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Gated container molecules

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Donald J. Cram, the great UCLA chemist, received the Nobel Prize for his discoveries about host-guest complexes [1]. Both theoretical and experimental studies have been conducted about the nature and strength of interactions between the host and guest molecules. The concepts of constrictive binding (the activation energy of the binding process) and intrinsic binding (the free energy difference between the complex and the free host and guest molecules) were introduced to characterize different binding properties (Figure 1) [2].

The exit of a guest from a host-guest complex involves overcoming the sum of the intrinsic and constrictive binding free energies. We have published a review on binding affinities of host-guest, protein-ligand and protein-transition-state complexes [3], in which the trends in the magnitude of binding constants and selectivity in the binding process were discussed. We described that the binding constants for neutral molecules in water can be estimated within several orders of magnitude from the surface areas buried upon complexation. Our group also discovered the phenomenon of “gating” in hemicarcerands, a process that opens a wall of a host to allow guests to enter and exit [4].

This article highlights recent experimental and theoretical studies of three types of gating: thermal, redox, and photochemical gating, indicating the current status in the areas. Gated container molecules and their gating phenomena with various guest molecules are discussed. The Badji group [5] has published an excellent review of gated container molecules.

Three kinds of thermal-gated container molecules are discussed here: (a) carcerands and hemicarcerands; (b) “sportsballs” by Rebek and coworkers; (c) molecular baskets. Our earlier work identified three types of host-guest complexes and established the general importance of gating in the determination of complexation propensities [4]. For hosts with portals too small (Figure 2, 1a) for the passage of solvent or guest molecules, the energy barriers for complexation, even with gate opening, are too high to form complexes. For hosts with portals too large (Figure 2, 1b), the guest molecules can enter or exit the cavity even without gating. Gating is important in the third class of host-guest complexes—hosts with proper sized portals (Figure 2, 1c) that allow the passage of a variety of guests upon a conformational change. Two types of gating are possible in hemicarcer and **1c**—French doors (inversion of the CH₂ groups shown in Figure 2) and sliding doors (enlargement of the opening site). Our simulations indicated that both French doors and sliding doors greatly affect the complexation and decomplexation process. Details about thermal gating in container molecules will be discussed below.

Carcerands and hemicarcerands are one kind of thermal-gated container molecules. The discovery of gating came from theoretical studies of the structures and dynamics of the carceplexes developed by Cram and co-workers [6]. Nakamura in the Houk group did

molecular mechanics-based dynamics simulations to reveal the mechanism of the acetonitrile escaping from the cavity of carcerand **2a** (Figure 3) [7]. We observed that the conformational flip of two CH₂ groups to CH₂-out conformations increases the side-portal size and lowers the activation energy for guest escape. Free energy perturbation (FEP) calculations were carried out to estimate the difference in free energy change for the guests escape processes. This work showed that gating is a control element in constrictive binding and the passage of guest molecules into or out of the cavity of carcerands.

Sheu *et al.* [8] studied the complexes of a flexible hemicarcerand **3a** (Figure 3) with various guest molecules. The binding energies of hemicarcerand **3b** with 40 aromatic and bicyclic guests (Figure 4) were predicted to be 12–23 kcal/mol by molecular mechanics calculations.

Molecular dynamic simulations were performed on the kinetics of complexation and decomplexation processes. Two complexation mechanisms, stepwise and one-step, were identified. The energy profiles for the complexation of host **3b** with two guests are shown in Figure 5. It can be interpreted from the energy profiles that the rate-determining step in complexation is the gate-opening process. These results showed why bicyclics can form complexes while large bicyclics do not. In general, it was found that the CH₂ flip gate-opening process is important for the complexation of bicyclic guests; smaller aromatic guests can pass in and out of the cavity without gate-opening.

Thermal gating has also been reported by Rebek and co-workers [9] (Figure 6) in the so-called “sportsballs” molecules with names such as “tennis ball” and “softball.”

