An Investigation into the Effects of Gating in Artificial Host Systems

DISSERTATION

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By

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Abstract

The translocation of molecules in natural systems is often regulated by modulation of dynamic moieties in a process referred to as gating. In the enzyme acetylcholinesterase, the tunnel leading to the active site is regulated by five freely-rotating aromatic residues which serve as gates. This passageway is effectively closed off by the gates roughly 98% of any given time, resulting in the rate of acetylcholine uptake to decrease by a factor of two in comparison to a model system possessing no gates. Strikingly, it was found that a guest whose volume is only 0.4 Å³ larger than acetylcholine will enter at a rate three orders of magnitudes less, thus acetylcholinesterase, though the process of gating, achieves a high degree of kinetic selectivity with only a small sacrifice of catalytic efficiency.

With the goal of incorporating gating into artificial host molecules, the Badjic group has designed and synthesized a series of molecules, termed molecular baskets, that consist of a bowl-shaped cavity with dynamic appendages (gates) tethered to the rim. In previous work within the Badjic group, phenol-based gates were shown to effectively close the basket, but the dynamics of the gates prevented an effective preorganized cavity to form and any resulting host-guest complex did not exist within a reasonable time-frame to allow study.
In an effort to more effectively close the basket and reduce gate dynamics, molecular baskets containing pyridyl gates were synthesized and their properties were analyzed after folding with Cu(I) (See Chapter 2). The resulting basket, however, only encapsulated linear coordinating guest molecules, which prevented the study of its gating properties.

Subsequently, a basket containing pyridylamido gates was synthesized and found to form a wider variety of host guest complexes. This basket was also found to incorporate gating successfully: the entrance and departure of guest molecules are primarily dependent on the rate by which the gates fold/unfold. By modifying the structure of the gates, it was found that the rates of guest ingress and egress can be controlled and tailored.

Through the use of linear free energy relationships (LFERs) between the activation energies for guest entrance and departure and the thermodynamic stability of the resulting host-guest complex, it was found (See Chapter 3) that the baskets displayed kinetic selectivity toward the size/shape of guest molecules: small molecules enter and leave at rates faster than larger molecules. To probe the relationship between the gate dynamics and kinetic selectivity, the experiment was repeated with molecular baskets possessing faster and slower gates. Interestingly, a correlation was found whereby faster gate dynamics resulted in increased kinetic selectivity.

In addition to gating, other interesting properties were found for the pyridylamido molecular baskets. Surprisingly, cyclohexane was found to interconvert between its two chair forms at a faster rate within the cavity than outside in the bulk solvent due to
favorable interactions between the host and half-chair transition state. The baskets were also found to effectively reversibly interconvert between the metal-chelation and intramolecular hydrogen bond modes of folding with an added stimulus (See Chapter 4). By studying gating in artificial host systems, unique features such as rate control and increased kinetic selectivity can potentially be incorporated into the next generation of supramolecular catalysts.
Dedication

To my wife and family
Acknowledgments

I would like to first thank my advisor, Dr. Jovica Bajdic, for his support and advice over the last six years. He has brought great enthusiasm to our research and I appreciate the independence I was granted to explore my own curiosities and ideas. I would also like to thank Dr. Christopher M. Hadad and Dr. Gideon Fraenkel and their corresponding group members for their collaborative efforts through the years.

I’m also thankful for the camaraderie and support offered from my own group members past and present. I’m especially thankful to Dr. Zhiqing Yan for initially showing me the ropes around the lab and Dr. Bao-yu Wang for our insightful discussions and experiments with molecular baskets. It was a lot of fun working with and brainstorming new ideas and experiments for these interesting systems. I am also grateful to Dr. Tanya Young of the Ohio State NMR facility for unraveling much of the mystery of those intricate instruments. I am certain such knowledge and experience will be of benefit for years to come.

Last, but certainly not least, I would like to thank my wife, Charlotte, and my parents for giving me support and motivation throughout the years. I’m fairly certain that if I didn’t have these, this document would not exist.
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**Fields of Study**

**Major Field:** Chemistry
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<table>
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<th>Abbreviation</th>
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<td>angstrom (1 x 10^{-10} m)</td>
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<td>Austin Model 1</td>
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<tr>
<td>AMBER</td>
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<td>br</td>
<td>broad (NMR)</td>
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<td>COSY</td>
<td>Correlation Spectroscopy (NMR)</td>
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<td>CPK</td>
<td>3-dimensional space-filling molecular modeling. Named after Robert Corey, Linus Pauling, and Walter Koltun</td>
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<td>DDQ</td>
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<td>Density Functional Theory</td>
</tr>
<tr>
<td>DMA</td>
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<td>DMAD</td>
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<td>ESI</td>
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</tr>
<tr>
<td>eu</td>
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</tr>
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<td>EXSY</td>
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h  hour
IR infrared
ITC Isothermal Calorimetry
$k_d$ rate constant describing the departure of a guest molecule from a host
$k_f$ rate constant describing the entrance of a guest molecule into a host
$k_{rac}$ rate constant describing the dynamic interconversion between the two closed stats in molecular baskets presented in Chapter 3.
LAH lithium aluminum hydride
LDA lithium diisopropylamide
LFER linear free energy relationship
M moles per liter
m meter; multiplet (NMR)
MALDI matrix-assisted laser desorption/ionization
MD molecular dynamics
min minute
MMFF Merck Molecular Force Field
MS mass spectrometry
NOE Nuclear Overhauser Effect
NOESY Nuclear Overhauser Effect Spectroscopy
NMR nuclear magnetic resonance
OTf trifluoromethanesulfonate (triflate)
PC packing coefficient \([\text{volume of guest / volume of host cavity}] \times 100\)
PES potential energy surface
PM3  parameterized model number 3
rds  rate determining step
ROESY  Rotating Frame Overhauser Effect Spectroscopy
s  second; singlet (NMR)
t  triplet (NMR)
\( t \)  time
THF  tetrahydrofuran
TFA  trifluoroacetic acid
TLC  thin-layer chromatography
Chapter 1: Molecular Baskets – Toward Functionalized Gated Artificial Host Systems

1.1 An Introduction to Gating

The control of the translocation of molecules is of significant importance to the functioning of living organisms. Cell membranes, for example, regulate the kinetics of molecules or ions passing in and out of the cell with respect to their size, shape, or functionality.\(^1\)\(^-\)\(^3\) Likewise, access to an active site of an enzyme is often regulated by the dynamic modulation of the entrance to its active site.\(^4\)\(^-\)\(^6\) Such processes, commonly referred to as gating, are akin to a traffic gate opening and closing at a constant rate, thus restricting how fast species may pass.

A particular example of an enzyme exhibiting gating is found in acetylcholinesterase (AchE), which is capable of efficiently hydrolyzing acetylcholine (Ach).\(^7\) The X-ray crystal structure of the enzyme reveals a 20 Å deep gorge leading to its active site\(^8\) whose access is regulated by five freely rotating aromatic rings which must reorientate themselves to allow the entrance of a guest molecule. McCammon and coworkers utilized molecular dynamics methods to ascertain the particular effects these gates have on the uptake of Ach and whether they contribute to the efficiency by which the enzyme operates.\(^4,\)\(^8\) Thus, it was calculated that the probability of the gates being fully open to allow the binding of Ach was small (2.4%). Despite this small fraction of time the gates
are open, however, the rate coefficient corresponding to the uptake of Ach was surprisingly found to only decrease by roughly a factor of two (from $1.7 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ to $0.7 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$). To account for this result, the authors suggested that the small probability of the gorge’s open state is likely compensated by a fast transition between the open and closed states. Worded differently, the gorge leading to the active site opens quickly numerous times and, during a binding event, Ach would make repeated attempts to enter until an attempt coincides with an opening, thus resulting in entry. Using a similar model, it was found that a slightly bulkier substrate possessing an additional 0.4 Å$^3$ volume would enter the active site at a rate three orders of magnitude less than Ach. Thus, through the process of gating, AchE achieves a high degree of kinetic selectivity among molecules of slightly different sizes without sacrificing much catalytic efficiency.

Prior to discussing the application of gating to artificial host systems, it is important to discuss the concepts of constrictive binding energy and intrinsic binding energy, which are fundamental to the field of host-guest chemistry. Intrinsic binding energy, equivalent to a host-guest complex’s thermodynamic stability ($\Delta G^\circ$), arises from non-covalent contacts between a host and guest (e.g. hydrogen bonding, electrostatics, C-H$^\cdots\pi$ interactions) as well as desolvation effects. Constrictive binding energy,\textsuperscript{9} equivalent to the energy required for guest entry ($\Delta G^\ddagger$), includes the energy associated with physical barriers such as dynamic appendages obstructing an entry or small openings in a host that guest molecules must squeeze through prior to entry. Thus, the constrictive binding energy can be seen primarily as the energy required for a host molecule to distort or rearrange itself to make encapsulation possible and is intrinsically related to gating. The
energy for a guest molecule to leave ($\Delta G^{\ddagger}_{d}$) is equivalent to the energy required to overcome both the intrinsic and constrictive binding energies ($\Delta G^\circ + \Delta G^{\ddagger}_{f}$) (Figure 1).

Figure 1: The Gibbs Free Energies associated with a host guest complex are the intrinsic binding energy, equivalent to the thermodynamic stability of the complex ($\Delta G^\circ$), and constrictive binding energy, equivalent to the energy required for guest entry ($\Delta G^{\ddagger}_{f}$). The sum of the magnitudes of intrinsic binding energy and constrictive binding energy is equivalent to the energy required for guest departure ($\Delta G^{\ddagger}_{d}$).

Similar to enzymes, artificial host molecules can also utilize gating by modulating constrictive binding energy. The regulation of guest uptake and dissociation can be due to dynamic structural units, but may also be imparted into hosts via molecules squeezing through small windows (aperatures) between the interior cavity and bulk solvent. These
two methods of gating in artificial host systems were first recognized during the study of hemicarcerand systems originally developed by Cram and co-workers.

In the 1980s, small molecules were trapped within host molecules derived from two resorcinarene-based bowls connected by four aliphatic or aromatic chains called carcerands. This irreversible encapsulation was achieved by synthesizing the complex in the presence of excess guest molecules, which served to template the reaction. The release of guest molecules to yield an empty host, however, was not observed even at high temperatures. Presumably, guest exchange, whereby the guest leaves the host and another guest or solvent molecule takes its place, is not possible unless the strong covalent bonds holding the capsule together are ruptured (Figure 2A).^{11}

![Figure 2](image.png)

Figure 2. A) Synthesis of a carcerand B) A hemicarcerand

The question that arises is how does one create a stable host-guest system, but still allow the potential for guest exchange? Cram solved this problem by developing hemicarcerands, or carcerands that either lack one of the four linkers or whose linkers are elongated and conformationally flexible (Figure 1B).^{12} Thus, a variety of host-guest
complexes were synthesized by heating a solution of hemicarcerand in the presence of excess guest molecules in a solvent whose volume is too large to occupy the interior. It is important to note that encapsulation of guest molecules was not observed at room temperature and thus, guest uptake is actually regulated by a barrier, termed constrictive binding energy, which must be overcome if guest molecules are to enter, and subsequently leave, the cavity of the hemicarcerand.⁹

What is the mechanism by which hemicarcerands regulate the guest exchange?

Houk and co-workers researched this by performing a series of molecular dynamics calculations on a hemicarcerand with a series of guest molecules to determine the activation energies associated with their encapsulation and departure.¹³ Of interest were two intrahemispheric OCH₂O linkages in the hemicarcerand changing from the chair conformer to the boat form (Figure 3A), which was estimated to be 17.5 kcal mol⁻¹. When the facing OCH₂O units block guest molecules DMF and DMA from departing the
hemicarcerand, the activation barrier was computed to be 60.5 and 55.4 kcal mol\(^{-1}\), respectively. Opening the OCH\(_2\)O gates, however, caused the overall barrier to drop to 32.4 kcal mol\(^{-1}\) for DMF and 27.7 kcal mol\(^{-1}\) for DMA, which was comparable to the experimentally measured activation energies. Thus, it was concluded that the guest exchange process is mediated by the constrictive binding energy imparted by the OCH\(_2\)O gates operating in what was defined as a French door mechanism. Additional constrictive binding energy is provided by the host slightly distorting to dilate the resulting aperture upon encapsulation in a sliding door mechanism (Figure 3B).\(^{13}\)

![Figure 4](image.png)

Figure 4: A) Chemical structure of a self-folding cavitand. B) Upon heating, the cavitand interconverts between the “vase” conformer (left) and “kite” conformer (right). Guest exchange is only observed in the kite conformation.

Guest exchange resulting from conformational change is not required to arise from a subunit as is the case of hemicarcerands, but can also arise from the dynamics of the entire system. For example, Rebek and co-workers have synthesized a resorcorcinarene-derived cavitand that possesses eight amido groups tethered to the periphery (Figure 4A).\(^{14}\) When these groups associate via hydrogen bonding, the cavitand will fold from a
flat “kite” conformation into a bowl-shaped “vase” conformation possessing a deep-cavity to accommodate appropriately sized guest molecules (Figure 4B). During a typical encapsulation experiment, the host is mixed with a guest molecule, such as adamantane, using a bulky solvent (p-xylene). As was the case with hemicarcerands, the choice of a bulky solvent is important because its large size makes it unfavorable toward encapsulation (the hypothetical host-solvent complex would possess low intrinsic binding energy), thus preventing a competing host-solvent exchange equilibrium when a more desirable guest is added.

Strikingly, the activation energy of folding/unfolding ($\Delta G^\ddagger = 17.4 \pm 0.5$ kcal/mol, 295 K) and the activation energy required for adamantane to depart the host ($\Delta G^\ddagger_d = 16.9 \pm 0.4$ kcal/mol, 295 K) are very similar. To explain this, one must take into account the likely mechanism of the guest exchange by which the cavitand must first unfold into the kite structure before guest exchange is possible (Figure 4B). While exchange should be hypothetical possible while in the vase conformation, such a process would lead to a desolvated host and is energetically costly. Clearly, the dynamics associated with the formation/deformation of the cavity itself is controlling the rate of guest self-exchange.

Although inherit control of guest exchange has been observed in hemicarcerands, cavitands, and many other diverse hosts, the full utilization of gating in artificial systems to impart the unique properties found in enzymes (control of reaction rate, kinetic selectivity based on size/shape) is yet to be realized. Given the unique nature of reactions that can be performed within a confined environment (presented in the next section),
development of gating in artificial hosts offers the potential for the creation of sophisticated supramolecular catalysts with a greater degree of efficiency and selectivity.

### 1.2 Artificial Host Systems as Molecular Reactors

Among their unique features, artificial host molecules achieve a separation between its interior and the external environment and thus, guest molecules will experience a different local environment as compared to the outside bulk solvent. Reactions that occur inside may be accelerated in some cases or they may yield products of different regiochemistry than expected.

![Schematic representation of a tetrahedral M₄L₆ capsule](image)

**Figure 5:** Schematic representation of a tetrahedral M₄L₆ capsule

An example of a host molecule catalyzing reactions is found in the metal coordination complexes developed by Raymond, Bergman, and co-workers. These tetrahedral capsules (M₄L₆) contain metal cations (M = Al⁺³, Ga⁺³, In⁺³, Ti⁴⁺, Ge⁴⁺, Fe⁺³) at its corners and bis-catechol ligands at the sides (L = N,N’-bis(2,3-dihydroxybenzoyl)-1,5-
diaminonapthalene) (Figure 5).\textsuperscript{18} In this system, it was found that the guest exchange is mediated by slippage, akin to the sliding door mechanism in Figure 3B, whereby the apertures are dilated by distortions in the ligand conformations around the capsule, which allow the guest to squeeze through to enter/depart the host.\textsuperscript{19}

These anionic water-soluble capsules provide an interior with a relatively high charge density. Thus small positively charged organic molecules were found to possess a high affinity for their interior, both due to electrostatic interactions and the hydrophobic effect. This selectivity in encapsulation was utilized in the catalyzed hydrolysis of acetals with capsule 1 (M = Ga\textsuperscript{III}) under conditions where normally the reaction would not occur (basic aqueous solution, pH = 10) due to the fact that the capsule stabilizes the positively charged intermediates formed throughout the course of the reaction (Figure 6). Interestingly, negative entropy of activation and an inverse secondary kinetic isotope effect with regard to the guest molecule was observed. Thus, it was rationalized that the rate determining step is not the initial protonation of the acetal, but rather a nucleophilic attack of water inside of the host.\textsuperscript{20}
As aforementioned, host molecules may also impart unusual regioselectivity in chemical reactions. For example, Fujita and co-workers developed a self-assembled metal-ligand architecture 2, or molecular cage, which self-assembles in water and encapsulates a wide variety of organic molecules (Figure 7). Diels-Alder reactions were found to be catalyzed within the interior due to the dramatic increase in the effective concentration, i.e. two reactant molecules inside will collide much more frequently than those solvated outside, which are separated by solvent molecules, and are thus more likely to react.
Interestingly, when Diels-Alder reactions were performed between anthracene derivative 3 and maleimide 4 inside 2, the addition takes place at the 1,4 position of the terminal benzene ring of anthracene giving 5 (Figure 8).\textsuperscript{23} If the reaction was run with the same reactants without the presence of 2, it would result in the addition at the more electron-rich 9,10 position, resulting in the otherwise expected Diels-Alder adduct 6. The unusual regioselectivity inside of the host can be attributed as a consequence of the early transition state of the Diels-Alder reaction: the reactant molecules fit inside the container is such a way that the double bond of 4 will not interact with the 9,10 carbons of the anthracene.\textsuperscript{23}
In summary, the inner space of artificial host molecules provides an isolated local environment that can alter various aspects of a reaction such as regiochemistry, reaction conditions, and reaction rates. At the heart of enzymatic rate acceleration is Menger’s spatiotemporal postulate: the longer two reactants reside within a critical distance, the greater the rate of reaction between the two. \(^{24,25}\) By utilizing gating in artificial host systems, control over the period of time molecules are in close proximity to one another can be achieved and thus, as was seen in the case of Diels-Alder reactions within Fujita’s molecular cage, rates can be accelerated. \(^{22}\) In the enzyme acetylcholinesterase, it was calculated that gating also greatly increases the kinetics selectivity of encapsulation without sacrificing much catalytic efficiency. \(^8\) The prospect of tailoring gated host molecules to serve as reactors with the purpose of selectively and efficiently obtaining desireable molecules under mild conditions that would otherwise be difficult or impossible to synthesize is an attractive one. Research into the incorporation and utilization of gating within the context of artificial hosts, however, has been lacking. With the goal of implementing the full potential of gating into functionalized artificial hosts, the Badjic group has designed, synthesized and studied artificial host molecules called molecular baskets, which allowed for the study of the fundamental aspects.
1.3 Design and Synthesis of a Molecular Basket

The structure of a molecular basket can be divided into three segments: a syn tris-norbornene concave scaffold that provides a cavity for the encapsulation of guest, phthalimide-like arms that act as walls for the cavity, and customizable gates that are envisioned to rotate about a CH$_2$ hinge to effectively regulate the guest traffic going into and out of the cavity (Figure 9).$^{26}$

Figure 9: Molecular structure of a molecular basket (left) and a x-ray crystal structure of a molecular basket with benzyl gates encapsulating a molecule of chloroform (right). Reprinted with permission from J. Am. Chem. Soc. 2006, 128, 5887 – 5894. Copyright 2006 American Chemical Society.

The common precursor to all molecular baskets thus far is the tris-anhydride 7, which allows the condensation of a variety of gates with amino functionalities. The current synthesis of 7 (Figure 10) first involves a Diels-Alder reaction between cis-1,4-
dichlorobutene and cyclopentadiene to form norbornene \(8\). Free radical bromination with bromine in nonane at high temperature furnishes \(9\), which is then dehydrohalogenated with an excess of potassium \(t\)-butoxide to obtain tri-alkene \(10\). Another Diels-Alder reaction is performed with DMAD to afford \(11\) after aromatization with DDQ. The resulting product is then stannylated by deprotonation with LDA and reacting the corresponding anion with trimethyltin chloride to yield \(12\), which is then cyclotrimerized with copper(II) nitrate\(^{27-31}\) to afford hexaester \(13\). The hexaester is saponified with lithium hydroxide and acidified to obtain hexacid \(14\), which is then dehydrated with hot acetic anhydride to give \(tris\)-anhydride \(7\).\(^{26,32}\)
Figure 10: Synthesis of tris-anhydride 7. Conditions: a) heavy wall sealed vessel, 180°C b) Br₂, 150°C c) excess potassium t-butoxide, 0°C d) DMAD, 120°C e) DDQ f) LDA, -78°C g) SnMe₃Cl, warm to rt h) Cu(NO₃)₂·2.5H₂O, 50°C i) LiOH, 80°C j) 10% HCl k) acetic anhydride, 150°C

With a scaffold by which gates can be tethered to by condensation with amines, our group focused their efforts on designing gates which can associate with one another to transiently close the system and thus mimic the gates found in enzymes. One of the first
such baskets was one which possessed phenol gates (Figure 9) whereby it was envisioned that folding would be induced by the formation of three intramolecular hydrogen bonds.\textsuperscript{26} Indeed, based on \textit{ab initio} calculations and experimental data obtained by infrared spectroscopy, it was found that the conformer in which all three gates associate to fully close the basket to be prevalent. Unfortunately, guest molecules that were envisioned to effectively fill the cavity such as chloroform were not observed to occupy the interior using low temperature NMR spectroscopy. Evidently, even though the lowest energy closed-basket conformation dominates the conformational equilibrium, the gates were still too dynamic, i.e. they possessed numerous degrees of freedom by which to rotate, resulting ultimately in a poorly defined cavity for guest molecules to occupy for long periods of time.\textsuperscript{26}

Utilization of NMR spectroscopy is a powerful in the study of host-guest complexes and we envisioned that kinetic measurements by NMR would be crucial for studying the gating phenomenon. Thus, we set out to synthesize gates that would not only have strong intramolecular interactions to heavily favor a closed conformation, but would also have constraints on their dynamics. It was postulated that the interior cavity of such a system would be better preorganized and the resulting kinetic stability of the resulting host-guest complexes would be increased. The successful gates we have found to accomplish these methods can be divided according to their method of folding: either by metal-chelation or intramolecular hydrogen bonding.
1.4 Chapter 1 Summary and Conclusions

Gating is widely seen in nature. Among the advantages imparted is the ability to significantly enhance kinetic selectivity of molecules of varying size and shape while still maintaining catalytic efficiency, as observed in enzymes such as acetylcholinesterase. In artificial systems, gating also presents itself as a means of controlling the guest exchange in host-guest complexes, as observed in Cram’s hemicarcerand host systems using molecular dynamics calculations by Houk and co-workers. A full utilization of gating in artificial systems offers the potential of regulating the traffic of guest molecules, controlling the kinetic stability of encapsulation complexes, and imposing kinetic selectivity among guest molecules of varying size and shape.

Artificial host systems can also serve as molecular reactors whereby reactions can differ in regiochemistry, reaction conditions, and/or rate with respect to the external bulk solvent, primarily due to the isolated local environment within the capsule that differs from the external environment found in the bulk solvent. The prospect of tailoring host molecules to serve as reactors with the purpose of selectively and efficiently obtaining molecules that would otherwise be difficult or impossible to synthesize is an attractive one and gating could play a crucial role. Its full implementation into artificial systems remains elusive, however, primarily due to a deficiency of knowledge regarding its incorporation into hosts and the quantitative relationships governing the process.

Thus, our group has synthesized a family of host molecules, named molecular baskets, which possesses a cavity formed by a tris-norbornene scaffold and phthalimide-
like arms. The precursor to any molecular basket is \textit{tris}-anhydride 7 to which gates are tethered via condensation reactions with amines. Our initial attempts at synthesizing gated molecular baskets involved the use of phenol gates. The corresponding basket was found to heavily favor the closed conformation, however, host-guest complexes were not observed with low-temperature NMR leading to the conclusion that the gates’ dynamics substantially lowered the complex’s kinetic stability. We have successfully solved the problem by utilizing gates, which will be presented in the next few chapters, that heavily favor the closed conformer and whose dynamics are minimized while closed.
Chapter 2: Molecular Baskets Folded by Metal-Chelation

2.1 Introduction: Pyridyl Gated Molecular Baskets and Their Chelation to Ag(I)

One method we envisioned to heavily favor a closed position in molecular baskets while substantially lowering the corresponding gate dynamics was to utilize metal-chelation instead of hydrogen bonding as the means of folding. Thus, we synthesized a series of pyridyl molecular baskets (Figure 11) which we envisioned would chelate to transition metal cations such as Ag(I) and Cu(I) resulting in the basket closing and creating a preorganized cavity for guest molecules to occupy.\textsuperscript{33,34} An advantage of this system is that a host-guest complex can potentially be further stabilized by the addition of a small chelating molecule as a guest, which will act as a fourth ligand while residing in

<table>
<thead>
<tr>
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<th>Y</th>
<th>Z</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>N</td>
<td>H</td>
<td>H</td>
<td>9:1 Toluene:Pyridine, 120°C, 15 h</td>
</tr>
<tr>
<td>16</td>
<td>H</td>
<td>N</td>
<td>H</td>
<td>9:1 Toluene:Pyridine, 120°C, 15 h</td>
</tr>
<tr>
<td>17</td>
<td>H</td>
<td>H</td>
<td>N</td>
<td>Glacial Acetic Acid, 120°C, 15 h</td>
</tr>
</tbody>
</table>

Figure 11: Synthesis of pyridyl gated baskets 15, 16, and 17
the interior. The Badjic group has previously explored how these systems respond to Ag(I) and the results of these studies will be presented briefly in this section.

Addition of AgOTf to a 1:1 CDCl$_3$:CD$_3$OD solution of basket 15 resulted in negligible changes in the $^1$H NMR chemical shifts of the basket. Interestingly however, the resonances corresponding to the protons of the gates broadened considerably which is indicative of aggregate formation whereby the gates of the basket are present in a wide variety of spatial orientations that interconvert at a fast rate relative to the NMR timescale.$^{34}$

![Diagram of basket 15 and 16 with NMR spectra](image)

Figure 12: A series of $^1$H NMR spectra (500 MHz, 298 K, 1:1 CDCl$_3$:CD$_3$OD) of a solution of 16 (5.4 mM) recorded after addition of a 124.0 mM standard of AgOTf (1:1 CDCl$_3$:CD$_3$OD). Reprinted from “A Close Inspection of Ag(I) coordination to molecular baskets. A study of salvation and guest encapsulation in solution and the solid state” *Tetrahedron*, **2009**, *65*, 7213 – 7219, with permission from Elsevier.

Basket 16 showed more promising results, in that the addition of AgOTf resulted in considerable changes in the $^1$H NMR chemical shifts in 1:1 CDCl$_3$:CD$_3$OD (Figure 12)
indicating the basket is indeed interacting with silver and there exists a fast rate of exchange between the silver-bound basket and silver-free basket. After one equivalent of silver, no further alterations were observed in the spectrum indicating the formation of a 1:1 complex. The proposed was verified by measuring the hydrodynamic radius using $^1$H DOSY$^{35,36}$, which gave a value consistent with a non-aggregating system (7.4 ± 0.2 Å). Through use of ITC, the binding constant, $K_a$, was found to be high (1.9 ± 0.3 x $10^5$ M$^{-1}$) and, interestingly, the complexation was found to be entropically driven ($\Delta H^\circ = 3.0 \pm 0.1$ kcal / mol ; $\Delta S^\circ = 34.0$ eu)$^{33}$.

Figure 13: Energy minimized (DFT, BP86) conformations of Ag(I):16 complexes. The calculated potential energy diagram for the interconversion of dynamic enantiomers 16$_a$ and 16$_b$ via synchronized rotation of pyridine flaps about their N-C-C-C dihedral angle. Reprinted with permission from Org. Lett. 2007, 9, 2301 - 2304. Copyright 2007 American Chemical Society.
Through use of density functional theory (DFT, BP86 functional) calculations, the optimized geometry of 16 bound to Ag(I) shows that the three pyridine gates are twisted with a propeller-like geometry, with either a $P$ or $M$ sense of twist (Figure 13). The activation barrier for the interconversion between these two dynamic enantiomers ($16_a$ and $16_b$) was calculated to be 2.7 kcal/mol. This low energy value was consistent with experimental data, whereby no decoalescence of the $^1$H NMR signal corresponding to the CH$_2$ hinge (protons H$_e$/H$_f$) was observed at low temperature (200 K).$^{33}$

![Figure 14: The energy-minimized structures (DFT, BP86) of Ag(I):16, 17$_a$, and 17$_b$. Reprinted from “A Close Inspection of Ag(I) coordination to molecular baskets. A study of salvation and guest encapsulation in solution and the solid state” *Tetrahedron*, 2009, 65, 7213 – 7219, with permission from Elsevier.]

Upon addition of Ag(I) to 17, significant changes in chemical shift in the $^1$H NMR spectra is again observed. These changes ceased to occur beyond one equivalent of Ag(I), suggesting the formation of a 1:1 complex. Interestingly, the resonance
corresponding to the bridge protons of the scaffold decoalesces from a singlet to an AB quartet upon complexation, which may be interpreted as the scaffold rigidifying once Ag(I) is bound. DFT calculations of the silver complex suggested the presence of two achiral confirmations: 17\textsubscript{a} and 17\textsubscript{b} (Figure 14). In contrast to Ag(I):16, the process of silver binding to 17 was found to be enthalpically driven through use of ITC ($\Delta H^o = -13.2 \pm 0.8$ kcal / mol ; $\Delta S^o = -20$ eu). This discrepancy can be rationalized by comparing the structures of each molecular basket complexed with Ag(I) (Figure 14). In the case of 17\textsubscript{a} and 17\textsubscript{b}, the silver is toward the edge of the outer-rim of the basket and is thus more susceptible to solvation, which is consistent with a negative folding entropy. For 16\textsubscript{a} and 16\textsubscript{b}, the silver is more buried within the interior of the basket and thus, solvent molecules are less capable of approaching the cation. Therefore, in the assembly process, solvent molecules are released thus yielding a positive change in entropy upon folding.\textsuperscript{34}

By using pyridinyl gates, molecular baskets 16 and 17 were able to fold and effectively close via metal-coordination upon addition of Ag(I). This resulted in a less dynamic host compared to that with phenol gates, although the pyridine rings on the gates still maintained the ability to rotate based on DFT calculations. In an effort to observe a host guest complex, a variety of small chelating molecules such as acetonitrile, methyl isocyanide, and imidazole were mixed in various proportions with Ag(I):16. Unfortunately, none were found to occupy the interior and the stronger chelators (isocyanides, imidazoles, and amines) were found to favor the removal Ag(I) from the basket, rather than encapsulation.
2.2 Chelation to Cu(I) and Encapsulation of Acetonitrile


We postulated that using a different transition metal other than Ag(I) may possibly yield stable host-guest complexes. Upon addition of Cu(CH$_3$CN)$_4$PF$_6$ to a solution of basket 16 in 5:3 acetone-d$_6$:chloroform-d, dramatic changes in the $^1$H NMR chemical shifts corresponding to the scaffold and gates were observed (Figure 15). All of the spectroscopic changes occurred before one equivalent was added; afterwards, no significant changes were observed, thus suggesting the formation of a 1:1 complex 18. It should be noted that we did not observe a new set of resonances appear upon the initial addition of Cu(I), but rather the resonances corresponding to 16 shifted toward the positions corresponding to 18 until one equivalent was added. As was previously seen with silver, apparently Cu(I) is exchanged quickly between 16 and 18 relative to the NMR timescale resulting in the average chemical shift between each proton involved in the exchange to be observed. However, in contrast to the addition of Ag(I) (See Figure 12), we found that the signals corresponding to the gates significantly broaden upon addition of Cu(I) and would not re-sharpen until the host is saturated. Thus, relative to the NMR timescale, it appears the exchange rate of Ag(I) between baskets 16 and Ag(I):16 is faster than that of Cu(I) between 16 and 18, suggesting that the Cu(I)-basket complex possesses greater kinetic stability toward other ligands dissociating the metal.
Figure 15: A) A series of $^1$H NMR spectra (400 MHz, 300 K, 5:3 acetone-d$_6$:chloroform-d) of a solution of 16 (2.60 mM) recorded after the gradual addition of a 53.0 mM solution of Cu(CH$_3$CN)$_4$PF$_6$. B) A nonlinear curve fitting of the $^1$H NMR chemical shifts of the H$_a$/H$_c$/H$_d$ resonances to a 1:1 equilibrium model.

