV-1 protease in its *semiopen* (green) and *closed* (blue) conformations. In the *closed* conformation, the two flaps are packed onto each other closely, restricting access to the active site. In the *semiopen* conformation, the two flaps slide away from each other slightly. Molecular dynamics studies suggested that the flaps can separate even further into an *open* conformation, in which the active site is completely exposed to the environment. It is postulated that the gating motion from open to closed results from the presence of the ligand in the active site.[7a]

Gating in synthetic hosts was first discovered in our lab as a result of computational investigations on Cram's hemi-carcerands.[8] Guest molecules encapsulated in the hydrophobic cavities of *hemicarcerands* can be released without breaking any covalent bonds when the hemicarceplex is heated to a higher temperature.[9] In contrast, *carcerands* refer to a group of host
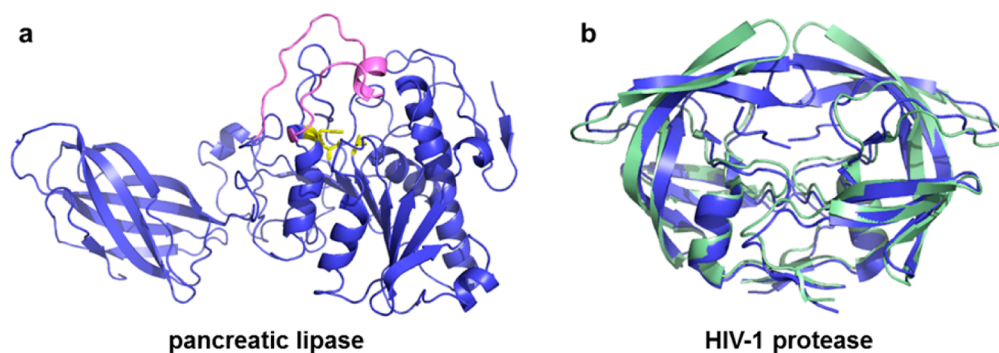
Figure 1. (a) Ribbon structure of pancreatic lipase (PDB entry 1HPL) with the active site (shown in yellow) covered by the lid (shown in purple). (b) Ribbon structures of HIV-1 protease in both closed (PDB entry 1TW7) and semiopen (PDB entry 2NPH) states (shown in blue and green, respectively).

molecules that form stable complexes with small organic molecules during synthesis; the incarcerated guests cannot escape without breaking covalent bonds in the hosts. The binding properties in such host–guest systems can be better described by introducing *intrinsic binding* (the free energy difference between the complex and the free host and guest) and *constrictive binding* (the additional activation free energy for decomplexation, arising from the physical barrier for egress of guest), as shown in Figure 2.[10] The constrictive binding free energy is also equal to the free energy of activation for binding. This quantity is near zero for an open receptor, known as a cavitand.
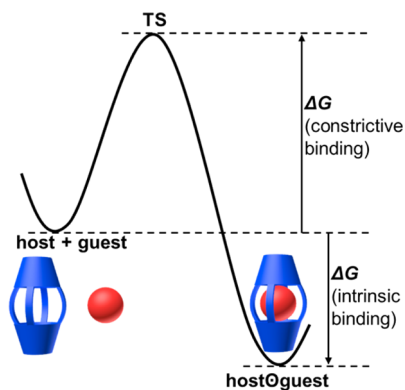

Figure 2. Energy definitions for host–guest complexation by a carcerand or hemicarcerand.

For all complexes, a more negative intrinsic binding energy produces a more stable complex and, therefore, a larger decomplexation barrier. Constrictive binding free energy does not affect intrinsic binding but does influence rates of complexation and decomplexation. If constrictive binding is higher than ∼25 kcal/mol, the host–guest complexation will take several days to occur under ambient conditions. With a closed gate, a hemicarceplex behaves like a carceplex, presenting a high decomplexation barrier, such that the imprisoned guest cannot escape. However, once the gate is opened, the decomplexation barrier of the hemicarcerplex is significantly lowered to allow release of the guest.

The mechanism of the controlled binding and release of guests in hemicarcerands was elucidated through computational studies by Nakamura in our group in the 1990s.[8] He showed that an increase in temperature results in a higher proportion of a different conformation of an eight-membered ring of the host

molecule. This occurs because there is a switch from a "chair" to a "boat" conformation, leading to the enlargement of the side portal and opening the passageway for the encapsulated guest. The concept of *gating* was introduced into the field of host–guest chemistry at that time to illustrate the idea of controllable passage of a guest entering and exiting the binding site of a host.[11]

Since then, our group has sought to achieve gating through various chemical processes. We have focused on three types of stimuli that lead to gating: thermal, redox, and photochemical, where the opening and closing of the gates involves conformational or chemical changes of the gates, stimulated by heat, redox reactions, or photolysis, respectively. This Account describes experimental and computational accomplishments from our group and others in the area of gated host–guest complexes.

