Gating as a Control Element in Constrictive Binding and Guest Release by Hemicarcerands

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Theoretical modeling of the dynamics of complexation and decomplexation of guest molecules by container molecules reveals that gating has a critical influence on the ease of formation and stability of host-guest complexes. Hosts equipped with gates can form very stable complexes with a variety of guests under readily achievable conditions. Gating involves conformational processes of the host molecule that alter the size of the portals through which guest molecules pass. "French door" and "sliding door" mechanisms of gate opening are identified.

Cram and co-workers identified "constrictive binding" as a factor controlling the stabilities of complexes involving guest molecules in carcerands and hemicarcerands (*1*). Constrictive binding is defined quantitatively as the difference between the activation energy for decomplexation and the complexation energy of a guest molecule. It arises from physical barriers to decomplexation. We have found that the magnitude of constrictive binding and the passage of most guest molecules into or out of hemicarcerands is controlled by "gating," a conformational process temporarily leading to an opening large enough to permit ready ingress and egress of guests. The size of the gate is controlled by motions related to "French doors" or "sliding doors" (Fig. 1). The phenomenon of gating explains how constrictive binding by hemicarcerands can lead to the formation of stable complexes with a variety of guest molecules and, at the same time, reversible complex formation at moderate temperatures (activation energies of decomplexation of 15 to 25 kcal/mol at 25° to 100°C). Without gating, carcerands with small portals would only be able to form complexes during synthesis, and guests could never leave the host. If the portal were large, constrictive binding would be absent, and the complexes would have very low stabilities. Conformational changes resulting in gating are important to the passage of substrates and inhibitors to the active sites of some enzymes; gating may facilitate catalytic processes in some enzymes (*2*). Flexible chelation has been proposed for host-guest complexes (*3*), and the effect on the kinetics of binding has been estimated (*4*). We show here that gating is a crucial design feature for the molecular recognition and dynamics of container molecules.

We recently reported the mechanism for the loss of acetonitrile from hemicarceplex **1**, which contains two acetonitrile molecules (Fig. 2). The rate-determining step is gate opening, which we now define as the French door type, which involves two chair-to-boat interconversions of dioxacyclooctadiene rings (**2**, Fig. 2) (*5*).

The ring inversion barrier was estimated (*5*) to be about 20 kcal/mol with use of the AMBER* force field (*6*). To obtain a better estimate for the inversion barrier, we fully optimized the transition state for the inversion of calix[9]resorcinarene (**3**) with the AM1 method (*7*) using the GAUSSIAN94 program (*8*). The activation energy was calculated to be 17.5 kcal/mol and the transition state is nonplanar (Fig. 3). The boat structure is 8.5 kcal/mol less stable than the chair structure, mainly because of the repulsion between the bowsprit (H_b) and flagpole (H_f) hydrogens.

In the absence of gating, the loss of acetonitrile from **1** could occur only with an activation energy on the order of 52 kcal/mol, which is the energy (AMBER*) required to force an acetonitrile from **1** (*5*). With the gate closed, the portal diameter (equivalent to the smallest H-H transportal distance) is 2.2 Å. With the gate open, the portal diameter is 3.9 Å, and the barrier drops to 26 kcal/mol. The constrictive binding energy is 25 kcal/mol with gating because the binding energy is only 1 kcal/mol. If the gate could not open, constrictive binding would be 51 kcal/mol, too large for guest loss except under severe conditions.

We have investigated a variety of carcerands and carceplexes with AMBER* in MACROMODEL, using a reaction coordinate procedure to study the reactions (*5*), as well as free energy perturbation calculations or the generalized Born–solvent accessible surface area solvation model to calculate solvation energies (*9*). We have identified three distinct types of host-guest complexes and have established the general importance of gating in the determination of complexation propensities.

1) Some hosts have portals too small for the passage of solvent or guest molecules into and out of the cavity. The thoroughly studied carceplexes **4** (shown in Scheme 1 with pyrazine inside) have been prepared with a variety of guests that are never lost (*10*, *11*). Calculations with AMBER* indicate that even with an open gate (portal diameter, 2.1 Å), the barrier to loss of dimethyl sulfoxide is much greater than the 90 kcal/mol required to break a C-C bond. Host-guest complexes like **4** are true carceplexes. The hypothetical complex of camphor with hemicarcerand **5** (shown in Scheme 1 with the smaller benzene inside) also belongs in this category: The energy barriers for complexation, both with (36 kcal/mol) and without (50 kcal/mol) gate opening, are too high to form a complex (*10*). If formed by synthesis of the host around the guest, the carceplex would be stable.