The formation of a 1:1 complex was verified through use of MALDI mass spectrometry (Figure 16A). An evaluation of the binding constant, $K_a$, through use of a nonlinear curve fitting of the $^1$H NMR chemical shifts (Figure 15B) and ITC (Figure 16B) showed that the basket possesses a high affinity for Cu(I) ($1.8 \times 10^5$ M$^{-1}$ and $1.7 \pm 0.1 \times 10^5$ M$^{-1}$ respectively). In contrast to Ag(I), the binding of Cu(I) to 16 is enthalpically driven ($\Delta H^o = -7.2 \pm 0.1$ kcal/mol; $\Delta S^o = -0.25$ eu). This can possibly be due to the inherit size difference between Ag(I) (1.29 Å) and Cu (0.8 Å), but caution should be exercised when directly comparing the values of these two systems due to the measurements taking place in different solvents (acetonitrile for Cu(I) and 1:1 CHCl$_3$:MeOH for Ag(I)).
Figure 16: A) Low resolution MALDI-TOF mass spectrum of an equimolar mixture of 16 and Cu(CH$_3$CN)$_4$PF$_6$, with a major signal at \( m/z = 963.14 \) amu, corresponding to the $[18]^+$ cation. B) Isothermal calorimetry data for the incremental addition of a 1.00 mM standard solution of Cu(CH$_3$CN)$_4$PF$_6$ to a 0.10 mM solution of 16 in CH$_3$CN under an atmosphere of nitrogen.

A variable temperature $^1$H NMR study was conducted on an equimolar solution of 16 and Cu(CH$_3$CN)PF$_6$ and a decoalescence of signals was observed at 248.1 K resulting in two sets of peaks, which we later found corresponded to two C3 symmetrical baskets 18$_a$ and 18$_b$, whose ratio changes with temperature (Figure 17). Furthermore, an upfield singlet (-1.7 ppm) is observed corresponding to a guest molecule residing within the interior of one of the baskets due to the imposed diamagnetic anisotropy of the four benzene rings surrounding the cavity. Upon integration of all of the signals, it was clear that one basket, herein defined as 18$_b$, encapsulated the guest molecule, which possessed three protons. It was deduced that the likely guest molecule was acetonitrile, given its size, shape, and coordinating properties. To verify this hypothesis, we performed a similar variable temperature experiment using deuterated acetonitrile as the solvent. In this experiment, the same signal splitting is observed, thus showing the formation of 18$_a$. 

\[ \Delta H^0 = -7.2 \pm 0.1 \text{ kcal/mol} \]
\[ \Delta S^0 = -0.25 \text{ e.u.} \]
\[ N = 0.76 \]
and \textbf{18b}. However, no upfield signal is observed, thus verifying acetonitrile is indeed the guest.

\begin{center}
\includegraphics[width=\textwidth]{figure17.png}
\end{center}

\textbf{Figure 17:} Variable temperature $^1$H NMR spectra (400 MHz, 5:3 acetone:d$_6$:chloroform-d) of an equimolar solution of \textbf{16} and Cu(CH$_3$CN)$_4$PF$_6$ (3.20 mM)
Figure 18: A) $^1$H NMR spectroscopic assignment of Cu(I)-folded molecular baskets $18_a$ (blue) and $18_b$ (red). The corresponding ROESY assignments are marked with green arrows. B) Selected regions of a $^1$H-$^1$H COSY spectrum (400 MHz, 5:3 acetone-d$_6$:chloroform-d, 190 K) of a 2.60 mM solution of $18_{a/b}$. C) Selected regions of a $^1$H-$^1$H ROESY spectrum (400 MHz, 5:3 acetone-d$_6$:chloroform-d, 190K) of a 2.60 mM solution of $18_{a/b}$.

In an effort to fully assign the $^1$H NMR resonances for $18_a$ and $18_b$, $^1$H-$^1$H COSY and $^1$H-$^1$H ROESY were performed at low temperature (190 K, Figure 18). The COSY spectrum revealed J-coupling between the signals corresponding to pyridine protons H$_a$, H$_b$, and H$_c$ as well as between the bridge and bridgehead protons H$_h$ and H$_{i/j}$. Utilizing this information, we assigned each proton resonance for both molecular baskets (See
Figure 18A). Further characterization with the ROESY spectrum revealed cross-peaks resulting from the magnetization transfer through space unsurprisingly between bridge and bridgehead protons H_b and H_{ij} and between bridgehead H_b and aryl proton H_g. Interestingly, another cross-peak is observed between hinge protons H_{ef} and pyridine proton H_d in basket 18_b, but not 18_a. A more dynamic system in the absence of acetonitrile would result in a substantial drop in the NOE cross-peak, which may explain this observation.

Also of note are the chemical shifts of pyridine protons H_a and H_b. The H_a resonance in 18_b experiences a considerable upper-field shift of 0.40 ppm with respect to the same proton in 18_a. This can be interpreted as the pyridine flaps in 18_b being positioned further into the cavity, and hence the shielding region, due to the coordination of acetonitrile. As a consequence, H_d must assume a position in between the hinge protons H_{ef}, whereby a magnetization transfer through space is facilitated. In contrast, H_a must be more remotely positioned with respect to the basket’s interior. Thus, the structure of 18_a is likely to resemble basket 16 coordinated to Ag(I) (See Figure 13).
Figure 19: A) Selected regions of $^1$H NMR spectra (400 MHz, 5:3 acetone-d$_6$:chloroform-d, 300 K) of a solution of a) Cu(CH$_3$CN)$_4$PF$_6$ (3.20 mM), b) CH$_3$CN (12.8 mM), and c) 18$_{a/b}$ (3.20 mM). B) $^1$H NMR chemical shifts for the methyl group in acetonitrile (400 MHz, 5:3 acetone-d$_6$:chloroform-d) as a function of temperature: (●) a solution of acetonitrile (12.8 mM), and (▲) a solution of 18$_{a/b}$ (3.20 mM).

On the basis of our experiments, it is evident that 18$_b$ consists of a tetracordinate Cu(I) with a molecule of acetonitrile in the interior. The question that soon arises, however, is what is the nature of Cu(I) in 18$_a$? That is to say, is a molecule of acetonitrile coordinated to Cu(I) located outside of the cavity in 18$_a$ or are the pyridine gates aligned around Cu(I) in a trigonal-planar fashion? The CH$_3$ protons of acetonitrile in Cu(CH$_3$CN)$_4$PF$_6$ and completely metal free acetonitrile resonate at 2.16 and 2.01 ppm (300 K, 5:3 acetone-d$_6$:chloroform-d) respectively. At 300 K, the $^1$H NMR spectrum of 18$_{a/b}$ revealed a broad methyl signal at 1.98 ppm, indicating an intermediate interconversion rate between free and encapsulated acetonitrile (Figure 19A). When the solution is cooled and the interconversion between free and encapsulated acetonitrile becomes slow (below 248 K), the remaining acetonitrile $^1$H NMR signal became identical.
to that of free acetonitrile (Figure 19B), thus showing $18_a$ to be a tricoordinated Cu(I) complex and verifying the equilibrium presented in Figure 18A. This equilibrium is further verified by running a variable temperature NMR with an excess (50.0 equivalents) of acetonitrile, which resulted in $18_b$ exclusively in accordance with Le Chatelier’s Principle (Figure 20).

Figure 20: Variable temperature $^1$H NMR spectra (400 MHz, 5:3 acetone-$d_6$:chloroform-$d_3$) of a 2.60 mM solution of $16$ with 53.0 eq of acetonitrile showing the exclusive formation of $18_b$.

With experimental evidence as to the structures of $18_a$ and $18_b$, we collaborated with the Hadad group to further investigate these structures and the underlying mechanistic details for their interconversion. Thus, utilizing DFT methods and the BP86 functional,$^{41,42}$ it was revealed that $18_b$ is more stable than $18_a$ by $-11.0$ kcal/mol ($\Delta E$). If one presumes that acetonitrile replaces that of a coordinating solvent molecule (e.g. $18_b$).
acetone) on the outside of the basket, then this number is increased to -3.5 kcal/mol, with 18b still being more thermodynamically stable. Furthermore, it was revealed that both 18b and 18a are helically twisted as was seen with Ag(I):16 and can be arranged in an M or P orientation. As was suggested by experimental evidence, the complexation of acetonitrile in 18b resulted in the relocation of Cu(I) to a deeper position within the cavity of the assembly. Interestingly, it was also found that the barrier for interconversion between the M and P forms via synchronized rotation of the pyridine flaps about their N-C-C-C dihedral angle for each basket to be relatively small (1.65 kcal/mol for 18b and 4.52 kcal/mol for 18a; Figure 21), which is consistent with the observation of a singlet for Hef in the 1H NMR spectra rather than an AB quartet.
Figure 21: Energy minimized (DFT, BP86) conformations of $18_a$ and $18_b$. Synchronized rotation of the pyridine flaps about their N-C-C-C dihedral angle ($\alpha$) was calculated to require 4.52 and 1.65 kcal/mol in $18_a$ and $18_b$ respectively.

With evidence of the inner workings of the interconversion of baskets $18_a$ and $18_b$, we focused our efforts on trying to determine the likely mechanism by which acetonitrile enters the basket to form $18_b$. An integration analysis of our initial variable temperature experiment (Figure 17) yielded equilibrium association constants, $K_a$, over a wide range
of temperatures. By plotting the natural logarithm of each value of $K_a$ vs. their corresponding inverse temperatures, a van’t Hoff plot was generated (Figure 22) whereby the slope and intercept yielded thermodynamic parameters ($\Delta H^\circ = -3.3 \pm 0.1$ kcal/mol; $\Delta S^\circ = -6.9 \pm 0.4$ e.u.).

![Van’t Hoff plot and thermodynamic parameters](image)

**Figure 22:** A) Van’t Hoff plot and B) the thermodynamic parameters for the $18_{a/b}$ interconversion

The binding of acetonitrile within the basket is strongly driven by enthalpy. The negative value of $\Delta H^\circ$ can be rationalized by the formation of an additional metal-to-ligand bond relative to tricoordinate basket $18_a$. Importantly, the value of -3.3 kcal/mol is comparable to that obtained by theoretical methods (-3.5 kcal/mol; see page 31). The observed loss in entropy is congruent with the immobilization of acetonitrile inside of the basket and the release of a loosely bound encapsulated solvent molecule.
Proton H₆ for both compounds 18ₐ and 18ₐ in the ^1H NMR spectrum should consist of a 1:1 doublet due to coupling to a neighboring proton H₆. With increasing temperature the two doublets progressively average to a singly doublet (see Figure 17). Clearly, this is a result of a fast equilibrium exchange process whose rate lies on the NMR timescale. Thus, we performed a complete band-shape analysis to obtain apparent rate constants k₁/k₋₁ which describe the process by which acetonitrile enters and leaves the basket respectively. The significantly broadened H₆ resonance in 18ₐ (Figure 23C), likely due to the relatively higher dynamics associated with this system, was accounted for. With apparent rate constants k₁/k₋₁ for a range of temperatures in hand, we were able to
obtain the activation parameters ($\Delta H^\ddagger = 6.5 \pm 0.5$ kcal/mol; $\Delta S^\ddagger = -20 \pm 2$ e.u.) describing the dynamic $18_{a/b}$ equilibrium through use of an Eyring plot (Figure 23A/B). The large decrease in entropy associated with the transition state is in agreement with a mechanism whereby a molecule of acetonitrile combines with the basket in the reaction’s rate-determining step.

Figure 24: A) Gated and B) slippage-based mechanisms for the $18_{a/b}$ interconversion have been proposed, and further assessed by DFT (BP86) calculations.

What is the mechanism of the interconversion between $18_a$ and $18_b$? Two mechanisms, one of which involves the gates playing an active role in the uptake of acetonitrile and one where they do not, can be envisioned (Figure 24). In the first mechanism, acetonitrile first coordinates to Cu(I) outside of the molecular basket. One pyridine gate will then dissociate resulting in a tri-coordinated Cu(I) complex and a
sizeable aperature for acetonitrile to enter the cavity before the cavity is sealed again upon association of the pyridine gate. If this mechanism were operating, the system would be gated in the sense that the energy required for dissociation of one gate would be equivalent to the constrictive binding energy required for guest entry. Thus, modifying the energy of dissociation by changing the electronic characteristics of the pyridine would offer the ability to control the rates of encapsulation. The second plausible mechanism is one whereby acetonitrile would squeeze through the apertures present without the dissociation of a gate. Such a pathway would require the dilation of the narrow aperature and thus some conformation strain, akin to the sliding doors mechanism presented in Section 1.1.

Experimental and theoretical evidence is in favor of the second mechanism. There is little evidence of the outer coordination of acetonitrile and, based on DFT calculations, the energy required for dissociation of a pyridine unit coordinated to Cu(I) and internalization of the acetonitrile guest requires at least 10.3 kcal/mol. This value is considerably different from the experimental value of $\Delta H^\ddagger = 6.5$ kcal/mol. Furthermore, gas-induced dissociation experiments by Rodgers and co-workers revealed that the bond dissociation energy ($\Delta H^\ddagger$, 0 K) for the removal of one pyridine unit from the $\text{Cu}^+(\text{pyridine})_3$ complex to be on the order of 20 kcal/mol.\textsuperscript{47,48} For the second mechanism, DFT calculations (BP86) probing the energy required for passage of acetonitrile through one of the side apertures revealed that it requires roughly 5 kcal/mol to drive the methyl group through without a considerable coordination-bond rupture to
Cu(I). This energy barrier is in better agreement with our experimentally measured value and thus, it is believed that this mechanism is operating.

2.3 Other Encapsulation Attempts in the Cu(I)-Bound Molecular Basket

By knowing that the likely mechanism is one whereby acetonitrile enters the basket through one of the side apertures in 18a, the constrictive binding energy (equivalent to $\Delta G^\ddagger_f$; see Figure 1) for this system can then be defined as the energy required for a guest molecule to squeeze through a dilated aperture to enter the system (sliding door mechanism). Thus, it is envisioned that the rate of encapsulation entering and leaving the capsule will vary considerably with minor changes in size of the guest. Furthermore, the intrinsic binding energy ($\Delta G^\circ$) would vary considerably depending on how strong the guest coordinates to Cu(I). In order to probe the interplay between these factors in 18a, we attempted to encapsulate a variety of small coordinating guest molecules.

The preparation of 18a, however, requires the use of Cu(CH$_3$CN)$_4$PF$_6$, which will inherently add four equivalents of the undesired guest acetonitrile upon addition of one equivalent of copper. This problem was circumvented by first preparing a 1:1 mixture of basket 16 and Cu(CH$_3$CN)$_4$PF$_6$ in degassed 5:3 acetone:chloroform and subsequently evaporating the solvent in vacuo under an atmosphere of nitrogen. The resulting solid was then redissolved in degassed 5:3 acetone:chloroform and evaporated once more before being dissolved in degassed 5:3 acetone-d$_6$:chloroform-d for any NMR studies.
Variable temperature NMR of this solution revealed the exclusive presence of 18a with no acetonitrile present (Figure 25).

Figure 25: Variable temperature NMR (400 MHz) of a 1.66 mM solution of 18a in 5:3 acetone-d₆:chloroform-d obtained after several evaporation/redissolving cycles under nitrogen to remove acetonitrile (see text for details).

To assess the propensity of basket 18a to encapsulate guest molecules 19-26, a small amount of guest (1.0 – 2.0 molar equivalents) was first added to a 3.4 mM solution of 18a in 5:3 acetone-d₆:chloroform-d. ¹H NMR spectra were acquired at low temperature (200 K > T > 300 K) to monitor any changes in the chemical shifts of the basket as well as to observe any potential upfield signals associated with an encapsulated guest molecule (> 0
ppm). If no encapsulation event was observed, the experiment was repeated with a higher concentration of guest (~ 50 molar equivalents).

Table 1: Encapsulation of guest molecules by $18_a$ in 5:3 acetone-d$_6$:chloroform-d.

<table>
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<tr>
<td>-</td>
<td>CH$_3$CN</td>
<td>53.2</td>
<td>Encapsulation</td>
</tr>
<tr>
<td>19</td>
<td>CH$_3$CH$_2$CN</td>
<td>71.5</td>
<td>No Encapsulation Observed</td>
</tr>
<tr>
<td>20</td>
<td>ClCH$_2$CN</td>
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<td>21</td>
<td>FCH$_2$CN</td>
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<td>Encapsulation</td>
</tr>
<tr>
<td>24</td>
<td>CH$_3$CH$_2$NC</td>
<td>77.5</td>
<td>Disassociates Cu(I) From Basket</td>
</tr>
<tr>
<td>25</td>
<td>CH$_3$NH$_2$</td>
<td>43.9</td>
<td>Disassociates Cu(I) From Basket</td>
</tr>
<tr>
<td>26</td>
<td>NH$_2$CN</td>
<td>46.1</td>
<td>Disassociates Cu(I) From Basket</td>
</tr>
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</table>

The first series of guests we trialed were ones who possess a larger volume than acetonitrile. Propionitrile 19 and chloroacetonitrile 20 were both found not to interact considerably with $18_a$. With either high or low concentrations of guest, no change in the basket $^1$H NMR chemical shifts were observed. Interestingly, the same result was found for fluoroacetonitrile 21, whose volume is only 5 Å$^3$ larger than acetonitrile. Besides the ability to squeeze through the side aperture of the basket, the other factors to consider with regards to the coordination/encapsulation of guest molecules is how the molecule may fit inside of the host and how strong it will coordinate to Cu(I). By examining the CPK model of the resulting host-guest complex with fluoroacetonitrile, it is clear that the van der Waal’s radii of the fluorine atom of the guest and the aryl ring on the sides of the host will be very close to one another. Also of note is that the fluorine atom will withdraw electron density away from the nitrile group and thus, fluoroacetonitrile will
coordinate weaker to Cu(I) with respect to acetonitrile. Likely, one of these factors, or a combination of both, is the reason why no host-guest complex was observed.

Since it appeared that nitriles bulkier than acetonitrile will not form stable host-guest complexes, we focused our efforts on small guests who are able to coordinate to Cu(I) strongly. Our first choice was acetonitrile’s constitutional isomer, methyl isocyanide 23. Unsurprisingly, 23 was encapsulated within 18 with an even greater affinity than that observed for acetonitrile ($K_{\text{CH}_{3}\text{NC},238K} = 34 \text{ M}^{-1}$; $K_{\text{CH}_{3}\text{CN},238K} = 7.5 \times 10^3 \text{ M}^{-1}$) (Figure 26).

When a larger isocyanide, ethyl isocyanide 24, was attempted, however, it was found that

Figure 26: Variable temperature $^1$H NMR spectra (400 MHz, 5:3 acetone-$d_6$:chloroform-$d$) of a 1.94 mM solution of 18 with 1.20 eq of CH$_3$NC.
the isocyanide will actually remove Cu(I) from 18 and presumably form isocyanide-
Cu(I) complexes. This effect was also observed when methylamine 25 and cyanamide 26
was attempted.

Overall, it was found that 18 was very selective in regards to the guest molecules it
would form stable host-guest complexes with. It appears that only small, linear,
coordinating ligands such as acetonitrile and methyl isocyanide can be encapsulated.
Since the size/shape of these two molecules do not vary considerably, it is likely methyl
isocyanide’s greater affinity toward 18 is due to the more favorable intrinsic binding
energy ($\Delta G^\circ$) as a result of the stronger coordination to Cu(I) while inside.

2.4 Chapter 2 Summary and Conclusions

In an effort to close a basket basket effectively and to minimize gate dynamics,
metal-chelating gates were tethered to tris-anhydride 7. It was conceived that upon
addition of a metal cation such as Ag(I) and Cu(I) the gates would chelate to the metal,
effectively close the basket, and provide a cavity for which a small ligating guest may
enter and act as a fourth ligand in the interior. Thus, pyridyl gated baskets 15-17 were
synthesized.

Basket 15 was found to aggregate upon addition of Ag(I), while baskets 16 and 17
were found to form 1:1 complexes. DFT calculations of these complexes suggested that
the Ag(I) cation rests above the rim and is partially solvated in basket 17 and is lowered
deeper into the cavity and desolvated in basket 16. Although Ag(I):16 seemed to be ideal
for encapsulating small chelating guest molecules, none were found to form stable host-guest complexes. We next tried a different transition metal, Cu(I), in the hopes of observing stable host-guest complexes.

Compound 16 was indeed found to bind to Cu(I) effectively ($K_a = 1.8 \times 10^5 \text{ M}^{-1}$). Upon cooling a 1:1 mixture of 16 and Cu(CH$_3$CN)$_4$PF$_6$ in 5:3 acetone-d$_6$-chloroform-d, the $^1$H NMR resonances of the basket decoalesced into two sets of NMR signals corresponding to molecular baskets 18$_a$ and 18$_b$. Through NMR integration and assignments by $^1$H-$^1$H COSY and $^1$H-$^1$H ROESY, it was found that 18$_b$ contained a molecule of acetonitrile and 18$_a$ presumably loosely held one solvent molecule. Careful inspection of the variable temperature NMR data also led to the conclusion that a molecule of acetonitrile is not binding to Cu(I) in 18$_a$ outside of the host, but rather the three pyridine gates are bound to Cu(I) in a trigonal-planar fashion. In an evaluation of the structure and dynamics of 18$_a$ and 18$_b$, DFT calculations revealed that the pyridine gates are helically twisted and can be arranged in either $M$ or $P$ fashion. The interconversion barrier for both 18$_a$ and 18$_b$ was found to be very low, however, making this process difficult to observe by NMR. In an effort to identify the mechanism for 18$_a$/18$_b$ interconversion, we utilized the NMR integration and a complete band-shape analysis to generate a Van’t Hoff plot and Eyring plot respectively. Both experimental and theoretical data were in favor of a mechanism whereby acetonitrile is encapsulated by squeezing through one of the side aperatures. Importantly, gate dissociation is not a prerequisite for acetonitrile entry.
With knowledge of the likely mechanism, a series of small coordinating molecules were attempted to be encapsulated inside of $18_a$ in order to probe the relationships between size, shape, coordinating ability, and the squeezing mechanism by which guests enter. However, $18_a$ proved to be exceedingly selective, whereby only acetonitrile and methyl isocynaide, which possesses the same linear geometry, were found to form a stable host-guest complex. Methyl isocyanide coordinates more strongly to Cu(I) than acetonitrile, thus the binding affinity was observed to be much higher.

Due to the apparent lack of variety in guest molecules that can be encapsulated in $18_a$, studies of the effects of gating in this system were severely hampered. In light of this, we refocused our efforts toward studying molecular baskets whose gates fold by means of hydrogen bonding. As was discussed in Chapter 1, our first attempts of utilizing this type of folding involved phenol gates. Unfortunately, the phenol gates revealed to be too dynamic to form stable host-guest complexes. While studying the mechanism of encapsulation of acetonitrile in $18_{ab}$, our group worked in parallel on the synthesis of a molecular basket which folds via intramolecular hydrogen bonding, but used dramatically less dynamic gates. Our results and observations for this system will be presented in the following chapter.
3.1 Introduction: Synthesis and Initial Studies of a New Molecular Basket

In the interests of creating a molecular basket that can fold by intramolecular hydrogen bonds to occlude space, encapsulate a variety of guest molecules, and regulate the rates of guest exchange, we targeted the synthesis of molecular basket 27, which we envisioned may close through the formation of either a clockwise or counterclockwise seam of intramolecular hydrogen bonds (Figure 27). Importantly, due to the hydrogen bonding occurring within two separate regions of the gate (the pyridyl nitrogen and amido hydrogen), the gate dynamics is substantially reduced relative to the molecular baskets folded by metal chelation presented in Chapter 2. It was postulated that the resulting decreased gate dynamics would lead to a better preorganized cavity, which should consequently result in slower guest dissociation rates.

We initially obtained this basket by condensation of tris-anhydride 7 and acetylated (aminomethyl)pyridine, but we eventually found that 27 can be more easily obtained through the scheme found in Figure 27, which, as we will later see, opened the door to a variety of amido-substituted molecular baskets. Thus, commercially available 28 was first reacted with thionyl chloride in methanol to obtain methyl ester 29, which was stirred in concentrated ammonium hydroxide to obtain amide 30. LAH reduction
afforded diamine 31, which was subsequently condensed with *tris*-anhydride 7 to obtain *tris*-amine 32. Finally, the *tris*-amine is reacted with acetic anhydride in the presence of triethylamine to afford 27.50

![Chemical structure and synthesis of molecular basket 27](image)

**Figure 27**: Chemical structure and synthesis of molecular basket 27. Top and side views of energy-minimized (DFT, B3LYP) structure of folded 27.

The ¹H NMR (400 MHz, CDCl₃ 298 K) spectrum of 27 contains a downfield singlet at approximately 10.98 ppm corresponding to the amido N-H proton, which remained consistent regardless of concentration (0.5 to 20 mM). Additionally, this peak also remained fairly constant with varying temperature (298 to 197 K, Δδ/ΔT = 6.1 ppb/K).

¹H NMR DOSY³⁵,³⁶ measurements (500 MHz, 298 K) also revealed that the apparent diffusion coefficients are practically invariant (5.6 and 5.9 x 10⁻¹⁰ m² s⁻¹) at concentrations
of 13.0 and 0.7 mM respectively. These observations are consistent with a molecular basket folded intramolecularly to form monomeric units, rather than aggregates.

Interestingly, upon cooling a CDCl₃ solution of 27, the ¹H NMR spectra revealed the decoalescence of hinge protons Hₑ/H_d from a singlet to an AB quartet at 225 K. This observation is indicative of the formation of two dynamic enantiomers, 27_a and 27_b, whose seam of intramolecular hydrogen bonds fold either clockwise or counterclockwise (Figure 28). In CD₂Cl₂, however, the decoalescence was observed to be less than 183 K. This observation is surprising since the interconversion process must entail the rupture of the hydrogen bonds, for which the stability should be similar in these two, non-coordinating, and low-polarity solvents. We thus hypothesized that the more sizeable chloroform (75 Å³) fits better inside of 27 (~ 221 Å³ cavity) than smaller dichloromethane (61 Å³). In a computational study (PM3, CAChe), it was found that the egress of dichloromethane along a reaction coordinate directed through the center of an
aperature of the folded host demands a lower activation energy (~ 7 kcal/mol) than the expulsion of chloroform (~ 14 kcal/mol). Thus, it was concluded that dichloromethane is much less competitive for occupying the inner space of the basket and would be better to use as a solvent for investigating host-guest complexes.

Figure 29: A) Selected regions of variable temperature $^1$H NMR spectra (400 MHz, CD$_2$Cl$_2$) of a solution of 27 (2.4 mM) and CCl$_4$ (3.7 mM). B) A selected region of VT $^{13}$C NMR spectra (100 MHz) of a solution of 27 (13.1 mM) and $^{13}$CCl$_4$ (19.6 mM). C) van’t Hoff plot and thermodynamic parameters for the 27(solvent)/27(CCl$_4$) equilibrium. Reprinted with permission from J. Am. Chem. Soc. 2008, 130, 15127 - 15133. Copyright 2008 American Chemical Society.
Upon the addition of CCl$_4$ to a solution of 27 (2.98 mM) in CD$_2$Cl$_2$, considerable changes were observed in its $^1$H NMR (400 MHz) spectrum. The amido N-H resonance shifted to a lower field ($\Delta \delta = 0.5$ ppm) as the concentration of CCl$_4$ was gradually increased. By utilizing a nonlinear-curve fitting of the binding isotherm to a 1:1 stoichiometric model$^{39,40}$, the apparent association constant, $K_a$, was found to be $109 \pm 1$ M$^{-1}$ at 298 K. After cooling a solution of 27 (2.4 mM) containing $^{13}$CCl$_4$ (3.7 mM) in CD$_2$Cl$_2$, decoalescence of signals were observed at $\sim 260$ K (Figure 29). Two different sets of peaks were ultimately observed at low temperature whose intensity ratio changes with temperature. Accordingly, each set was assigned as a $C_3$-symmetrical basket: one occupied with solvent (CD$_2$Cl$_2$) and another with CCl$_4$. When $^{13}$CCl$_4$ was employed in such an experiment, the decoalescence of signals in the $^{13}$C NMR spectra (100 MHz) was found to occur at practically the same temperature as that of the previously taken $^1$H NMR spectra (260 K).

The integration of the N-H signals at each temperature afforded the corresponding association constants and thermodynamic parameters for the conversion of 27(CD$_2$Cl$_2$) into 27(CCl$_4$) (Figure 29C). The encapsulation of CCl$_4$ is driven by enthalpy ($\Delta H^o = -3.1 \pm 0.2$ kcal/mol) with a negligible loss in entropy ($\Delta S^o = -1.2 \pm 0.8$ eu) which is in accordance with an exchange of an encapsulated dichloromethane molecule with CCl$_4$.

