# Gated Molecular Baskets

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<th>Journal:</th>
<th>Chemical Society Reviews</th>
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<td>Manuscript ID:</td>
<td>CS-REV-04-2014-000140.R1</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Review Article</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>24-May-2014</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Hadad, Christopher; The Ohio State University, Chemistry Hermann, Keith; The Ohio State University, Chemistry Ruan, Yian; The Ohio State University, Hardin, Alex; The Ohio State University, Chemistry; The Ohio State University, Badjic, Jovica; Ohio State University, Department of Chemistry</td>
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Gated Molecular Baskets

Keith Hermann, Yian Ruan, Alex M. Hardin, Christopher M. Hadad and Jovica D. Badjić*

In this review, we describe the construction of gated molecular baskets, discuss their mechanism of action in regulating the exchange of guests and illustrate the potential of these concave hosts to act as catalysts for controlling chemical reactions. Importantly, a number of computational and experimental studies have suggested that gated baskets ought to unfold their gates at the rim for permitting the passage of guests to/from their inner space. These dynamic hosts are therefore offered as useful models for investigating the process of gating in artificial systems. Furthermore, gated baskets should permit examining the benefit of controlling the rate by which reactants access a gated catalyst for promoting chemical reactions occurring in its confined space.

Introduction

Chemists have, for more than four decades, studied the characteristics and explored the utility of compounds with an enforced cavity. At the present time, we recognize that cavitands would trap guest molecules that are complementary in shape, size and electronic attributes to their concave interior. In addition, the formation of such host-guest complexes is often driven by desolvation, which plays an important role in complexation events. In his seminal paper about cavitand I, D. J. Cram discussed a prospective of using concave compounds for promoting chemical reactions, stabilizing reactive intermediates and controlling the rates by which encapsulated molecules are undergoing in/out trafficking: "can cavitands be prepared with "pores" in their "skins" that allow the entrance and departure of certain guest from their interior, but forbid passage to others?" This intriguing question was of a great interest, soon thereafter the preparation of carcerands (Figure 1).

Several years later, soluble carcerand 2 was prepared and, with $^1$H NMR spectroscopy, was shown to contain a molecule of templating solvent ((CH$_3$)$_2$SO, (CH$_3$)$_2$NCOCH$_3$, (CH$_3$)$_2$NCHO) in its cavity. Indeed, when large C$_2$H$_{10}$NCHO solvent was used in the synthesis of 2 there was no formation of the host. Interestingly, [2-(CH$_3$)$_2$SO] possessed a long lifetime with the entrapped DMSO molecule "unable" to depart from its inner space at 150ºC for 24h! It was deduced that DMSO was permanently trapped in the cavity of 2 with its departure necessitating a cleavage of covalent bonds (>90 kcal/mol). The phenomenon is akin to mechanical bonds in rotaxanes for which a high activation barrier prevents the slippage of a macrocyclic ring over the bulky termini of its "axle-like" component.

![Figure 1. Chemical structures of carcerands 1 (A) and 2 (B). Three solvent molecules (red) were trapped in the cavity of 2 during its preparation.](Image)

The UCLA group reported the synthesis of D$_{4h}$ symmetric host 1 (Figure 1A) with an enforced interior, although this molecular capsule was found to be poorly soluble in numerous solvents.

![Figure 2. Dioxacyclooctadiene rings in hemicarcerand 3 (R = CH$_3$CH$_2$Ph) undergo chair-to-boat conformational changes. Two OCH$_3$O bridges (brown) alter the position to create a sizeable portal for a more facile trafficking of guests ((CH$_3$)$_2$NCHO is shown).](Image)

To reduce the high activation energy of the complexation/decomplexation of carcerands, Cram and co-workers designed hemicarcerands (Figure 2). Molecular
capsule 3 (R = CH₂CH₂C₆H₅, Figure 2) was made³⁴ to carry three OCH₃O bridging units connecting its northern and southern cups. With one OCH₃O group missing, the side portal was, in hemicarcerand 3, big enough to permit decomplexation (ΔG° > 20 kcal/mol) of several guests ((CH₃)₂SO, (CH₃)₂NCOCH₃, (CH₃)₂NCHO).²⁵, ²⁶ The activation energy of the process was indeed large, given a small affinity of guests for populating the host. Cram coined the term "constrictive binding"²⁷ to describe an apparent "physical barrier" corresponding to the guest departure. It derives from the Latin word constrictus meaning "narrowing of a passage". Questions about the nature of constrictive binding were posed, yet it was difficult addressing them with space-filling molecular models.²⁸ Houk and co-workers, however, were the first to show that conformational changes occurring within hemicarcerands ought to be considered for understanding the trafficking of molecules.²⁹ In particular, chair-to-boat interconversion of one dioxacyclooctadiene ring within carcerands/hemicarcerands was computed to require a considerable activation energy (≥12 kcal/mol). The opening of two OCH₃O-gates (>20 kcal/mol, Figure 2) was then proposed to promote access/departure of guests to/from the inner space of hemicarcerands (Figure 2).²⁸ If the host's dioxacyclooctadiene rings solely assume the chair conformation, the activation barrier for guest departure becomes insurmountable at experimentally accessible temperatures.³⁰ Almost two decades after the Houk's original proposal, the process of gating appears to be important for the operation of various dynamic hosts.¹⁶ In addition, the gating could be used for developing supramolecular systems capable of controlling the outcome of chemical reactions.³³, ³⁴ or delivery/trafficking of useful molecules.³⁵, ³⁶ In this review, we focus on describing the action of gated molecular baskets developed in our laboratory. These dynamic hosts are useful models for studying gated molecular encapsulation and its importance for controlling chemical reactivity.