■ THERMALLY GATED HEMICARCERANDS

The synthesis of thermally gated hemicarcerands can be achieved by linking two hemispheres by four bridges of proper length.[12] The synthesis of host **1a** is an example of this strategy (Figure 3a). One of the four side portals of **1a** is highlighted in blue, while a polar portal is highlighted in red. This host, **1a**, forms complexes with one or two acetonitriles molecules during its synthesis from a tetrathiolate hemisphere plus a tetrachloro hemisphere in acetonitrile solvent. The complex with two acetonitriles loses one guest molecule upon heating at 110 °C for 3 days, but the escape of the second acetonitrile was not observed.[13] Based on CPK space-filling models, Cram proposed that the acetonitrile could only escape through the polar portal, since it is larger than the side portal as shown in Figure 3b.

However, CPK models failed to explain why the escape of a second acetonitrile is not favored, nor can these models provide any information about the activation energy for the decomplexation. With force-field computations, Nakamura in our group was able to reveal some structural and dynamic properties not observable from the space-filling model or experiments.[8] To reduce the computational effort, calculations were carried out on **1b** instead of the actual host **1a**, since preliminary studies showed that the "feet" (R groups) have little effect on the portal sizes. All possible structures of **1b** were optimized with the AMBER* force field in the Macromodel program.[14] It was found that each eight-membered ring in **1** (Figure 3a, one unit is highlighted in green) has two conformations: CH_2-in and CH_2-out (Figure 3c). The CH_2-
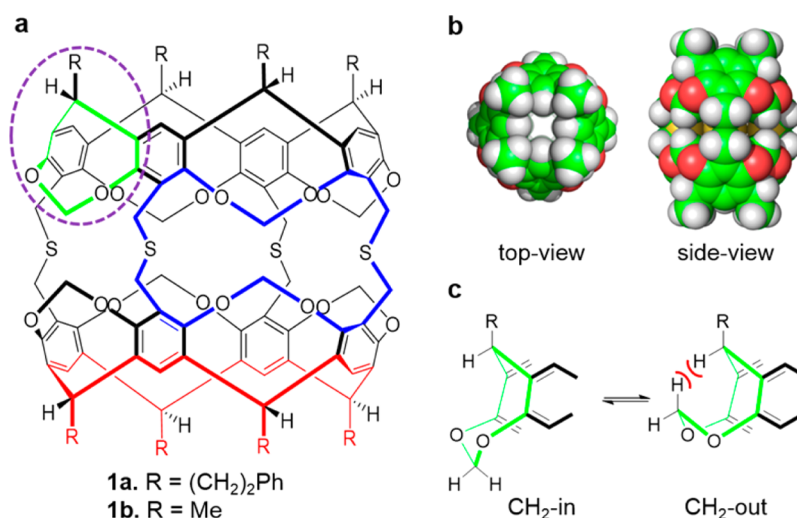
Figure 3. (a) Structure of thermally gated hemicarcerand **1** with one side portal colored in blue, one polar portal colored in red, and one eight-membered ring colored in green and circled (there are eight units of this type in **1**). (b) CPK model of **1b** showing the polar portal is slightly larger than the side portals. (c) The CH_2-in and CH_2-out conformational change in an eight membered ring in **1** (the unit that is circled in part a) that leads to the closing and opening of the thermal gate.

out conformation is calculated to be about 7 kcal/mol higher in energy than the CH_2-in conformation, due to the steric repulsion between the two clashing hydrogens in the CH_2-out conformation (Figure 3c). At room temperature, the equilibrium between CH_2-in and CH_2-out is greater than 10^5 to 1 (CH_2-out less than 0.001%). When temperature is raised to 110 °C, the proportion of CH_2-out increases by about 2 orders of magnitude.

Figure 4 shows an acetonitrile escaping from the hemi-carceplex through equatorial or polar portals. These structures
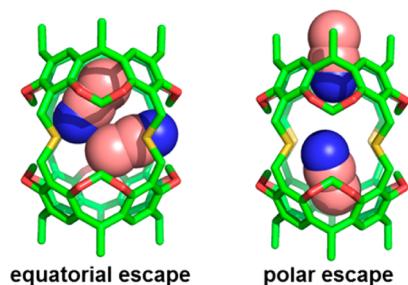

Figure 4. Equatorial and polar escape pathways of acetonitrile from host **1b**. The acetonitriles are shown in space-filling models.

were obtained by constrained optimizations. The activation energies for these two pathways obtained with all CH_2-in conformations were very high, 52 and 46 kcal/mol, respectively. This result suggested that the trapped acetonitriles are not able to escape the cavity from either the side portal or the polar portal with the host in its CH_2-in (closed) form.