To probe the kinetics of the folding process and, consequently, CCl$_4$ translocation, the decoalescence of H$_e$/H$_d$, a result of the conformational equilibrium of 27$_a$/27$_b$ (Figure 28), in the presence of excess CCl$_4$ was subjected to a total band-shape analysis$^{43-47}$ yielding apparent first-order rate constant $k_{rac}$ for a range of temperatures.$^{53}$ The excess
of CCl₄ was used to fully populate the host and thus the corresponding activation parameters obtained from the Eyring plots ($\Delta H^\ddagger_{rac} = 10.4 \pm 0.3$ kcal/mol; $\Delta S^\ddagger_{rac} = 1.4 \pm 0.1$ e.u.) describes the interconversion process of molecular basket 27 with a molecule of CCl₄ occupying the interior. Furthermore, we examined the apparent rate constants for guest departure, $k_d$, by simulating the line shapes of the two exchanging and unequally populated N-H spins (Figure 29A): one corresponding to 27_{(solvent)} and another to 27_{(CCl₄)} basket.⁴³⁻⁴⁷,⁵³ From the corresponding Eyring plots (Figure 30), the activation parameters corresponding to CCl₄ departure were obtained ($\Delta H^\ddagger_d = 8.6 \pm 0.5$ kcal/mol; $\Delta S^\ddagger_d = -15.0 \pm 0.8$ e.u.).

![Eyring plot and the activation parameters for CCl₄ departing 27_{(CCl₄)} obtained from dynamic ¹H NMR measurements in CD₂Cl₂. Reprinted with permission from J. Am. Chem. Soc. 2008, 130, 15127 - 15133. Copyright 2008 American Chemical Society.](image)

The question arises as to whether the opening/closing motions of the basket, expressed as the 27ₐ/27ₛ interconversion, regulate the kinetics of the egress/ingress of CCl₄. Note that using the acquired activation parameters for the 27ₐ/27ₛ interconversion
yields a value of Gibbs free energy of activation at 298 K ($\Delta G_{\text{rac,298K}}^{\dagger} = \Delta H^{\dagger} - [298\ K]\Delta S^{\dagger}$) to be approximately 10.0 kcal/mol. Strikingly, this value is comparable to the energy value obtained by subtracting the thermodynamic bias of encapsulation ($\Delta G^\circ = 2.7$ kcal/mol) from the Gibbs free energy of activation of CCl$_4$ departure at 298 K ($\Delta G_{d,298K}^{\dagger} \sim 13.1$ kcal/mol). This correlation in energy values supports a mechanism whereby guest departure demands that the basket must unfold via dissociation of the three intramolecular hydrogen bonds in order for CCl$_4$ to depart the cavity (Figure 31). The constrictive binding energy, equivalent to the energy for guest entrance ($\Delta G_{f}^{\dagger}$, see Figure 1), appears to primarily arise from the unfolding motions of the basket.

Figure 31: Energy diagram showing the partitioned standard ($\Delta G^\circ$), at 298 K, for synchronized gated transfer of CCl$_4$ in/out of molecular basket 27. Reprinted with
With data in support of the mechanism shown in Figure 31, it can be concluded that the basket does indeed regulate the association and dissociation of guest molecules (in this case CCl₄) and this property is regulated by the opening/closing dynamics provided by the gates. Before further study could be performed on the effects of gating on molecular encapsulation, however, it was necessary to first perform a complete evaluation on the propensity of basket 27 to encapsulate guest molecules.⁵⁴ The questions that needed to be answered were (1) what are the three-dimensional requirements (i.e. size/shape) for encapsulation, (2) is there a relationship between the steric/electronic properties of the guest and its affinity toward 27, and (3) can we predict the propensity of future molecules to be encapsulated from our resulting data?

For encapsulations that are guided by nonspecific host/guest intermolecular contacts, Rebek and co-workers have noted that, in an ideal situation, a guest’s volume will occupy 55.0 ± 0.8% of the host cavity. This ratio between the guest volume and cavity volume is referred to as the packing coefficient (PC).⁵⁵,⁵⁶ Thus, it is reasonable that an analysis of the volume of basket 27 would impart information regarding the types of molecules that may be encapsulated. Accordingly, it was found that the volume of an optimized structure of folded 27 obtained through density functional theory (DFT, B3LYP/6-31G(d)) possesses an estimated interior volume of 221 ± 9 Å³ (Spartan) with an error corresponding to six independent computations.⁵⁶ It should be noted that there is likely an added uncertainty due to the transient nature of the cavity (c.a. 10%) contributing to a
fluctuation in volume.\textsuperscript{55} Regardless, based on the 55\% rule, guests possessing a volume of 80 – 120 Å\textsuperscript{3} (36 – 55\% of the total volume of fully closed 27) would be favored to reside within the cavity.

Although there are no strong non-covalent contact points (e.g. hydrogen bonding donors/acceptors) within the cavity, the interior is surrounded by three phthalimide rings on the sides and one benzene ring in the bottom. These functionalities could impart increased intrinsic binding energy (\(\Delta G^\circ\)) through the use of favorable interactions with the guest, including electrostatic and C-H\cdots\pi interactions.\textsuperscript{57} To characterize this component, the electrostatic potential surface of the host surface was calculated (Spartan, Figure 32A). The basket was observed to possess domains with a negative potential, -17 kcal/mol at the center of its bottom, -5 kcal/mol on the sides, and -10 kcal/mol on the top. With knowledge regarding the size/shape and electrostatic potential surface of the interior, it is clear that halomethane derivates, such as 28-38, would make excellent candidate guests due to their volume, spherical shape, and electrostatic potential surface that qualitatively complements the basket’s interior (Figure 32B).
The capacity of these guest molecules for occupying molecular basket 27 was examined by NMR spectroscopy in a similar manner to that previously used for CCl₄ (34). Thus, upon cooling a CD₂Cl₂ solution of guest, two sets of resonances, one corresponding to a solvent-filled 27 and the other to guest-filled 27, was observed in the ¹H NMR spectra. Integration of the resonances afforded the binding constant (K), and from a Van’t Hoff plot (Figure 33A), the thermodynamic parameters (ΔH°, ΔS°) for the encapsulation were obtained (Table 2).
Table 2: Thermodynamic Parameters for the Entrapment of Halomethanes 28-38 Inside Molecular Basket 1

<table>
<thead>
<tr>
<th>Guest</th>
<th>Volume (Å³)ᵃ</th>
<th>PCᵇ (%)</th>
<th>ΔH° (kcal/mol)ᶜ</th>
<th>ΔS° (kcal/mol)ᶜ</th>
<th>ΔG° (kcal/mol)ᶜ,ᵈ</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 CBr₄</td>
<td>106.2</td>
<td>48</td>
<td>-4.85 ± 0.09</td>
<td>-0.2 ± 0.4</td>
<td>-4.8 ± 0.1</td>
</tr>
<tr>
<td>29 CBr₃Cl</td>
<td>101.9</td>
<td>46</td>
<td>-6.8 ± 0.2</td>
<td>-7.6 ± 0.8</td>
<td>-4.5 ± 0.1</td>
</tr>
<tr>
<td>30 CBr₂Cl₂</td>
<td>97.5</td>
<td>44</td>
<td>-5.42 ± 0.06</td>
<td>-5.8 ± 0.2</td>
<td>-3.7 ± 0.1</td>
</tr>
<tr>
<td>31 CBr₃F</td>
<td>94.3</td>
<td>43</td>
<td>-5.3 ± 0.1</td>
<td>-7.3 ± 0.4</td>
<td>-3.1 ± 0.2</td>
</tr>
<tr>
<td>32 CCl₁Br</td>
<td>92.9</td>
<td>42</td>
<td>-5.5 ± 0.1</td>
<td>-7.2 ± 0.4</td>
<td>-3.4 ± 0.2</td>
</tr>
<tr>
<td>33 CBr₂ClF</td>
<td>89.6</td>
<td>41</td>
<td>-4.1 ± 0.4</td>
<td>-5 ± 2</td>
<td>-2.6 ± 0.9</td>
</tr>
<tr>
<td>34 CCl₄</td>
<td>88.3</td>
<td>40</td>
<td>-3.1 ± 0.2</td>
<td>-1.2 ± 0.8</td>
<td>-3 ± 1</td>
</tr>
<tr>
<td>35 CBr₁H</td>
<td>87.8</td>
<td>40</td>
<td>-1.73 ± 0.08</td>
<td>-2.3 ± 0.4</td>
<td>-1.0 ± 0.1</td>
</tr>
<tr>
<td>36 CBr₂CH</td>
<td>83.5</td>
<td>38</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>37 CCl₃F</td>
<td>80.8</td>
<td>37</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>38 CCl₁H</td>
<td>74.4</td>
<td>34</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

ᵃ Calculated with Spartan. ᵇ Packing coefficients were computed following a published procedure. ᶜ Obtained from the corresponding van’t Hoff plots. The error margins in ΔH° and ΔS° were propagated from a linear least-squares analysis of the experimental data (SigmaPlot 10.0) and represent one standard deviation in the values. ᵈ At 298 K.

Notably, the propensity of the basket for sequestering halomethanes is a function of their size (Figure 33). Thus, CBr₄, the largest guest, showed the highest affinity for occupying 27 (Table 2). However, the enthalpic contribution (ΔH°) for this guest was found to be less favorable than that of slightly smaller tribromochloromethane (ΔΔH° = 2.0 kcal / mol; Table 2). In fact, when the binding enthalpies for 28-38 is plotted as a function of guest volume (Figure 33B), an apparent bell-shaped dependence was obtained.⁵⁸ Evidently, molecules with a “distorted” spherical shape present a better match for the egg-shaped pocket of the basket, affording more favorable non-covalent contacts. Importantly, the size-based selectivity is in good agreement with Rebek’s “55% rule”⁵³ as encapsulation is observed to occur for guests possessing a volume of 84 – 110 Å³.
Interestingly, guests 31 and 33 were encapsulated, but the apparent stabilities were somewhat lower than expected on the basis of guest size (Table 2). Notably, the two molecules contain a fluorine atom, each with a negative potential at its northern pole (Figure 32). It can be reasoned that the adverse electrostatic forces disfavored the host/guest interaction.\textsuperscript{59,60}
Figure 34: Chemical structures of 28 and 39 – 41, and the corresponding thermodynamic parameters for the encapsulation within molecular basket 27. Computed binding energies (ΔE, kcal/mol), at the M05-2X/6-31+G(d,p)/M05-2X/6-31G(d) level of theory. Reprinted with permission from Org. Lett. 2008, 10, 5361 - 5364. Copyright 2008 American Chemical Society.

Subsequently, guest molecules 28 and 39 – 41 were closely examined to compare guests who encompass comparable volumes and shapes, albeit each with a different number of methyl groups. As before, the thermodynamics of the encapsulations was studied by use of variable temperature $^1$H NMR spectroscopy. Strikingly, the stabilities of the complexes (ΔG°, 298 K) changed radically along the series (Figure 34). A closer
examination of the thermodynamic parameters revealed that although the change in enthalpy upon association ($\Delta H^\circ$) is fairly constant (~ -4 kcal/mol), the entropies ($\Delta S^\circ$) vary considerably: the greater the number of methyl groups, the more negative the entropic contribution was (0 to -11 e.u.). Evidently, swapping the bromines in CBr$_4$, with methyl groups in 39 – 41 did not cause considerable disparities in the host/guest contacts: the two groups are almost identical in size and polarizability to account for comparable enthalpic outputs.

Indeed, the results of density functional theory (Figure 34) calculations verified this experimental observation. With the assistance of the hybrid exchange-correlation density functional (M05-2X), which has been optimized for dispersive interactions$^{61}$, the binding energies ($\Delta E$) were computed to parallel the experimental enthalpies. The restricted motion of the rotatable methyl groups within a guest, perhaps obstructed the binding, giving rise to the observed unfavorable entropies. Markedly, the entropic “forces” direct the overall stability of these sort of encapsulation complexes: the effect is additive, and increases with the number of methyl groups.$^{62}$

Overall, the guests that were identified to preferentially occupy the cavity of molecular basket 27 were halomethane guests whose volume lies within the range of ~ 80 to 120 Å$^3$, such as 28 – 35. Based on the above analysis, the primary contributions toward the intrinsic binding energy ($\Delta G^\circ$), are the electrostatic interactions between the host and guest and the complementary size of the guest to that of the cavity (packing coefficient of 38 – 55%) relative to that of the solvent (dichloromethane, PC = 28%). The substitution of bromine with methyl groups, despite their similar van der Waals size,
results in a considerable decrease in affinity primarily due to the unfavorable entropy likely associated with an obstruction of the rotation of the methyl groups.

3.2 Controlling the Gate Dynamics


With proof that the folding/unfolding motions in molecular basket 27 regulates the egress/ingress of guest molecules and the identification of several suitable guest molecules, it was now possible to study the gating properties of this system. To effectively study the effects of gating as a function of gate dynamics, and thus constrictive binding energy, however, a means of controlling the rates of unfolding/folding must be achieved. This may be accomplished by simply modifying the temperature, but, given the vast differences in the temperature-dependent thermodynamic and kinetic parameters unique to each host-guest system, this simple method would also alter the intrinsic binding energy ($\Delta G^\circ$) and actually complicate the overall analysis. Thus, a method was needed to observe the effects of folding/unfolding at various rates, but at the same temperature to allow direct comparison of various guest molecules. Such control of the gate dynamics would effectively result in a host-guest series of similar intrinsic binding energies ($\Delta G^\circ$), but variable constrictive binding energies ($\Delta G_{f}^{\ddagger}$). To accomplish this task, molecular basket 27 was modified such that the R substituent of the
amide is varied sterically and electronically to vary the strength of the resulting hydrogen bond array and, consequently, the rate of folding/unfolding (Figure 28).

Thus, six R groups were deliberately chosen and installed to give baskets 27 and 42 – 46. The synthesis proceeded via the previously presented methodology whereby tris-anhydride 7 was reacted with 5-(aminomethyl)pyridine-3-amine 31 to yield modular tris-amine 32. Subsequently, an alkanoylation of 32 gave desired 27 and new hydrogen-bond folded baskets 42 – 46 in satisfactory yields (70 – 85%; Figure 35).
The electron density perturbation in these molecular baskets, caused by substituents R, ought to anisotropically impact the electrostatic N-H...N contacts and thereby have an effect on the intramolecular hydrogen bonding.\(^\text{60,63,64}\) That is to say, the depletion (or build up) of the charge at the HB-donor position (N-H) must be accompanied by a negligible charge perturbation at the HB-acceptor site (Pyr-N). Indeed, the electrostatic potentials of the energy minimized model compounds (AM1/HF(6-31G**), Spartan)\(^\text{65}\) suggested a fluctuation in the charge density at the donor but rather consistent values at the acceptor atom (Table 3).

<table>
<thead>
<tr>
<th>R</th>
<th>N-H(^a) (kcal/mol)</th>
<th>Pyr-N(^a) (kcal/mol)</th>
<th>(\delta) (N-H)(^b) (ppm)</th>
<th>(\delta) (N-H)(^c) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>((\text{CH}_3)_3\text{C})</td>
<td>58</td>
<td>-49</td>
<td>9.7</td>
<td>10.4</td>
</tr>
<tr>
<td>\text{CH}_3</td>
<td>62</td>
<td>-48</td>
<td>10.8</td>
<td>11.4</td>
</tr>
<tr>
<td>\text{CH}_3\text{CH=CH}</td>
<td>61</td>
<td>-49</td>
<td>10.8</td>
<td>11.4</td>
</tr>
<tr>
<td>\text{C}_6\text{H}_5</td>
<td>59</td>
<td>-49</td>
<td>11.2</td>
<td>11.8</td>
</tr>
<tr>
<td>\text{CF}_3</td>
<td>69</td>
<td>-44</td>
<td>12.2</td>
<td>12.6</td>
</tr>
</tbody>
</table>

\(^a\)Model compounds consist of one phthalimide “arm”. \(^b\)298 K. \(^c\)213 K.

\(^1\)H NMR chemical shifts of the N−H signals in 27 and 42 − 46 are indicators for the strength and the proportion of the intramolecular hydrogen bonding (Table 3). Markedly, bulky \((\text{CH}_3)_3\text{C}−\) groups enforced weaker \((\delta_{\text{N-H}} = 9.7−10.4 \text{ ppm})\) whereas all other substituents stronger \((\delta_{\text{N-H}} = 10.8−12.6 \text{ ppm})\) noncovalent contacts. FT-IR spectroscopic studies of 27, 42, and 46, in addition, suggested the existence of a fully closed \(C_3\) symmetric basket with other conformers populating the equilibrium to a lesser degree.
These findings are, importantly, supported by Schneider’s suggestion\(^{66}\) that \(\sim 2\) kcal/mol of the free energy (\(\Delta G^\circ\), 298 K, CDCl\(_3\)) is to be attributed to a hydrogen bond lacking secondary electrostatic interactions; that is to say, \(\Delta G^\circ\) (298 K, CDCl\(_3\)) of \(\sim 6\) kcal/mol can be expected to describe the formation of a “fully closed” basket.

To quantify the effect the R groups impart on the opening/closing motions of the baskets, the first-order rate constants (\(k_{rac}\)) for the interconversion of dynamic enantiomers A and B (Figure 28) were determined by completing the line-shape analysis of the diastereotopic H\(_{d/c}\) resonances at variable temperatures. Importantly, an excess of \(t\)-BuBr (guest) was used in each experiment to ensure a sole exchange of the guest-populated baskets. The rate constants (\(k_{rac}\)) for “averaging” the H\(_{a/b}\) signals, i.e., revolving of the gates, were further incorporated into an Eyring plot to afford \(k_{rac}\)’s at 226.0 K (Table 4). It is obvious that substituents had an effect on the gates’ dynamics: the electron-withdrawing CF\(_3\) retarded (4 ± 0.4 s\(^{-1}\)) while the electron-donating CH\(_3\) (108 ± 22 s\(^{-1}\)) accelerated the rotation of the gates.

Table 4: Table 4: Kinetic parameters for the revolving of gates (\(k_{rac}\), \(^1\)H NMR line-shape analysis) in molecular baskets 27 and 42 – 46 (CD\(_2\)Cl\(_2\)), at 226.0 ± 0.1 K.

<table>
<thead>
<tr>
<th>Basket</th>
<th>R</th>
<th>(k_{rac}) (s(^{-1}))(^{a,b})</th>
<th>(\Delta G_{rac})(^{‡}) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>CH(_3)</td>
<td>108 ± 22</td>
<td>11.0 ± 0.1</td>
</tr>
<tr>
<td>42</td>
<td>(CH(_3))(_2)C</td>
<td>78 ± 16</td>
<td>11.1 ± 0.1</td>
</tr>
<tr>
<td>43</td>
<td>CH(_3)(CH(_2))(_5)</td>
<td>97 ± 20</td>
<td>11.0 ± 0.1</td>
</tr>
<tr>
<td>44</td>
<td>((E))-CH(_2)CH=CH</td>
<td>83 ± 17</td>
<td>11.1 ± 0.1</td>
</tr>
<tr>
<td>45</td>
<td>C(_6)H(_5)</td>
<td>20 ± 4</td>
<td>11.7 ± 0.1</td>
</tr>
<tr>
<td>46</td>
<td>CF(_3)</td>
<td>4 ± 1</td>
<td>12.4 ± 0.1</td>
</tr>
</tbody>
</table>

\(^{a}\) Error margins (20%) were obtained on the basis of four independent measurements. \(^{b}\) Each measurement was repeated twice, and the error margins were propagated from the linear least-squares analysis of the experimental data.
The dependence of the reaction’s free energy ($\Delta G^\circ$ or $\Delta G^{\ddagger}$) on the reactant’s substituents is described with substituent constants ($\sigma$) and accounted for by proportional free energy relationships (LFERs).\textsuperscript{67} The concept has, interestingly, been used for examining noncovalent interactions, and typically, the electronic effects are solely evaluated.\textsuperscript{68} In the case of these baskets, however, the gates’ dynamics seems to be a function of not only electronic but also steric factors (Table 4). Moreover, the ground and the excited states for the A/B interconversion appear crowded when sizable R groups are introduced (Figure 28). Taft’s LFER scale, conveniently, defines polar ($\sigma^*$) and steric ($E_s$) substituent constants and has been recommended for studying aliphatic systems.\textsuperscript{69,70} We used this two-parameter model to fit a plot of $\log(k_{\text{rac}}^{(\text{subs.})}/k_{\text{rac}}^{(\text{Me})})$ versus $\rho^*\sigma^* + \delta E_s$ (Figure 36). The correlation was acceptable ($R^2 = 0.94$), with the revolving rates susceptible to both inductive/field ($\rho^* = -0.5$) and steric ($\delta = 0.13$) factors. Molecular basket 42 with the sterically demanding (CH$_3$)$_3$C− group, thus, underwent a rather “slow” A/B interconversion ($k_{\text{rac}} = 78 \pm 16$ s$^{-1}$) despite its weak N–H···N hydrogen bonding contacts (Table 3).
Figure 36: Linear free energy relationship (LFER) for the revolving of gates (A) in baskets 27 and 42 - 46. The correlation was obtained using Taft’s two-parameter regression model with polar (σ*) and steric (E_s) substituent constants (B).

The rate constants for t-BuBr (guest) entering (k_f) and departing (k_d) baskets 27 and 42 - 46 were ascertained by completing quantitative ^1H−^1H EXSY NMR measurements. The volumes of the cross and diagonal peaks for proton resonances of t-BuBr inside and outside the basket were evaluated to give first-order magnetization rate constants (k*_f and k*_d) for the exchange, at different mixing times (τ_m); τ_m’s were originally estimated by measuring T_1 relaxations of t-BuBr protons. The association k_f and dissociation k_d rate constants were then obtained as k_f = k*_f/[basket] and kout = k*_d (Table 5).
Table 5: Kinetic parameters for the translocation of t-BuBr ($k_f$, $k_d$, 2-D EXSY NMR) in molecular baskets 27 and 42 – 46 (CD$_2$Cl$_2$), at 226.0 ± 0.1 K. Thermodynamic stabilities ($\Delta G^\circ$, 226.0 K) of the encapsulation complexes.

<table>
<thead>
<tr>
<th>Basket</th>
<th>R</th>
<th>$k_f$ (M$^{-1}$ s$^{-1}$)</th>
<th>$k_d$ (s$^{-1}$)</th>
<th>$\Delta G_d$‡ (kcal/mol)</th>
<th>$\Delta G^\circ$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>CH$_3$</td>
<td>524 ± 110</td>
<td>4.7 ± 0.7</td>
<td>12.4 ± 0.1</td>
<td>-2.1 ± 0.1</td>
</tr>
<tr>
<td>42</td>
<td>(CH$_3$)$_2$C</td>
<td>1964 ± 392</td>
<td>11.5 ± 0.9</td>
<td>12.0 ± 0.1</td>
<td>-2.3 ± 0.1</td>
</tr>
<tr>
<td>43</td>
<td>CH$_3$(CH$_2$)$_5$</td>
<td>407 ± 73</td>
<td>4.3 ± 0.4</td>
<td>12.4 ± 0.1</td>
<td>-2.0 ± 0.1</td>
</tr>
<tr>
<td>44</td>
<td>(E)-CH$_3$CH=CH</td>
<td>239 ± 68</td>
<td>2.8 ± 0.1</td>
<td>12.6 ± 0.1</td>
<td>-2.0 ± 0.1</td>
</tr>
<tr>
<td>45</td>
<td>C$_6$H$_5$</td>
<td>38 ± 12</td>
<td>0.4 ± 0.1</td>
<td>11.7 ± 0.1</td>
<td>-2.0 ± 0.2</td>
</tr>
<tr>
<td>46</td>
<td>CF$_3$</td>
<td>0.7 ± 0.1</td>
<td>0.07 ± 0.02</td>
<td>14.2 ± 0.2</td>
<td>-1.0 ± 0.2</td>
</tr>
</tbody>
</table>

a The error margins represent the standard deviation of eight independent measurements.

Taft’s linear free energy scale was used to correlate the kinetic data for the departure ($k_{out}$) of t-BuBr (Figure 37). The plot of log($k_d$(sub)s)/$k_d$(Me) versus $\rho^*\sigma^* + \delta E_s$ correlates well ($R^2 = 0.95$). The polar ($\rho^* = -0.6$) and steric ($\delta = 0.21$) sensitivity factors characterizing the rate of t-BuBr dissociating from the molecular baskets are similar to the factors describing the rotation of the gates ($\rho^* = -0.5$ and $\delta = 0.13$). The result, importantly, validates the interdependence between the internal dynamics of the gates (rotary motion) and the kinetic stability of guests (translation). Thus far, the electron-withdrawing CF$_3$ retarded ($k_{out} = 0.07 \pm 0.02$ s$^{-1}$) while the electron-donating CH$_3$ ($k_{out} = 4.7 \pm 0.7$ s$^{-1}$) accelerated the departure of t-BuBr from the baskets. The behavior of basket 42 containing bulky (CH$_3$)$_3$C$^-$ units, however, did not follow the linear trend described in Figure 37. The guest (t-BuBr) departed this basket at a rate ($k_d = 11.5 \pm 0.9$ s$^{-1}$) higher than expected considering the “slow” flipping of its gates ($k_{rac} = 78 \pm 16$ s$^{-1}$). It is, perhaps, that weaker hydrogen bonds at the seam of this basket (Table 3) authorized the guest departure by an alternative mechanism. One scenario could involve the slipping...
of $t$-BuBr through an aperture created by single-gate unfolding, but this remains to be further investigated.

Figure 37: (A) Linear free energy relationship (LFER) for the dissociation of $t$-BuBr from baskets 27 and 42 – 46 (B). The correlation was obtained using Taft’s two parameter regression model with polar ($\sigma^*$) and steric ($E_s$) substituent constants (Figure 36B).

The stability of $t$-BuBr complexes with 27 and 42 – 46 ($\Delta G^\circ$, Table 5) remained fairly consistent ($\sim -2.0$ kcal/mol) with the notable exception of trifluoro substituted 46. Possibly, the resulting strong hydrogen bonds result in a more tightly closed basket with a “smaller” inner space, and thereby higher affinity toward solvent and lower toward $t$-BuBr. More importantly, the lack of deviation in thermodynamic stability is indicative that altering the steric and electronics of the R group in the gates greatly alters the constrictive binding energy ($\Delta G_f^\circ$) without modifying the intrinsic binding energy ($\Delta G^\circ$) considerably.
The lifetime $t (1/k_d)$ of the encapsulated $t$-BuBr is clearly a function of the basket’s dynamics (Figure 38) and can, in this gated environment, be controlled and predicted by choosing a proper R substituent. With explicit control over the constrictive binding energy, it was now possible to eventually investigate the gating properties of this system using a series of guest molecules with varying gate dynamics at the same temperature.
3.3 The Dynamic Discrimination of Guest Molecules in Molecular Baskets


One of the most fundamental properties of gating in natural systems is the ability to dynamically discriminate between guest molecules of varying size and shape.\textsuperscript{1,4,5,7,13} As illustrated in Chapter 1, the gates of acetylcholinesterase are only open a small fraction of time (~ 2.4%), which results in a decrease in the rate of binding of acetylcholine by a factor of two. However, a slightly bulkier substrate whose volume is only 0.4 Å\textsuperscript{3} greater than acetylcholine will enter at a rate three orders of magnitude less than acetylcholine, resulting in a system that possesses very high selectivity without sacrificing much catalytic efficiency.\textsuperscript{13} Molecular baskets can be viewed as model systems that possess gates that can open/close at varying rates. With an effective means of tailoring the dynamics of the gates and knowledge of a variety of molecules of differing sizes and shapes that could be encapsulated, it was now possible to study (1) whether or not the gating phenomenon can be incorporated into artificial systems and (2) if there is a relationship between encapsulation selectivity and gate dynamics. For both of these objectives, an experimental protocol first needed to be developed to provide quantitative relationships between the kinetics of encapsulation, the kinetics of the opening/closing motions of the gates, and the intrinsic binding energy ($\Delta G^\circ$).
Figure 39: A) Reaction coordinate diagram showing an equilibrium with homosteric guest series 28, 39 – 40, and 47 – 48 (CBr₄ is displayed) entering ($k_f$) and departing ($k_d$) gated molecular basket 45 (internal volume: 220 Å³). Solvent molecules (CD₂Cl₂, right) occupy basket 45 devoid of external guests. B) Energy minimized structures (B3LYP/3-21G) of guests 47–49.