A Case of Gated Encapsulation with the Formation of an Open-Host Intermediate

The entrapment of guests by gated hosts could, in some situations, be described with a mechanism (Figure 3) whereby the opening of the host (H) gives an unstable intermediate (I).³⁷

Accordingly, a conformational change in H could lead to I (Figure 3A/B), which then traps guest G in the step that follows. Accordingly, one can use the steady-state approximation to derive the corresponding rate law (Figure 3).³⁸ If the opening of host H is rate determining (step 1, Figure 3A), it follows that the encapsulation rate becomes solely a function of the concentration of host H (rate = k₁[H]). Conversely, if the entrance of guest G into intermediate I is rate-determining (step 2, Figure 3B), then the rate becomes a function of the concentrations of both host H and guest G (rate = k₂obs[H][G], Figure 3B). Rebek and co-workers used conventional kinetic analysis to examine the substitution of adamantane (A) inside "softball" host 4 with [2.2]paracyclophane (P) (Figure 4).³⁹ Self-assembled capsule 4 comprises a sizeable interior (~313 Å³) and is also made of two complementary subunits forming a seam of 16 hydrogen bonds (Figure 4).⁴⁰ Importantly, the affinity of 4 for entrapping [2.2]paracyclophane is greater than for adamantane to permit practically irreversible conversion of [4–A] into [4–P] (Figure 4). The substitution was found to be slow enough and was monitored with conventional ¹H NMR spectroscopy using variable concentrations of compound P. At low concentrations of P, the reaction appeared to be first order in P, while at high concentrations of P, the complexation was zeroth order in this reactant! The saturation curve (k₂obs vs [P])⁴⁰ was taken as a sign for the formation of an intermediate and also a change in the rate-determining step of the substitution. The data were, subsequently, fit to the mechanistic scenario described in Figure 3 to give k₁ = 0.0027 s⁻¹ (ΔG°₁ = 20.3 kcal/mol at 289 K). At high concentrations of P, the opening of capsule 4 is energetically demanding and limits the rate by which the supramolecular substitution takes place (Figure 3A). To examine the nature of the experimentally observed intermediate, Houk and co-workers computed⁴¹ that the formation of double-door 1 (Figure 4) would require ~24 kcal/mol, which is close to the experimentally observed ΔG°₁ (20.3 kcal/mol).

In line with the discussion, the opening of hemicarcerands of type 3 (Figure 2) was computed³⁰ to constitute the rate-limiting step in the formation of hemicarceplexes.⁴² Additional experimental measurements, however, remain to be completed to test such computational predictions.⁴³ Finally, the operation of gated molecular baskets (see below) constitute another mechanistic alternative with, perhaps, one elementary step including: the ingress of a guest, from bulk solvent, causing the egress of the residing guest and opening of the
basket’s gates. The mechanism of action of gated molecular baskets is described in sections that follow.

**Gated Molecular Baskets**

**Design and Preparation:** We originally designed molecular baskets of type 5 (Figure 5, R = CH₃) in our laboratory.⁴⁵ The key reaction for the preparation of these dynamic hosts is the tris-annulation of racemic norbornene compounds using transition metal catalyst(s), either Cu(I) or Pd(0) (Figure 5A).⁴⁶, ⁴⁷ In particular, De Lucchi and co-workers have developed⁴⁸ a variety of useful cyclotrimerization protocols. The reaction gives a mixture of syn/anti diastereomeric products (Figure 5A) for which the undesired anti compound usually dominates. To overcome this difficulty, we optimized a methodology for

![Figure 5](image)

Figure 5. (A) The tris-annulation of stannylated norbornenes is promoted with Cu(I) or Pd(0) catalysts to give a mixture of syn and anti cyclotrimers. (B) Chemical structure of gated molecular baskets (5, R = CH₃) with three intramolecular N–H–N hydrogen bonds. (C) ORTEP representation of the solid-state structure of a gated basket; note that a molecule of CHCl₃ resides in the cavity of this host having three phenyl gates at the rim.

Furthermore, the amide groups were found to adopt a Z configuration about each C–N bond with the basket’s pyridine gates forming three intramolecular N–H–N hydrogen bonds (Figure 5B).⁴⁹ ¹H NMR chemical shifts of the singlet corresponding to the N–H protons are typically found at δ > 11 ppm.

**Encapsulation Thermodynamics:** To evaluate the internal volume of energy-optimized 5 (DFT, B3LYP/6–31G(d)),⁵⁷ with its pyridine gates in their “closed” position (226 Å³, Figure 6A), we used the 3V software.⁵¹ While this particular freeware was originally recommended for investigating drug-binding sites in biological molecules,⁵² it can also be used for studying artificial hosts.⁵¹ The computed electrostatic potential surface (AM1, Spartan) of the interior of C₃ symmetric 5 encompasses domains with negative potentials⁵³ making it complementary to tetrahedral haloalkanes (V = 80–110 Å³, Figure 6B). In fact, haloalkane guests are poised⁵⁷ to place one of their polarizable groups against the cup-shaped framework of 5 with the remaining three units pointing to side portals (Figure 6C). With the assistance of variable temperature ¹H NMR spectroscopy,⁵⁷ we demonstrated that a small haloalkane (CCl₄, CBr₄, CH₂CBr₄, etc.) would occupy the inner space of 5 in solvophobic CH₂Cl₂ (61 Å³).⁵⁴ Notably, the binding energy was found to be a function of the guest's size with ΔG° = −4.85 ± 0.1 kcal/mol (298.0 K) for bigger CBr₄ (106 Å³) and ΔG° = −1.0 ± 0.1 kcal/mol (298.0 K) for smaller CH₂Br₂.⁵⁴ The affinity tracked the population of the inner space of gated 5 (expressed via so-called packing coefficient, PC = V₁/V₁₀₀)⁵⁵ whereby the PC of CBr₄ is 0.47 while for CH₂Br₂ is 0.39. Interestingly,
all encapsulations were driven by enthalpy ($\Delta H^\circ<0$) due to, perhaps, the complementarity of host and guests in shape and electrostatic characteristics (Figure 6A/B). We further examined the binding of four guests with similar volumes having a variable number of CH$_3$ groups (Figure 6D). The enthalpy of the interaction was comparable along the series ($\Delta H^\circ \approx -4$ kcal/mol), and in line with the computed energies ($E$, Figure 6D). The entropic contribution, however, changed: the greater the number of CH$_3$ groups, the more negative $\Delta S^\circ$ (from $-0.2$ to $-10.7$ e.u., Figure 6D). Presumably, the motion of methyl groups becomes restricted in the cavity of gated basket 5 to contribute to the effect. There is roughly $0.6$–$1$ kcal/mol loss in energy ($\Delta S^\circ$) per each additional CH$_3$ group at 298 K.