However, the conformational change of the eight-membered ring from CH_2-in to CH_2-out dramatically lowers the barrier of equatorial-escape, as shown in Figure 5. Ground state hemicarceplex (Figure 5, left) has to overcome the barriers for sequential conformational flips of two −OCH_2O- moieties (22 and 26 kcal/mol, respectively) to achieve an intermediate (Figure 5, middle) with its side portal wide open. The escape of an acetonitrile through the open portal requires only 22 kcal/mol, less than the barrier for gate opening (Figure 5, right). The overall barrier for decomplexation through gating is 26 kcal/

mol, which corresponds to a half-life of 15 days at ambient temperature, but only 1 min at 110 °C. This result agrees well with the experimental observation. Molecular dynamics simulations also showed that the escape of the first acetonitrile is exergonic, while the escape of a second acetonitrile is endergonic. This explains why the second acetonitrile does not exit the cavity. Our interpretation of gating as the rate-limiting step in decomplexation was supported by the lack of a steric isotope effect in a similar hemicarceplex. Liu and Warmuth reported no isotope effect for the escape of deuterated *p*-xylene or naphthalene from a gated hemicarceplex.[15]

The term "gating" was introduced at that time to describe this conformational process that controls the entrance and exit of a guest in synthetic host molecules. Two types of gating exist in hemicarceplexes, and we named these French door and sliding door. The types of doors that inspire these names are shown in Figure 6. French door gating describes two edge-to-edge door openings, and in **1b** refers to the sequential flips of two −OCH_2O− moieties that lead to the opening of a portal. The sliding door often involves the conformational change of the whole molecular skeleton, resulting in the enlargement of the side portal, without any pronounced outward motion of the doors, as shown schematically at the bottom right of Figure 6.

From the analysis of gating processes in four different hemicarcerands, we found that the importance of gating in the complexation and decomplexation processes varies, depending on the nature of guests and the size of the hemicarcerand portals.[11] Some hosts have portals so large that the guests readily pass into and out of the cavity with almost no barriers. In such cases, gating does not influence the entry and exit of guests. An example is the complexation of hemicarcerand **2** (Figure 7, left) with benzene. Calculations with the AMBER* force field showed that there is no barrier to complexation, and the decomplexation barrier is only about 8 kcal/mol with solvation corrections, which suggests rapid entry and exit of the benzene without gating. In contrast, some hosts have portals too small to allow the passage of guest molecules even with an open gate. The barrier to loss of dimethyl sulfoxide from **3b** (Figure 7, right) is calculated to be greater than the energy to break a C−C bond (∼90 kcal/mol). Some hosts have portals
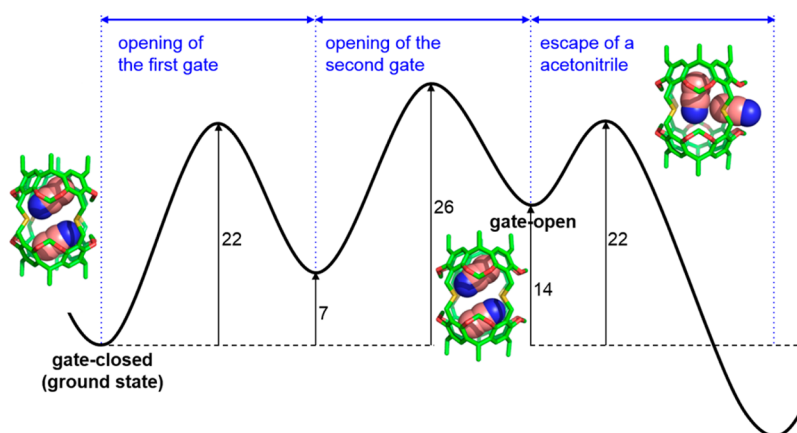
Figure 5. Energy profiles for the escape of acetonitrile from **1b** through gating. Energies in kcal/mol.
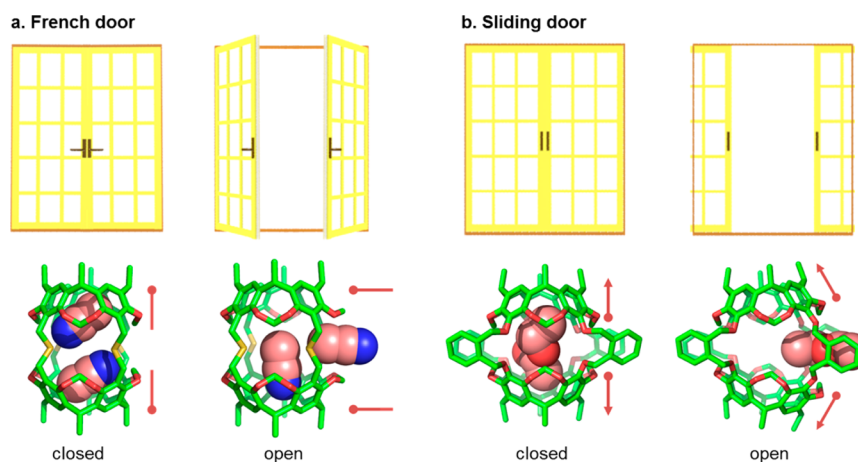