For this study, we chose phenyl basket 45 and molecules 28, 39 – 41, and 47 – 49 as guests (Figure 39B). The guest series 47, 40, 39, 48, and 28 have identical volume (size) with van der Waals volumes of Br and CH₃ groups contributing to uniform size (106–107 Å³).
Å$^3$) and spherical shape across the series. Two heterosteric guests molecules, 41 and 49, were also included to identify any changes in the encapsulated kinetics upon deviating from the size/shape profile of the isosteric guest series. Basket 45 (Figure 39A) was used in the study, and its affinity ($\Delta G^\circ$) toward the isosteric guests was more favorable (more exoergic) as the number of CH$_3$ units decreased (Table 6). As elucidated previously, the encapsulation limits the rotational and vibrational degrees of freedom of CH$_3$ groups, which obstructs the binding via an unfavorable entropy ($\Delta S^\circ < 0$; See Figure 34). Notably, the range of binding energies $\Delta G^\circ$ (250 K, Table 6) spans ~4 kcal/mol for these very similar guests, thereby allowing a critical evaluation of the possible linear free energy relationships (LFER).$^{67}$

Table 6: Activation parameters for the trafficking of guests 28, 39 – 41, and 47 – 49 (2D EXSY NMR, CD$_2$Cl$_2$, 250.0 ± 0.1 K) in ($k_f$, $\Delta G_f^{\ddagger}$) and out ($k_d$, $\Delta G_d^{\ddagger}$) from basket 45 and the 45 A/B interconversion ($\Delta G_{rac}^{\ddagger}$; see Figure 28) as well as thermodynamic stabilities ($\Delta G^\circ$, 250.0 ± 0.1 K) of [45 ⊂ guest] encapsulation complexes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Guest</th>
<th>$k_f$ ($M^{-1}s^{-1}$)$^a$</th>
<th>$k_d$ (s$^{-1}$)</th>
<th>$\Delta G_f^{\ddagger}$ (kcal/mol)</th>
<th>$\Delta G_d^{\ddagger}$ (kcal/mol)</th>
<th>$\Delta G_{rac}^{\ddagger}$ (kcal/mol)</th>
<th>$\Delta G^\circ$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>(CH$_3$)$_4$C</td>
<td>1100 ± 115</td>
<td>30.3 ± 0.9</td>
<td>11.03 ± 0.05</td>
<td>12.81 ± 0.01</td>
<td>11.5 ± 0.1</td>
<td>-1.77 ± 0.05</td>
</tr>
<tr>
<td>40</td>
<td>(CH$_3$)$_2$CBr</td>
<td>1160 ± 134</td>
<td>16.2 ± 0.8</td>
<td>11.00 ± 0.06</td>
<td>13.12 ± 0.02</td>
<td>11.8 ± 0.1</td>
<td>-2.11 ± 0.06</td>
</tr>
<tr>
<td>39</td>
<td>(CH$_3$)$_2$CBr$_2$</td>
<td>1525 ± 200</td>
<td>3.41 ± 0.23</td>
<td>10.87 ± 0.07</td>
<td>13.89 ± 0.03</td>
<td>11.9 ± 0.1</td>
<td>-3.02 ± 0.07</td>
</tr>
<tr>
<td>48</td>
<td>(CH$_3$)CBr$_3$</td>
<td>2460 ± 251</td>
<td>0.48 ± 0.01</td>
<td>10.63 ± 0.05</td>
<td>14.86 ± 0.01</td>
<td>12.3 ± 0.1</td>
<td>-4.23 ± 0.05</td>
</tr>
<tr>
<td>28</td>
<td>CBr$_4$</td>
<td>8500 ± 3010</td>
<td>0.10 ± 0.03</td>
<td>10.02 ± 0.18</td>
<td>15.63 ± 0.15</td>
<td>12.6 ± 0.1</td>
<td>-5.6 ± 0.1</td>
</tr>
<tr>
<td>49</td>
<td>(CH$_3$)CCl$_3$</td>
<td>8040 ± 873</td>
<td>22.8 ± 0.8</td>
<td>10.04 ± 0.05</td>
<td>12.95 ± 0.02</td>
<td>11.6 ± 0.1</td>
<td>-2.90 ± 0.06</td>
</tr>
<tr>
<td>41</td>
<td>(CH$_3$)$_3$Si</td>
<td>480 ± 48</td>
<td>14.4 ± 0.5</td>
<td>11.44 ± 0.05</td>
<td>13.17 ± 0.02</td>
<td>12.5 ± 0.1</td>
<td>-1.73 ± 0.06</td>
</tr>
</tbody>
</table>

$^a$ Error margins were obtained on the basis of four independent measurements. $^b$ Each measurement was repeated twice.
Two-dimensional $^1\text{H}-^1\text{H}$ and $^{13}\text{C}-^{13}\text{C}$ NMR magnetization transfer measurements (EXSY)$^{70,72}$ were completed to obtain the rate coefficients for the homosteric guests entering ($k_f$) and departing ($k_d$) basket 45 in CD$_2$Cl$_2$ at 250.0 ± 0.1 K (Table 6). The encapsulation (Figure 39A) was in accord with an dissociative mechanism$^{73}$ whereby the association was first order in the guest ($v_f = k_f [\text{guest}][\text{basket}]$) while the dissociation process was zeroth order in the guest ($v_d = k_d [\text{basket} \subset \text{guest}]$).
Figure 40: Activation energies for isosteric guests 28, 39, 40, 47, and 48 (106 – 107 Å³) entering ($\Delta G^{\ddagger}_{f}$) and departing ($\Delta G^{\ddagger}_{d}$) basket 45 were found to be a linear function of the corresponding binding energies ($\Delta G^{\circ}$, 250.0 ± 0.1 K). The kinetic behavior of smaller 49 (93 Å³) and bigger 41 (121 Å³) deviates from the observed linear free energy relationships ($\Delta G^{\ddagger} = \rho \Delta G^{\circ} + \delta$). The activation energies characterizing the revolving of gates ($\Delta G^{\ddagger}_{rac}$) also exhibit a LFER.
After the host–guest affinities ($\Delta G^\circ = k_f/k_d$) were plotted against the corresponding free energies of activation ($\Delta G_{\text{f/d}}^\dagger$), well-correlated linear relationships were observed (Figure 40); note that the binding energies $\Delta G^\circ$ from the EXSY measurements match those obtained by the integration of $^1$H NMR signals. Evidently, there exists quantitative relationships between the thermodynamic potential for the encapsulation and the free energy of activation for the isosteric guest series entering/exiting basket 45 in competition with the solvent (CD$_2$Cl$_2$). We analyzed these relationships with the following equation $\Delta G^\dagger = \rho \Delta G^\circ + \delta$. The slopes of the fitted lines, which we denote as $\rho$, correspond to the susceptibility by which the free energies of activation respond to the change in the thermodynamic affinity of guests toward molecular basket 45. For the values of $\rho$, the ingress of guests generates a smaller slope ($\rho_f = 0.25$), while the egress has a larger magnitude of its slope ($|\rho_d| = 0.74$, Figure 40). An early transition state would suggest that the guest entrapment ($\Delta G_f^\dagger$) would be less responsive to $\Delta G^\circ$ than $\Delta G_d^\dagger$, as is observed. The intercept of the fitted lines, which we denote as $\delta$, represents the activation barrier ($\Delta G^\dagger$) for the encapsulation of a hypothetical guest possessing the same size/shape as the isosteric guest series and a binding energy of $\Delta G^\circ = 0$; note that under this circumstance, $\delta = \Delta G_f^\dagger = \Delta G_d^\dagger = 11.56 \pm 0.14$ kcal/mol.

First-order rate constants ($k_{\text{rac}}$) for the interconversion of dynamic enantiomers 45A and 45B (Figure 28) were obtained by completing NMR line-shape simulations of the coalescence of diastereotopic H$_{\text{d/e}}$ resonances at variable temperatures (220–270 K, Table 6). After the data were placed into the free energy correlation plot (Figure 40), the activation energies for 45A/B interconversion ($\Delta G_{\text{rac}}^\dagger$) were shown as well to be a linear
function $(R^2 = 0.972)$ of the thermodynamic stability of the host-guest complexes. The slope of the fitted line is small ($|\rho_{\text{rac}}| = 0.26$) while the intercept ($11.13 \pm 0.09$ kcal/mol) is very similar to the $\delta$ value above ($11.56 \pm 0.14$ kcal/mol, Figure 40). The existing LFER corroborates the synergy between the internal dynamics of the gates and the thermodynamic stability of guests bound in the cavity of host 45. Furthermore, the energy required for revolving the gates at $\Delta G^o = 0$ is almost equal to the constrictive binding ($\Delta G_{\text{in}}^\ddagger = \Delta G_{\text{out}}^\ddagger = 11.56 \pm 0.14$ kcal/mol)–physical barrier that a guest encounters in escaping the basket. The host’s conformational change, i.e., gating, is evidently controlling the uptake/release of guest molecules.

Figure 41: Snapshots of CBr4 departing 45, along a force vector aligned with the basket’s side aperture, obtained from steered molecular dynamics (SMD) simulations of the process (0, 440, and 1000 ps; top). The variation of intramolecular N---H distances (assigned as I, II, and III) in basket 45 as a function of time during the SMD simulation (bottom).
The departure of sizable CBr$_4$ (or any guest of the isosteric guest series for that matter), via a trajectory along the side aperture of the basket, was computed using steered molecular dynamics (SMD)\textsuperscript{76} and the AMBER program. Importantly, a simultaneous cleavage of all three N–H---N hydrogen bonds is required for a guest (106–107 Å$^3$) to leave the basket’s cavity (Figure 41). Furthermore, the results of the SMD simulation indicated that smaller CHCl$_3$ (75 Å$^3$) can enter and exit 45, without considerably perturbing the position of the gates. If the trafficking of smaller guests does not require a considerable perturbation of the gates, then one could expect a faster 45A/B interconversion (Figure 28) on the account of greater effective space available to the revolving gates and weaker (distance-dependent) basket-to-guest electrostatic interactions. Indeed, our experimental studies suggested a more rapid rotation of gates in [45-CD$_2$Cl$_2$]: $\Delta G_{rac}^\ddagger = 9.2 \pm 0.1$ kcal/mol at 250.0 K.

The relationships described in Figure 40 pertain to guests (28, 39, 40, 47, and 48) that have the same size and shape. Will guest molecules, having profiles slightly different from these obey the $\Delta G^\circ/\Delta G^\ddagger$ linear correlations? Guests 41 and 49 were chosen to examine this aspect (Figure 39B). 1,1,1-Trichloroethane 49 is a nonspherical compound and is smaller (93 Å$^3$) than the homosteric guest series (∼107 Å$^3$). Interestingly, 49 entered/departed basket 45 faster than one would predict on the basis of the LFER in Figure 40. Larger tetramethylsilane 41 (120 Å$^3$) was, however, found to access/leave the basket’s cavity at a rate slower than expected on the basis of the LFER in Figure 40. The results of the kinetic measurements for 41 and 49 can be interpreted by considering the mechanism of conformational gating in acetylcholinesterase (AChE).\textsuperscript{8} A guest will make
repeated attempts to access the cavity of dynamic [45-CD₂Cl₂] via Brownian motion. The gates switch between open and closed states and, when an attempt coincides with the open state, the encapsulation happens (Figure 41). The likelihood that the gates open wide enough to admit a substrate is evidently related to the substrate’s size. Hence, larger substrate 41 has a lower probability while smaller substrate 49 has a higher probability for entering “the transient aperture” created by the gates.

Thus, the experimental results suggest that the encapsulation kinetics mediated by gated basket 45 is governed by the guest’s profile and the host/guest interaction potential ($\Delta G^\circ$). When the size/shape of guests is kept constant, the encapsulation potential ($\Delta G^\circ$) is a linear function of the rate by which they enter/depart basket 45 ($\Delta G_{f/d}^\circ$). However, when the potential is fixed, basket 45 discriminates guests on a basis of their size/shape via dynamic modulation of the binding site’s access, thereby resembling enzymes such as acetylcholinesterase.⁴,⁷,⁸

### 3.4 The Effect of Gate Dynamics on Guest Selectivity: The Revolving-Door Effect

The following is adapted from the pre-peer reviewed version of the following article: Rieth, S. and Badjic, J. D. “The Effect of Gate Dynamics of Revolving Gates on the Kinetics of Molecular Encapsulation – The Activity/Selectivity Relationship” Chem. Eur. J. 2011, 17, 2562 - 2565. Copyright 2011 Wiley-VCH verlag GmbH & Co. KGaA. Reproduced in part with permission.

In the previous section, an experimental protocol to identify and quantify the kinetic selectivity of encapsulation imparted into the system as a result of gating was developed. Importantly, it was verified that, much like the enzyme acetylcholinesterase,⁸ gating plays
a crucial role in the kinetic selectivity of the encapsulation of guest molecules with varying size and shape. With this new methodology, it was now possible to study the changes in this phenomenon as a function of the gate dynamics. In other words, if we increase $k_{\text{rac}}$ (related to the motion of the gates), will the differences in entrance and departure rates ($k_f$ and $k_d$) of guest molecules of differing size and shape increase or decrease? If such an effect is quantifiable, the answer gained will be of critical importance in the future design of artificial hosts incorporating gating.

Thus, we used baskets 27, 45, and 46 that have R residues with different steric and electronic characteristics within the amido groups (Figure 35) for controlling the hydrogen-bonding array and thereby the dynamics of the gates ($k_{\text{rac}}$, Table 7). Thus, basket 46 (R=CF$_3$) had its gates opening and closing at a lower rate, whereas basket 27 (R=CH$_3$) had its gates opening and closing at a higher rate in dichloromethane at (250.0 ± 0.1) K (Table 7); the gates’ dynamics gradually increased from 46 to 45 to 27 as the strength of the hydrogen bonding around the rim was decreased (Table 7).

Table 7: Rates of racemization ($k_{\text{rac}}$) of molecular baskets 27, 45, and 46 in CD$_2$Cl$_2$ at (250.0 ± 0.1) K representing the interconversion between two dynamic enantiomers (Figure 28) measured using dynamic NMR spectroscopy and the values of $\rho$ and $\delta$ for the entrance and departure of the homosteric guest series following the free energy relationship $\Delta G^\ddagger_{\text{f/d}} = \rho \Delta G^\circ + \delta$.

<table>
<thead>
<tr>
<th>Basket</th>
<th>$k_{\text{rac}}$ (s$^{-1}$)</th>
<th>$\rho_f$</th>
<th>$\rho_d$</th>
<th>$\delta$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46 (R = CF$_3$)</td>
<td>2.95 x 10$^3$</td>
<td>0.08 ± 0.04</td>
<td>-0.93 ± 0.04</td>
<td>12.4 ± 0.1</td>
</tr>
<tr>
<td>45 (R = Ph)</td>
<td>4.85 x 10$^4$</td>
<td>0.25 ± 0.04</td>
<td>-0.75 ± 0.04</td>
<td>11.6 ± 0.1</td>
</tr>
<tr>
<td>27 (R = CH$_3$)</td>
<td>&gt; 5 x 10$^4$</td>
<td>0.24 ± 0.04</td>
<td>-0.77 ± 0.04</td>
<td>10.7 ±0.1</td>
</tr>
</tbody>
</table>
We have chosen eight guests, 28, 39 – 41, and 47 – 50, for our study (Figure 42). Compounds 28, 48, 39, 40, and 47 are isosteric (≈106 Å³), having analogous size and shape. On the other hand, compounds 49 (93 Å³), 41 (120 Å³) and 50 (102 Å³) differ. Notably, each of these guests was trapped by baskets 27, 45, and 46 (interior cavity ≈ 220 Å³) at 250 K in dichloromethane, as observed by an upfield ¹H/¹³C NMR chemical shift of the encapsulated nuclei surrounded with the host’s aromatic arms. Moreover, almost each guest itself was found to have a comparable affinity (ΔG°) for occupying both less dynamic 46 and more dynamic 45 and 27 (Table 8 and Figure 43). Importantly, it is evident that the current study is showing the changes in encapsulation behavior as a function of constrictive binding energy (ΔG‡, related to ΔG‡rac) as opposed to intrinsic binding energy (ΔG°). The encapsulation affinities of the largest guest 41, which perhaps forms the closest contacts with the molecular baskets, presented a notable exception from such a trend. The noncovalent guest-to-basket contacts have thus remained fluctuating to a small degree, despite increasingly greater gate dynamics and somewhat different electrostatics characteristics of the hosts. The encapsulation favorability (ΔG°) of the isosteric guests toward baskets 27, 45, and 46, however, showed an apparent trend whereby carbon tetrabromide (28) was the strongest binder (Table 8). This phenomenon was addressed earlier and described as entropic in its origin: a guest molecule with a greater number of CH₃ rotors possesses a lower propensity for residing inside the basket.
Figure 42: Chemical structures of guest molecules grouped according to volume. The homosteric guest series 28, 48, 39, 40, and 47 are spherical and of the same volume due to the identical van der Waals radius of bromine and methyl groups. Heterosteric guest molecules 49, 41, and 50 are used as examples of guest molecules that reside outside of this size/shape profile.

The rate coefficients corresponding to the guests entering ($k_f$) and departing ($k_d$) baskets 27, 45, and 46 were obtained with quantitative $^1$H–$^1$H or $^{13}$C–$^{13}$C NMR exchange spectroscopy (EXSY)\textsuperscript{71,72} and $^1$H NMR selective inversion recovery measurements\textsuperscript{77} at 250.0 ± 0.1 K (Table 8); note that we used the selective inversion recovery method for measuring the encapsulation kinetics in cases when considerable T1 noise limited an accurate evaluation of the EXSY cross-peak integrals.\textsuperscript{77} The NMR data were fit to the host/guest exchange mechanism in which a guest replaces a solvent molecule inside the basket during association ($v_f$=$k_f$[guest][basket]), whereas exactly the opposite occurs upon dissociation ($v_d$=$k_d$[basket⊂guest]).
Table 8: Gibbs free energies of activation corresponding to the entrance ($\Delta G_f^{\ddagger}$) and departure ($\Delta G_d^{\ddagger}$) of guests along with the thermodynamic stabilities ($\Delta G^\circ$) of each complex at (250.0 ± 0.1) K in CD$_2$Cl$_2$. Data were obtained from quantitative NMR magnetization transfer experiments; each data point was obtained from six independent EXSY measurements with the error margin corresponding to the standard deviation of those measurements.

<table>
<thead>
<tr>
<th>Basket</th>
<th>Guest</th>
<th>$\Delta G_f^{\ddagger}$ (kcal/mol)$^a$</th>
<th>$\Delta G_d^{\ddagger}$ (kcal/mol)$^a$</th>
<th>$\Delta G^\circ$ (kcal/mol)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>CBr$_3$CH$_3$</td>
<td>12.14 ± 0.08</td>
<td>16.34 ± 0.06</td>
<td>-4.20 ± 0.05</td>
</tr>
<tr>
<td>46</td>
<td>CBr$_2$(CH$_3$)$_2$</td>
<td>12.17 ± 0.07</td>
<td>15.14 ± 0.06</td>
<td>-2.97 ± 0.09</td>
</tr>
<tr>
<td>46</td>
<td>CBr(CH$_3$)$_3$</td>
<td>12.39 ± 0.06</td>
<td>14.32 ± 0.02</td>
<td>-1.93 ± 0.06</td>
</tr>
<tr>
<td>46</td>
<td>C(CH$_3$)$_4$</td>
<td>12.30 ± 0.08</td>
<td>13.66 ± 0.03</td>
<td>-1.37 ± 0.09</td>
</tr>
<tr>
<td>46</td>
<td>Si(CH$_3$)$_4$</td>
<td>12.69 ± 0.06</td>
<td>13.74 ± 0.03</td>
<td>-1.05 ± 0.06</td>
</tr>
<tr>
<td>46</td>
<td>CBr$_2$ClCH$_3$</td>
<td>12.11 ± 0.10</td>
<td>15.59 ± 0.09</td>
<td>-3.48 ± 0.04</td>
</tr>
<tr>
<td>45</td>
<td>CBr$_4$</td>
<td>10.0 ± 0.2</td>
<td>15.6 ± 0.1</td>
<td>-5.6 ± 0.1</td>
</tr>
<tr>
<td>45</td>
<td>CBr$_3$CH$_3$</td>
<td>10.63 ± 0.05</td>
<td>14.86 ± 0.01</td>
<td>-4.23 ± 0.05</td>
</tr>
<tr>
<td>45</td>
<td>CBr$_2$(CH$_3$)$_2$</td>
<td>10.87 ± 0.07</td>
<td>13.89 ± 0.03</td>
<td>-3.02 ± 0.07</td>
</tr>
<tr>
<td>45</td>
<td>CBr(CH$_3$)$_3$</td>
<td>11.00 ± 0.06</td>
<td>13.12 ± 0.02</td>
<td>-2.11 ± 0.06</td>
</tr>
<tr>
<td>45</td>
<td>C(CH$_3$)$_4$</td>
<td>11.03 ± 0.05</td>
<td>12.81 ± 0.01</td>
<td>-1.77 ± 0.05</td>
</tr>
<tr>
<td>45</td>
<td>CCl$_3$CH$_3$</td>
<td>10.65 ± 0.05</td>
<td>13.06 ± 0.04</td>
<td>-2.41 ± 0.05</td>
</tr>
<tr>
<td>45</td>
<td>Si(CH$_3$)$_4$</td>
<td>11.42 ± 0.05</td>
<td>13.24 ± 0.01</td>
<td>-1.81 ± 0.06</td>
</tr>
<tr>
<td>45</td>
<td>CBr$_2$ClCH$_3$</td>
<td>10.46 ± 0.05</td>
<td>14.27 ± 0.03</td>
<td>-3.80 ± 0.06</td>
</tr>
<tr>
<td>27</td>
<td>CBr$_4$</td>
<td>9.2 ± 0.2</td>
<td>15.0 ± 0.2</td>
<td>-5.8 ± 0.1</td>
</tr>
<tr>
<td>27</td>
<td>CBr$_3$CH$_3$</td>
<td>9.66 ± 0.06</td>
<td>14.05 ± 0.02</td>
<td>-4.39 ± 0.06</td>
</tr>
<tr>
<td>27</td>
<td>CBr$_2$(CH$_3$)$_2$</td>
<td>9.76 ± 0.07</td>
<td>13.07 ± 0.06</td>
<td>-3.31 ± 0.09</td>
</tr>
<tr>
<td>27</td>
<td>CBr(CH$_3$)$_3$</td>
<td>10.24 ± 0.07</td>
<td>12.40 ± 0.05</td>
<td>-2.16 ± 0.08</td>
</tr>
<tr>
<td>27</td>
<td>CCl$_3$CH$_3$</td>
<td>9.68 ± 0.10</td>
<td>11.94 ± 0.04</td>
<td>-2.26 ± 0.09</td>
</tr>
<tr>
<td>27</td>
<td>Si(CH$_3$)$_4$</td>
<td>10.65 ± 0.06</td>
<td>12.36 ± 0.04</td>
<td>-1.71 ± 0.07</td>
</tr>
<tr>
<td>27</td>
<td>CBr$_2$ClCH$_3$</td>
<td>9.86 ± 0.06</td>
<td>13.53 ± 0.02</td>
<td>-3.67 ± 0.06</td>
</tr>
</tbody>
</table>

$^a$ The experimental rate coefficients $k_f/d$ were converted to $\Delta G_f/d$ by using the Eyring equation. 

$^b$ The free energies of interaction $\Delta G^\circ = -RT\ln \left( \frac{k_f}{k_d} \right)$ were calculated from the NMR magnetization transfer experiments and are in good agreement with those obtained from NMR integration and van’t Hoff plots.
Figure 43: The activation energies for the entrapment ($\Delta G^\ddagger_{f}$) and the departure ($\Delta G^\ddagger_{d}$) of isosteric guests 4–8 (black circles) abide to a linear free energy relationship described with the equation $\Delta G^\ddagger_{f/d} = \rho \Delta G^\circ + \delta$. Note that the experimental data were fit to a linear function corresponding to A) basket 46 ($R^2 = 0.69; R^2 = 1.00$), B) basket 45 ($R^2 = 0.93; R^2 = 0.99$) and C) basket 27 ($R^2 = 0.94; R^2 = 0.99$). The kinetic data for the exchange of heterosteric guest molecules 41, 49, and 50 are shown in blue. The computed 90% confidence bands (SigmaPlot) of the linear regression lines are also shown in blue.
In accord with our prior study presented in section 3.3, we found that isosteric 28, 48, 39, 40, and 47 enter/depart baskets 46, 45, and 27 at rates corresponding to the linear free energy relationship (LFER) \[ \Delta G^{\ddagger}_{f/d} = \rho \Delta G^\circ + \delta, \] (Figure 43): the activation energies for the entrance (\( \Delta G^\ddagger_f \)) and departure (\( \Delta G^\ddagger_d \)) of these guests were strictly a linear function of the binding energies (\( \Delta G^\circ \)). We reason that the slope (\( \rho \)) of the fitted lines depicts the susceptibility by which \( \Delta G^{\ddagger}_{f/d} \) responds to the changes in \( \Delta G^\circ \), therefore reporting on the nature of the encapsulation’s transition state; thus, a small slope \( \rho_{in} \) would concur with an early transition state. Second, the intercept (\( \delta \)) describes the energy required for the entry/departure of a hypothetical guest having the same size/shape as the isosteric guest series, but no binding affinity (\( \Delta G^\circ=0 \)). For each host, the two \( \Delta G^{\ddagger}_{f/d}/\Delta G^\circ \) regression lines converge at \( \delta \), whose value increased with slower gate dynamics (Figure 43).

Interestingly, baskets 27 and 45, having more dynamic gates (R = CH₃ and Ph), exhibited similar \( \rho \) values of roughly \( \rho_f = 0.25 \) for the ingress and \( \rho_d = -0.76 \) for the egress of the isosteric guests (Table 7). Basket 46, however, with slower revolving gates (R = CF₃) showed distinctively different values: \( \rho_f = 0.08 \) and \( \rho_d = -0.93 \). Evidently, host 46 with gates revolving at the slowest rate had also the lowest capacity for distinguishing between guests in the isosteric guest series. That is to say, the encapsulation of 28, 48, 39, 40, and 47 by basket 46 occurred at more similar rates than by baskets 27 and 45. The greater gate activity is therefore associated with greater encapsulation selectivity and vice versa. The binding of the isosteric guest series to basket 46 (R = CF₃) is furthermore slowed down when compared to basket 27 (R = CH₃). A trend whereby a host with more dynamic gates also exchanges guests at a faster rate ought to be reasoned from the
standpoint of the gate dynamics. Namely, the aromatic gates revolving at a slower rate, that is, 46, would spend longer time in the “closed” position, hence more effectively restricting the access to the host’s inner space.

To further inspect the relationship between the entrapment selectivity and the basket’s gate dynamics, we scrutinized the rates describing the entrance/departure of guests 41, 49, and 50 (Figure 42). Comparatively smaller 49 (93 Å³) was found to enter/exit baskets 27, 45, and 46 at rates greater than expected from the linear relationship established for the isosteric guest series (106–107 Å³, Figure 43). The entrance/departure of bigger tetramethyilsilane (41) would, however, take place at slower rates. At this point, we reasoned that the magnitude of the deviation of the exchange rate of heterosteric guest molecules 41, 49, and 50 from the established linear relationship for the isosteric guests (described with the equation ΔG^‡_in-out = ρΔG° + δ) would suggest the selectivity by which the basket operates. In other words, a gated basket incapable of effectively discriminating guests on the basis of the size/shape would solely promote their in/out exchange on the basis of the encapsulation potential ΔG°, and closely abiding to the established LFER.
Table 9: Difference in the experimental activation energy $\Delta G^\dagger_{fd}$ of guests 41 and 49 entering/departing baskets 46 (R = CF₃), 45 (R = Ph), and 27 (R = Me), and computed $\Delta \Delta G^\dagger_{fd}$ of hypothetical guests having the same affinity ($\Delta G^\circ$) for the encapsulation as 41 and 49 but the size and shape corresponding to the isosteric guest series.

| Guest     | Basket | $|\Delta G^\dagger_{fd}|$ (kcal/mol) | $|\Delta \Delta G^\dagger_{fd}|$ (kcal/mol) |
|-----------|--------|-------------------------------------|--------------------------------------------|
| CCl₃CH₃   | 46     | 0.07 ± 0.06                         | 0.08 ± 0.13                                |
| CCl₃CH₃   | 45     | 0.30 ± 0.05                         | 0.31 ± 0.04                                |
| CCl₃CH₃   | 27     | 0.46 ± 0.10                         | 0.46 ± 0.04                                |
| Si(CH₃)₄ | 46     | 0.32 ± 0.06                         | 0.33 ± 0.06                                |
| Si(CH₃)₄ | 45     | 0.32 ± 0.01                         | 0.31 ± 0.01                                |
| Si(CH₃)₄ | 27     | 0.38 ± 0.06                         | 0.39 ± 0.04                                |

To quantitatively ascertain the distribution of the encapsulation rates for 41, 49, and 50, we first computed 90% confidence band (SigmaPlot) for each of the fitted regression lines pertaining to the isosteric guests entering/departing baskets 27, 45, and 46 (Figure 43). This particular statistical method is useful for revealing the distribution of data having 90% certainty with reference to the experimental values. Accordingly, the activation energies $\Delta G^\dagger_{fd}$ of the heterosteric guests entering/exiting the less dynamic basket 46 (R = CF₃) appeared more within the band when compared to those regarding baskets 45 (R = Ph) and 27 (R = CH₃)(Figure 43); the rates for 1,1-dibromo-1-chloroethane (50) were, for all three baskets, positioned quite close to the fitted lines, which is likely due to the very small difference in volume between this (102 Å³) and the guests from the isosteric series (106–107 Å³). Furthermore, we determined the difference ($\Delta \Delta G^\dagger_{fd}$) between the experimental activation energy, $\Delta G^\dagger_{fd}$, for the entrance/departure of 41/49 and the corresponding hypothetical guests having identical $\Delta G^\circ$ while abiding to the free energy relationship $\Delta G^\dagger_{fd} = \rho \Delta G^\circ + \delta$ (Table 9). In particular, one notes an increasingly larger $|\Delta \Delta G^\dagger_{fd}|$ values and, therefore, greater deviations for non-spherical
guest 1,1,1-trichloroethane (49) going from the less dynamic 46 to the more dynamic 27 (Table 9). The spherical tetramethylsilane (41), akin to the isosteric guests), however, was to a much smaller degree (if any) discriminated by baskets 27, 45, and 46. Nonetheless, the experimental observations still indicate a feasible correlation between the dynamics of the gates and the basket’s kinetic selectivity such that more dynamic gates afford greater entrapment selectivity with regard to size and shape.

Thus, our results are all in favor of the notion that baskets with more dynamic gates (activity) are also capable of greater kinetic discrimination (selectivity) in trapping compounds. Indeed, the effect appeared small, but is quantifiable and its generality/magnitude remains to be investigated.\textsuperscript{78} The observed correlation between size selectivity and gate dynamics can be rationalized by envisioning a revolving door. When the door rotates around its axis at a relatively slow rate, small and large objects can easily translocate through. When the rotation rate is increased, however, larger objects will have greater difficulty passing through without being hit by the door due to a decrease in the resulting “dynamic aperture”.

Interest toward understanding the gating\textsuperscript{79} of molecules and quantitative rules\textsuperscript{80} that describe the process continues. The phenomenon could indeed be useful for controlling chemical reactions occurring in artificial hosts\textsuperscript{81,82} and developing new ways for the delivery of active compounds.\textsuperscript{83}
3.5 Molecular Recognition of a Transition State


The conformational interconversion of encapsulated guest(s) has been previously studied in artificial hosts, and complexation was almost uniformly identified to retard or to have no effect, relative to a proper reference system. The deceleration has been speculated to arise from steric and electronic characteristics of the hosts affecting the reactant as well as the transition state(s) of the interconverting guest. The activation barrier for the ring flipping of 1,4-thioxane and 1,4-dioxane required an additional 1.6–1.8 kcal mol$^{-1}$ ($\Delta\Delta G^\ddagger$) within the restrictive interior of carcerands. The chair–chair interconversion process for cyclohexane was noted to occur slower in “jelly doughnut” ($\Delta\Delta G^\ddagger \approx 0.3$ kcal mol$^{-1}$) and resorcin[4]arene ($\Delta\Delta G^\ddagger = 0.25 \pm 0.10$ kcal mol$^{-1}$) based cavitands. In the first case, this was rationalized by invoking favorable C-H⋅⋅⋅π interactions to stabilize the chair ground state. Analogous studies on the rotation of the amide bond in encapsulated environments showed such an interconversion occurred at a faster/slower rate in hydrophobic, supramolecular assemblies than in polar or nonpolar ($\Delta\Delta G^\ddagger \approx 1–3$ kcal mol$^{-1}$) solvents, respectively. In light of these discoveries, we chose to investigate the ring-flipping process of cyclohexane-d$_{11}$ within molecular baskets. Surprisingly, ring-flipping rate acceleration is observed rather than retardation. We thus measured the kinetics of the conformational interconversion of cyclohexane-d$_{11}$ by
quantitative NMR spectroscopy and used electronic structure methods to identify the origin of the observed acceleration.

Figure 44: An energy diagram for the conformational interconversion of cyclohexane. The interconversion of ground- and transition-state conformers can be described with two degrees of freedom $\phi_1$ and $\phi_2$. Note that only one cycle of the pseudorotation is shown.