Finally, we quantified the potential of 5 (R = CF$_3$, Figure 7) for trapping 2,2-dibromopropane (107 A$^3$, $PC = 0.47$) in four differently sized solvents having comparable polarities: CD$_2$Cl$_2$ (61 A$^3$), CDCl$_4$ (75 A$^3$), CFCl$_3$ (81 A$^3$) and CCl$_4$ (89 A$^3$). The stability of [5–(CH$_3$)$_2$CBr$_2$] was found to be higher in CD$_2$Cl$_2$ while lower in CDCl$_4$/CFCl$_3$ and very small in CCl$_4$ (Figure 7A). Apparently, the smallest dichloromethane is the least competitive solvent in the series with the lowest affinity for occupying the basket (Figure 7B). We reasoned that in line with the encapsulation stoichiometry (Figure 7B), one CD$_2$Cl$_2$ is too small ($PC = 0.28$), while two are incompatible in shape with the interior of 5 to populate it. When more sizeable solvents (C$_6$D$_6$ (99 A$^3$), C$_6$D$_2$CD$_3$ (117 A$^3$), m-C$_6$D$_4$(CD$_2$)$_2$ (136 A$^3$) and 1,3,5-C$_6$D$_3$(CD$_2$)$_3$ (154 A$^3$) were probed as a medium for the encapsulation of halocarbons, the solubility of "free" basket 5 dropped, albeit it improved considerably in the presence of guests (i.e. [5–guest] complexes). Importantly, the affinity of 5 for trapping 1,1,1-tribromoethane increased in the series with mesitylene being the most solvophobic medium ($K_a = 412$ M$^{-1}$, 300.0 K). The finding bodes well with the encapsulation stoichiometry (Figure 7B) in which a trapped guest molecule is substituted with the solvent: [5–mesitylene] complex possesses the lowest stability ($PC = 0.68$) to contribute to a greater quantity of [5–guest]. Furthermore, the finding is in line with the W. C. Still’s pioneering study$^7$ on elucidating the importance of solvent size for the formation of encapsulation complexes.

**Stimuli-Responsive Behaviour:** The preparation and study of switchable hosts could be of interest for developing more sophisticated catalysts, energy conversion devices, and sensors. Despite much advancement in the field, attaining control over conformational dynamics and functional behaviour of molecules, or their assemblies, remains a challenge. Accordingly, we studied switchable characteristics of gated molecular baskets and found that these hosts can be reversibly interconverted among conformational states 5A, 5B and 5C (Figure 8). Importantly, each state has unique encapsulation characteristics and distinct internal dynamics. Gated basket 5A (226 A$^3$) contains three pyridine-based gates for forming a seam of intramolecular N-H---N hydrogen bonds and occluding space. This host was found (1 H NMR spectroscopy) to selectively trap 2,2-dibromopropane ((CH$_3$)$_2$CBr$_2$, 107 A$^3$) in the presence of methylisocyanoide (CH$_3$NC, 58 A$^3$). Upon addition of an equimolar amount of (CuOTf)$_2$PhMe, however,
we observed (¹H NMR spectroscopy) the conversion of basket 5A into 5B (Figure 8). Importantly, 5B contains Cu(I) cation at its rim coordinating to sp² nitrogen atoms of the pyridine gates and also a molecule of CH₃NC occupying the host's cavity. The use of external chemical stimulus (Cu(I)) therefore caused a disruption of three N—H—N hydrogen bonds in 5A, reorganization of its gates and finally exchange of guests to give rise to 5B. To reverse these chemical changes, we used Na₂S which coordinated to Cu(I) and thereby triggered the conversion of 5B back into 5A. Following, we added trifluoroacetic acid (TFA, pH = 0.25 to 5A to induce the protonation of pyridine gates (pKₐ = 5.25). Indeed, the protonation took place, and we observed the dimerization of the host to give 5C (Figure 8): the assembly comprised three nitrogen atoms of the pyridine gates, assuming propeller-like orientations, should permit the interconversion of dynamic enantiomers 5⁰ and 5⁴. Finally, the addition of K₂CO₃ to 5C led to its deep deprotonation and the formation of 5A for completing the acid-base cycle (Figure 8).

![Figure 9](image_url)  
**Figure 9.** (A) Top views of stereoisomeric baskets 5⁰ and 5⁴ (MMFFs, Spartan). (B) A segment of simulated (WinDNMR) and experimental VT ¹H NMR spectra of basket 5 (R = CH₃) in CDCl₃, showing the coalescence of the AB quartet, corresponding to CH₃ protons, into a singlet.⁴⁹