2) Some hosts have portals so large that gating does not influence the entry of most guests. In such cases, constrictive binding is small, and stable complexes are not formed. Hemicarcerand **5** has a large enough portal (portal diameter, 4.4 to 5.0 Å in different conformations) that small aromatic, monocyclic and bicyclic guests pass into and out of the host cavity without gating (*12*). In this case, stable complexes cannot be isolated; there is no barrier to complexation, and the barrier to decomplexation is determined only by the complexation energy. A typical example is the complexation of hemicarcerand **5** with benzene (Scheme 1); the calculated complex stabilization energy is 15 kcal/mol in the gas phase and 7.7 kcal/mol after correction for solvation of benzene in neat benzene (*13*). Other simple benzene derivatives such as iodobenzene and *p*-xylene also fall into this category. These molecules do not form isolable complexes (*12*).

3) Some hosts have portals that are too

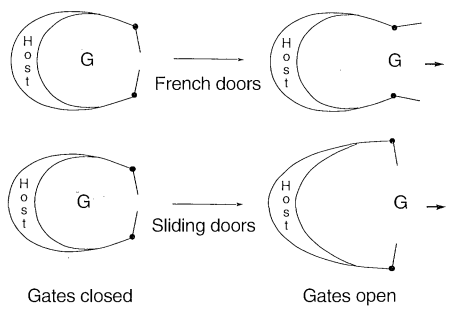

Fig. 1. Two types of gating in hemicarceplexes: the French door and sliding door mechanisms. G, guest molecule.

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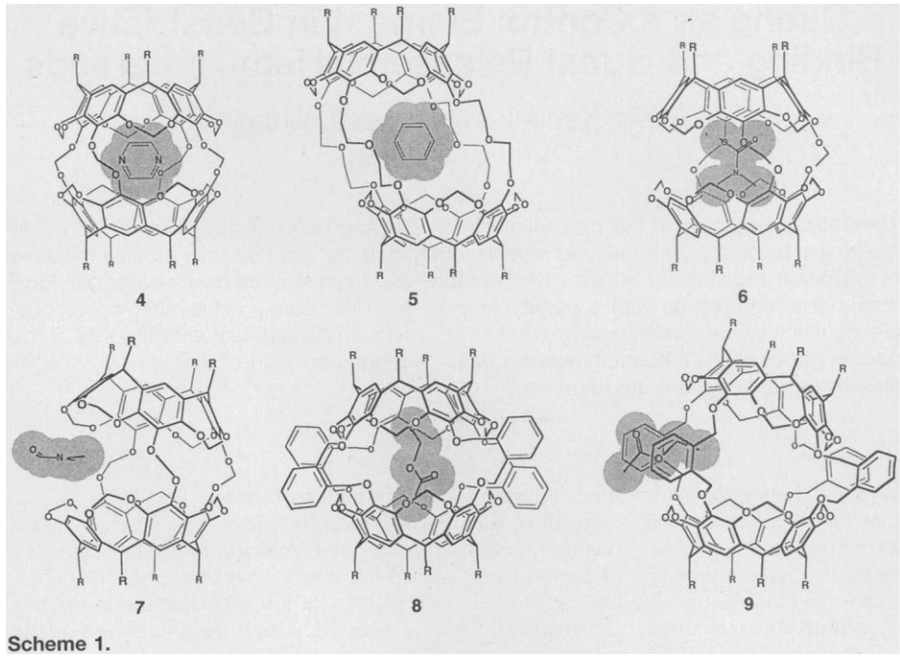
small to admit most guests, but upon a conformational change leading to gating, a variety of guests can pass into and out of the host. Such hosts form stable, but reversible, complexes with a large number of guests. In such cases, the energy barrier for the complexation process is approximately equal to the energy barrier for gate opening, and the decomplexation barrier is equal to the complexation energy plus the activation energy for gate opening. One example is the complexation of norbornane with hemicarcerand **5**: The complexation and decomplexation energy barriers (including solvation energy) are calculated by AMBER* to be 35 and 42 kcal/mol when the gate is kept closed; when the gate is held open, these energies are only 4 and 11 kcal/mol; and when combined with the gating process, the barriers are 18 and 25 kcal/mol, respectively (*5*). With gating, a large variety of hemicarceplexes can be made and isolated.