The potential energy surface (PES) for the interconversion of cyclohexane, which has been intensively studied both theoretically and computationally, is described with two degrees of freedom ($\phi_1$ and $\phi_2$, Figure 44) and contains $D_{3d}$-symmetric chair and $D_2$-symmetric twist-boat conformations as energy minima connected by $C_2$-symmetric half-chair and $C_{2v}$-symmetric boat transition states (Figure 44). The chair-to-chair interconversion is characterized by the first-order rate constant $k$, which on the basis of
the mechanism is twice the value of the experimental $k_{obs}$. By using NMR spectroscopy, Anet et al. measured the interconversion of C$_6$D$_{11}$H in CS$_2$ as a solvent and found that it occurs with an activation enthalpy ($\Delta H^\ddagger$) of $(10.71 \pm 0.04)$ kcal mol$^{-1}$ and an activation entropy ($\Delta S^\ddagger$) of $(2.2 \pm 0.2)$ eu (Table 10). Importantly, the activation energy ($\Delta G^\ddagger$) for the process is barely a function of the liquid phase (methylcyclohexane, acetone, and CS$_2$); although the value of $\Delta G^\ddagger$ is somewhat higher in the gas phase (Table 10).

Table 10: Activation parameters $\Delta H^\ddagger$, $\Delta S^\ddagger$, and $\Delta G^\ddagger$ (188.8 K) for the conformational interconversion of cyclohexane-d$_{11}$(2-D EXSY NMR, 400 MHz, CD$_2$Cl$_2$, 188.8 $\pm$ 0.1 K) inside baskets 27, 45, and 46 in CS$_2$, the gas phase, CD$_2$Cl$_2$, and C$_6$D$_5$CD$_3$.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$\Delta H^\ddagger$ (kcal/mol)</th>
<th>$\Delta S^\ddagger$ (eu)</th>
<th>$\Delta G^\ddagger$ (kcal/mol)</th>
<th>$k$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS$_2^a$</td>
<td>10.71 $\pm$ 0.04</td>
<td>2.2 $\pm$ 0.2</td>
<td>10.29 $\pm$ 0.06</td>
<td>4.7 $\pm$ 0.7</td>
</tr>
<tr>
<td>Gas phase$^b$</td>
<td>12.1 $\pm$ 0.5</td>
<td>5.7 $\pm$ 0.5</td>
<td>10.6 $\pm$ 0.5</td>
<td>2.1 $\pm$ 1.5</td>
</tr>
<tr>
<td>Basket 27</td>
<td>-</td>
<td>-</td>
<td>9.43 $\pm$ 0.03</td>
<td>43 $\pm$ 3</td>
</tr>
<tr>
<td>Basket 45</td>
<td>-</td>
<td>-</td>
<td>9.45 $\pm$ 0.02</td>
<td>41 $\pm$ 2</td>
</tr>
<tr>
<td>Basket 46</td>
<td>-</td>
<td>-</td>
<td>9.56 $\pm$ 0.04</td>
<td>30 $\pm$ 3</td>
</tr>
<tr>
<td>CH$_2$Cl$_2^c$</td>
<td>10.2 $\pm$ 0.1</td>
<td>0.4 $\pm$ 0.4</td>
<td>10.1 $\pm$ 0.1</td>
<td>6.9 $\pm$ 2.2</td>
</tr>
<tr>
<td>C$_6$D$_5$CD$_3^c$</td>
<td>10.3 $\pm$ 0.2</td>
<td>1.2 $\pm$ 0.7</td>
<td>10.1 $\pm$ 0.2</td>
<td>7.9 $\pm$ 4.3</td>
</tr>
</tbody>
</table>

$^a$ See Ref. 90  $^b$ See Ref. 92  $^c$ Obtained from Eyring plots and line-shape analysis of $^1$H NMR signals (197 to 236 K).

There is moderate thermodynamic affinity for cyclohexane-d$_{11}$ occupying the interior of baskets 27 (R = Me), 45 (R = Ph), and 46 (R = CF$_3$) (Table 11). The binding free energy $\Delta G^\circ$ is less favorable as more electron-withdrawing R groups (EWGs) are installed at the amide position. It could be that the EWGs render the host’s shell less polarizable, thereby disrupting its dispersion interactions with the guest; these interactions, together with other factors, contribute to the $\Delta G^\circ$ values.
Table 11: Thermodynamic parameters $\Delta H^\circ$, $\Delta S^\circ$, and $\Delta G^\circ$ for the binding of cyclohexane-$d_{11}$ to baskets 27, 45, and 46 ($\Delta G^\circ$ and $K$ at 188.8 K) in CD$_2$Cl$_2$ obtained from variable-temperature $^1$H NMR data (186–228 K) and van’t Hoff plots.

<table>
<thead>
<tr>
<th>Basket</th>
<th>$\Delta H^\circ$ (kcal/mol)</th>
<th>$\Delta S^\circ$ (eu)</th>
<th>$\Delta G^\circ$ (kcal/mol)</th>
<th>$K$ (M$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>-3.88 ± 0.07</td>
<td>-9.2 ± 0.3</td>
<td>-2.15 ± 0.03</td>
<td>314 ± 29</td>
</tr>
<tr>
<td>45</td>
<td>-3.92 ± 0.04</td>
<td>-10.3 ± 0.2</td>
<td>-1.96 ± 0.02</td>
<td>191 ±13</td>
</tr>
<tr>
<td>46</td>
<td>-3.31 ± 0.05</td>
<td>-9.7 ± 0.2</td>
<td>-1.48 ± 0.04</td>
<td>52 ± 5</td>
</tr>
</tbody>
</table>

a Obtained from $\ln K$ versus $1/T$ linear functions at 188.8 K.

The rate coefficient $k$ for cyclohexane-$d_{11}$ undergoing a chair flipping motion inside baskets 27, 45, and 47 was determined by using $^1$H-$^1$H NMR EXSY spectroscopy$^{71,72}$ at (188.8 ± 0.1) K (Table 10): the first-order magnetization rate constant $k^*_\text{obs}$ ($k^*_\text{obs} = k_{\text{obs}} = 1/2 k$) was obtained for the chemical exchange of the proton residing at the axial and the equatorial positions (Figure 45). At this low temperature, the rates for the entrapment and the release of cyclohexane by the host were reduced below the EXSY detection limit, as evidenced by the absence of the appropriate cross-signal in the spectrum (Figure 45). The interconversion kinetics of cyclohexane-$d_{11}$ in bulk dichloromethane (CD$_2$Cl$_2$) and toluene ($C_6H_5CD_3$) were measured concurrently by using both the classical line-shape and the EXSY methodology: the results from both analyses are consistent and in good agreement with published data (Table 10).$^{89,90}$ On the basis of the measurements (Table 10), it was determined that the interconversion of cyclohexane occurs roughly five times faster inside baskets 27, 45, and 46 than in the reference bulk solvents CD$_2$Cl$_2$ and C$_6$D$_5$CD$_3$. What is the origin of the acceleration?
Figure 45: A 2-D NMR EXSY spectrum (400 MHz, 188.8 ± 0.1 K) of a 14.0 mM solution (CD$_2$Cl$_2$) of cyclohexane-d$_{11}$ and basket 2 (1.40 mM). The volumes of the diagonal and cross-signals were used to extract the magnetization rate constant $k^*_\text{obs}$ that characterized the conformational interconversion.

An elevated pressure was earlier demonstrated to facilitate the interconversion of cyclohexane.\textsuperscript{91} Originally, the stochastic model for isomerization reactions\textsuperscript{88g,f} was used to explain such a result. In contrast to conventional transition-state theory, this model takes into account the recrossing of the activation barrier and proposes a dependence of the transmission coefficient $\kappa$ (the fraction of successful trajectories) on the collisional frequency of molecules; in conventional transition-state theory $\kappa=1$. That is to say, the reaction coordinate becomes coupled to the surrounding medium through collisions between solvent and solute molecules. The unimolecular kinetics that describes the
isomerization of cyclohexane\textsuperscript{88c} in the liquid phase conflicts with statistical RRKM theory, and the transmission coefficient $\kappa$ is a function of the external pressure or coupling of the solvent and solute. As the framework of the basket is in intimate and prolonged contact with the entrapped and rapidly fluctuating cyclohexane, the collisional contribution to the reaction coordinate could be sufficient to affect the interconversion and thereby control the isomerization rate. Computational results obtained through collaboration with the Hadad Group, however, offer an alternative explanation.

The acceleration of cyclohexane’s interconversion in the interior of these molecular baskets is due to a) a reduced energy barrier from the chair local minimum to the half-chair transition state or b) to a more efficient transmission coefficient $\kappa$.\textsuperscript{88b} The basket could contribute energetically in two ways: the destabilization of the chair conformer and the stabilization of the half-chair transition state (Figure 46).
The Hadad Group first employed the ONIOM\textsuperscript{94} (MP2/6-31G(d):AM1) method to investigate the complex formed between the basket and cyclohexane as a guest. Unfortunately, only very small differences in the geometry and energy for both the chair and half-chair conformers were seen between calculations on cyclohexane in a vacuum and in the basket. They speculated an inadequate treatment of the host–guest interactions may be the main reason for the inability of the ONIOM method to provide an explanation to this experimental observation. Unfortunately, it was difficult to evaluate the system with the MP2 level of theory because of its size.\textsuperscript{95} Thus, they employed density functional theory (DFT) calculations using the M06-2X functional,\textsuperscript{96,97} as this method has been optimized for studying noncovalent interactions between organic molecules. To assess the role of the basket as a host, they obtained optimized geometries for the cyclohexane guest inside the basket (for chair and half-chair TS structures) and then
recomputed the energies of the static chair and half-chair in a vacuum (that is, without the basket) relative to fully optimized M06-2X calculations of cyclohexane in a vacuum. According to the DFT results, the chair is slightly destabilized in the basket relative to the isolated chair conformer in a vacuum ($\Delta E = 0.25$ kcal mol$^{-1}$; Figure 46B). Further inspection of the interatomic distances (Figure 46A) reveal three (cyclohexane) C-H⋯π (basket) contacts ($<2.7$ Å from hydrogen to the π centroid)$^{98}$ for the encapsulated chair conformation, which leads to the $C_1$ symmetry of the chair in the basket but a $D_{3d}$ symmetry in a vacuum. Conversely, relative to the half-chair conformer in a vacuum, the half-chair transition state of the guest is a more stabilized structure ($\Delta E = -0.90$ kcal mol$^{-1}$) in the interior of basket 27. Examination of the encapsulated half-chair conformation (Figure 46C) showed that three dihedral angles of the carbon skeleton changed significantly as a consequence of the “fourth” C-H⋯π interaction with the upper pyridine gate. This additional C-H⋯π contact may play a role in assisting the “distortion” of the half-chair conformation, thereby moving it along the reaction coordinate to more closely resemble the twist-boat product. The Hadad Group’s computational studies implied that the encapsulated chair conformation is slightly destabilized and that the half-chair TS is stabilized in the basket relative to that in a vacuum. The activation barrier $\Delta E^\ddagger$ for the interconversion of cyclohexane was thus computed to be 10.87 kcal mol$^{-1}$ in the interior of basket 1 (Table 12), which is a significant reduction from the calculated barrier (12.02 kcal mol$^{-1}$) in a vacuum. A more favorable conversion of the chair into the half-chair TS while inside the basket ($\Delta\Delta E^\ddagger =$
1.15 kcal mol$^{-1}$, Figure 46B) is somewhat consistent with the experimental finding ($\Delta \Delta G^\ddagger \approx 0.5$ kcal mol$^{-1}$).

Table 12: Computed energies (M06-2X/6-311++G(d,p)//M06-2X/6-31G(d)) for the conformational interconversion of cyclohexane in a vacuum and inside basket 27.

<table>
<thead>
<tr>
<th>Conformation</th>
<th>Vacuum (kcal / mol)</th>
<th>Basket 27 (kcal / mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair</td>
<td>0$^a$</td>
<td>0</td>
</tr>
<tr>
<td>Half-chair</td>
<td>12.02</td>
<td>10.87</td>
</tr>
<tr>
<td>Twist-boat</td>
<td>6.19</td>
<td>6.05</td>
</tr>
<tr>
<td>Boat</td>
<td>7.51</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ For comparison, the computed energy corresponding to the chair conformational state was in each case set at zero.

The computational study revealed two H$_{eq}$ atoms and one H$_{ax}$ atom of the chair conformation making C-H⋯π contacts with the basket (Figure 46A). This result is in agreement with a greater difference in the chemical shift $\Delta \delta_{ax/eq}$ of the axial/equatorial protons of cyclohexane-d$_{11}$ inside baskets 27, 45, and 46 (227 Hz) than in bulk solvent (190 Hz, Figure 45). Moreover, the splitting pattern of the $^1$H NMR signals of the entrapped cyclohexane-d$_{11}$ did not alter at lower temperatures, thus suggesting a low activation barrier for this compound tumbling in the interior of 27, 45, and 46. The results of molecular dynamics (MD) simulations are consistent with this observation, disclosing a random fluctuation of cyclohexane (111 Å$^3$) inside closed baskets (ca. 221 Å$^3$) over a period of 10 ns.

Overall, the acceleration of the ring-flipping process of cyclohexane is found to be a result of more favorable noncovalent binding, and hence stabilization of the transition state, of the encapsulated compound. Incorporation of such control elements into the
design of artificial hosts with the purpose of facilitating dynamical change is desireable, but remains challenging given the subtle nature of weak noncovalent contacts. Serendipitous discoveries, however, provide critical information for enhancing our understanding of the fine details pertaining to the rational design of encapsulation-based catalysts.

3.6 Chapter 3 Summary and Conclusions

From our previous developments of molecular baskets folded by intramolecular hydrogen bonds using phenol groups (Section 1.3) and by metal chelation (Chapter 2) it was clear that in order to create kinetically stable host-guest complexes, the dynamics of the gates had to be minimized to create a better preorganized cavity. Thus, a family of molecular baskets folded by intramolecular hydrogen bonds using pyridinyl-amido gates were synthesized. The gates of these baskets possess two hydrogen bond contact points (the pyridine nitrogen and amido hydrogen) to aid in reducing dynamics. The folding of the baskets resulted in a pair of dynamic enantiomers whereby the resulting hydrogen bond array can be orientated clockwise or counterclockwise. Throughout our studies, dynamic NMR studies have been utilized to quantify the barrier to interconversion, which is related to the barrier of the basket opening and closing.

Through our initial studies of the new molecular baskets, it was found that the encapsulation of guest molecules follows an associative mechanism whereby the gates must unfold prior to guest exchange. Indeed, it was found that the dissociation of guest
molecule CCl₄ is roughly the sum of the intrinsic binding energy (ΔG°) and the energy required for the interconversion (opening) of the gates.

Additionally, a series of guest molecules were trialed with the molecular basket to identify what critical structures/features were necessary to drive the encapsulation. From the electrostatic potential surface of the host, it was clear that halocarbons would exhibit favorable electrostatic interactions within the interior. Furthermore, it was found that molecules possessing a packing coefficient of 40 – 48% (roughly 88 to 106 Å³) fit nicely inside. Overall, the ideal guest molecules, which were used in further studies, were found to be spherical halogenated methanes as well as spherical molecules within the aforementioned packing coefficient range. An important observation is the addition of methyl groups to isosteric guest molecules (e.g. tetrabromomethane and t-butyl bromide) results in a decrease of host-guest affinity primarily due to a relative disfavored entropy of formation.

With knowledge of the types of guests that can be effectively encapsulated within the interior of basket 27, we then sought to modify how fast the basket opens and closes. To accomplish this, the R group of the amide tethered to the gates was modified with a variety of substituents of differing steric and electronic effect such that they would perturb the resulting hydrogen bond array upon folding. Through the use of Taft plots, it was found that electron withdrawing groups slowed the rate of unfolding considerably while sterics had little effect.

Possessed with a means of obtaining molecular baskets with the same cavity volume, but with gates opening/closing at different rates at the same temperature, it was now
possible to evaluate the gating properties of this system. Thus, linear free energy relationships were constructed between the rates of ingress and egress of isosteric guest molecules ($\Delta^{\pm}G_f$ and $\Delta^{\pm}G_{\text{d}}$) and the corresponding host-guest affinity ($\Delta G^\circ$). After comparing the rates against guest molecules who differ in profile (i.e. they possess a different size/shape) it is found that the basket kinetically discriminates according to the size of a molecule whereby molecules smaller in volume enter/leave the cavity at a faster rate than larger molecules. After studying this phenomenon in molecular baskets that open/close at a variety of rates, it was found that the more dynamic baskets ($k_{\text{rac}}$ is high) discriminates between guest sizes more effectively than those with less dynamics.

Another interesting property found in molecular basket 27 is its unusual ability to catalyze the rate of interconversion between the two chair states in cyclohexane within its interior. Previously, such processes were observed to be slower within the confined environment of a host. Through a computational study performed by the Hadad Group, it was found that the rate acceleration is primarily due to the stabilization of the half-chair transition state and slight destabilization of the chair ground state within the interior.

As discussed in Chapter 1, gating provides natural systems, such as the enzyme acetylcholinesterase, with the ability to dramatically increase the size/shape selectivity of guest molecules while sacrificing little catalytic efficiency. In our studies with the intramolecular hydrogen bond folded baskets presented within this chapter, it was found that the consequences of gating are not unique to natural systems, but these properties manifest themselves into simple artificial host systems as well. The development of novel, useful, efficient, and selective artificial supramolecular reactors demands a
fundamental understanding of the functions that give rise to desired properties in natural systems. Progress in the understanding and application of one of these critical functions, gating, will aide in the development of future sophisticated artificial systems.
4.1 A Four-State Molecular Switch

Chapters 2 and 3 described molecular baskets folded by metal chelation and intramolecular hydrogen bonds respectively. Of importance, is the fact that each mode of folding presented a unique size/shape selectivity among guests (e.g. for Cu(I) coordinated basket 18, small linear coordinating molecules such as acetonitrile are preferred\(^{32}\), as opposed to spherical halomethane molecules for hydrogen-bond folded 27).\(^{54}\) Interestingly, the gate structures for these two baskets (3-pyridyl and 3-pyridyl-5-amido respectively) are remarkably similar and, since both are pyridine-based, can be potentially folded with metal cations. Thus, we studied whether we could achieve a stimulus-mediated interconversion\(^{99}\) between the two folded states using basket 27 (Figure 47).
Figure 47: Chemical structures of hydrogen bonded (27_{A/B}, A) and Cu(I) folded (27:Cu(I), B) basket 27. Side views of energy minimized (DFT, B3LYP) structures of 27_{A/B} (top) and 27:Cu(I) (bottom).

As described previously, molecular basket 27 has been designed to contain three pyridine-based gates, linked via intramolecular hydrogen bonding from meta amido groups, to occlude space and thus form a dynamic and gated environment (Figure 47A). The downfield $^1{H}$ NMR chemical shift ($\delta = 10.8$ ppm, Figure 48A) of the N–H resonances indicates the intramolecular HB contacts. The “hinge” H_{d/e} spins appeared as a singlet at high temperatures and as an AB quartet at low temperatures, thus demonstrating the interconversion of two C$_3$ symmetric enantiomers, 27$_{A}$ and 27$_{B}$, each containing hydrogen bonds displayed in the clockwise or the counter-clockwise
orientation. In essence, the 27\textsubscript{A/B} interconversion necessitates that each of the gates revolve 180° about the “vertical” axis. The activation energy ($\Delta G^{\ddagger}\text{rac,298}$) for this internal motion was found to be on the order of 10.8 kcal/mol, from NMR line-shape analysis.

Figure 48: (A) Selected regions of $^1$H NMR spectra (400 MHz, 298 K) of 27 (1.9 mM, CD\textsubscript{2}Cl\textsubscript{2}/C\textsubscript{6}D\textsubscript{6} = 2:1) recorded after addition of: (a) 6, (b) 12, (c) 18, (d) 24, (e) 30, (f) 36, (g) 42, (h) 48, and (i) 54 μL of 17.4 mM solution of (CuOTf)\textsubscript{2}PhMe. (B) $^1$H NMR chemical shifts of the $\text{H}_f$ resonance in 27 (1.9 mM) as a function of the titrated (CuOTf)\textsubscript{2}PhMe (17.4 mM). (C) $^1$H NMR chemical shifts of the $\text{H}_a$ resonance in 16 (2.5 mM) as a function of the titrated (CuOTf)\textsubscript{2}PhMe (32.5 mM).

Upon an incremental addition of a standard solution of (CuOTf)\textsubscript{2}PhMe to 27\textsubscript{A/B} in 2:1 CD\textsubscript{2}Cl\textsubscript{2}/C\textsubscript{6}D\textsubscript{6}, the basket’s $^1$H NMR spectrum changed: (a) the N–H resonance shifted upfield ($\Delta \delta = 2.0$ ppm) and (b) the aromatic $\text{H}_{b/c/d/f}$ resonances moved downfield (Figure 48).
Evidently, the addition of Cu(I) disrupted the intramolecular N–H…N contacts in 27A/B and promoted the formation of another C₃ symmetric assembly. Indeed, the results of ¹H NMR DOSY,³⁵,³⁶ COSY, NOESY spectroscopic and MALDI³⁷,³⁸ spectrometric measurements suggested the existence of 27:Cu(I) (Figure 47). When the chemical shift for the H₁ resonance was plotted against the molar equivalents of Cu(I) added to 27A/B, a sigmoidal dependence was evident (Figure 48B). Perhaps, the formation of the 27:Cu(I) complex occurred stepwise with some degree of cooperativity.¹⁰⁰,¹⁰¹ Molecular basket 16, with freely rotating pyridine gates (i.e., without amido groups), was previously shown to bind Cu(I), thereby yielding the 18ₐ complex (Figure 48C, see section 2.2 and 2.3). Interestingly, the assembling of 18ₐ (Figure 48C) required a greater quantity of copper than the formation of 27:Cu(I) (Figure 48B) in this solvent system. The finding that it is “easier” to coordinate 27 than 16 to Cu(I) is intriguing; the electronic/steric substituent effects of the meta amides, evidently, played a role in the binding thermodynamics.
Figure 49: Selected regions of $^1$H NMR spectra (400 MHz, 243 K) of a solution of basket 27 (1.22 mM, CD$_2$Cl$_2$/C$_6$D$_5$CD$_3$ = 2:1) containing CH$_3$CBr$_2$CH$_3$ (19.5 mM) and CH$_3$NC (1.22 mM), and recorded after an addition of 13.0 mM (CuOTf)$_2$PhMe and 26.0 mM CH$_3$NC. Molar equivalents of Cu(I) and CH$_3$NC are shown on the left.

Basket $^{27}_{A/B}$ trapped 2,2-dibromopropane in the presence of methyl isocyanide (Figure 49). The upfield $^1$H NMR singlet at $\delta \sim -0.7$ ppm, corresponding to C$_3$H$_6$Br$_2$ inside of 27, corroborated such an occurrence. Upon addition of Cu(I) to $^{27}_{A/B}$, however, the basket transformed into $^{27}$:Cu(I) entrapping CH$_3$NC inside its cavity. The disappearance of the resonance at $-0.7$ ppm and the appearance of another singlet at $-0.3$ ppm (CH$_3$NC) is in accord with that scenario (Figure 49). Interestingly, during the titration, the emergence of Cu(CH$_3$NC)$_4^+$ ($\delta = 3.3$ ppm, Figure 49) was observed to precede the formation of $^{27}$:Cu(I):CH$_3$NC. An excess of CH$_3$NC, however, led to the
reappearance of \(27_{A/B}\) (Figure 49). The removal of Cu(I) from \(27: Cu(I): CH_3NC\), along with the re-encapsulation of \(C_3H_6Br_2\), was also accomplished with the addition of \(Na_2S\). Evidently, the basket can be reversibly switched between two structural states with comparable interior volumes of \(\sim 221 \, \text{Å}^3\) and each expressing a unique functional behavior of encapsulation: \(27: Cu(I)\) showed no affinity for trapping 2,2-dibromopropane, while \(27_{A/B}\) was not amenable toward encapsulating \(CH_3NC\). Stoichiometrically balanced equations for the guest-mediated interconversion of Cu(I) folded and hydrogen bonded baskets are shown in Figure 50.
Figure 50: Stoichiometrically balanced equations describing the products obtained during the addition events in Figure 47, including A) the first 0.125 molar equivalents of Cu$_2$(PhMe)OTf$_2$, B) the additional 0.375 molar equivalents of Cu$_2$(PhMe)OTf$_2$, and C) the addition of three molar equivalents of CH$_3$NC. The chemical structures of D) 27:C(CH$_3$)$_2$Br$_2$ and E) [27:Cu(I):CH$_3$NC]OTf.
Presumably, the internal basket’s dynamics (in addition to other factors) played an important role for expressing the guest selectivity via preorganization. The $27_{A/B}$ interconversion (Figure 47) necessitates the cleavage of $\text{N}−\text{H}−\text{N}$ hydrogen bond(s) and is energetically demanding (expt $\Delta G^\ddagger_{\text{rac,298}} = 10.8 \text{ kcal/mol}$). The analogous conformational change in $27: \text{Cu(I)}: \text{CH}_3\text{NC}$, however, is more facile and can occur without rupturing the Cu−N coordinative bonds. This dynamic process was not observed experimentally, but computed (DFT, B3LYP) to require a small activation energy ($\Delta G^\ddagger = 3.9 \text{ kcal/mol}$).

The basket’s stimuli-responsive characteristics were further examined under acidic conditions. The nitrogen atoms, at the pyridine gates in $27_{A/B}$, were expected to abstract hydrogen(s) from strong proton donors thereby obstructing the internal hydrogen bonding at the rim of the basket and the encapsulation. An incremental addition of CF$_3$CO$_2$H (TFA) to a solution of $27_{A/B}$, containing 2,2-dibromopropane, prompted considerable $^1$H NMR spectroscopic changes (Figure 51). The addition of one molar equivalent of TFA led to the formation of [27$\subset$H]$^+$; note the occurrence of red-colored signals in Figure 51. $^1$H NMR DOSY, COSY and NOESY spectroscopic measurements suggest the existence of [27$\subset$H]$^+$. The single protonation, interestingly, initiated the expulsion of 2,2-dibromopropane (Figure 51). At first, the entrapment of trifluoroacetate anion was suspected for contributing to the guest’s dismissal. However, the CF$_3$ fluorine resonance ($^{19}$F NMR) remained unaffected during the titration, indicating the absence of the TFA encapsulation. In fact, the shape complementary CH$_3$SO$_3^-$ anion (from CH$_3$SO$_3$H) was also shown to reside outside of [27$\subset$H]$^+$. A molecule of solvent (CD$_2$Cl$_2$) must, therefore, be occupying the singly protonated basket.
Figure 51: Series of $^1$H NMR spectra (400 MHz, 243 K) of a solution of 27 (1.3 mM, CD$_2$Cl$_2$) containing CH$_3$CBr$_2$CH$_3$ (2.2 mM) and recorded after addition of 65.0 mM standard solution of TFA. Diffusion coefficients ($D_{obs}$) and the corresponding hydrodynamic radii ($r_H$) were obtained from $^1$H NMR DOSY measurements (500 MHz, 300 ± 1 K).

Variable temperature $^1$H NMR spectra of [27$\text{C}$H]$^+$ exhibited a set of resonances corresponding to a $C_3$ symmetric compound. In particular, a sharp singlet for the hinge $H_{d/e}$ protons and a downfield shifted N–H resonance ($\delta = 11.2$ ppm) were prominent: the protonated basket comprises a set of rapidly revolving gates interacting via hydrogen bonds; alternatively, more elaborate $^1$H NMR spectra, corresponding to less symmetric structure(s), would be expected.

A Monte Carlo conformational study of [27$\text{C}$H]$^+$ (MMFF force field) provided an insight into the host’s dynamics. Three hydrogen bonded and $C_s$ symmetric conformers,
with a comparable thermodynamic stability of $E_{\text{st}} = 0-3$ kcal/mol, were found. Accordingly, the experimental $^1$H NMR results could be interpreted by a rapid gate-flipping motion assisted with proton shuttling that averaged the hydrogen spins to give a spectrum corresponding to a $C_3$ symmetric structure. The enhanced dynamics at the rim of $[27\subset\text{H}]^+$ contributed to the development of a poorly preorganized inner space and, evidently, altered the basket’s capacity for acting as a host.

Further protonation of $[27\subset\text{H}]^+$ caused the appearance of a new set of $^1$H NMR signals, representing another $C_3$ symmetric assembly on average, as shown in blue in Figure 51. Notably, the addition of TFA restored the capacity for entrapping 2,2-dibromopropane, whose $^1$H NMR signal shifted further downfield ($\delta = -0.8$ ppm, Figure 51). Evidently, 2,2-dibromopropane experienced less diamagnetic shielding inside the newly formed host. The trend in the hydrodynamic radii (Figure 51) pointed to the basket’s aggregation, and possibly assembling into a more sizable dimer. Indeed, when 2,2-dibromopropane was used in excess (to saturate the host), the encapsulation was complete and the integrated basket:guest signal ratio was 2:1 (Figure 52B)! Moreover, the $C_3$ symmetric nature of $[27\subset\text{H}_3]^+$ concurred with the recorded $^1$H NMR spectrum: two equally strong signals, for each of the $H_b/H_c/H_f$ protons, correspond to the nuclei residing in the northern and the southern portion of the dimer (Figure 52A). A close proximity of the $H_b$ and $H_c$ protons was also manifested by the NOE cross signal. The inner volume of $[27\subset\text{H}_3]^+$, with the gates pointing to the bulk solvent, was estimated to be 307 Å$^3$. Guests such as 2,2-dibromopropane (105 Å$^3$) and dichloromethane (83 Å$^3$) occupy ~61% of the inner space of $[27\subset\text{H}_3]^+$, accounting for the experimentally
observed encapsulation. Ultimately, the addition of K$_2$CO$_3$ to [27$_2$$<$H$_3$]$^{3+}$ led to the formation of 27$_{A/B}$, with the transient appearance of [27$<$H]$. The guest-exchange capacity of the basket can thus be reversibly controlled at yet another level using an acid/base stimulus.

![Figure 52](image_url)

Figure 52: (A) Variable temperature $^1$H NMR spectra (500 MHz) of a CD$_2$Cl$_2$ solution of 27 (0.7 mM) containing 34.0 mM CH$_3$CB$_2$CH$_3$ and 2.7 mM TFA. (B) Integration proportion ($^1$H NMR) of H$_a$ or H$_b$ resonances in 27 and the proton nuclei in the encapsulated CH$_3$CB$_2$CH$_3$ were used to obtain basket/guest ratio as a function of temperature. (C) Top and side views of energy minimized (MMFF) structure of [27$_2$$<$3H]$^{3+}$. 