Figure 6. (a) French door cartoon and analogous gating in **1b**. (b) Sliding door cartoon and analogous gating in a four *o*-xylyl bridged hemicarcerand.
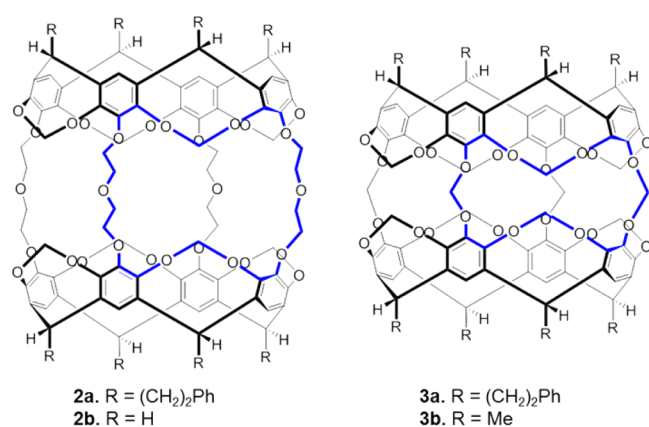

Figure 7. Structures of hosts with large portals (left) and small portals (right); one of the four side portals in each structure is highlighted in blue.

small enough to incorporate and bind guests, but still big enough for the exit of the guests upon a conformational change, as the release of acetonitrile from hemicarcerand **1**. Gating becomes a crucial factor in forming stable, and yet reversible, complexes of such hosts with appropriate guests.

We explored the involvement of gating in complexation in detail in a study of the complexation of hemicarcerand **2b** with 40 aromatic or bicyclic guests.[16] The structural optimizations

and molecular dynamics simulations with the MM3* force field showed that thermal gating is not required for the entry of smaller aromatic guests such as toluene and *p*-xylene; gating is a crucial factor only in the complexation and decomplexation of hemicarcerand **2b** with larger bicyclic guests such as norbornene. These results are in accord with the experimental fact that simple aromatics either fail to complex with hemicarcerand **2a** or escape the host cavity upon attempted isolation, while larger bicyclics form isolable complexes with **2a**.[17]

Conformational processes in crown ether hosts for ammonium and metal cations had been studied earlier by Stoddart.[18] Gating has also been explored in Klärner's molecular tweezers,[19] Badjić's molecular baskets,[20] and Cram's "vase-kite" cavitands[21] (Figure 8). These types of hosts have been reviewed recently by Badjić and by our group.[22]

Another example of a gated host is Rebek's "softball" **4a** (Figure 9),[23] a spherical dimeric container molecule held together by hydrogen bonds. This structure bears multiple thermal gates that could operate via several different gating patterns. Wang in our group studied the guest exchange mechanism in Rebek's complexes with force-field calculations.[24] The complete dissociation of the "softball" dimer requires breaking up 16 hydrogen bonds, and the energy cost is calculated to be as high as 70 kcal/mol. This indicates that the guest exchange has to occur through a gating process rather
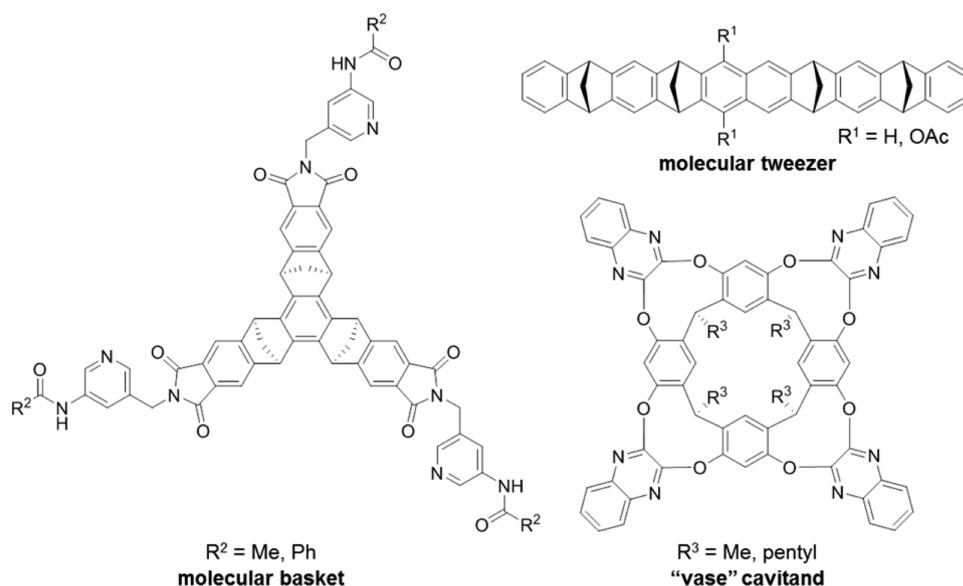
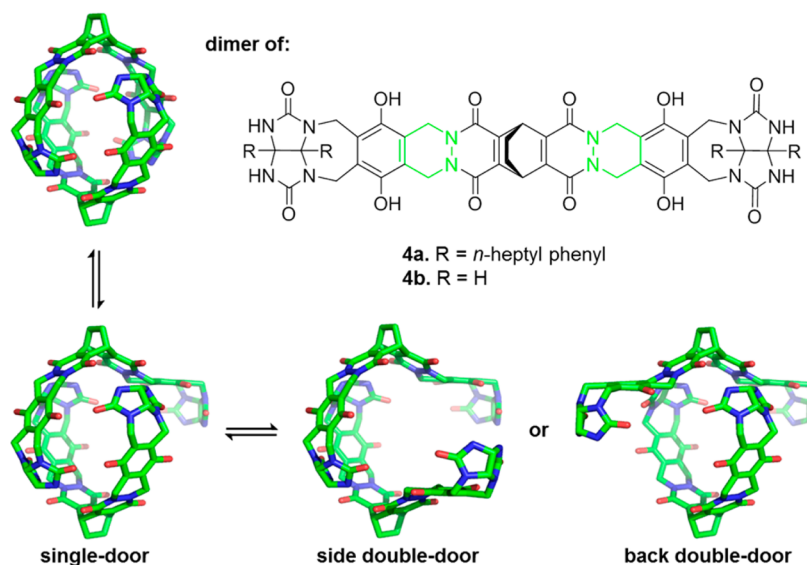**Figure 8.** Structures of additional hosts with thermal gates.