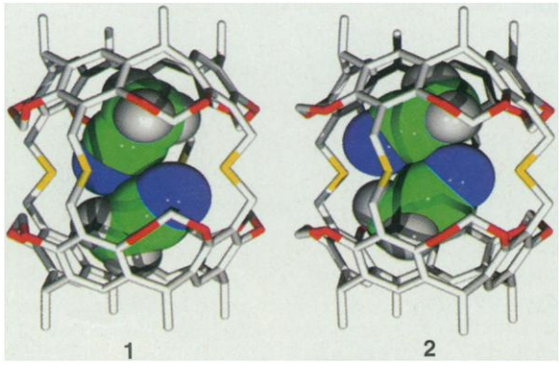
A variety of phenomena observed by the Cram group can be interpreted in terms of gating. For the hemicarcerand **6** with three $-O-CH_2-O-$ linkers, the activation enthalpies for the escape of *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMA) have been measured to be 23.9 and 20.1 kcal/mol, respectively (*14*). Surprisingly, the larger guest molecule (DMA) has the lower activation energy for passage through the portal of the hemicarcerand. Because one linker is missing in the hemicarcerand, there are four methylene groups forming a double French door in the largest cavity of **6**. Without gate opening, the activation energies for DMF and DMA escape are calculated to be 60.5 and 55.4 kcal/mol, respectively. These values are in the same order as those found by experiment, but they are much higher than the experimental values. Opening two of the doors of the double French door causes the overall barriers to drop to 32.4 kcal/mol for DMF and 27.7 kcal/mol for the larger DMA. A combination of French and sliding door gating is involved in the escape (structure **7**). The difference in barriers is in accord with experiment; the calculated barriers are too high, probably because of the neglect of solvation of the emerging guest molecule (*15*).



Scheme 1.

Why is the loss of DMA easier than that of the less bulky DMF? The complexation energies for DMF and DMA are calculated to be 18.0 and 13.3 kcal/mol, respectively. Because DMA is too bulky to fit well inside the carcerand, its complexation energy is 4.7 kcal/mol less favorable. The barriers for the inward passage of DMF and DMA through the open gate are virtually identical because they have similar cross sections, but the escape barrier for DMA is smaller because its complex is less stable. In the absence of gating, the decomplexation and complexation energies would be on the order of the guest size and too high to be readily achievable.

The hemicarcerand with *o*-xylyl linkers, **8** (shown in Scheme 1 with ethyl acetate inside), demonstrates how sliding door and French door gating both contribute to the control of guest loss from a hemicarceplex. Experimental activation enthalpies for loss of guest molecules toluene, DMA, 2-butanone, and ethyl acetate are 14.3, 20.5, 20.8, and 22.2 kcal/mol, respectively (*16*). These molecules have two types of exit routes from the hemicarceplex. Our simulations indicate that the favored process involves exit of the guest into an antechamber formed by the xylyl linkers, rather than directly to the exterior. Structure **9** shows ethyl acetate in this chamber; the complex must undergo a second conformational process to free the guest from interactions with the benzene rings, allowing complete escape. For all guests, sliding door gating was an important mechanism for decomplexation. The extent to which French door gating affects the escape barriers depends on the nature of the guest. For toluene, which is flat, French door gating plays a small role, lowering the barrier for escape by only about 1 kcal/mol; for ethyl acetate, howev-



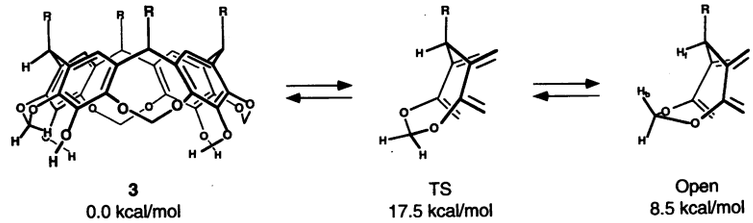


Fig. 2 (left). Equilibrium structure of hemicarceplex **1** incorporating two acetonitriles. French door gating has enlarged the portal to form conformation **2**. **Fig. 3 (above).** Conformational processes involved in gate opening. Compound **3** is a resorcinarene model compound. TS, transition state.

er, our calculations predict that opening of the French door gate lowers the barrier from 26 to 20 kcal/mol. Both French door and sliding door gating are evident in **9**, which shows the highest energy point in the estimated escape trajectory of ethyl acetate. The portal diameters are 3.5 Å in **8** and 7.6 Å in **9**. Both DMA and 2-butanone are intermediate cases showing small effects from French door gating of about 1.5 and 2.5 kcal/mol, respectively.