**Conformational Stereoisomerism and Racemization:** In 5, the seam of N—H—N hydrogen bonds can be oriented in two directions (P or M) to give stereoisomeric baskets 5⁰ and 5⁴ (Figure 9A).⁴⁹ Thus, in solution, the rotation of the pyridine gates, assuming propeller-like orientations, should permit the interconversion of dynamic enantiomers 5⁰ and 5⁴. In line with this reasoning, ¹H NMR signals corresponding to CH₂ hydrogen nuclei in 5 are expected to become diastereotopic during a slow racemization (Figure 9A). When the exchange of CH₂ signals is, however, fast on the NMR time scale, these protons become enantiotropic and therefore indistinguishable by dynamic ¹H NMR spectroscopy. Indeed, variable temperature ¹H NMR spectroscopy (VT ¹H-NMR) corroborated the anticipated scenario for the racemization of 5⁰/M: the resonance corresponding to CH₂ group appeared as a singlet at high but AB quartet at low temperatures (Figure 9B).⁷⁸, ⁷⁹ Interestingly, the rate of racemization appeared to be a function of the guest's affinity for occupying the basket's cavity: the greater the affinity (ΔG°), the slower the 5⁰/M interconversion (ΔG°).⁷⁹ To account for the observation, we reason that a greater host-guest affinity means a stronger intermolecular attraction and thereby a greater "pull" on the gates by the guest to decrease the rate by which the basket opens and closes its gates; note that the situation is somewhat complicated by the fact that guest exchange could also contribute to the revolving of three aromatic gates (see below).⁶⁶ To further investigate the mechanism of 5⁰/M interconversion, we used VT ¹H-NMR spectroscopy to quantify the racemization of 5 (R = CF₃, Figure 5) in four differently sized solvents (CD₂Cl₂ (61 Å³), CDC₁₇ (75 Å³), CFCl₃ (81 Å³) and CCl₄ (89 Å³)).⁵¹ Interestingly, the racemization was found to be fastest in CD₂Cl₂ (ΔH° rac = 10.9 ± 0.3 kcal/mol at 298.0 K) while slowest in CCl₄ (ΔH° rac = 12.8 ± 0.2 kcal/mol at 298.0 K). When ΔH° rac was plotted against...
ΔS_{rac} (red line in Figure 10A), however, we found an isokinetic relationship for the interconversion of $^5$H$_{2}$M in CCl$_3$, CFCI and CCl$_4$ suggesting the same mechanism of racemization$^{51}$ The interconversion of $^5$H$_{2}$M in CCl$_2$ was, however, found to fit to another isokinetic relationship (blue line in Figure 10A) suggesting a different racemization pathway;$^{51}$ note that this particular linear dependence corresponded to the racemization of a more spacious gated basket in the same four solvents. Markedly, the population of the basket's cavity varies for the examined solvents, acting as guests: while the PC for CCl$_3$, CFCI and CCl$_4$ varies from 0.33 to 0.39, it is 0.27 for CCl$_2$. In line with the experimental evidence (Figure 10A), we went on to suggest that the size of guests residing inside gated baskets of type 5 matter in the opening/closing event by imposing on the operation of gates revolving at the rim. That is to say, when PC > 0.30, the racemization of basket follows the mechanistic pathway whereby all three gates revolve simultaneously (RM$_3$, Figure 10B). However, for PC < 0.30, the revolving mechanism comprises one pyridine gate “breaking away” from the N–H–⋯N hydrogen bonding to form an intermediate state followed by the concomitant flip of the remaining two gates (RM$_1$, Figure 10). The reasoning is in line with our computational study whereby the RM$_1$ pathway dominates for the racemization of baskets having pyridine gates forming stronger intramolecular N–H–⋯N hydrogen bonding contacts.$^{51}$

**Encapsulation Kinetics:** To examine the rate law characterizing the exchange of 1,1,1-trichloroethane (CH$_3$CCl$_3$) to/from gated basket 5 (R = Ph, Figure 5), we completed $^1$H,$^1$H-[CH$_3$CCl$_3$]$^{80}$ we arrived to the following dependence: $k^*_{in} = k_{in}$ [5–CH$_2$Cl$_2$]. If the proposed kinetic model is valid, the experimentally determined $k^*_{in}$ must be a linear function of the concentration of basket [5–CH$_2$Cl$_2$]. Indeed, we found a linear dependence between $k^*_{in}$ and [CH$_3$CCl$_3$] with the slope of the fitted curve equal to $k_{in} = 2.1 \pm 0.3 \times 10^3$ M$^{-1}$s$^{-1}$ ($\Delta G^2_{in} = 10.7$ kcal/mol, Figure 11B)$^{56, 79}$ Following, the rate law corresponding to CH$_3$CCl$_3$ guest departing [5–CH$_3$CCl$_3$] complex was, in a similar manner,$^{56}$ probed by varying the concentration of [CH$_3$CCl$_3$] and measuring $k^*_{out}$ ($^1$H NMR spectroscopy). Importantly, there was no interdependence between the experimentally determined $k^*_{out}$ and [CH$_3$CCl$_3$] to suggest that the departure of this guest from [5–CH$_3$CCl$_3$] is zeroth order in its concentration with the rate law $v_{out} = k_{out}$ [5–CH$_3$CCl$_3$] ($k^*_{out} = k_{out} = 10$ s$^{-1}$; $\Delta G^2_{out} \approx 13.4$ kcal/mol). At last, the activation energy for the racemization of [5–CH$_3$CCl$_3$] was (from dynamic $^1$H NMR spectroscopy)$^{59}$ determined to be $\Delta G^2_{rac} = 11.7$ kcal/mol; the racemization of [5–CH$_2$Cl$_2$] was, however, more facile with $\Delta G^2_{rac} = 9.2$ kcal/mol.