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4.2 Chapter 4 Summary and Conclusions

Molecular basket 27, composed of a semi-rigid $C_{3v}$ symmetric tris-norbornadiene platform and three pyridine gates with acetamide groups was evaluated as to whether it can interconvert between the intramolecular hydrogen bond mode of folding to metal chelation through use of an added stimulus. Thus, the pyridine gates have been shown to fold via intramolecular hydrogen bonds such that tert-butyl bromide is effectively encapsulated. Upon addition of Cu(I), the mode of folding switches to that of metal chelation, resulting in the expulsion of the tert-butyl bromide and the exclusive encapsulation of methyl isocyanide; a process that may be reversed by addition of Na$_2$S. The hydrogen-bond assembly was also found to be easily disrupted by addition of trifluoroacetic acid, forming a highly dynamic system with one equivalent and a dimer encapsulating one molecule of tert-butyl bromide and one molecule of dichloromethane with 1.5 equivalents. The transformations involving TFA have also been found to be readily reversible with K$_2$CO$_3$, thus showing the original basket may function as a unique four-state molecular switch.

The design and preparation of switchable systems with stimuli-responsive behavior gives access to a variety of versatile materials.$^{103}$ The results of our study contribute to such efforts, and demonstrate the adaptive nature of dynamic and gated hosts. Furthermore, the implementation of function into artificial structures demands a tunable element of design making the described four-state mode of action here a useful paradigm.
Chapter 5: Experimental

5.1 General Methods

All chemicals were purchased from commercial sources, and used as received unless stated otherwise. All solvents were dried prior to use according to standard literature protocols. Chromatography purifications were performed using silica gel 60 (Sorbent Technologies 40-75μm, 200 x 400 mesh). Thin-layer chromatography (TLC) was performed on silica-gel plate w/UV254 (200μm). Chromatograms were visualized by UV-light and stained using 20% phosphomolybdic acid in ethanol if needed. Melting points were determined on an Electrothermal melting point apparatus in open capillaries and are reported uncorrected. $^1$H and $^{13}$C NMR spectra were recorded, at 400 MHz and 100 MHz respectively, on a Bruker DPX-400 spectrometer unless otherwise noted. They were referenced using the solvent residual signal as an internal standard. NMR samples were prepared using CD$_2$Cl$_2$ and CDCl$_3$ purchased from Cambridge Isotope Laboratories. The chemical shift values are expressed as δ values and the couple constants values (J) are in Hertz (Hz). The following abbreviations were used for signal multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; and br, broad. Temperatures were corrected through use of a 100% methanol standard.
5.2 Synthetic Procedures

A solution of 14 (15 mg, 0.03 mmol) and Ac₂O (2 mL) was heated at 130 °C for 2 h. The solvent was removed in high vacuo to afford 7 as a white solid (13.0 mg, 90%). M.p. >300 °C; ¹H NMR (400 MHz, CD₃SOCD₃, 25 °C): δ = 7.99 (s, 6H), 4.77 (s, 6H), and 2.56 ppm (s, 6H); ¹³C NMR (100 MHz, CD₃SOCD₃, 25 °C): δ = 163.0 (C), 159.8 (C), 138.0 (C), 129.4 (C), 117.9 (CH), 65.0 (CH2), 48.3 (CH); HRMS(ESI): m/z calcd for C₃₉H₁₈O₉Na 653.0843 [M+Na]+; found: 653.0826.

A mixture of freshly distilled cyclopentadiene (2.65 g, 0.04 mol) and cis-1,4-dichloro-2-butene (4.16 g, 0.033 mol) in benzene (3 mL) was heated at 180 °C for 5 h in a sealed tube. The reaction mixture was cooled to room temperature and benzene was
evaporated under reduced pressure. The remaining residue was distilled in vacuo to afford 8 as a colorless oil (4.5 g, 71%). B.p. = 85.0 °C at 0.5 mm Hg; $^1$H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 6.25 (dd, 2H, $J_1 = J_2 = 1.8$ Hz), 3.31 (dd, 2H, $J_1 = 5.7$ Hz, $J_2 = 10.7$ Hz), 3.14-3.09 (m, 4H), 2.63-2.60 (m,2H), 1.55 (m, 1H), and 1.37 ppm (d, 1H, $J = 8.6$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$, 25 °C): δ =135.6 (CH), 48.4 (CH$_2$), 46.6 (CH), 45.6 (CH), and 45.0 ppm (CH$_2$). MS(ESI): $m/z$ calcd for C$_9$H$_{12}$Cl$_2$Na: 213.0 [M+Na]$^+$; found: 213.0.

9. To a solution of 8 (21.6 g, 113 mmol) in 390 mL of n-nonane at 150°C was added Br$_2$ (5.80 mL, 18.1 g, 113 mmol) dropwise. The resulting mixture was heated/stirred for an additional 15 min before being cooled to 0°C. The resulting precipitate was collected by vacuum filtrated and washed with cold hexanes (2 x 100 mL) to yield 9 (14.0 g, 35%) as a white solid. Any unreacted starting material may be recovered via column chromatography (5:1 hexanes:dichloromethane). M. p. 96 °C; $^1$H NMR (400 MHz, CDCl$_3$, 25 °C): δ =4.46 (d, 2H, $J = 2.0$ Hz), 3.66 (dd, 2H, $J_1 = 6.6$ Hz, $J_2 = 11.4$ Hz), 3.41 (dd, 2H, $J_1 = 9.8$ Hz, $J_2 = 11.3$ Hz), 2.89 (t, 2H, $J = 1.8$ Hz), 2.54-2.51 (m, 2H), 2.40 (d, 1H, $J = 11.0$ Hz), and 1.56 ppm (dt, 1H, $J_1 = 1.6$ Hz, $J_2 = 11.0$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 52.7 (CH), 50.9 (CH), 43.5 (CH), 40.9 (CH$_2$), and 34.4 ppm (CH$_2$); HRMS(ESI): $m/z$ calcd for C$_9$H$_{12}$Br$_2$Cl$_2$Na: 372.8558 [M+Na]$^+$; found: 372.8571.
To a solution of 9 (2.4 g, 6.8 mmol) in THF (68 mL) at 0 ºC, potassium tert-butoxide (14.5 g, 0.14 mol) was added under an argon atmosphere. The reaction mixture was left to stir for 2 h, before being quenched with water (6 mL) and extracted with hexanes (3 x 50 mL). The organic phase was dried (MgSO₄) and evaporated under reduced pressure. The solid residue was purified by column chromatography (SiO₂, hexanes) to afford 10 as a colorless oil (1.1 g, 82%). ¹H NMR (400 MHz, CDCl₃, 25 ºC): δ = 6.20 (d, 1H, J = 3.1 Hz), 5.31 (s, 1H), 5.25 (s, 1H), 5.13 (s, 1H), 5.00 (s, 1H), 3.36 (s, 1H), and 3.30 ppm (s, 1H); ¹³C NMR (100 MHz, CDCl₃, 25 ºC): δ = 135.4 (CH), 103.4 (CH₂), 102.4 (CH₂), 58.7 (CH), 52.2 (CH) and 50.9 ppm (CH₂); HRMS(ESI): m/z calcd for C₉H₁₀Br: 196.9960 [M+H]+; found: 197.0033.

A carbon tetrachloride (150 mL) solution of 10 (5.37 g, 27.2 mmol) and freshly distilled dimethyl acetylenedicarboxylate (5.32 g, 37.4 mmol) was allowed to stir at reflux for 12 h. The solvent was removed under reduced pressure to yield an amber oil (9.24 g). The oil was dissolved in dichloromethane (200 mL) and solid 2,3-dichloro-5,6-dicyano-p-benzoquinone (7.10 g, 31.3 mmol) was added. The mixture was mechanically
stirred under argon (12 h, rt), before it was “washed” with a saturated aqueous NaHCO$_3$ solution (3 × 200 mL) and dried (MgSO$_4$), and the organic layer was concentrated in vacuo. The solid residue was purified by column chromatography (SiO$_2$, CH$_2$Cl$_2$) to yield 11 (6.54 g, 71%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$, 298 K): δ 2.35 (1H, d, $J$ = 7.6 Hz), 2.63 (1H, d, $J$ = 8.0 Hz), 3.85 (1H, s), 3.88 (6H, s), 4.00 (1H, s), 6.73 (1H, d, $J$ = 3.2 Hz), 7.51 (1H, s), and 7.65 ppm (1H, s); $^{13}$C NMR (100 MHz, CDCl$_3$, 298 K): δ 51.7, 52.6, 52.7, 58.2, 68.8, 121.5, 122.1, 128.9, 130.1, 135.8, 139.8, 153.3, 153.9, 168.1, and 168.4 ppm; HRMS (EI): $m$/z calcd for C$_{15}$H$_{14}$BrO$_4$ 337.0075 [M + H]$^+$; found 337.0061.

12. To a solution of dry diisopropylamine (830 μL, 5.90 mmol) in THF (20 mL) at −78°C was added $n$-butyl lithium (1.6 M in hexanes, 3.60 mL, 5.76 mmol), and the mixture was stirred for 40 min under an atmosphere of argon. A solution of 11 (1.50 g, 4.45 mmol) in THF (10 mL) was then added dropwise over a period of 10 min, and the resulting mixture was stirred for an additional 30 min. Following, a solution of trimethyltin chloride (937 mg, 4.76 mmol) in THF (10 mL) was added dropwise over a period of 10 min, and the resulting mixture was gradually warmed to room temperature over a period of 3 h. Aqueous NH$_4$Cl (4 mL) was used to quench the base, followed with the removal of the organic layer in vacuo. The solid residue was washed with water (60
mL) and extracted with diethyl ether (2 × 70 mL). The combined organic phase was dried (MgSO₄) and concentrated in vacuo. The solid residue was purified by column chromatography (SiO₂, hexanes/ethyl acetate, 2:1) to yield 12 as a white solid (1.59 g, 72%). Mp 139–140 °C; ¹H NMR (400 MHz, CDCl₃, 27 °C): δ 0.24 (9H, t, \( J = 40 \) Hz), 2.27 (1H, d, \( J = 7.6 \) Hz), 2.57 (1H, d, \( J = 7.6 \) Hz), 3.91 (7H, s), 4.09 (1H, s), 7.47 (1H, s), and 7.65 ppm (1H, s); ¹³C NMR (100 MHz, CDCl₃, 27 °C): δ −9.3, 52.5, 52.6, 57.0, 60.2, 68.4, 121.1, 122.0, 129.0, 129.8, 147.0, 152.2, 153.6, 154.0, 168.4, and 168.5 ppm; HRMS (EI): \( m/z \) calcd for C₁₆H₁₆BrO₄Sn 500.9723 [M + H]⁺; found 500.9687.

13.³² A mixture of 12 (1.09 g, 2.18 mmol) and Cu(NO₃)₂·2.5H₂O (2.53 g, 10.9 mmol) in acetone (53 mL) was stirred at 50 °C overnight. The solvent was removed in vacuo and the remaining residue was washed with a 10% aqueous NH₃ solution (60 mL) and extracted with diethyl ether (3 × 100 mL). The combined phase was dried (MgSO₄) and concentrated in vacuo. The solid residue was purified by column chromatography (SiO₂, dichloromethane/acetone, 9:1) to yield 13 (75.8 mg, 13.6%) as a white solid. Mp 215 °C;
$^1$H NMR (400 MHz, CDCl$_3$, 27 °C): δ 2.54 (6H, s), 3.80 (18H, S), 4.43 (6H, s), and 7.45 ppm (6H, s); $^{13}$C NMR (100 MHz, CDCl$_3$, 27 °C): δ 48.8, 52.3, 65.4, 121.6, 129.8, 137.8, 152.8, and 168.1 ppm. HRMS (ESI): $m/z$ calcd for C$_{45}$H$_{36}$O$_{12}$Na 791.2099 [M + Na]$^+$; found 791.2098.

![Chemical structure of the compound](image)

$^{14}$ An aqueous solution of LiOH • xH$_2$O (60 mg, 1.43 mmol; 2 mL) was added to a solution of $^{13}$ (30 mg, 0.04 mmol) in THF (2 ml), and subsequently heated at 80 °C for 2 h. The aqueous phase was acidified with a 10% aqueous HCl solution (1 mL), and the resulting precipitate filtered, washed with water (2 mL), and dried at 90 °C under high vacuum to yield $^{14}$ as a white solid (25.4 mg, 95 %). M.p. >300 °C; $^1$H NMR (400 MHz, CD$_3$SOCD$_3$, 25 °C): δ = 12.67 (br, 6H), 7.46 (s, 6H), 4.62 (s, 6H), and 2.42 ppm (s, 6H); $^{13}$C NMR (100 MHz, CD$_3$SOCD$_3$, 25 °C): δ = 168.8 (C), 153.3 (C), 138.3 (C), 130.6 (C), 121.5 (CH), 5.3 (CH$_2$), and 48.3 ppm (CH); HRMS(ESI): $m/z$ calcd for C$_{39}$H$_{24}$O$_{12}$Na 707.1150 [M+Na]$^+$; found: 707.1165.
To a solution of trisanhydride 7 (2.5 mg, 0.004 mmol) in toluene (1.0 ml), was added a solution of 3-(aminomethyl)pyridine (2.6 mg, 0.024 mmol) in toluene (0.5 ml). Then neat pyridine (150.0 μl) was added, before the solution was heated to reflux for 12 h. The reaction mixture was then cooled to room temperature, evaporated in vacuo, and the residue purified by column chromatography (SiO2, benzene/acetone, 3:1) to yield 18 as a white solid (3.6 mg, 87%). $^1$H NMR (500 MHz, CDCl$_3$, 27 °C): $\delta = 8.25$ (s, 3H), 8.16 (s, 3H), 7.46 (d, 3H), 7.30 (s, 6H), 7.03 (dd, 3H), 4.44 (s, 6H), 4.32 (s, 6H), and 2.34 (s, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$, 27 °C): $\delta = 167.6$ (C=O), 156.8 (CH), 137.8 (CH), 136.3 (C), 129.0 (CH), 128.2 (CH), 125.3 (CH), 123.4 (C), 122.7 (C), 118.5 (C), 68.2 (CH$_2$), 49.3 (CH), and 42.7 (CH$_2$) ppm. MALDI-TOF $m/z$ calcd for C$_{57}$H$_{36}$N$_6$O$_6$Na: 923.260 [M+Na]$^+$, found: 923.331.
A solution of acetic anhydride (1.7 mg, 17.0 μmol) in THF (100 μL) was added dropwise to a stirred solution (THF, 0.5 mL) of compound 32 (3.0 mg, 3.2 μmol) containing triethylamine (3.2 mg, 32.0 μmol) at 0 °C. The stirring was continued for 1.5 h, after which the solvent was evaporated in vacuum and the residue was purified by preparatory TLC (SiO₂, CH₂Cl₂/CH₃OH = 10:1) to yield a white solid product (1.9 mg, 55 %). ¹H NMR (400 MHz, CDCl₃, 298 K): δ = 10.98 (s, 3-NH), 8.29 (t, J = 1.6 Hz, 3H), 8.24 (d, J = 1.6 Hz, 3H), 8.16 (d, J = 2.4 Hz, 3H), 7.43 (s, 6H), 4.74 (s, 6H), 4.23 (s, 6H), 2.54 (q, J = 3.6 Hz, 6H) and 2.23 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ = 169.7, 167.0, 156.7, 145.1, 142.3, 135.2, 135.6, 134.9, 133.3, 130.1, 116.1, 66.1, 49.0, 38.3 and 23.7 ppm; HR MALDI-TOF m/z calcd for C₆₃H₄₆N₉O₉: 1072.3418 [M+H]⁺, found: 1072.2285.
To a solution of 5-amino-nicotinic acid (450 mg, 3.26 mmol) in 20 mL of methanol at 0°C was added thionyl chloride (4.50 mL, 7.37 g, 61.9 mmol) dropwise. The resulting mixture was refluxed and the reaction monitored by TLC (10:1 dichloromethane:methanol). After completion (c.a. 2 h), the mixture was cooled to room temperature and the solvent was removed in vacuo. 15 mL of water was added to the resulting residue and the mixture is neutralized by careful addition of 7 mL of a saturated sodium bicarbonate solution. The mixture is extracted with ethyl acetate (5 x 30 mL) and the combined organic fractions were dried (Na$_2$SO$_4$) and concentrated in vacuo to yield crude 29 (328.5 mg, 66%) as a white solid which was used without further purification.

$^1$H NMR (DMSO-d$_6$, 400 MHz, 300 K) $\delta$ = 8.04 (1H, d, $J$ = 5.4 Hz), 6.95 (1H, s), 6.87 (1H, dd, $J$ = 1.5, 5.4 Hz), 6.28 (2H, s), 3.83 (3H, s); $^{13}$C NMR (DMSO-d$_6$, 100 MHz, 300 K) $\delta$ = 165.72, 160.51, 148.91, 137.75, 109.99, 107.4, 52.3.

Ester 29 (328.5 mg, 2.16 mmol) was stirred in 13 mL of concentrated ammonium hydroxide at room temperature for 24 h. The solvent was removed in vacuo and resulting residue was purified by column chromatography (5:1 dichloromethane:methanol + 1%
triethylamine) to yield 30 (260.6 mg, 88%) as a white solid. NMR (DMSO-d$_6$, 400 MHz, 300 K) $\delta$ = 7.97-7.93 (2H, m), 7.43 (1H, s), 6.83-6.81 (2H, d, $J = 5.7$ Hz), 6.08 (2H, s);

$^{13}$C NMR (DMSO-d$_6$, 100 MHz, 300 K) $\delta$ = 167.23, 160.21, 148.09, 142.77, 109.31, 106.22.

![Chemical Structure](image)

31. To a solution of 30 (100.0 mg, 0.729 mmol) in 150 mL of THF at 58°C was added 60 mg (1.58 mmol) of lithium aluminum hydride (LAH). The mixture was stirred for three days with monitoring by TLC (1:1 dichloromethane:methanol) and adding 60 mg more of LAH every 24 h (180 mg total). The completed reaction is cooled to 0°C, carefully quenched with 1.0 mL of water, filtered with methanol rinsings, and concentrated in vacuo. The resulting crude mixture was purified by column chromatography (5:1 dichloromethane:methanol + 1% triethylamine to isolate any starting material followed by 1:1 dichloromethane:methanol + 1% triethylamine to eluate the product) to yield 31 (32.5 mg, 36%) as a yellow oil. NMR (DMSO-d$_6$, 400 MHz, 300 K) $\delta$ = 7.11 (1H, s), 7.02 (1H, s), 6.20 (1H, s), 4.54 (2H, s), 3.00 (2H, s, br), 2.92 (2H, s).
Tris-anhydride 7 (6.3 mg, 10.0 μmol) was added portionwise to a stirred solution of dry DMSO (1.0 mL) containing 31 (4.9 mg, 40.0 μmol) at room temperature. After 2 h, neat pyridine (0.1 mL) was added dropwise and the temperature was raised to 115 ºC. The reaction was allowed to complete over ~12 h (overnight), after which the solvent was evaporated in vacuum and the residue was purified by column chromatography (SiO2, CH2Cl2/CH3OH = 6:1) to yield a white solid product (6.6 mg, 70 %). H NMR (500 MHz, DMSO-d6, 300 K): δ = 7.81 (s, 6H), 7.79 (s, 3H), 7.63 (s, 3H), 6.64 (s, 3H), 5.24 (s, 6-NH), 4.73 (s, 6H), 4.48 (s, 6H), 2.52 (s, 6H); 13C NMR (126 MHz, DMSO-d6, 300 K): δ = 167.5, 157.8, 144.7, 137.9, 135.9, 135.5, 132.2, 129.7, 118.0, 116.2, 65.2, 48.2, 38.3 ppm; HR MALDI-TOF m/z calcd for C57H39N9O6K: 984.266 [M+K]+, found: 984.229.
A solution of trimethylacetyl chloride (2.3 mg, 19.2 μmol) in THF (100 μL) was added dropwise to a stirred solution of 32 (3.0 mg, 3.2 μmol) in THF (0.5 mL) containing triethylamine (3.2 mg, 32.0 μmol) at 0 °C. The stirring was continued for 1.5 h, after which the solvent was evaporated in vacuum and the residue was purified by preparatory TLC (SiO₂, CH₂Cl₂/CH₃OH = 15:1) to yield a white solid product (3.3 mg, 85 %).

1H NMR (400 MHz, CDCl₃, 300 K): δ = 10.09 (s, 3-NH), 8.29 (d, J = 2.4 Hz, 3H), 8.20 (d, J = 1.6 Hz, 3H), 8.12 (dd, J = 1.6 Hz, 2.4 Hz, 3H), 7.39 (s, 6H), 4.69 (s, 6H), 4.43 (s, 6H), 2.55 (s, 6H);

13C NMR (63 MHz, CDCl₃, 300 K): δ = 178.8, 167.0, 156.7, 146.2, 143.9, 137.6, 136.1, 135.0, 132.7, 130.1, 116.0, 66.7, 48.9, 39.3, 38.3, 27.7 ppm; HR MALDI-TOF m/z calcd for C₇₂H₆₃N₉O₉Na: 1220.465 [M+Na]⁺, found: 1220.456.
A solution of \( n \)-heptanoyl chloride (2.9 mg, 19.2 mmol) in THF (100 μL) was added dropwise to a stirred solution (THF, 0.5 mL) of compound 32 (3.0 mg, 3.2 μmol) containing triethylamine (3.2 mg, 32.0 μmol) at -10 °C. The stirring was continued for 1.5 h, after which the solvent was evaporated in vacuum and the residue was purified by preparatory TLC (SiO\(_2\), CH\(_2\)Cl\(_2\)/CH\(_3\)OH = 13:1) to yield a white solid product (3.3 mg, 80 %). \(^1\)H NMR (400 MHz, CDCl\(_3\), 300 K): \( \delta = 10.87 \) (s, 3-NH), 8.28 (s, 3H), 8.22 (s, 3H), 8.18 (s, 3H), 7.42 (s, 6H), 4.73 (s, 6H), 4.42 (s, 6H), 2.54 (dd, \( J = 12.0 \), 6.7 Hz, 6H), 2.43 (t, \( J = 6.6 \) Hz, 6H), 1.76 (m, 6H), 1.33 (m, 18H), 0.89 (s, 9H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\), 300 K): \( \delta = 173.0, 167.0, 156.7, 145.1, 142.4, 137.5, 135.3, 135.0, 133.2, 130.2, 116.1, 66.1, 49.0, 38.3, 37.0, 31.6, 29.1, 25.5, 22.5, 14.1 \) ppm; HR MALDI-TOF \( m/z \) calcd for C\(_{78}\)H\(_{75}\)N\(_9\)O\(_9\)Na: 1304.559 [M+Na]+, found: 1304.715.
A solution of trans-crotonyl chloride (1.7 mg, 16.0 μmol) in THF (100 μL) was added dropwise to a stirred solution (THF, 0.5 mL) of compound 32 (3 mg, 3.2 μmol) containing triethylamine (3.2 mg, 32.0 μmol) at -10 °C. The stirring was continued for 1.0 h, after which the solvent was evaporated in vacuum and the residue was purified by preparatory TLC (SiO₂, CH₂Cl₂/CH₃OH = 13:1) to yield a white solid product (2.9 mg, 80 %).

¹H NMR (500 MHz, CDCl₃, 300 K): δ = 10.93 (s, 3-NH), 8.36 (s, 3H), 8.23 (d, J = 2.0 Hz, 3H), 8.22 (d, J = 2.5 Hz, 3H), 7.41 (s, 6H), 7.05 (m, 3H), 6.04 (dd, J = 15.0 Hz, 1.5 Hz, 3H), 4.74 (s, 6H), 4.42 (s, 6H), 2.53 (s, 6H), 1.91 (dd, J = 6.5 Hz, 1.5 Hz, 9H);

¹³C NMR (126 MHz, CDCl₃, 300 K): δ = 167.0, 165.4, 156.4, 156.1, 145.1, 142.5, 141.8, 137.5, 135.4, 135.0, 133.2, 130.2, 125.0, 116.1, 66.1, 49.0, 38.4, 18.0 ppm; HR MALDI-TOF m/z calcd for C₆⁹H₅¹N₉O₉Na: 1172.371 [M+Na]+, found: 1172.492.
A solution of benzoyl chloride (2.3 mg, 16.4 μmol) in THF (100 μL) was added dropwise to a stirred solution (THF, 0.5 mL) of compound 32 (3.0 mg, 3.2 μmol) containing triethylamine (3.2 mg, 32.0 μmol) at 0 °C. The stirring was continued for 1.5 h, after which the solvent was evaporated in vacuum and the residue was purified by preparatory TLC (SiO₂, CH₂Cl₂/CH₃OH = 15:1) to yield a white solid product (3.2 mg, 80 %). ¹H NMR (400 MHz, CDCl₃, 300 K): δ = 11.38 (s, 3-NH), 8.53 (s, 6H), 8.06 (s, 3H), 8.04 (s, 3H), 7.98 (s, 3H), 7.40-7.55 (m, 15H), 4.66 (s, 6H), 4.41 (s, 6H), 2.53 (s, 6H); ¹³C NMR (63 MHz, CDCl₃, 27 °C): δ = 167.2, 166.9, 156.7, 145.6, 143.1, 137.5, 135.4, 135.3, 133.9, 133.1, 132.0, 130.1, 128.5, 127.8, 116.0, 65.8, 49.0, 38.3 ppm; HR MALDI-TOF m/z calcd for C₇₈H₅₁N₉O₉Na: 1280.371 [M+Na]⁺, found: 1280.404.
A solution of trifluoroacetic anhydride (8.4 mg, 40.0 μmol) in THF (100 μL) was added dropwise to a stirred solution (THF, 0.8 mL) of compound 32 (4.7 mg, 5.0 μmol) containing triethylamine (5.1 mg, 50.0 μmol) at 0 °C. The stirring was continued for 1.0 h, after which the solvent was evaporated in vacuum and the residue was purified by preparatory TLC (SiO₂, CH₂Cl₂/CH₃OH = 20:1) to yield a white solid product (4.3 mg, 70 %). H NMR (400 MHz, CDCl₃, 300 K): δ = 12.22 (s, 3-NH), 8.32 (s, 3H), 8.31 (s, 6H), 7.42 (s, 6H), 4.78 (s, 6H), 4.44 (s, 6H), 2.55 (dd, J = 11.6 Hz, 8.4 Hz, 6H); C NMR (126 MHz, CDCl₃, 300 K): δ = 166.8, 156.9, 157 (q, CF₃C=O), 147.0, 142.5, 137.6, 135.7, 133.9, 132.7, 130.1, 117 (q, CF₃), 116.1, 66.0, 49.0, 38.1 ppm; HR MALDI-TOF m/z calcd for C₆₃H₃₆F₉N₉O₉K: 1272.213 [M+K]⁺, found: 1272.207.
To a solution of diisopropylamine (3.0 mL, 2.2 g, 21.4 mmol) in dry THF (30 mL) at −30°C was added dropwise \( n \)-butyllithium (1.6 M in hexanes, 13.0 mL, 20.8 mmol). The resulting solution was warmed to 0°C, stirred for 10 min, and then cooled to −95°C. Bromoform (1.75 mL, 5.06 g, 20.0 mmol) was added dropwise and the mixture was stirred for 10 min before a solution of methyl iodide (1.4 mL, 3.2 g, 22.5 mmol) in THF (10 mL) was added dropwise. The resulting mixture was stirred at −95° for 1.5 hr, slowly warmed to −70°C, quenched with 1.0 mL of aqueous NH\(_3\)/NH\(_4\)Cl buffer (pH 9.0), and warmed to room temperature. The mixture was partitioned with 1:1 H\(_2\)O:Et\(_2\)O (80 mL), separated, and the aqueous layer was washed once with Et\(_2\)O (40 mL). The organic fractions were combined, dried with Na\(_2\)SO\(_4\), concentrated in vacuum, and the resulting crude mixture was purified by Kügelrohr distillation (50°C, 80 mm Hg, the product deposits unto dry-ice cooled bulbs) to yield 1,1,1-tribromoethane (3.17 g, 59%) as a colorless liquid.

\(^1\)H NMR (400 MHz, CDCl\(_3\), 300 K): \( \delta = 3.38 \) (s) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\), 300 K): \( \delta = 51.9, 31.4 \) ppm.

To a solution of diisopropylamine (3.0 mL, 2.2 g, 21.4 mmol) in dry THF (30 mL) at −30°C was added dropwise \( n \)-butyllithium (2.5 M in hexanes, 8.0 mL, 20.0 mmol). The resulting solution was warmed to 0°C, stirred for 10 min, and then cooled to −95°C.
Dibromochloromethane (1.53 mL, 3.75 g, 18.0 mmol) was added dropwise and the mixture was stirred for 10 min before a solution of methyl iodide (1.31 mL, 2.98 g, 21.0 mmol) in THF (10 mL) was added dropwise. The resulting mixture was stirred at −95° for 30 min, slowly warmed to −70°C, quenched with 3.0 mL of a saturated aqueous NH₄Cl solution and warmed to room temperature. The mixture was concentrated under reduced pressure and the residue was partitioned with 1:1 H₂O:Et₂O (80 mL), separated, and the aqueous layer was washed once with Et₂O (40 mL). The organic fractions were combined, dried with Na₂SO₄, concentrated under reduced pressure, and the resulting crude mixture was purified by distillation (55 − 58°C, 70 mm Hg) to yield 1,1-dibromo-1-chloroethane (872 mg, 22%) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃, 300 K): δ = 3.13 (s) ppm; ¹³C NMR (100 MHz, CDCl₃, 300 K): δ = 54.7, 49.9 ppm.
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A.1 Supplementary Data for Chapter 3.2

Sample Preparation for 2-D EXSY Experiments

All NMR solutions and standards were prepared under nitrogen atmosphere in a glove box. All NMR samples were prepared in J. Young NMR tubes purchased from Norell. CD$_2$Cl$_2$ was degassed using the freeze-thaw method and stored under nitrogen in a glove box.

General Procedure for 2-D EXSY Measurements of $k^*_{f}$ and $k^*_{d}$

A solution of basket and $t$-butyl bromide in CD$_2$Cl$_2$ (J. Young NMR tube) was cooled to 226.0 ± 0.1 K inside the NMR probe and allowed to equilibrate for 1.0 h. The $^1$H spin-lattice relaxation times ($T_1$) for the free and encapsulated guest molecules were determined by a standard inversion-recovery pulse sequence with a relaxation delay ($\tau_d$) of at least 5*$T_1$. Following, a series of gradient NOESY experiments were run with a relaxation delay of 5*$T_1$ and mixing times ($\tau_m$) of 0 ms and four others ranging from 25 to 450 ms such that the crosspeaks were clearly resolved. Each of the 128 F1 increments was the accumulation of 2 scans. The peak volumes were determined using XWinNMR.
software from Bruker, after phase and baseline corrections in both dimensions. The magnetization exchange rate constant \( (k^*_f \text{ and } k^*_d) \) were, at each mixing time \( \tau_m \), calculated using the EXSYCalc program (Mestrelab Research).\(^{104}\) The association \( k_f \) and dissociation \( k_d \) rate constants were then obtained as: \( k_f = k^*_f / [\text{basket}] \) and \( k_d = k^*_d \). The mean value was reported using the standard deviation as an experimental error. For each basket, the quantitative NOESY experiments were repeated twice.