Gating is a general phenomenon that contributes to the stabilities and rates of complexation of hemicarcerands. In the absence of gating, only guests of nearly exactly the size of the portal can enter the host under normal conditions and still form stable complexes due to constrictive binding. The container molecules recently reported by Meissner *et al.* (*17*) must partially disunite the complementary halves either by sliding door gating or full dissociation to allow the passage of molecules into or out of the cavity. Gating makes it possible for a single host to form stable complexes with guests with a range of sizes. This concept provides a new design criterion for complexes and catalysts.

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15. The absolute solvation energies of DMF and DMA in chloroform calculated by BOSS Monte Carlo simulations (BOSS, 3.5; W. L. Jorgensen, Yale University) are −7.1 and −5.8 kcal/mol, respectively. From simple addition of the solvation energies to the calculated activation energies for guest loss, $\Delta E\ddagger$, the activation energies for escape are estimated to be 24.6 kcal/mol for DMF and 21.9 kcal/mol for DMA. These values are close to the experimental values, considering that (i) solvation effects at the transition states are less than those of free guest molecules and (ii) the solvent used in the experiment (nitrobenzene) is more polar than that used in the calculation (chloroform).
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Photoinduced Chemical Dynamics of High-Spin Alkali Trimers

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Nanometer-sized helium droplets, each containing about 10^4 helium atoms, were used as an inert substrate on which to form previously unobserved, spin-3/2 (quartet state) alkali trimers. Dispersed fluorescence measurements reveal that, upon electronic excitation, the quartet trimers undergo intersystem crossing to the doublet manifold, followed by dissociation of the doublet trimer into an atom and a covalently bound singlet dimer. As shown by this work, aggregates of spin-polarized alkali metals represent ideal species for the optical study of fundamental chemical dynamics processes including nonadiabatic spin conversion, change of bonding nature, and unimolecular dissociation.

Spectroscopic studies of unimolecular reactions provide detailed insight into the mechanism of formation and decay of reaction complexes (*1*). For example, electronic excitation of a van der Waals complex followed by unimolecular dissociation allows the observation of different decay channels. These channels yield information on both the weakly bound complex and the dissociation process. This dissociation can be particularly interesting if it is accompanied by a change in the bonding nature of the products. Small alkali clusters are good candidates for this kind of study because they can exhibit multiple bonding configurations that are dependent on the alignment of the spins of the valence electrons in the molecule. In the absence of spin polarization, the unpaired valence electron of the group IA alkali atoms can participate in the formation of chemical bonds in the dimer, trimer, and larger clusters of these atoms. Aggregates of atoms with parallel electron spins exhibit instead only van der Waals bonding, resulting from the balance between the attractive dispersion (correlation) forces and the Pauli repulsion between the highly deformable valence electron distributions. With the exception of the noble gas trimers, spin-3/2 alkali trimers are the simplest three-atom van der Waals aggregates. In addition to shedding light on the chemical dynamics experiments reported below, these systems are likely to be useful for the investigation of three-body intermolecular forces.

Numerous experimental (*2–10*) and computational (*11–13*) studies have been conducted on the structure and spectroscopy of the doublet states of the Na trimer (Na_3), but the quartet electronic states of Na_3 have not yet been probed. Using He nanodroplets as an inert substrate, we prepared Na_3 aggregates in their lowest quartet state and used them to investigate one of the simplest three-body nonadiabatic dynamic processes available in nature. We found by dispersed fluorescence measurements that laser excitation to an excited quartet electronic state of an alkali trimer may lead to a curve-crossing into the doublet manifold. This is followed by a dissociation of the doublet trimer into an atom and a covalently bound singlet dimer. After the intersystem crossing into the doublet manifold, the molecule will be in an excited state that is expected to dissociate (*3*).

A beam of large He nanodroplets, each droplet containing ~10^4 He atoms, was

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