**The Mechanism of Gated Encapsulation:** The results of steered molecular dynamics calculations showed that “opening” of three pyridine-based gates is required for the trafficking of guests to/from baskets (Figure 12A)$^{79}$ In particular, pulling CH$_3$CCl$_3$ from the interior of [5–CH$_3$CCl$_3$], along various reaction trajectories, would cause a rupture of N–H–⋯N hydrogen bonds.$^{56}$ Ergo, the unfolding of pyridine gates within gated baskets must occur with the departure of guests. As discussed in the previous section, the rate law corresponding to EXSY and selective inversion-transfer NMR measurements.$^{56}$ These experiments were conducted under equilibrium conditions, with the exchange rate constants $k^*_{in}$ (s$^{-1}$) and $k^*_{out}$ (s$^{-1}$) characterizing the transfer of longitudinal magnetization of CH$_3$CCl$_3$ nuclei from bulk solvent to the interior of gated basket and vice versa (Figure 11A)$^{80, 81}$ On the basis of already established 1:1 host/guest binding stoichiometry (*vide supra*),$^{37}$ we assumed that the formation of [5–CH$_3$CCl$_3$] is first order in [5–CH$_2$Cl$_2$] and [CH$_3$CCl$_3$] so that $v_{in} = k_{in}$ [5–CH$_2$Cl$_2$] [CH$_3$CCl$_3$]; note that CD$_2$Cl$_2$ is bulk solvent, occupying “free” basket 5. Since the rate of the forward reaction, from the magnetization transfer experiments, is formulated as $v_{in} = k^*_{in}$
the formation of $[5\text{-CH}_2\text{CCL}_3]$ complex ($\nu_{\text{in}} = k_{\text{in}}$ $[5\text{-CH}_2\text{CCL}_3][\text{CH}_2\text{CCL}_3]$) was found to be first-order in guest suggesting that ingress/egress of CH$_2$CCL$_3$ constitutes the rate-limiting step of gated encapsulation (Figure 12B). Finally, the racemization of $[5\text{-CH}_2\text{CCL}_3]$ ($\Delta G^\ddagger_{\text{rac}} = 11.7\text{ kcal/mol}$) was found to be more facile than the departure of CH$_2$CCL$_3$ from $[5\text{-CH}_2\text{CCL}_3]$ complex ($\Delta G^\ddagger_{\text{out}} = 13.4\text{ kcal/mol}$). Apparently, gated host $[5\text{-CH}_2\text{CCL}_3]$ incessantly flutters its pyridine gates at the rim ($\Delta G^\ddagger_{\text{rac}} = 11.7\text{ kcal/mol}$). An occasional egress of CH$_2$CCL$_3$ and ingress of CD$_2$CCL$_3$ ($\Delta G^\ddagger_{\text{out}} = 13.4\text{ kcal/mol}$) takes place to give $[5\text{-CH}_2\text{CCL}_3]$! The presumption is that CD$_2$CCL$_3$ enters gated basket of type 5 via a sizeable side aperture to substitute CH$_2$CCL$_3$ in a single elementary step (Figure 12C); indeed, there could be an intermediate (i.e. partly-unfolded basket) forming along the way. More experiments are needed to refute/confirm such a mechanistic scenario. Lastly, we discovered that the rate of the solvent/guest supramolecular substitution (Figure 12C) is, in gated encapsulations, a function of the size of solvent molecules displacing the entrapped guest: the bigger the solvent the slower the displacement. The negative entropy of activation ($\Delta S_{\text{act}}^{\ddagger}$) is, furthermore, characterizing such transformations with a transition state (Figure 12C) comprising both guest and solvent molecules within the gated host.

**Controlling the Encapsulation Kinetics:** There has been some interest toward understanding the persistency (lifetime) of encapsulation complexes. Indeed, a control of the host's dynamics could be useful for regulating the outcome of chemical reactions and delivering compounds at a precise rate. In line with studying molecular gating, we realized that learning about conformational changes in cavitation-based hosts and understanding how to fine-tune such processes should allow the preparation of novel supramolecular catalysts (vide infra).

Gated baskets of type 5 operate by unfolding pyridine-based gates at the rim for permitting in/out exchange of guests. It follows that adjusting the rate ($k_{\text{out}}$) by which guests revolve ought to affect the residing time ($t = 1/k_{\text{out}}$) of trapped compounds. In accord with this reasoning, we decided to alter the electronic and steric characteristics of R amido groups in basket $5^R$ (Figure 13A), with the notion that these substituents would, to a variable degree, affect the stability of the N–H–N hydrogen bonds. By altering the racemization rate of $5^R$, we should change the kinetic liability of noncovalent complexes. Since weak/moderate hydrogen bonds are electrostatic in nature, the electron-density perturbations of $5^R$ had to be anisotropic to affect the host's dynamics in the desired manner: a depletion of the charge at N–H$_0$ positions should be accompanied by a negligible perturbation at the Pyr–N$_7$ sites. Indeed, computed electrostatic potentials (HF(6–31G(d,p))) suggested a fluctuation in the charge density at the hydrogen atom of N–H$_0$ groups, but rather consistent values at the pyridine nitrogen atoms.

With the assistance of $^1$H NMR spectroscopy ($^1$H–H-EXSY) we found that electron-withdrawing CF$_3$ groups in $5^{CF_3}$ retarded, while electron-donating CH$_3$ groups in $5^{CH_3}$ accelerated, the racemization of these baskets. More importantly, the rate coefficient ($k_{\text{out}}$, Table 1) characterizing the departure of (CH$_3$)$_2$CBr guest from $[5^{R=\text{(CH}_3)_2\text{CBr}}]$ encapsulation complexes followed the same trend! The kinetic stability of $[5^{R=\text{(CH}_3)_2\text{CBr}}]$ decreased in the series in spite of a comparable thermodynamic stability of these complexes ($\Delta G^\ddagger = \sim 2$ kcal/mol, Table 1). In fact, the thermodynamically least stable complex $[5^{CF_3}\text{-(CH}_3)_2\text{CBr}]$ ($\Delta G^\ddagger = \sim 1.0 \pm 0.2$ kcal/mol, Table 1) was also the most persistent one ($k_{\text{out}} = 0.07 \pm 0.02$ s$^{-1}$). The lifetime ($t=1/k_{\text{out}}$ Figure 13A) of encapsulation complexes $[5^{R=\text{(CH}_3)_2\text{CBr}}]$ is thus a function of the dynamics of the pyridine-based gates: the more sluggish the gates, the more persistent the encapsulation complex. Lastly, the kinetic data for the departure of (CH$_3$)$_2$CBr was placed on a quantitative scale using Taft's linear free-energy relationship (Figure 13B).