Figure 9. Structure of "softball" dimer and the three proposed "gate-open" forms.

than dissociation. Three proposed gating patterns were evaluated computationally (Figure 9) on the simplified model softball **4b**: single-door (only one gate being involved), side double-door (one gate on each monomer being involved), and back double-door (two gates on the same monomer being involved). The barriers of these three pathways are 22, 24, and 38 kcal/mol, respectively. The back double-door is not likely to take place under experimental conditions. We predicted that the single-door and side double-door processes can both occur.

Intrigued and stimulated by these observations, we set out to go beyond thermal gating and to build container molecules with gates that could be controlled by chemical and photochemical stimuli.

■ REDOX AND CHEMICAL REACTION-GATED HEMICARCERANDS

Disulfide-dithiol interchange is ubiquitous in biological proteins, and the equilibrium is known to be determined by the environmental thiol concentration. Sherman and co-

workers reported a carcerand with four disulfide bridges, which performs guest exchange under redox conditions.[25] Building on this observation, we designed a gated hemicarcerand bearing a disulfide-dithiol redox-controllable "gate".[26] Most of Cram's hemicarcerands possess four identical bridging groups, which is synthetically easier to achieve than dual- or triply-bridged hosts. These triply-bridged hemicarcerands can be obtained using similar macrocyclization reactions in relatively low yield, followed by modification of the remaining substituents to form the gate. The redox-gated hemicarcerand **5a** was synthesized with a unique fourth bridging group that undergoes disulfide-dithiol interchange in the presence of base and thiol compounds (Figure 10).