**EXSY \( k^*_f \text{ and } k^*_d \) for Basket 46.** 2-D EXSY experiment described above was for basket 46 performed at 235.0 ± 0.1, 243.0 ± 0.1, and 250.0 ± 0.1 K, yielding \( k^*_f \text{ and } k^*_d \) at each temperature (see table below). The rate constants at 226.0 K were then estimated by extrapolation of an Eyring plot from a linear and weighted least-squares analysis.

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>( k_f ) (M(^{-1})s(^{-1}))</th>
<th>( k^*_d ) (s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>235 ± 0.1</td>
<td>2.7 ± 0.7</td>
<td>0.17 ± 0.08</td>
</tr>
<tr>
<td>243 ± 0.1</td>
<td>19.3 ± 3.9</td>
<td>0.66 ± 0.12</td>
</tr>
<tr>
<td>250 ± 0.1</td>
<td>36 ± 6</td>
<td>1.3 ± 0.1</td>
</tr>
</tbody>
</table>
Figure 53: 2-D EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.4 mM solution of basket 46 containing 4.1 molar equivalents of $t$-BuBr (9.84 mM) in CD$_2$Cl$_2$; the concentration of “free” basket [basket] = 1.7 ± 0.2 mM, was obtained by integrating $^1$H NMR signals for the guest ($t$-BuBr) and solvent occupied 46. Note that $k_{ba}^*$ = $k_d^*$ and $k_{ab}^* = k_{r}^*$. 

Figure 54: 2-D EXSY Spectrum (400 MHz, 243.0 ± 0.1 K) of a 2.4 mM Solution of Basket 46 containing 4.5 molar equivalents of $t$-BuBr (10.8 mM) in CD$_2$Cl$_2$; the
concentration of “free” basket [basket] = 1.8 ± 0.2 mM, was obtained by integrating $^1$H NMR signals for the guest ($t$-BuBr) and solvent occupied 46. Note that $k_{ba}^* = k_{d}^*$ and $k_{ab}^* = k_{f}^*$.

Figure 55: 2-D EXSY Spectrum (400 MHz, 235.0 ± 0.1 K) of a 2.4 mM Solution of Basket 46 containing 4.1 molar equivalents of $t$-BuBr (9.84 mM) in CD$_2$Cl$_2$; the concentration of “free” basket [basket] = 1.5 ± 0.2 mM, was obtained by integrating $^1$H NMR signals for the guest ($t$-BuBr) and solvent occupied 46. Note that $k_{ba}^* = k_{d}^*$ and $k_{ab}^* = k_{f}^*$.
Figure 56: An Eyring Plot describing the temperature dependence of $k^*_d$. The exchange rate at 226.0 K was estimated to be $0.068 \pm 0.022 \text{ s}^{-1}$.

Figure 57: An Eyring Plot describing the temperature dependence of $k_f$. The exchange rate at 226.0 K was thus estimated to be $0.69 \pm 0.15 \text{ M}^{-1} \text{s}^{-1}$. 
Figure 58: 2-D EXSY Spectrum (400 MHz, 226.0 ± 0.1 K) of a 1.1 mM Solution of Basket 27 containing 2.3 molar equivalents of t-BuBr (2.53 mM) in CD₂Cl₂; the concentration of “free” basket [basket] = 0.84 ± 0.08 mM, was obtained by integrating ¹H NMR signals for the guest (t-BuBr) and solvent occupied 27. Note that k*ₗₐₗₜ₈ = k*ₗₐₜ and k*ₐₗₜ₈ = k*ₗₜ₈.

Figure 59: 2-D EXSY Spectrum (400 MHz, 226.0 ± 0.1 K) of a 1.9 mM Solution of basket 42 containing 2.6 molar equivalents of t-BuBr (4.94 mM) in CD₂Cl₂; the
concentration of “free” basket \([\text{basket}] = 1.0 \pm 0.1 \text{ mM}\), was obtained by integrating \(^1\text{H}\) NMR signals for the guest \((t\text{-BuBr})\) and solvent occupied \(42\). Note that \(k_{ba}^* = k_d^*\) and \(k_{ab}^* = k_f^*\).

Figure 60: 2-D EXSY Spectrum \((400 \text{ MHz, } 226.0 \pm 0.1 \text{ K})\) of a 1.9 mM solution of basket \(43\) containing 3.3 molar equivalents of \(t\text{-BuBr} (6.27 \text{ mM})\) in CDCl\(_2\); the concentration of “free” basket \([\text{basket}] = 0.097 \pm 0.010 \text{ mM}\), was obtained by integrating \(^1\text{H}\) NMR signals for the guest \((t\text{-BuBr})\) and solvent occupied \(43\). Note that \(k_{ba}^* = k_d^*\) and \(k_{ab}^* = k_f^*\).
Figure 61: 2-D EXSY Spectrum (400 MHz, 226.0 ± 0.1 K) of a 1.3 mM solution of basket 44 containing 3.3 molar equivalents of t-BuBr (4.29 mM) in CD$_2$Cl$_2$; the concentration of “free” basket [basket] = 0.086 ± 0.009 mM, was obtained by integrating $^1$H NMR signals for the guest (t-BuBr) and solvent occupied 44. Note that $k_{ba}^* = k_{da}^*$ and $k_{ab}^* = k_{fb}^*$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k_{ba}^*$</th>
<th>$k_{ab}^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 ms</td>
<td>2.7</td>
<td>211</td>
</tr>
<tr>
<td>60 ms</td>
<td>2.9</td>
<td>192</td>
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<tr>
<td>70 ms</td>
<td>2.6</td>
<td>208</td>
</tr>
<tr>
<td>80 ms</td>
<td>2.8</td>
<td>260</td>
</tr>
</tbody>
</table>

$k_{ba}^*$: 2.8 ± 0.1 s$^{-1}$

$k_{ab}^*$: 239 ± 68 s$^{-1}$M$^{-1}$
Figure 62: 2-D EXSY Spectrum (400 MHz, 226.0 ± 0.1 K) of a 1.8 mM Solution of Basket 45 containing 3.7 molar equivalents of t-BuBr (6.66 mM) in CD$_2$Cl$_2$; the concentration of “free” basket [basket] = 0.083 ± 0.008 mM, was obtained by integrating $^1$H NMR signals for the guest (t-BuBr) and solvent occupied 45. Note that $k^{*}_{ba} = k^{*}_d$ and $k^{*}_{ab} = k^{*}_f$.

$^1$H Line Shape Analysis of the A/B Interconversion

First-order rate constants $k_f$ and $k_{by}$ for the A/B interconversion of 27 and 42-46 (see below), were obtained by simulating the line-shapes of H$_{a/b}$ signals at various temperatures (WINDNMR-Pro). A statistical correction was not applied, assuming that the A/B interconversion does include any intermediate state. The exchange rate constants from the simulation were, importantly, shown to be independent on the concentration of the guest (t-BuBr). Accordingly, they were made equivalent to the chemical rate constant describing the A/B interconversion ($k_{rac}$). $k_{rac}$ at 226.0 K was, for each basket 27, 42-46,
calculated from Eyring plot ($\ln(kb/T) = \text{slope}/T + \text{intercept}$). The reported error margin of 20% was obtained from four independent measurements.

199.6 ± 0.1 K

204.1 ± 0.1 K

207.4 ± 0.1 K

210.7 ± 0.1 K

214.0 ± 0.1 K

217.3 ± 0.1 K
Figure 63: Simulated and experimental (WINDNMR-Pro) resonances for the H_{a/b} protons in 27 (2.98 mM) in CD$_2$Cl$_2$ containing 100.0 molar equivalents of t-BuBr (298 mM).
Figure 64: Eyring plot for 27A/27B interconversion, obtained with $k_{\text{rac}}$ from dynamic $^1$H NMR measurements above; $k_{\text{rac}}$ at 226.0 K (with an error margin of 20 %) was obtained from the linear least square analysis of the experimental data above.
Figure 65: Eyring plot for 42A/42B interconversion, obtained from dynamic $^1$H NMR measurements of 42 (3.31 mM) in CD$_2$Cl$_2$ containing 60.0 molar equivalents of t-BuBr; $k_{\text{rac}}$ at 226.0 K (with an error margin of 20 %) was obtained from the linear least-square analysis of the experimental data above (in this particular case, however, $k_{\text{rac}}$ at 226 K was reported (Table 4) as a mean of three independent measurements: 83 ± 17, 91 ± 18 and 59 ± 12 s$^{-1}$).
Figure 66: Eyring plot for 43A/43B interconversion, obtained from dynamic $^1$H NMR measurements of 43 (1.41 mM) in CD$_2$Cl$_2$ containing 150.0 molar equivalents of $t$-BuBr; $k_{\text{rac}}$ at 226.0 K (with an error margin of 20 %) was obtained from the linear least-square analysis of the experimental data above.
Figure 67: Eyring plot for 44A/44B interconversion, obtained from dynamic $^1$H NMR measurements of 44 (1.41 mM) in CD$_2$Cl$_2$ containing 100.0 molar equivalents of $t$-BuBr; $k_{\text{rac}}$ at 226.0 K (with an error margin of 20 %) was obtained from the linear least-square analysis of the experimental data above.
Figure 68: Eyring plots for 45A/45B interconversion, obtained from dynamic $^1$H NMR measurements of 45 in CD$_2$Cl$_2$ (2.14 mM) containing 74.0 (red), 125.0 (blue), 175.0 (green) and 225.0 (gray) molar equivalents of t-BuBr; $k_{\text{rac}}$ at 226.0 K (with an error margin of 20%) was obtained from the linear least-square analysis of the experimental data below. (red, slope = -5633.7322 and intercept = 22.1632); blue, slope = -4956.9507 and intercept = 19.4412; green, slope = -4791.6522 and intercept = 18.8017; gray, slope = -4854.2705 and intercept = 19.1374).
Figure 69: Eyring plot for 46A/46B interconversion, obtained from dynamic $^1$H NMR measurements of 46 (1.16 mM) in CD$_2$Cl$_2$ containing 250.0 molar equivalents of $t$-BuBr; $k_{\text{rac}}$ at 226.0 K (with an error margin of 20 %) was obtained from the linear least-square analysis of the experimental data above.

A.2 Supplementary Data for Chapter 3.3

Sample Preparation for 2-D EXSY Experiments

All NMR solutions and standards were prepared under nitrogen in a glove box. All NMR samples were prepared in J. Young NMR tubes purchased from Norell. CD$_2$Cl$_2$ was degassed using the freeze-thaw method and stored under nitrogen in a glove box.
Procedure for 2-D $^1$H EXSY Experiment

A solution of basket and guest in CD$_2$Cl$_2$ (J. Young NMR tube) was cooled to 250.0 ± 0.1 K inside the NMR probe and allowed to equilibrate for 1.0 h. The $^1$H spin-lattice relaxation times ($T_1$) for the free and encapsulated guest molecules were determined by a standard inversion-recovery pulse sequence with a relaxation delay ($\tau_d$) of at least 5*$T_1$. Following, a series of gradient NOESY experiments were run with a relaxation delay of 5*$T_1$ and mixing times ($\tau_m$) of 0 ms and three others ranging from 40 ms to 250 ms such that the cross-peaks were clearly resolved. Each of the 128 F1 increments was the accumulation of 2 scans. The peak amplitudes were determined using XWinNMR software from Bruker, after the phase and baseline corrections in both dimensions. The magnetization exchange rate constant ($k^*_f$ and $k^*_d$) were, at each mixing time $\tau_m$, calculated using the EXSYCalc program (Mestrelab Research). The association $k_{in}$ and dissociation $k_d$ rate constants were then obtained as: $k_f = k^*_f/\text{[basket]}$ and $k_d = k^*_d$. All quantitative NOESY experiments were repeated twice. The mean value was reported with standard deviation as an experimental error.

Procedure for 2-D $^{13}$C EXSY Experiment

A solution of basket and guest in CD$_2$Cl$_2$ (J. Young NMR tube) was cooled to 250.0 ± 0.5 K inside the NMR probe and allowed to equilibrate for 1.0 h. The $^{13}$C spin-lattice relaxation times ($T_1$) for the free and encapsulated guest molecules were determined by a standard inversion-recovery pulse sequence with a relaxation delay ($\tau_d$) of at least 5*$T_1$. 

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Following, a series of gradient NOESY experiments were run with a relaxation delay of $5*T_1$ and mixing times ($\tau_m$) of 0 ms, 350 ms, and 400 ms. Each of the 128 F1 increments was the accumulation of 28 scans. The peak amplitudes were determined using XWinNMR software from Bruker, after the phase and baseline corrections in both dimensions. The magnetization exchange rate constant ($k^*_d$) was, at each mixing time $\tau_m$, calculated using the EXSYCalc program (Mestrelab Research). The dissociation $k_{out}$ rate constant was then obtained as: $k_d = k^*_d$. The mean value was reported with standard deviation as an experimental error. The quantitative NOESY experiments were repeated twice. The association $k_{in}$ rate constant was obtained as $k_f = (k^*_d)(K)$, where K is the equilibrium constant obtained from a Van’t Hoff Plot.

Figure 70: 2-D $^{13}$C EXSY Spectrum (126 MHz, 250.0 ± 0.1 K) of a 2.6 mM solution of basket 45 containing 1.5 molar equivalents of 28 ($^{13}$CBr4, 3.9 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. Note $k^*_{out} = k^*_d$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k^*_{out}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>350 ms</td>
<td>0.130</td>
</tr>
<tr>
<td></td>
<td>0.095</td>
</tr>
<tr>
<td>400 ms</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td>0.070</td>
</tr>
</tbody>
</table>
Figure 71: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.5 mM solution of basket 45 containing 1.0 molar equivalent of 48 (C(CH$_3$)$_3$Br$_3$, 2.5 mM) in CD$_2$Cl$_2$. The concentration of “free” basket, [basket] = 0.57 mM ± 0.06 mM, was obtained by $^1$H NMR integration. The sample spectrum shown has been symmetrized for clarity. Note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{i}}$. 

<table>
<thead>
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<th>Mixing Time</th>
<th>$k^*_{\text{out}}$</th>
<th>$k^*_{\text{in}}$</th>
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</thead>
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<td>0.491</td>
<td>1.401</td>
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<tr>
<td></td>
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<td>220 ms</td>
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<td>1.424</td>
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<td></td>
<td>0.493</td>
<td>1.428</td>
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<tr>
<td>240 ms</td>
<td>0.465</td>
<td>1.404</td>
</tr>
</tbody>
</table>
Figure 72: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.5 mM solution of basket 45 containing 2.0 molar equivalents of 39 (C(CH$_3$)$_2$Br$_2$, 5.0 mM) in CD$_2$Cl$_2$. The concentration of “free” basket, [basket] = 0.83 mM ± 0.08 mM, was obtained by $^1$H NMR integration. The sample spectrum shown has been symmetrized for clarity. Note $k^*_\text{out} = k^*_\text{d}$ and $k^*_\text{in} = k^*_\text{r}$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
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<th>$k^*_\text{in}$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>3.13</td>
<td>1.126</td>
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<tr>
<td></td>
<td>3.17</td>
<td>1.126</td>
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<tr>
<td>110 ms</td>
<td>3.47</td>
<td>1.276</td>
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<tr>
<td></td>
<td>3.40</td>
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<tr>
<td>120 ms</td>
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<tr>
<td></td>
<td>3.62</td>
<td>1.361</td>
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</table>
Figure 73: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.5 mM solution of basket 45 containing 10.2 molar equivalents of 40 (C(CH$_3$)$_3$Br, 25.5 mM) in CD$_2$Cl$_2$. The concentration of “free” basket, [basket] = 0.83 mM ± 0.08 mM, was obtained by $^1$H NMR integration. The sample spectrum shown has been symmetrized for clarity. Note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{i}}$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
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<th>$k^*_{\text{in}}$</th>
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</thead>
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<tr>
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<td>15.82</td>
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<td>70 ms</td>
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<td>0.930</td>
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<tr>
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<td>15.48</td>
<td>0.950</td>
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<tr>
<td>90 ms</td>
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<tr>
<td></td>
<td>17.49</td>
<td>1.048</td>
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Figure 74: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.5 mM solution of basket 45 containing 7.0 molar equivalents of 47 (C(CH$_3$)$_4$, 17.5 mM) in CD$_2$Cl$_2$. The concentration of “free” basket, [basket] = 1.36 mM ± 0.14 mM, was obtained by $^1$H NMR integration. The sample spectrum shown has been symmetrized for clarity. Note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{f}}$. 

<table>
<thead>
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</thead>
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<td>30.42</td>
<td>1.809</td>
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<td>50 ms</td>
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<tr>
<td></td>
<td>29.79</td>
<td>1.523</td>
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<tr>
<td>60 ms</td>
<td>29.04</td>
<td>1.499</td>
</tr>
<tr>
<td></td>
<td>31.22</td>
<td>1.403</td>
</tr>
</tbody>
</table>
Figure 75: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.5 mM solution of basket 45 containing 2.75 molar equivalents of 41 (Si(CH$_3$)$_4$, 6.9 mM) in CD$_2$Cl$_2$. The concentration of “free” basket, [basket] = 1.96 mM ± 0.20 mM, was obtained by $^1$H NMR integration. The sample spectrum shown has been symmetrized for clarity. Note $k^*_\text{out} = k^*_{d}$ and $k^*_\text{in} = k^*_f$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k^*_\text{out}$</th>
<th>$k^*_\text{in}$</th>
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</thead>
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<tr>
<td>40 ms</td>
<td>15.11</td>
<td>0.930</td>
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<tr>
<td></td>
<td>15.03</td>
<td>0.928</td>
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<tr>
<td>50 ms</td>
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<td>0.929</td>
</tr>
<tr>
<td></td>
<td>14.00</td>
<td>0.929</td>
</tr>
<tr>
<td>60 ms</td>
<td>14.17</td>
<td>0.930</td>
</tr>
<tr>
<td></td>
<td>14.21</td>
<td>0.929</td>
</tr>
</tbody>
</table>
Figure 76: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 0.2 mM solution of basket 45 containing 9.9 molar equivalents of 49 (C(CH$_3$)$_2$Cl, 2.2 mM) in CD$_2$Cl$_2$. The concentration of “free” basket, [basket] = 0.11 mM ± 0.01 mM, was obtained by $^1$H NMR integration. The sample spectrum shown has been symmetrized for clarity. Note $k_{\text{out}}^* = k_{\text{d}}^*$ and $k_{\text{in}}^* = k_{\text{f}}^*$.

Van’t Hoff Analysis of Basket 45 Encapsulating $^{13}$CBr$_4$

Figure 77: A series of $^1$H NMR (left column, 500 MHz) and $^{13}$C NMR (right column, 126 MHz) spectra of a 3.40 mM solution of 45 containing 0.78 molar equivalents (2.6
mM) of $^{13}\text{CBr}_4$ in CD$_2$Cl$_2$; note two sets of signals, one set corresponding to [45$\subset$CD$_2$Cl$_2$] and another to [45$\subset^{13}\text{CBr}_4$].

![Van’t Hoff plot](image)

**Figure 78:** Van’t Hoff plot describing the temperature dependence of the natural logarithm of equilibrium constant $K$, for the encapsulation of $^{13}\text{CBr}_4$. The $^1$H NMR integration of the amide N–H signals of basket 45 ($\delta = 11.6$ and 11.3 ppm) was used to obtain the value for $K$ (see the equation below). The error bar was calculated as the 95% prediction interval.

$$K = \frac{[^{1}\text{CBr}_4]}{[1][\text{CBr}_4]}$$

$$K_{250K} = 8.5 \times 10^4 \pm 1.6 \times 10^4 \text{ M}^{-1}$$
Table 13: Activation Parameters for the Trafficking of Guests (2D EXSY NMR, CD$_2$Cl$_2$, 250.0 ± 0.1 K) in ($k_f$, $\Delta G^\ddagger_f$) and out ($k_d$, $\Delta G^\ddagger_d$) from Basket 45 and the 45A/B Interconversion ($\Delta G^\ddagger_{rac}$) as well as Thermodynamic Stabilities (250.0 ± 0.1 K) of Encapsulation Complexes obtained from 2D EXSY measurements ($\Delta G^{\circ}_{EXSY}$, $K_{EXSY}$) and the Integration of $^1$H NMR Signals ($\Delta G^{\circ}_{NMR}$, $K_{NMR}$).

<table>
<thead>
<tr>
<th></th>
<th>Neo-Pentane</th>
<th>2,2-Dibromopropane</th>
<th>1,1,1-Tribromoethane</th>
</tr>
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<tbody>
<tr>
<td>$k_f$</td>
<td>1100 ± 115 s$^{-1}$M$^{-1}$</td>
<td>1161 ± 134 s$^{-1}$M$^{-1}$</td>
<td>1525 ± 200 s$^{-1}$M$^{-1}$</td>
</tr>
<tr>
<td>$k_d$</td>
<td>30.3 ± 0.9 s$^{-1}$</td>
<td>16.2 ± 0.8 s$^{-1}$</td>
<td>3.41 ± 0.23 s$^{-1}$</td>
</tr>
<tr>
<td>$\Delta G^\ddagger_f$</td>
<td>11.03 ± 0.05 kcal/mol</td>
<td>11.00 ± 0.06 kcal/mol</td>
<td>10.87 ± 0.07 kcal/mol</td>
</tr>
<tr>
<td>$\Delta G^\ddagger_d$</td>
<td>12.81 ± 0.01 kcal/mol</td>
<td>13.12 ± 0.02 kcal/mol</td>
<td>13.89 ± 0.03 kcal/mol</td>
</tr>
<tr>
<td>$k_{rac}$</td>
<td>426 ± 85</td>
<td>244 ± 49</td>
<td>186 ± 37</td>
</tr>
<tr>
<td>$\Delta G^\ddagger_{rac}$</td>
<td>11.50 ± 0.10 kcal/mol</td>
<td>11.77 ± 0.10 kcal/mol</td>
<td>11.91 ± 0.10 kcal/mol</td>
</tr>
<tr>
<td>$K_{EXSY}$</td>
<td>36 ± 4</td>
<td>71 ± 9</td>
<td>447 ± 66</td>
</tr>
<tr>
<td>$K_{NMR}$</td>
<td>51 ± 9</td>
<td>85 ± 15</td>
<td>615 ± 107</td>
</tr>
<tr>
<td>$\Delta G^{\circ}_{EXSY}$</td>
<td>-1.77 ± 0.05 kcal/mol</td>
<td>-2.11 ± 0.06 kcal/mol</td>
<td>-3.02 ± 0.07 kcal/mol</td>
</tr>
<tr>
<td>$\Delta G^{\circ}_{NMR}$</td>
<td>-1.95 ± 0.08 kcal/mol</td>
<td>-2.20 ± 0.09 kcal/mol</td>
<td>-3.18 ± 0.09 kcal/mol</td>
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<table>
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<tr>
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<th>CBr$_4$</th>
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<tr>
<td>$k_f$</td>
<td>8500 ± 3010 s$^{-1}$M$^{-1}$</td>
<td>1525 ± 200 s$^{-1}$M$^{-1}$</td>
<td></td>
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<tr>
<td>$k_d$</td>
<td>0.10 ± 0.03 s$^{-1}$</td>
<td>3.41 ± 0.23 s$^{-1}$</td>
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</tr>
<tr>
<td>$\Delta G^\ddagger_f$</td>
<td>10.02 ± 0.18 kcal/mol</td>
<td>10.04 ± 0.05 kcal/mol</td>
<td></td>
</tr>
<tr>
<td>$\Delta G^\ddagger_d$</td>
<td>15.63 ± 0.15 kcal/mol</td>
<td>12.95 ± 0.02 kcal/mol</td>
<td></td>
</tr>
<tr>
<td>$k_{rac}$</td>
<td>50 ± 10</td>
<td>12.56 ± 0.10 kcal/mol</td>
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</tr>
<tr>
<td>$\Delta G^\ddagger_{rac}$</td>
<td>12.56 ± 0.10 kcal/mol</td>
<td>11.6 ± 0.1 kcal/mol</td>
<td></td>
</tr>
<tr>
<td>$K_{Van't Hoff Plot}$</td>
<td>8.5 x10$^4$ ± 1.6 x10$^4$ M$^{-1}$</td>
<td>321 ± 64</td>
<td></td>
</tr>
<tr>
<td>$\Delta G^{\circ}_{Van't Hoff Plot}$</td>
<td>-5.6 ± 0.1 kcal/mol</td>
<td>11.6 ± 0.1 kcal/mol</td>
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</table>

<table>
<thead>
<tr>
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<th>Tetramethylsilane</th>
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<tr>
<td>$k_f$</td>
<td>480 ± 48 s$^{-1}$M$^{-1}$</td>
<td>8040 ± 873 s$^{-1}$M$^{-1}$</td>
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<tr>
<td>$k_d$</td>
<td>14.4 ± 0.5 s$^{-1}$</td>
<td>22.8 ± 0.8 s$^{-1}$</td>
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<tr>
<td>$\Delta G^\ddagger_f$</td>
<td>11.44 ± 0.05 kcal/mol</td>
<td>10.04 ± 0.05 kcal/mol</td>
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<td>$\Delta G^\ddagger_d$</td>
<td>13.17 ± 0.02 kcal/mol</td>
<td>12.95 ± 0.02 kcal/mol</td>
</tr>
<tr>
<td>$k_{rac}$</td>
<td>59 ± 12</td>
<td>321 ± 64</td>
</tr>
<tr>
<td>$\Delta G^\ddagger_{rac}$</td>
<td>12.5 ± 0.1 kcal/mol</td>
<td>11.6 ± 0.1 kcal/mol</td>
</tr>
<tr>
<td>$K_{EXSY}$</td>
<td>33 ± 4</td>
<td>353 ± 40</td>
</tr>
<tr>
<td>$K_{NMR}$</td>
<td>45 ± 6</td>
<td>428 ± 74</td>
</tr>
<tr>
<td>$\Delta G^{\circ}_{EXSY}$</td>
<td>-1.73 ± 0.06 kcal/mol</td>
<td>-2.90 ± 0.06 kcal/mol</td>
</tr>
<tr>
<td>$\Delta G^{\circ}_{NMR}$</td>
<td>-1.88 ± 0.07 kcal/mol</td>
<td>-3.00 ± 0.09 kcal/mol</td>
</tr>
</tbody>
</table>
**Rate Law Analysis**

Here is our rate law analysis: A. From the EXSY measurement \( \text{rate low}_{\text{forward}} = k^* \cdot \text{[C(CH}_3\text{Br}_3]} \) so if we assume \( \text{rate low}_{\text{forward}} = k_f \cdot \text{[C(CH}_3\text{Br}_3]} \) [1] (equation A1) then \( k^* = k_f \) [1] (equation A2); (B) From the EXSY measurement \( \text{rate low}_{\text{backward}} = k^* \cdot \text{[1-C(CH}_3\text{Br}_3]} \) so if assume \( \text{rate low}_{\text{backward}} = k_d \cdot \text{[1-C(CH}_3\text{Br}_3]} \) (equation A1) then \( k^* = k_d \) (equation A3).

We varied the concentration of guest 48 (C(CH$_3$)Br$_3$) and measured the rates (EXSY) for it entering and departing basket 45. The magnetization rate constant \( k^*_{\text{d}} \) was found to be independent on any concentration. The magnetization rate constant \( k^*_{\text{f}} \) was, however, found to be a linear function of the concentration of 45. Accordingly, the data fits the kinetic model with the forward reaction being first and the backward zeroth order in the guest (see equation A1)

\[
\begin{align*}
45 + \text{C(CH}_3\text{Br}_3} & \quad \xleftrightarrow{\text{k}^*_{\text{f}}} \quad 45 \cdot \text{C(CH}_3\text{Br}_3} \\
\text{k}^*_{\text{f}} & = k_f[45] \\
\text{k}^*_{\text{d}} & = k_d
\end{align*}
\]

(A1) (A2) (A3)

**Table 14:** Equilibrium concentrations of 45, C(CH$_3$)Br$_3$, [45$\rightleftharpoons$C(CH$_3$)Br$_3$] and magnetization exchange rate constants obtained from $^1$H NMR integration and 2-D $^1$H EXSY spectroscopic measurements, respectively (400 MHz, 250 ± 0.1 K).

<table>
<thead>
<tr>
<th>Sample</th>
<th>$[\text{C(CH}_3\text{Br}_3] \cdot 48$</th>
<th>$[45$]</th>
<th>$[45$ $\cdot$ C(CH$_3$)Br$_3$]</th>
<th>$k^* \cdot$ f</th>
<th>$k^* \cdot$ d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.29 ± 0.03 mM</td>
<td>0.66 ± 0.07 mM</td>
<td>0.73 ± 0.07 mM</td>
<td>1.90 ± 0.06 s$^{-1}$</td>
<td>0.58 ± 0.01 s$^{-1}$</td>
</tr>
<tr>
<td>2</td>
<td>0.65 ± 0.07 mM</td>
<td>0.57 ± 0.06 mM</td>
<td>1.94 ± 0.19 mM</td>
<td>1.63 ± 0.01 s$^{-1}$</td>
<td>0.56 ± 0.01 s$^{-1}$</td>
</tr>
<tr>
<td>3</td>
<td>0.58 ± 0.06 mM</td>
<td>0.43 ± 0.04 mM</td>
<td>0.96 ± 0.10 mM</td>
<td>1.33 ± 0.05 s$^{-1}$</td>
<td>0.56 ± 0.01 s$^{-1}$</td>
</tr>
</tbody>
</table>
Figure 79: The magnetization rate constant \( k^* \) as a function of the concentration of 45. Note that the fitted curve has a slope, which in accord with the equation A2 above, is equivalent to \( k_f \). The intercept of 0.27 is close to 0.

\[^1\text{H} \text{NMR Line-Shape Analysis of the A/B Interconversion}\]

First-order rate constants \( k_A \) and \( k_B \), for the A/B interconversion of 45 (Figure 28) were obtained by simulating the line-shapes of diastereotopic H\(_{de}\) signals at various temperatures (WINDNMR-Pro\(^53\)) in the presence of guest molecules in excess. First-order rate constant \( k_{\text{rac}} \) was, for each system, calculated from Eyring plot (250 K). The reported error margin of 20% was obtained from four independent measurements.
227.5 ± 0.1 K
234.0 ± 0.1 K
238.5 ± 0.1 K
241.2 ± 0.1 K
244.0 ± 0.1 K
246.8 ± 0.1 K
249.5 ± 0.1 K
252.3 ± 0.1 K
Figure 80: Simulated (WinDNMR-Pro)\textsuperscript{53} and experimental $^1$H NMR (400 MHz) resonances for the H\textsubscript{d/e} protons in 45 (2.5 mM) in CD\textsubscript{2}Cl\textsubscript{2} containing 53.0 molar equivalents of CBr\textsubscript{4} (133 mM); please note that $k_{AB} = k_{\text{rac}}$. 