The Taft's scale defines polar ($\sigma^*$) and steric ($E^*$) constants of a variety of substituents and has been useful for studying the perturbation of both equilibria and rates of chemical reactions. We used this two-parameter model to fit a linear dependence between log($k_{\text{out}}$/s) and $\sigma^*$ + $E^*$ (Figure 13B). The correlation was acceptable ($R^2 = 0.94$), with the departure rates being a function of both electronic ($\rho^* = -0.6$) and steric

![Figure 13.](image)
On the Shape Selectivity: If two guests possess the same affinity for occupying a gated basket \((\Delta G^0)\), will they enter such host at the same rate \(\Delta G^+_{\text{in}}\)? How do size, shape and/or number of alkyl groups to encompass a different affinity for occupying 5 \((\Delta G^0 = -(1.8-5.6) \text{ kcal/mol, Figure } 14B)\). Interestingly, these spherical compounds were measured to enter 5 at rates \((\Delta G^+_{\text{in}})\) corresponding to binding affinities \(AG^0\) (Figure 14B): the greater the potential for occupying the basket, the faster the ingress.\(^{79}\) Moreover, we found that the encapsulation kinetics/thermodynamics of I–V could be described with a quantitative relationship using the following linear equation \(\Delta G^+_{\text{in}} = \rho \Delta G^0 + \delta\) (Figure 14B). A question arose: would guest molecules, having profiles slightly different from I–V, obey the same \(\Delta G^0/\Delta G^+_{\text{in}}\) linear free-energy relationship (LFER)? Guests VI–VII were chosen to examine this aspect of the gating (Figure 14A). 1,1,1-Trichloroethane VI is a non-spherical molecule, smaller (93 Å\(^3\)) than I–V (−107 Å\(^3\)). Interestingly, VI entered basket 5 at the rate faster than one would predict on the basis of the LFER in Figure 14B. Larger tetramethylsilane VII (120 Å\(^3\)) was, however, found to access the basket’s cavity at a rate slower than expected on the basis of the LFER in Figure 14B. Clearly, gated basket 5 selected guests on the basis of their size/shape: for isosteric guests, the encapsulation rates would track the intrinsic binding potential \((AG^0)\), and in accordance with the linear free-energy relationship (Figure 14B). For smaller/bigger guests, however, the rates do not fit the free-energy \((\Delta G^+_{\text{in}} = \rho \Delta G^0 + \delta)\) dependence. It follows that for two guests possessing the same affinity \(\Delta G^0\) for occupying a gated host, the rate by which they access its interior \((\Delta G^+_{\text{in}})\) is a function of their size: the smaller compound is expected to enter the host at a faster while bigger molecule at a slower rate. Indeed, the quantified shape/size selectivity could be a function of the frequency by which the revolving gates flutter at the rim of 5,\(^{78}\) to resemble the action of some enzymes.\(^{100}\) On the basis of this postulate, one should find that a faster racemization of baskets contributes to a greater kinetic selectivity of trapping guests\(^{78}\) yet more research is needed to test the existence of such conformational/gating selectivity\(^{33}\) in artificial settings.

Stereoselective Encapsulation and Gating: As described in prior sections, three pyridine-based gates revolve at the rim of gated baskets to contribute to the formation of a racemic mixture of P/M capsules (Figure 9).\(^{51}\) In this vein, C\(_3\) symmetric 5\(^r\) and 5\(^l\) possess so-called inherent chirality\(^{101}\) that is reversed by the process of racemization. By restricting the orientation of the gates to either P or M propeller-like form, however, the gated basket could perhaps become capable of kinetically discriminating (resolving) chiral molecules.\(^{102}\) That is to say, an enantiomeric guest \((R)\) may access/depart 5\(^r\) at a different rate than the opposite enantiomer (S). In fact, transition states for access/departure of \(R\) or \(S\) guest to/from 5\(^r\) basket should be diastereomeric and therefore comprise different stabilities! Indeed, chiral hemiarcencarbons\(^{12}\) and cryptophanes\(^{103}\) trap/release enantiomeric guests at different rates, yet our fundamental understanding of the process and its control remain insufficient for implementing this element of design into functional hosts.\(^{104}\)

The computed structure of 5\(^r\) basket (Figure 15A)\(^{105}\) showed that three pyridine-based gates are somewhat shifted to
the right, driving each hydrogen $H_i$ of the CH$_2$ groups, away from the carbonyl oxygen atom. We, therefore, anticipated that substituting $H_1$ with more sizeable CH$_3$ group (Figure 15B) should bias the helicity and give (S)–5$^p$ stereoisomer. In other words, by installing stereogenic S center at the "hinge" position the pyridine gates ought to assume the $P$ orientation for (S)–5$^p$ possessed an almost identical potential for complexing $R$–6 ($\Delta G^\ddagger(\text{R}) = -0.92 \pm 0.08$ kcal/mol) and $S$–6 ($\Delta G^\ddagger(\text{S}) = -0.86 \pm 0.06$ kcal/mol). In spite of comparable intrinsic affinities ($\Delta \Delta G^\ddagger(R/S) = 0.06$ kcal/mol), gated basket (S)–5$^p$ kinetically differentiated ($^1$H-NMR spectroscopy)$^{105}$ enantiomeric 1,2-

minimizing the van der Waals strain.$^{76}$ Finally, we computed (DFT: RI-BP86/SV(P), Figure 15C) that (S)–5$^p$ is 2.19 kcal/mol more stable than the corresponding (S)–5$^M$ diastereomer.$^{105}$ The $^1$H NMR spectrum of (S)–5 showed one set of signals corresponding to C$_3$ symmetric species, with no decoalescence of resonances at lower temperatures (up to 210 K). The results suggested a predominance of either (S)–5$^p$ or (R)–5$^M$ diastereomer. We then went on to use circular dichroism (CD) spectroscopy,$^{77}$ to confirm the exclusive formation of the expected (S)–5$^p$ diastereomer in CD$_2$Cl$_2$.$^{105}$

When enantioenriched (R)–6 guest (>85 % ee, Figure 16A) was added to a solution of (S)–5$^p$ in CD$_2$Cl$_2$, we observed a single set of $^1$H NMR signals at $\delta < 0$ ppm corresponding to the haloalkane within (S)–5$^p$$\subset$(R)–6 complex (Figure 16B); likewise, the formation of (S)–5$^p$$\subset$(S)–6 ensued upon mixing (S)–5$^p$ and (S)–6 (Figure 16B). Importantly, we found that dibromopropanes to a greater degree $\Delta \Delta G^\ddagger_{\text{in}}$ (R/S) = 0.3 kcal/mol! Thus, the $R$–6 guest would enter (S)–5$^p$ two times faster than the $S$–6 compound. To explain the observation, we suggested that pyridine-based gates, residing in their principal $P$ orientation within (S)–5$^p$, unfold in a unidirectional manner during the trafficking of (R/S)–6 (Figure 16A). In this way, the observed stereoselectivity arose from diastereomeric transition states formed in the gating.$^{105}$