Computational studies [10] of the guest exchange in “tennis ball” and “softball” container molecules by Wang in the Houk group showed that in the “tennis ball” dimer, the gate-opening is achieved by the inversion of one of the envelope-shaped seven-membered rings (colored in green in Figure 6). The overall energy required for gate-opening is much larger than the dissociation energy of the “tennis ball”, and it is likely that the guest exchange in “tennis ball” occurs by the dissociation mechanism. On the contrary, the overall energy cost of the gate-opening process, which involves the inversion of one or two six-membered rings (colored in green in Figure 6) of the “softball”, is much lower than the computed dissociation energy. We proposed three gating mechanisms (Figure 7, bottom): single-door-gating process that involves the inversion of only one six-membered ring (Figure 7, bottom A), side double-door-gating process that involves the inversion of one six-membered ring on each monomer (Figure 7, bottom B) and back double-door-gating process that involves the inversion of two six-membered rings on the same monomer (Figure 7, bottom C). Wang’s calculations showed that gating has a significant influence on the guest exchange process in “softball” dimer.

Thermal gating has been observed in the molecular baskets as well which were created by Badji and co-workers. They found a correlation between the complexation and the size, shape and electronic characteristics of guest molecules [11]. Through kinetics studies of the encapsulation of various haloalkenes, they found that guest molecules with proper size could be entrapped in the cavity of **4a** (Figure 8, top left), which is in good agreement with Rebek’s 55% rule [12]. The gate-opening is achieved by the rotation of three C–N single bonds (Figure 8, top right and bottom), and they reported three switching modes including copper coordination and acid-base stimulus [13]. The recognition characteristics of the molecular basket can be tuned by controlling the external stimulus. Another interesting aspect of gated molecular baskets is that a linear correlation between intrinsic binding energy and constrictive binding energy has found for guest encapsulation in basket **4b** (Figure 8, top left) [14].

Redox reactions are another means to control gating. A novel design of gated hemicarcerands based on disulfide-dithiol interchange was recently reported by our group [15]. Three out of seven guest molecules formed stable complexes with hemicarcerand **5a** (Figure 9). Helgeson and Hayden in the Houk group studied the disulfide gate-opening process by reacting the hemicarceplexes (**5a**⊙**1**, **5a**⊙**2** and **5a**⊙**3**) with dithiols. Decomplexation was observed under addition of base (DBU) and dithiol, indicating that the disulfide on hemicarcerand **5a** is reduced to dithiol and results in the opening of the cavity to give **5b**.

Molecular mechanics level computational studies were performed on the complexation and decomplexation between guests **1–7** and hemicarcerands **5a** and **5b** to calculate the constrictive and intrinsic binding energies between hosts and guests. The result suggested that guests **1–6** could form complexes with hemicarcerands in either open or closed state. However, the constrictive binding energy of the less bulky guest **5** is too small, indicating that **5** readily goes in and out the portal of the hosts without gating. This explains why **5a**⊙**5** was not observed in experiments. Our computations have aided in the explanation and support of the experimental observations.

Photochemical reactions are a third major gating process. The concept of photoswitchably gated hemicarcerands has been demonstrated by Deshayes in only one example [16]. He and co-workers reported a photoactive hemicarceplex **6a** (Figure 10). Host **6a** is able to undergo bond cleavage of nitrophenyl ether group upon irradiation with UV light. They demonstrated that the hemicarceplex **6a** (G = NMP, DMA) is thermally stable at room temperature in the dark. However, it undergoes slow decomplexation when exposed to ambient light with photocleavage of the 3-nitro-*o*-xyly bridge and releasing the incarcerated guests, leading to the tris-bridged open-form host **6b** and the free guests. The rate of the cleavage reaction can be monitored by the rate of the appearance of formyl proton signal for the photoproduct aldehyde, and it was shown that the rate of guest release for both complexes has a linear dependence on light intensity. Moreover, they prepared another kind of hemicarceplex with four 3-nitro-*o*-xylyl bridges. These hemicarceplexes have both thermal stability and photoactivity, and hence they may be useful in controlled drug delivery systems.