Hemicarcerand **5a** (disulfide form) was heated in neat guests (Figure 10, yellow box) above 100 °C followed by precipitation in MeOH. In this way, stable complexes between **5a** and three (colored in blue in Figure 10) out of seven guests were observed from the ^{1}H NMR spectrum. The other four guests failed to form isolable complexes with **5a** because they are
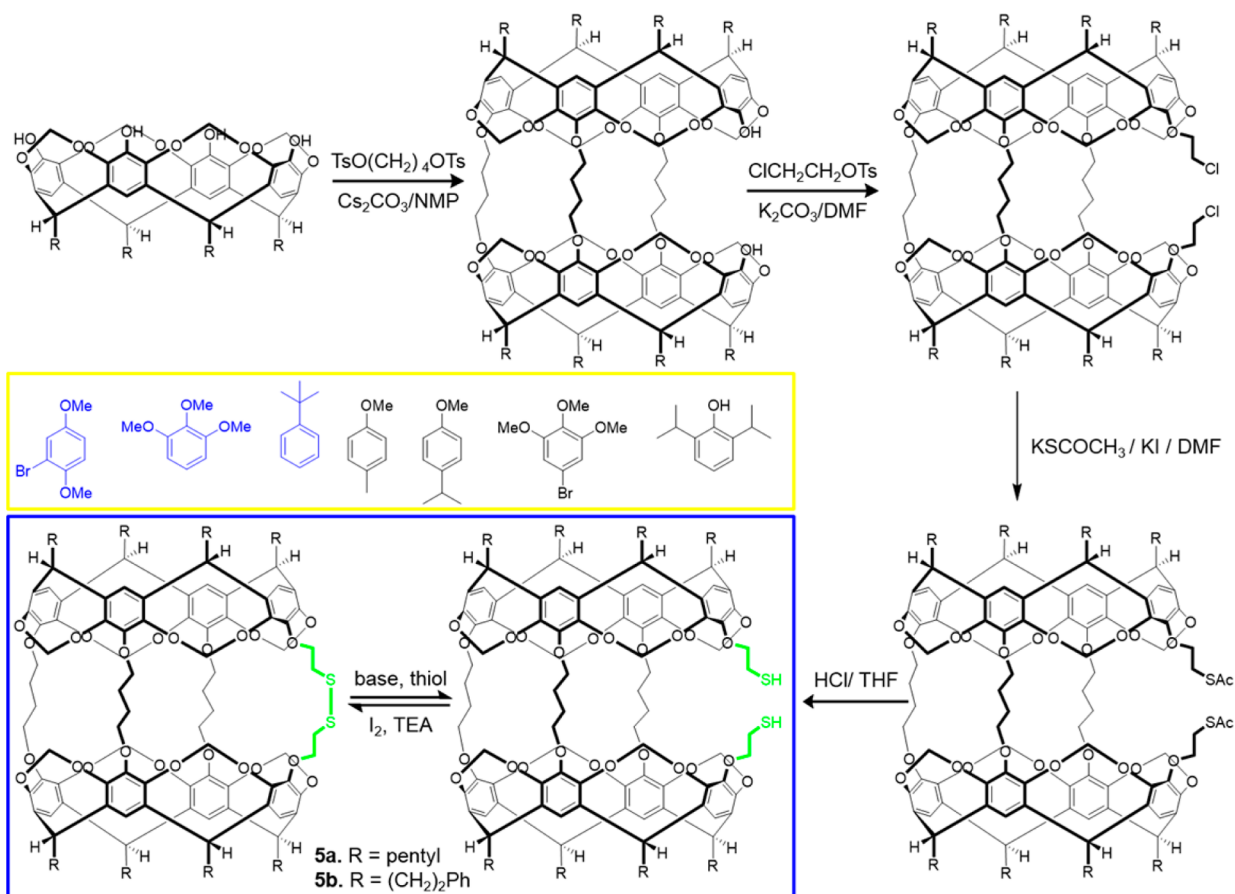
Figure 10. Synthesis of hemicarcerands **5a** (**5b** was studied computationally). Blue box: reversible gate-closing and gate-opening. The disulfide-dithiol gates are colored in green. Yellow box: guest molecules tested in complexation experiments. The first three guests (colored in blue) formed stable complexes with **5a**.
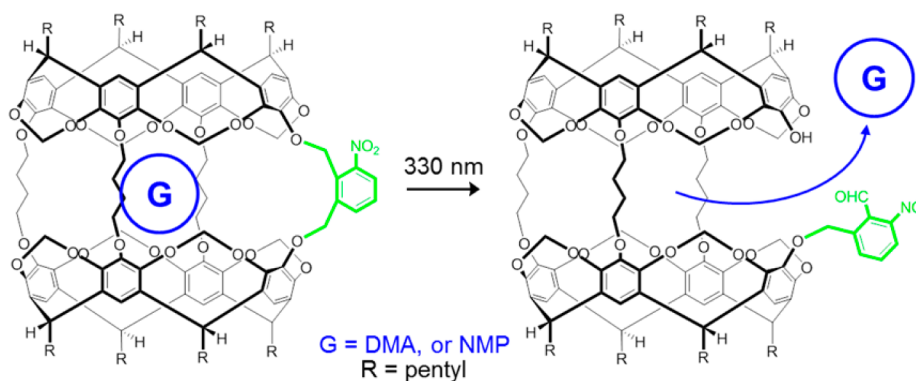

Figure 11. Photoinduced release of a guest molecule G from a photoactive hemicarceplex.

either too large to enter, or too small to be retained in the host cavity. The stable complexes were studied under reducing conditions: when subjected to dithiol (dithiothreitol (DTT) or $HS(CH_2)_4SH$) and base (DBU), the disulfide is converted to dithiol, and decomplexation occurs, as monitored by ^1H NMR spectra. Gate-opening and guest-release is accelerated by increasing concentrations of dithiol.

The disulfide-dithiol gate in **5a** provides a prototype for the development of a potential drug-delivery vehicle based on Cram container chemistry combined with gating. Since the glutathione (GSH) concentration in human cancerous cells is found to be two to five times higher than that in normal cells,[27]

the gate-opening of hemicarcerand **5** in cancerous cells should be more rapid than that in normal cells. Such disulfide-dithiol gated hemicarcerands have potential applications as anticancer-drug delivery vehicles.