Recently, we delineated an effective synthetic strategy for rapid preparation of C$_3$ symmetric 7 possessing a twisted framework and therefore a chiral inner space (Figure 17).$^{106}$ In particular, we used methanesulfonic acid (CH$_3$SO$_3$H) to promote a tandem of intramolecular annulation reactions (cyclialkylations)$^{107}$ with the conversion of indene derivative 8 into 7 (85% yield, Figure 17A). The cup-shaped 7 encompasses three [3.2.1] bicyclic rings twisted in the same direction so that the molecule is helical with either right- (P) or left-handed (M) sense of twist (Figure 17B). Twisted cavitands have unique topology$^{108}$ and are more sizeable than gated hosts of type 5 (Figure 5). At present, we are investigating these concave compounds for promoting stereoselective encapsulations, obtaining chiral sensors and supramolecular catalysts.$^{99, 104, 109, 113}$

**Gated Baskets and Reactivity:** Self-assembled or covalent molecular capsules offer a unique environment$^2$ for destabilizing reactants and/or stabilizing reactive
intermediates/transition states of chemical reactions.\textsuperscript{10, 11, 13} Given the subtlety of noncovalent interactions,\textsuperscript{97} however, it is

![Image](image_url)

Figure 17. (A) The cycloalkylation of 8 is promoted with CH$_3$SO$_3$H to give twisted cavitand 7 (85%, CH$_3$COCH$_2$Cl);\textsuperscript{105} an electron-pushing scheme describes the first annihilation reaction. (B) C$_5$ symmetric $\eta^7$ and $\eta^8$ (MMFFs, Spartan) possess a screw-shaped structure with either a right (P) or left-handed (M) sense of twist.

indeed challenging to rationally design a supramolecular (encapsulation-based) catalyst\textsuperscript{114, 115} whereby a combination of electrostatic forces (\textasciitilde 1 kcal/mol or more) is expected to stabilize the transition state of a desired chemical transformation. In particular, the conformational changes of encapsulated guest(s) have almost uniformly been found to slow down or stay unchanged relative to those occurring in an isotropic solvent system.\textsuperscript{116-118} We recently reported a case of accelerated ring flipping of cyclohexane-d$_{11}$ (C$_{12}$D$_{11}$H) within gated basket 5 (Figure 18A).\textsuperscript{57} The rate coefficient $k$ (s$^{-1}$) of cyclohexane-d$_{11}$ undergoing chair-to-chair interconversion (Figure 18B) was, in CD$_2$Cl$_2$ ($k = 6.9 \pm 2.2$ s$^{-1}$; $\Delta G^\ddagger = 10.1 \pm 0.1$ kcal/mol) and within basket 5 ($k = 43 \pm 3$ s$^{-1}$; $\Delta G^\ddagger = 9.43 \pm 0.03$ kcal/mol), quantified with $^1$H,$^1$H-EXSY as well as dynamic NMR measurements at 189 K. As the conformational change of C$_{12}$D$_{11}$H was roughly five times faster inside gated basket than in the reference bulk solvent, we used electronic structure methods (DFT: M06-2X, Figure 18B) to identify the origin of the observed acceleration.\textsuperscript{57} In essence, the optimized geometry of chair cyclohexane was slightly destabilized inside the basket relative to vacuum ($\Delta E = 0.25$ kcal/mol, Figure 18B). Three C–H$\cdots$π interactions (<2.7 Å, from each hydrogen to juxtaposed π centroid, Figure 18B) were

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Figure 18. (A) Energy minimized structure of basket 5 containing cyclohexane (M06-2X/6-31G(d)); note that the front side of the basket is omitted for clarity. An energy diagram for the conformational interconversion of cyclohexane (right). (B) Energy optimized structures of chair (left) and half-chair (right) conformers inside gated molecular basket 5 (M06-2X/6-31G(d)); some structural features are omitted for clarity.

suggested affect the geometry of cyclohexane altering from being $D_{3h}$ symmetric in vacuum to $C_1$ inside 5. Conversely, the half-chair transition state of cyclohexane was found to be "more stable" in basket 5 than in vacuum ($\Delta E = -0.90$ kcal/mol, Figure 18B). The formation of another host-guest C–H$\cdots$π interaction distorted three dihedral angles of the half-chair carbon framework moving it along the reaction coordinate to more closely resemble the twist-boat product! The activation barriers for the chair-to-chair interconversion of cyclohexane were, in this way, computed to be $\Delta E^\ddagger = 10.87$ kcal/mol in the interior of 5 while $\Delta E^\ddagger = 12.02$ kcal/mol in vacuum ($\Delta \Delta E^\ddagger = 1.15$ kcal/mol). Importantly, the result was in good agreement with our experimental measurements ($\Delta \Delta G^\ddagger = 0.5$ kcal/mol). To sum up, molecular recognition of the transition state corresponding to the interconversion of cyclohexane facilitated the transformation thereby concurring with the Pauling paradigm: "enzymes are molecules that are complementary in structure to the activated complexes of the reactions that they catalyze...".\textsuperscript{119}