Finally we would like to comment on recent studies of the “sliding door” gating mechanism. In our earlier publications two gating mechanisms were indicated—“French door” and “sliding door” [4]. The container molecules discussed so far are mostly “French door”-gated. Host molecules have been reported recently that create a pathway for guest entry and exit based on the slippage of part of the host. The Badji group [5] has provided a very thorough review of all types of gating in cavitands and container molecules. Computational simulations on the slippage approach to rotaxanes [17] revealed two main energy barriers for the slipping-off process of macrocycle (Figure 11) over the *R-S* stoppers. The trend in the calculated energy barriers with different *R-S* stoppers showed good agreement with the experimental yields.

This comment highlights thermal, redox, and photo-chemical gating mechanisms. Gating in container molecules should also be achievable by other stimuli such as acid-base and hydrogen bond interactions. Such mechanisms could be built into container molecules to develop new nanometer-scale molecular devices.

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Biography

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Figure 1.
Energy diagram for host and guest complexation.

Figure 2.

Upper left: structure of carcerand **1a**, one of the portals colored in blue; guest = pyrazine. Upper right: structure of hemicarcerand **1b** with one of the portals colored in blue; guest = benzene. Bottom: structure of hemicarcerand **1c**, gating sites are color in red (closed state) and green (open state); guest = DMA, DMF.

Figure 3.

Left: structure of carcerand **2a**, calculations were done on **2b** for simplification. Reprinted with permission from ref. [7]. Copyright 1995 American Chemical Society. Right: structure of hemicarcerand **3a**, calculations were done on model **3b**. CH_2 -in conformation shown in red (chair-conformation); CH_2 -out conformation shown in dot green (boat-conformation). Reprinted with permission from ref. [8]. Copyright 1996 American Chemical Society.

Figure 4.

Guests **A1–A12** form isolable complexes with hemicarcerand **3a**; guests **B1–B28** do not form isolable complexes with **3a**. Reprinted with permission from ref. [8]. Copyright 1996 American Chemical Society.

Figure 5.

Energy profiles for stepwise and one-step complexation/decomplexation processes between host **3b** and guests **A1** (blue) and **B25** (black). (a) Hemiacerand **3a**; (c) hemiacerand **3a** with one boat form; (e) hemiacerand **3a** with two boat forms; (g) complex **3a**⊙**A1** with two boat forms; (i) **3a**⊙**A1** with one boat form; (k) **3a**⊙**A1**; (b), (d), (f) and (i) are transition states for chair-boat (or boat-chair) flip. Reprinted with permission from ref. [8]. Copyright 1996 American Chemical Society.

Figure 6.
Molecular structures of “tennis ball” and “softball”.

Figure 7.

Up: gating mechanism and dissociation-recombination mechanism for guest exchange in "tennis ball". Bottom: three gating mechanisms for guest exchange in "softball". Reprinted with permission from ref. [10]. Copyright 1999 American Chemical Society.

Figure 8.

Upper left: molecular structure of molecular basket **4a** and **4b**. Reprinted with permission from ref. [11]. Copyright 2008 American Chemical Society. Upper right: molecular modeling of basket **4a**. Bottom: gating mechanism and guest encapsulation.

Figure 9.

Up: structures of hemicarcerands **5a** and **5b** (disulfide-dithiol interchange). Bottom: guest molecules studied; guests **1–7** formed stable complexes with **5a**.

Figure 10. The photo-induced release of a guest molecule (DMA or NMP) from hemicarceplex **6a**. Photochemical reaction sites are indicated in red.

Figure 11. Energy profile calculated for the slippage process of a macrocycle. Two energy barriers were indicated in red.