Computational studies on hemicarcerand **5b** and all seven guests were carried out with the MM3* force field to determine the activation energies of complexation and decomplexation. Constrictive binding energies of the last three guests shown in the yellow box in Figure 10 are calculated to be more than 20 kcal/mol, which is in agreement with the absence of complexation upon heating the host in guest solutions. The smaller 4-methoxytoluene has a low constrictive binding
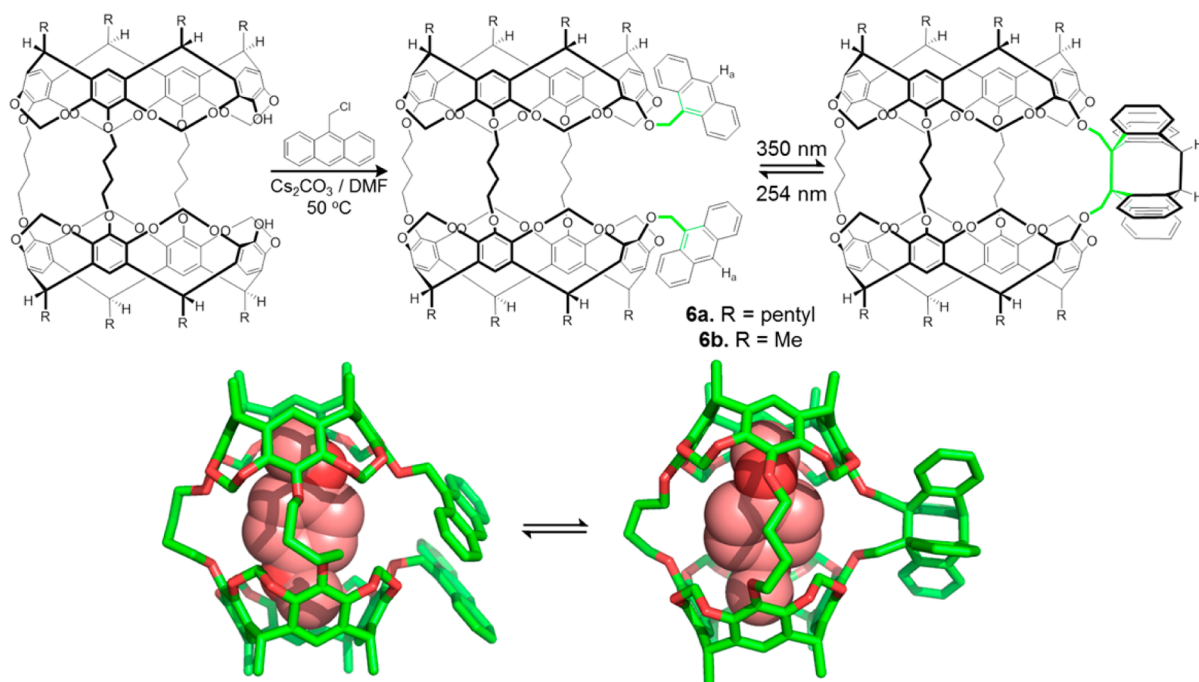
Figure 12. Top: synthesis of hemicarcerands **6a** and its the reversible gate-closing and gate-opening. The photochemical gates are colored in green. Bottom: computed structures of complexes formed between *para*-dimethoxybenzene and **6b**.

energy, but it readily escapes the cavity through the side portals upon attempt isolation. The dissociation energies for complexes of the three molecules colored in blue with **5b** in the closed form are above 20 kcal/mol, and these values are lowered by about 10 kcal/mol when the gate opens.

■ PHOTOCHEMICALLY GATED HEMICARCERANDS

Two carceplexes that can be converted to hemicarceplexes by UV radiation were reported by Deshayes and co-workers. One is shown in Figure 11.[28] This host has one bridge with a nitrobenzyl ether group. Upon irradiation at 330 nm, intramolecular hydrogen transfer to the nitro and irreversible CO bond cleavage take place. This opens the gate and allows escape of the trapped guests, either dimethylacetamide (DMA) or *N*-methyl-2-pyrrolidinone (NMP).

While this demonstrates the photochemical gate-opening that converts a carceplex into a hemicarceplex, we undertook the synthesis and study of a reversibly gated hemicarcerand. We designed a photoswitchable gated hemicarcerand **6a** (Figure 12) based on the reversible dimerization of anthracene upon irradiation.[29] The dimerization of anthracene is known to occur upon irradiation at relative long wavelength, while the retro-cycloaddition occurs at the shorter wavelength of 254 nm.[30] The synthesis of **6a** was achieved by treating the diol with 9-chloromethylanthracene in DMF using cesium carbonate as the base (Figure 12). Dimerization of anthracene occurs upon irradiation at 350 nm, resulting in the gate closing. Irradiation at 254 nm causes the gate to open and regenerate the bis-anthracene. The reversibility of gate-opening and closing processes of the hemicarcerand **6a** was confirmed by ^{1}H NMR and ^{13}C NMR spectra, as well as fluorescence spectroscopy. During one cycle of alternate irradiation at 350 and 254 nm, the emission band of anthracene decreases in intensity and then recovers to 99% of the original level. Good reversibility was observed from successive photochemical cycles.