With the process of molecular gating under control, one wonders about a potential relationship between the gating of reactants and chemical reactivity. That is to say, will dynamic regulation of substrate access to a catalytic center, embedded in a gated molecular basket, have an effect on the rate of a chemical reaction taking place in the basket's interior (Figure 19A)? So far, the process of gating allows for controlling the time that molecules stay in an intimate contact.\textsuperscript{96} By increasing
the lifetime of such an encounter complex, the reaction could become more effective on the basis of an increased probability for overcoming the activation barrier via a higher number of successful collisions (see the Menger’s spatiotemporal postulate).\(^{120}\) In another possible scenario, the gating could be adjusted to limit the rate of a particular chemical transformation, which could further be manipulated for controlling the outcome of a series of reactions. Since there have been no studies about gated catalysis, we set to create a family of gated catalysts.\(^{121}\) It, thus, occurred to us that a stereoselective installation of four norborne "walls" around a porphyrin "floor" would give a basket-like host containing a porphyrin ring (Figure 19). Accordingly, we optimized a synthetic methodology for obtaining basket \(9\) by promoting head-to-tail tetramerization of enantiopure pyromethanecarbinol \(10\) with Brønsted acids (\(p\)-TsOH).\(^{122}\) The reaction was under kinetic control as longer reaction times and higher concentrations of the acid led to the formation of other diastereomeric porphyrin systems (Figure 19). Importantly, basket Mn(III)–9 (Figure 20) was expected to react with a sacrificial terminal oxidant (\(t\)-BuSO\(_2\)PhIO) to give an elusive Mn(V)=O species capable of transferring an oxygen atom to olefins in its spacious inner space (\(V \approx 570 \text{ Å}^3\)). If the residing time of olefins is indeed controlled via gating, there should be a possibility to investigate the relationship between molecular gating and reactivity.

First, we incorporated Zn(II) into basket \(9\) to form Zn(II)–9 capable of axial coordination of imidazole-based ligands. Smaller 1-methylimidazole (64 \text{ Å}^3) was found to predominantly bind to Zn(II)–9 inside of its cavity while larger 1,5-diadamantylimidazole (361 \text{ Å}^3) would coordinate at its outer side. The rationale for these studies rested in the notion that the complexation of \(N\)-heterocycles to the outer side of Mn(III)–9 would enforce the epoxidation to occur in the cavity of the basket (Figure 21A).\(^{122}\) \(N\)-Heterocycles are known to bind to Mn(III) porphyrins forming five- and six-coordinate complexes. With the assistance of UV-Vis spectroscopy, we determined that Mn(III)–9 basket would predominantly bind (a) 1-methylimidazole at its inner side (\(K_{a1} = 58 \pm 13 \text{ M}^{-1}\), \(K_{a2} < 5 \text{ M}^{-1}\)) to give \(L_{\text{in}}\)-Mn(III)–9 and (b) 1,5-diadamantylimidazole to the outer side (\(K_{a1} = 332 \pm 26 \text{ M}^{-1}\), \(K_{a2} \approx 0 \text{ M}^{-1}\)) forming \(L_{\text{out}}\)-Mn(III)–9 (Figure 21A). The epoxidation of an equimolar mixture of differently sized/shaped \(cis\)-2-octene \(10\) (187 \text{ Å}^3) and \(cis\)-cyclooctene \(11\) (142 \text{ Å}^3) was in the presence of \(L_{\text{in}}\)-Mn(III)–9 and \(L_{\text{out}}\)-Mn(III)–9, promoted with soluble iodosylarene \(t\)-BuSO\(_2\)PhIO in CH\(_2\)Cl\(_2\) at room temperature (Figure 21A/B). When the reaction occurred outside the cavity of \(L_{\text{in}}\)-Mn(III)–9, the oxidation of the linear alkene \(10\) was 1.2 times faster than the cyclic one \(11\). When the epoxidation reaction was taking place inside the cavity of \(L_{\text{out}}\)-Mn(III)–9, however, the conversion of linear alkene \(10\) was 2.0 times faster than the cyclic one \(11\). What is the origin of the observed shape selectivity? Why would linear alkene react at a faster rate (\(\Delta G^2 = 0.3 \text{ kcal/mol}\)) than the cyclic one in the inner space of the supramolecular catalyst? Since we could not detect the encapsulation of \(10\) or \(11\) within basket \(9\) (\(^1\)H NMR spectroscopy), the observed kinetic resolution could emanate from the catalyst’s topology and/or its dynamic nature (gates revolving at the rim). At present, we are working on placing pyridine-based gates into \(9\) for forming intramolecular hydrogen-bonding contacts. The utility of such gated hosts as well as its catalytic characteristics will be evaluated.
but could become useful for modulating the outcome of trafficking of guests. Controlling the process of this so-called molecular gating\textsuperscript{123} is still a matter of scientific curiosity but could become useful for modulating the outcome of chemical reactions (especially for the optimized design and operation of supramolecular catalysts) and promoting a delivery of molecules. Gated molecular baskets, described in this review, operate via unfolding their pyridine-based gates at the rim for permitting the passage of guests. These compounds are now established as useful models for not only investigating encapsulation mechanisms but also understanding the utility of gating in controlling the outcome of chemical reactions.

**Conclusions**

In the last two decades, we have witnessed a growing interest toward elucidating mechanisms by which the process of molecular encapsulation takes place. At present, we recognize that conformational changes in capsular hosts could facilitate in/out trafficking of guests. Controlling the process of this so-called molecular gating\textsuperscript{123} is still a matter of scientific curiosity but could become useful for modulating the outcome of chemical reactions (especially for the optimized design and operation of supramolecular catalysts) and promoting a delivery of molecules. Gated molecular baskets, described in this review, operate via unfolding their pyridine-based gates at the rim for permitting the passage of guests. These compounds are now established as useful models for not only investigating encapsulation mechanisms but also understanding the utility of gating in controlling the outcome of chemical reactions.

**Acknowledgements**

This work was financially supported with funds obtained from the National Science Foundation under CHE-1305179 to J.D.B. The Ohio Supercomputer Center is gratefully acknowledged for providing generous computational resources.

**Notes and references**

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The process of molecular gating is important for controlling the trafficking of guests to and from artificial molecular capsules.
Biography

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Yian Ruan received her B.S. in chemistry and biology from Tsinghua University in China (2008). She obtained her PhD degree in organic chemistry from the Ohio State University (2014) by designing, preparing and investigating the characteristics of molecular baskets capable of trapping nerve agents. Her research interests include molecular encapsulation and self-assembled materials.
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