At the same time, the structures of the open and closed host were studied with the OPLS force field. Calculations showed that the two anthracene moieties in an open-state are parallel to each other, separated by a proper distance so that they are able to dimerize to close the gate without introducing much strain. Several small organic molecules were studied with molecular mechanics calculations to predict whether a stable complex could be formed with the designed hemicarcerand. Figure 12 shows the optimized complexes formed between *para*-dimethoxybenzene and host **6b** in both open and closed states. In both cases, the methoxy groups sit perfectly in the cavities with no obvious strain, indicating that *para*-dimethoxybenzene can form stable complexes with host **6**. The participation of solvent in complexation was also taken into consideration. By increasing the number of chloroform molecules inside the cavity, it was determined that the most stable complex between **6b** and chloroform molecules is **6b**·CHCl$_3$. This complex is calculated to be more stable than **6b**·1,4-(MeO)$_2$C$_6$H$_4$, indicating the complexation between 1,4-(MeO)$_2$C$_6$H$_4$ and **6a** is not likely to take place in chloroform.

This prediction was confirmed by a complexation study of hemicarcerand **6a** with 1,4-(MeO)$_2$C$_6$H$_4$ monitored with ^{1}H NMR spectroscopy. No complexation was observed when chloroform was used as the solvent. A bulky solvent was then used in the following study. An excess of 1,4-(MeO)$_2$C$_6$H$_4$ was added to a Ph$_2$O solution of **6a** (open form). An upfield shift of the methyl protons on 1,4-(MeO)$_2$C$_6$H$_4$ was observed on the ^{1}H NMR spectrum of the mixture, indicating the formation of complex. When the mixture was irradiated at 350 nm for 1h, the upfield shift of methyl protons was maintained, and the disappearance of the anthracene peaks (H$_a$) showed that a carceplex was formed involving the gate-closed form of **6a** and the guest. The carceplex was stable indefinitely at ambient temperature without detectable release of the guest. Upon irradiation at 254 nm, a downfield shift of the methyl protons was observed along with the appearance of the anthracene

resonances, which indicates the opening of the gate and release of the guest. A series of small aromatic molecules, including toluene, *o*-xylene, *m*-xylene, and *p*-xylene, were tested in parallel with *para*-dimethoxybenzene, and they behave similarly in complexation with hemicarcerand **6a**. This example demonstrates that precise control of gating in hemicarcerands can be achieved photochemically.

■ SUMMARY

Gating, a common phenomenon in enzyme−substrate binding processes, has been introduced into artificial host−guest complexes in various forms. Starting from the observation of thermal gating in Cram's hemicarcerands, and using the tools of computational chemistry, we designed ways to stimulate the binding and release of small molecules by gating. Currently, the cavities of these gated hemicarcerands are small and only a few aromatic compounds can be accommodated. We are interested in developing gated hemicarcerands with larger cavities so that they can be used to encapsulate and deliver drug molecules. In addition, water solubility must be enhanced before such delivery vehicles can be used in biological systems. The use of gating controlled by various stimuli adds a dynamic dimension to the field of host−guest chemistry.

■ AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

Biographies

Fang Liu received her B.S. in chemistry from Nankai University, China, in 2009. She came to UCLA as an undergraduate as part of the CSST program and is now a graduate student with K. N. Houk at UCLA, studying gating in container molecules and the factors controlling reactivity in bioorthogonal cycloadditions.

Roger C. Helgeson received his B.S. at the University of Washington in 1961 and his Ph.D. degree at UCLA in 1965 under Donald J. Cram. He was a NIH postdoctoral fellow at Harvard University with Paul D. Bartlett. After 4 years as an assistant professor in chemistry department at the University of Wisconsin—Milwaukee, he returned to UCLA to work with Donald Cram from 1971 to 1997. After spending 4 years at UCLA with Fred Wudl, he joined the Houk research group where he performs experimental research on container molecules and organic reactivity and catalysis.

K. N. Houk is the Saul Winstein Chair in Organic Chemistry at UCLA. He is a computational organic chemist. He received his Ph.D. with R. B. Woodward in 1968, and overlapped with Roger Helgeson for 2 years at Harvard. He has published extensively on pericyclic reactions, stereoselectivity, molecular recognition, and enzyme design. He is a Fellow of the American Academy of Arts and Sciences, a member of the National Academy of Sciences, and is a Senior Editor of this journal.

■ ACKNOWLEDGMENTS

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