$255.0 \pm 0.1 \text{ K}$  

$257.8 \pm 0.1 \text{ K}$  

$260.5 \pm 0.1 \text{ K}$  

$263.3 \pm 0.1 \text{ K}$  

$266.0 \pm 0.1 \text{ K}$  

$268.8 \pm 0.1 \text{ K}$
$k_{\text{rac,250K}} = 50 \pm 10 \text{ s}^{-1}$

Figure 81: Eyring plot describing the temperature dependence of $k_{\text{rac}}$ of a 2.5 mM solution of 45 containing 53.0 molar equivalents of CBr$_4$ (133 mM) in CD$_2$Cl$_2$. Please note $k_b = k_{\text{rac}}$. 
$k_{\text{fac,250K}} = 87 \pm 17 \text{ s}^{-1}$

Figure 82: Eyring plot describing the temperature dependence of $k_{\text{fac}}$ of a 2.5 mM solution of 45 containing 120.0 molar equivalents of C(CH$_3$)Br$_3$ (300 mM) in CD$_2$Cl$_2$. Please note $k_b = k_{\text{fac}}$. 


$k_{\text{rac,250K}} = 186 \pm 37 \text{ s}^{-1}$

Figure 83: Eyring plot describing the temperature dependence of $k_{\text{rac}}$ of a 2.5 mM solution of 45 containing 60.0 molar equivalents of C(CH$_3$)$_2$Br$_2$ (150 mM) in CD$_2$Cl$_2$. Please note $k_b = k_{\text{rac}}$
\( k_{\text{rac,}250\text{K}} = 244 \pm 49 \text{ s}^{-1} \)

Figure 84: Eyring plot describing the temperature dependence of \( k_{\text{rac}} \) of a 2.14 mM solution of 45 containing 150.0 molar equivalents of C(CH\(_3\))\(_3\)Br (231 mM) in CD\(_2\)Cl\(_2\). Please note \( k_b = k_{\text{rac}} \)
Figure 85: Eyring plot describing the temperature dependence of $k_{\text{rac}}$ of a 1.6 mM solution of 45 containing 275.0 molar equivalents of $\text{C(CH}_3\text{)}_4$ (440 mM) in CD$_2$Cl$_2$. Please note $k_b = k_{\text{rac}}$

$k_{\text{rac,250K}} = 426 \pm 85 \text{ s}^{-1}$
$k_{\text{rac,250K}} = 321 \pm 64 \text{ s}^{-1}$

Figure 86: Eyring plot describing the temperature dependence of $k_{\text{rac}}$ of a 1.4 mM solution of 45 containing 180.0 molar equivalents of C(CH$_3$)$_3$Cl$_3$ (252 mM) in CD$_2$Cl$_2$. Please note $k_b = k_{\text{rac}}$
Figure 87: Eyring plot describing the temperature dependence of $k_{\text{rac}}$ of a 1.4 mM solution of 45 containing 200.0 molar equivalents of Si(CH$_3$)$_4$ (280 mM) in CD$_2$Cl$_2$. Please note $k_b = k_{\text{rac}}$.

$$k_{\text{rac,250K}} = 59 \pm 12 \text{ s}^{-1}$$

Figure 88: Eyring plot describing the temperature dependence of $k_{\text{rac}}$ of a 1.5 mM solution of 45 in CD$_2$Cl$_2$.

$$k_{\text{rac,250K}} = 4.85 \cdot 10^4 \text{ s}^{-1}$$
A.3 Supplementary Data for Chapter 3.4

Sample Preparation for 2-D EXSY Experiments

All NMR solutions and standards were prepared under nitrogen in a glove box. All NMR samples were prepared in J. Young NMR tubes purchased from Norell. CD$_2$Cl$_2$ was degassed using the freeze-thaw method and stored under nitrogen in a glove box.

Procedure for 2-D $^1$H EXSY Experiment

A solution of basket and guest in CD$_2$Cl$_2$ (J. Young NMR tube) was cooled to 250.0 ± 0.1 K inside the NMR probe and allowed to equilibrate for 1.0 h. The $^1$H spin-lattice relaxation times ($T_1$) for the free and encapsulated guest molecules were determined by a standard inversion-recovery pulse sequence with a relaxation delay ($\tau_d$) of at least 5*T$_1$. Following, a series of gradient NOESY experiments were run with a relaxation delay of 5*T$_1$ and mixing times ($\tau_m$) of 0 ms and three others ranging from 40 ms to 250 ms such that the cross-peaks were clearly resolved. Each of the 128 F1 increments was the accumulation of at least 2 scans. The corresponding integrals were determined using MestReNova software from Mestrelab Research, after the phase and baseline corrections in both dimensions. The magnetization exchange rate constants ($k^*_f$ and $k^*_d$) were, at each mixing time $\tau_m$, calculated using the EXSYCalc program (Mestrelab Research).\textsuperscript{104} The association $k_f$ and dissociation $k_d$ rate constants were then obtained as: $k_f = k^*_f/[\text{bask}et]$ and $k_d = k^*_d$. All quantitative NOESY experiments were repeated twice. The mean value was reported with standard deviation as an experimental error.
Procedure for $^{13}$C EXSY Experiment

A solution of basket and guest in CD$_2$Cl$_2$ (J. Young NMR tube) was cooled to 250.0 ± 0.5 K inside the NMR probe and allowed to equilibrate for 1.0 h. The $^{13}$C spin-lattice relaxation times ($T_1$) for the free and encapsulated guest molecules were determined by a standard inversion-recovery pulse sequence with a relaxation delay ($\tau_d$) of at least 5*$T_1$. Following, a series of gradient NOESY experiments were run with a relaxation delay of 5*$T_1$ and mixing times ($\tau_m$) of 0 ms and either 350 ms or 400 ms. Each of the 128 F1 increments was the accumulation of at least 28 scans. The corresponding integrals were determined using MestReNova software from Mestrelab Research, after the phase and baseline corrections in both dimensions. The magnetization exchange rate constant ($k_{*d}$) was, at each mixing time $\tau_m$, calculated using the EXSYCalc program (Mestrelab Research).$^{104}$ The dissociation $k_d$ rate constant was then obtained as: $k_d = k_{*d}$. The mean value was reported with standard deviation as an experimental error. The quantitative NOESY experiments were repeated twice. The association $k_{in}$ rate constant was obtained as $k_{in} = (k_{*d})(K)$, where K is the equilibrium constant obtained from a Van’t Hoff Plot.

Procedure for $^1$H Selective Inversion-Recovery Experiment

A solution of basket and guest in CD$_2$Cl$_2$ (J. Young NMR tube) was cooled to 250.0 ± 0.1 K inside the NMR probe and allowed to equilibrate for 1.0 h. The $^1$H spin-lattice relaxation times ($T_1$) for the free and encapsulated guest molecules were determined by a standard inversion-recovery pulse sequence with a relaxation delay ($\tau_d$) of at least 5*$T_1$. 

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Using a selective 1D inversion-recovery pulse sequence \([\tau_d - 180^\circ \text{(selective)} - \tau_m - 90^\circ \text{(nonselective)}]\), 32 transients is obtained for each mixing time \((\tau_m)\) with a relaxation delay \((\tau_d)\) of at least \(5*T_1\). The absolute integrals corresponding to encapsulated and free guest molecules were, at each mixing time, determined using TopSpin software from Bruker and the resulting data was fitted using the two-site exchange equations described by Led et al\(^{77}\) to obtain magnetization exchange rate constants \(k^*_f\) and \(k^*_d\). The association \(k_f\) and dissociation \(k_d\) rate constants were then obtained as: \(k_f = k^*_f/[\text{basket}]\) and \(k_d = k^*_d\).

**Rate Constant Tables**

Guests:

<table>
<thead>
<tr>
<th>Guest</th>
<th>28 – CBr(_4)</th>
<th>48 – CBr(_3)CH(_3)</th>
<th>39 – CBr(_2)(CH(_3))(_2)</th>
<th>40 – CBr(CH(_3))(_3)</th>
<th>47 – C(CH(_3))(_4)</th>
<th>49 – CCl(_3)(CH(_3))</th>
<th>41 – Si(CH(_3))(_4)</th>
<th>50 – CBr(_2)Cl(CH(_3))</th>
</tr>
</thead>
</table>

Table 15: Rate constants \(k_f\) and \(k_d\) measured for guests in basket 46 at 250.0 K in CD\(_2\)Cl\(_2\) and the corresponding association constants obtained by NMR \((K_{NMR})\) or by \(k_f/k_d\).

<table>
<thead>
<tr>
<th>Guest</th>
<th>48</th>
<th>39</th>
<th>40</th>
<th>47</th>
<th>49</th>
<th>41</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_f) (s(^{-1})M(^{-1}))</td>
<td>116 ± 19</td>
<td>109 ± 19</td>
<td>69.8 ± 7.9</td>
<td>85 ± 14</td>
<td>102 ± 12</td>
<td>38.4 ± 4.5</td>
<td>124 ± 25</td>
</tr>
<tr>
<td>(k_d) (s(^{-1}))</td>
<td>0.024 ± 0.003</td>
<td>0.27 ± 0.03</td>
<td>1.42 ± 0.07</td>
<td>5.39 ± 0.37</td>
<td>1.23 ± 0.31</td>
<td>4.60 ± 0.30</td>
<td>0.11 ± 0.02</td>
</tr>
<tr>
<td>(K_{NMR}) (M(^{-1}))</td>
<td>4.85 ± 0.49 x 10(^3)</td>
<td>397 ± 69</td>
<td>51 ± 9</td>
<td>14.3 ± 2.5</td>
<td>84 ± 15</td>
<td>13.2 ± 2.3</td>
<td>1125 ± 96</td>
</tr>
<tr>
<td>(k_f/k_d) (M(^{-1}))</td>
<td>4.85 ± 0.49 x 10(^3)</td>
<td>403 ± 71</td>
<td>49 ± 6</td>
<td>15.8 ± 2.9</td>
<td>83 ± 23</td>
<td>8.3 ± 1.1</td>
<td>1125 ± 96</td>
</tr>
</tbody>
</table>
Table 16: Rate constants $k_f$ and $k_d$ measured for guests in basket 45 at 250.0 K in CD$_2$Cl$_2$ and the corresponding association constants obtained by NMR ($K_{NMR}$) or by $k_f/k_d$.

<table>
<thead>
<tr>
<th>Guest</th>
<th>28</th>
<th>48</th>
<th>39</th>
<th>40</th>
<th>47</th>
<th>49</th>
<th>41</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_f$</td>
<td>7609 ± 2240</td>
<td>2460 ± 251</td>
<td>1525 ± 200</td>
<td>1161 ± 134</td>
<td>1100 ± 115</td>
<td>2381 ± 239</td>
<td>494 ± 50</td>
<td>3438 ± 354</td>
</tr>
<tr>
<td>$k_d$</td>
<td>0.09 ± 0.02</td>
<td>0.48 ± 0.01</td>
<td>3.41 ± 0.23</td>
<td>16.2 ± 0.8</td>
<td>30.3 ± 0.9</td>
<td>18.1 ± 0.1</td>
<td>12.5 ± 0.2</td>
<td>1.58 ± 0.10</td>
</tr>
<tr>
<td>$K_{NMR}$</td>
<td>8.5 ± 1.6 x 10^4</td>
<td>5277 ± 914</td>
<td>615 ± 107</td>
<td>85 ± 15</td>
<td>51 ± 9</td>
<td>133 ± 23</td>
<td>43 ± 7</td>
<td>2541 ± 440</td>
</tr>
<tr>
<td>$k_f/k_d$</td>
<td>8.5 ± 1.6 x 10^4</td>
<td>5125 ± 534</td>
<td>447 ± 66</td>
<td>71 ± 9</td>
<td>36 ± 4</td>
<td>131 ± 13</td>
<td>39 ± 4</td>
<td>2176 ± 263</td>
</tr>
</tbody>
</table>

Table 17: Rate constants $k_f$ and $k_d$ measured for guests in basket 27 at 250.0 K in CD$_2$Cl$_2$ and the corresponding association constants obtained by NMR ($K_{NMR}$) or by $k_f/k_d$.

<table>
<thead>
<tr>
<th>Guest</th>
<th>28</th>
<th>48</th>
<th>39</th>
<th>40</th>
<th>47</th>
<th>49</th>
<th>41</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_f$</td>
<td>4.4 ± 1.8 x 10^4</td>
<td>1.74 ± 0.21 x 10^4</td>
<td>1.42 ± 0.21 x 10^4</td>
<td>5393 ± 748</td>
<td>1.68 ± 0.32 x 10^4</td>
<td>2376 ± 285</td>
<td>11610 ± 1234</td>
<td></td>
</tr>
<tr>
<td>$k_d$</td>
<td>0.40 ± 0.13</td>
<td>2.44 ± 0.12</td>
<td>17.9 ± 0.07</td>
<td>69 ± 6.6</td>
<td>173 ± 13</td>
<td>74.5 ± 5.5</td>
<td>7.04 ± 0.29</td>
<td></td>
</tr>
<tr>
<td>$K_{NMR}$</td>
<td>1.1 ± 0.3 x 10^5</td>
<td>8784 ± 1521</td>
<td>605 ± 105</td>
<td>78 ± 14</td>
<td>97 ± 17</td>
<td>34.1 ± 5.9</td>
<td>2419 ± 419</td>
<td></td>
</tr>
<tr>
<td>$k_f/k_d$</td>
<td>1.1 ± 0.3 x 10^5</td>
<td>7146 ± 923</td>
<td>795 ± 149</td>
<td>78 ± 13</td>
<td>97 ± 17</td>
<td>31.9 ± 4.5</td>
<td>1649 ± 188</td>
<td></td>
</tr>
</tbody>
</table>

**Experimental Data: Molecular Basket 46 (R = CF$_3$)**

Guests 39, 40, 47, and 49: Rate constants $k_f$ and $k_d$ were obtained through a 2-D EXSY experiment at 250.0 K as outlined in page 176.

Guest 41: Rate constants $k_f$ and $k_d$ were obtained through an 1-D selective inversion-recovery experiment at 250.0 K as outlined in page 176.

Guests 48 and 50: The exchange at 250.0 K was found to be too slow to be quantified by NMR. Thus, the 2-D EXSY experiment outlined in page 176 was performed at 266.0,
271.0, and 276.0 K and $k^*_{d, 250K}$ was obtained by extrapolation of an Eyring Plot. The association rate constant, $k_f$, was obtained as $k_f = (k^*_d)(K)$, where $K$ is the equilibrium constant obtained from a Van’t Hoff Plot.

Figure 89: 2-D $^1$H EXSY Spectrum (400 MHz, 266.0 ± 0.1 K) of a 0.60 mM solution of basket 46 containing 0.83 molar equivalents of 48 (C(CH$_3$)$_3$Br$_3$, 0.50 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. Please note $k^*_{out} = k^*_d$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k^*_{out}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 ms</td>
<td>0.184, 0.435</td>
</tr>
<tr>
<td>325 ms</td>
<td>0.275, 0.225</td>
</tr>
<tr>
<td>350 ms</td>
<td>0.260, 0.185</td>
</tr>
</tbody>
</table>
Figure 90: 2-D $^1$H EXSY Spectrum (400 MHz, 271.0 ± 0.1 K) of a 0.60 mM solution of basket 46 containing 0.83 molar equivalents of 48 (C(CH$_3$)$_3$Br, 0.50 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. Please note $k^*_\text{out} = k^*_\text{d}$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k^*_\text{out}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 ms</td>
<td>0.479</td>
</tr>
<tr>
<td></td>
<td>0.470</td>
</tr>
<tr>
<td>225 ms</td>
<td>0.490</td>
</tr>
<tr>
<td></td>
<td>0.441</td>
</tr>
<tr>
<td>250 ms</td>
<td>0.478</td>
</tr>
<tr>
<td></td>
<td>0.413</td>
</tr>
</tbody>
</table>
Figure 91: 2-D $^1$H EXSY Spectrum (400 MHz, 276.0 ± 0.1 K) of a 0.60 mM solution of basket 46 containing 0.83 molar equivalents of 48 (C(CH$_3$)$_3$Br, 0.50 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. Please note $k^*_{\text{out}} = k^*_{\text{d}}$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k^*_{\text{out}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 ms</td>
<td>0.771</td>
</tr>
<tr>
<td></td>
<td>0.882</td>
</tr>
<tr>
<td>225 ms</td>
<td>0.970</td>
</tr>
<tr>
<td></td>
<td>0.967</td>
</tr>
<tr>
<td>250 ms</td>
<td>1.041</td>
</tr>
<tr>
<td></td>
<td>0.973</td>
</tr>
</tbody>
</table>
Figure 92: Eyring plot describing the temperature dependence of $k_d$ of a 0.60 mM solution of 46 containing 0.83 molar equivalents of 48 (C(CH$_3$)$_3$Br$_3$, 0.50 mM) in CD$_2$Cl$_2$.

$k_{d,250K} = 0.024 \pm 0.003$ s$^{-1}$
Figure 93: A series of $^1$H NMR Spectra (400 MHz) of a 0.60 mM solution of basket 46 containing 0.83 molar equivalents of 48 (C(CH$_3$)Br$_3$, 0.50 mM) in CD$_2$Cl$_2$.

$$K_{250K} = 4.85 \pm 0.49 \times 10^3 \text{ M}^{-1}$$
Figure 94: Van’t Hoff plot describing the temperature dependence of the natural logarithm of equilibrium constant $K$, for the encapsulation of 48 in basket 46. The $^1$H NMR integration of the amide NH signals of basket 1 ($\delta = 12.7$ and 12.5 ppm) was used to obtain the value for $K$.

![Van’t Hoff plot](image)

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k^*_{\text{out}}$</th>
<th>$k^*_{\text{in}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 ms</td>
<td>0.275</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>0.224</td>
<td>0.030</td>
</tr>
<tr>
<td>250 ms</td>
<td>0.299</td>
<td>0.040</td>
</tr>
<tr>
<td></td>
<td>0.278</td>
<td>0.037</td>
</tr>
<tr>
<td>300 ms</td>
<td>0.250</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>0.264</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Figure 95: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 0.60 mM solution of basket 46 containing 4.05 molar equivalents of 39 (C(CH$_3$)$_2$Br$_2$, 2.43 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.32 ± 0.03 mM by NMR integration. Please note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{f}}$. 
Figure 96: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 0.60 mM solution of basket 46 containing 7.50 molar equivalents of 40 (C(CH$_3$)$_3$Br, 4.5 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.45 ± 0.05 mM by NMR integration. Please note $k_{\text{out}}^* = k_{\text{d}}^*$ and $k_{\text{in}}^* = k_{\text{f}}^*$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k_{\text{out}}^*$</th>
<th>$k_{\text{in}}^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 ms</td>
<td>1.507</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>1.386</td>
<td>0.031</td>
</tr>
<tr>
<td>250 ms</td>
<td>1.380</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>1.374</td>
<td>0.030</td>
</tr>
<tr>
<td>300 ms</td>
<td>1.371</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>1.531</td>
<td>0.034</td>
</tr>
</tbody>
</table>
Figure 97: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 0.60 mM solution of basket 46 containing 15.9 molar equivalents of 47 (C(CH$_3$)$_4$, 9.54 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.53 ± 0.05 mM by NMR integration. Please note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{f}}$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k^*_{\text{out}}$</th>
<th>$k^*_{\text{in}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 ms</td>
<td>6.013</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>5.498</td>
<td>0.046</td>
</tr>
<tr>
<td>170 ms</td>
<td>4.978</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>4.967</td>
<td>0.042</td>
</tr>
<tr>
<td>190 ms</td>
<td>5.352</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td>5.298</td>
<td>0.044</td>
</tr>
</tbody>
</table>
Figure 98: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 0.60 mM solution of basket 46 containing 7.8 molar equivalents of 49 (C(CH$_3$)$_3$Cl, 4.7 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.38 ± 0.04 mM by NMR integration. Please note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{f}}$.

$k^*_{\text{f}} = 0.0179 ± 0.0011 \text{ s}^{-1}$ \hspace{1cm} $k^*_{\text{d}} = 4.60 ± 0.30 \text{ s}^{-1}$
Figure 99: Experimental $^1$H selective inversion-recovery NMR (400 MHz, 250 K) data and the corresponding fittings for free (left) and encapsulated (right) 41 (Si(CH$_3$)$_4$) in a 0.56 mM solution of 46 containing 29.43 molar equivalents of 10 (16.5 mM) in CD$_2$Cl$_2$. The concentration of free basket, [basket], was determined to be 0.46 ± 0.05 mM by NMR integration.

Figure 100: 2-D $^1$H EXSY Spectrum (400 MHz, 266.0 ± 0.1 K) of a 0.56 mM solution of basket 46 containing 1.18 molar equivalents of 50 (C(CH$_3$)Br$_2$Cl, 0.66 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. Please note $k^*_\text{out} = k^*_\text{d}$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k^*_\text{out}$</th>
<th>$k^*_\text{d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 ms</td>
<td>0.737</td>
<td>1.036</td>
</tr>
<tr>
<td>350 ms</td>
<td>1.018</td>
<td>0.863</td>
</tr>
<tr>
<td>400 ms</td>
<td>1.307</td>
<td>1.037</td>
</tr>
</tbody>
</table>
Figure 101: 2-D $^1$H EXSY Spectrum (400 MHz, 271.0 ± 0.1 K) of a 0.56 mM solution of basket 46 containing 1.18 molar equivalents of 50 (C(CH$_3$)Br$_2$Cl, 0.66 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. Please note $k^*_{out} = k^*_d$. 
Figure 102: 2-D $^1$H EXSY Spectrum (400 MHz, 276.0 ± 0.1 K) of a 0.56 mM solution of basket 46 containing 1.18 molar equivalents of 50 (C(CH$_3$)Br$_2$Cl, 0.66 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. Please note $k_{out}^* = k_{d}^*$. 

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>$k_{out}^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 ms</td>
<td>3.436</td>
</tr>
<tr>
<td></td>
<td>3.690</td>
</tr>
<tr>
<td>100 ms</td>
<td>3.405</td>
</tr>
<tr>
<td></td>
<td>3.443</td>
</tr>
<tr>
<td>125 ms</td>
<td>3.378</td>
</tr>
<tr>
<td></td>
<td>3.526</td>
</tr>
</tbody>
</table>
$k_{d,250K} = 0.11 \pm 0.02 \text{ s}^{-1}$

Figure 103: Eyring plot describing the temperature dependence of $k_d$ of a 0.56 mM solution of 46 containing 1.18 molar equivalents of 50 (C(CH$_3$)Br$_2$Cl, 0.66 mM) in CD$_2$Cl$_2$. 
Figure 104: A series of $^1$H NMR Spectra (400 MHz) of a 0.56 mM solution of basket 46 containing 1.18 molar equivalents of 50 \( \text{(C(CH}_3\text{)Br}_2\text{Cl}, 0.50 \text{ mM)} \) in CD$_2$Cl$_2$.

\[ K_{250K} = 1.13 \pm 0.10 \times 10^3 \text{ M}^{-1} \]
Figure 105: Van’t Hoff plot describing the temperature dependence of the natural logarithm of equilibrium constant $K$, for the encapsulation of 50 in basket 46. The $^1$H NMR integration of the amide NH signals of basket 1 ($\delta = 12.7$ and 12.5 ppm) was used to obtain the value for $K$.

**Experimental Data: Molecular Basket 45 ($R = Ph$)**

Guests 28, 48, 39, 40, 47, 49, 41, and 50: Rate constants $k_f$ and $k_d$ were obtained through a 2-D EXSY experiment at 250.0 K as outlined in page 176.

![2-D EXSY Spectrum](image)

Table: 1H EXSY Values for guests

<table>
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<th>$k^{*}_{in}$</th>
</tr>
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</tr>
<tr>
<td>400 ms</td>
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<td>0.095</td>
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Figure 106: 2-D $^{13}$C EXSY Spectrum (126 MHz, 250.0 ± 0.1 K) of a 2.60 mM solution of basket 45 containing 1.5 molar equivalents of 28 ($^{13}$CBr$_4$, 3.9 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. Please note $k^{*}_{out} = k^{*}_{in}$.
Figure 107: A series of $^1$H NMR Spectra (400 MHz) of a 3.40 mM solution of basket 45 containing 0.78 molar equivalents of 28 ($^{13}$CBr$_4$, 2.6 mM) in CD$_2$Cl$_2$.

$K_{250K} = 8.5 \pm 1.6 \times 10^4 \text{ M}^{-1}$

Figure 108: Van’t Hoff plot describing the temperature dependence of the natural logarithm of equilibrium constant $K$, for the encapsulation of 28 in basket 45. The $^1$H
NMR integration of the amide $\tilde{\text{N}}$H signals of basket 1 ($\delta = 11.6$ and 11.3 ppm) was used to obtain the value for $K$.

![EXSY Spectrum](image)

Figure 109: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.5 mM solution of basket 45 containing 1.0 molar equivalents of 48 (CBr$_3$CH$_3$, 2.5 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.57 ± 0.06 mM by NMR integration. Please note $k^*_\text{out} = k^*_{\text{d}}$ and $k^*_\text{in} = k^*_{\text{r}}$. 

<table>
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<td>240 ms</td>
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Figure 110: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.5 mM solution of basket 45 containing 2.0 molar equivalents of 39 (CBr$_2$(CH$_3$)$_2$, 5.0 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.83 ± 0.08 mM by NMR integration. Please note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{f}}$.

<table>
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Figure 111: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.5 mM solution of basket 45 containing 10.2 molar equivalents of 40 (C(CH$_3$)$_3$Br, 25.5 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free
basket, [basket], was determined to be 0.83 ± 0.08 mM by NMR integration. Please note $k_{\text{out}}^* = k_{\text{d}}^*$ and $k_{\text{in}}^* = k_{\text{f}}^*$.

Figure 112: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.5 mM solution of basket 45 containing 7.0 molar equivalents of 47 (C(CH$_3$)$_4$, 17.5 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 1.36 ± 0.14 mM by NMR integration. Please note $k_{\text{out}}^* = k_{\text{d}}^*$ and $k_{\text{in}}^* = k_{\text{f}}^*$.
Figure 113: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 1.64 mM solution of basket 45 containing 9.68 molar equivalents of 49 (C(CH$_3$)$_3$Cl, 15.9 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.55 ± 0.06 mM by NMR integration. Please note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{r}}$. 

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<td>17.943</td>
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Figure 114: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 2.5 mM solution of basket 45 containing 2.75 molar equivalents of 41 (Si(CH$_3$)$_4$, 6.9 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 1.96 ± 0.20 mM by NMR integration. Please note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{f}}$.

Figure 115: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 1.65 mM solution of basket 45 containing 1.08 molar equivalents of 50 (C(CH$_3$)$_2$Br$_2$Cl, 1.78 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free
basket, [basket], was determined to be $0.59 \pm 0.06$ mM by NMR integration. Please note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{r}}$.

*Experimental Data: Molecular Basket 27 (R = Me)*

Guests 28, 48, 39, 40, and 50: Rate constants $k_f$ and $k_d$ were obtained through a 2-D EXSY experiment at 250.0 K as outlined in page 176.

Guest 49 and 41: Rate constants $k_f$ and $k_d$ were obtained through an 1-D selective inversion-recovery experiment at 250.0 K as outlined in page 176. For guest 49, the association rate constant, $k_f$, was obtained as $k_f = (k^*_{\text{d}})(K)$, where $K$ is the equilibrium constant obtained from a Van’t Hoff Plot.
Figure 116: 2-D $^{13}$C EXSY Spectrum (126 MHz, 250.0 ± 0.1 K) of a 2.36 mM solution of basket 27 containing 0.70 molar equivalents of 28 ($^{13}$CBr$_4$, 1.65 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. Please note $k^\text{h}_{\text{out}} = k^\text{h}_{\text{d}}$. 
Figure 117: A series of $^1$H NMR Spectra (400 MHz) of a 2.36 mM solution of basket 27 containing 0.70 molar equivalents of 28 ($^{13}$CBr$_4$, 1.65 mM) in CD$_2$Cl$_2$. 
Figure 118: Van’t Hoff plot describing the temperature dependence of the natural logarithm of equilibrium constant $K$, for the encapsulation of 28 in basket 27. The $^1$H NMR integration of the amide NH signals of basket 1 ($\delta = 11.4$ and 11.2 ppm) was used to obtain the value for $K$. 

$$K_{250K} = 1.1 \pm 0.3 \times 10^5 \text{ M}^{-1}$$
Figure 119: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 0.69 mM solution of basket 27 containing 1.19 molar equivalents of 48 (CBr$_3$CH$_3$, 0.83 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.18 ± 0.02 mM by NMR integration. Please note $k^*_{\text{out}} = k^*_{d}$ and $k^*_{\text{in}} = k^*_{f}$.

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Figure 120: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 0.69 mM solution of basket 27 containing 1.31 molar equivalents of 39 (CBr$_2$(CH$_3$)$_2$, 0.90 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.48 ± 0.05 mM by NMR integration. Please note $k^*_{\text{out}} = k^*_{d}$ and $k^*_{\text{in}} = k^*_{f}$.

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<tr>
<td>75 ms</td>
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<td>20.43</td>
<td>7.45</td>
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Figure 121: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 0.69 mM solution of basket 27 containing 4.59 molar equivalents of 40 (C(CH$_3$)$_3$Br, 3.17 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.56 ± 0.06 mM by NMR integration. Please note $k^\ast_{\text{out}} = k^\ast_d$ and $k^\ast_{\text{in}} = k^\ast_i$. 

<table>
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<tr>
<td></td>
<td>62.02</td>
<td>2.70</td>
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Figure 122: Experimental $^1$H selective inversion-recovery NMR (400 MHz, 250 K) data and the corresponding fittings for free (left) and encapsulated (right) 49 (CCl$_3$CH$_3$) in a 1.64 mM solution of 27 containing 6.65 molar equivalents of 9 (11.81 mM) in CD$_2$Cl$_2$.

$k^*_{out} = 173 \pm 13 \text{ s}^{-1}$
Figure 123: A series of $^1$H NMR Spectra (400 MHz) of a 1.64 mM solution of basket 27 containing 6.65 molar equivalents of 49 (C(CH3)Cl3, 11.81 mM) in CD$_2$Cl$_2$. 
Figure 124: Van’t Hoff plot describing the temperature dependence of the natural logarithm of equilibrium constant $K$, for the encapsulation of 49 in basket 27. The $^1$H NMR integration of the amide NH signals of basket 3 ($\delta = 11.6$ and 11.3 ppm) was used to obtain the value for $K$ (see the equation below).

$$K_{250K} = 97 \pm 17$$
\[ k_{in} = 4.55 \pm 0.30 \text{ s}^{-1} \quad k_{out} = 74.5 \pm 5.5 \text{ s}^{-1} \]

Figure 125: Experimental \(^1\)H selective inversion-recovery NMR (400 MHz, 250 K) data and the corresponding fittings for free (left) and encapsulated (right) 41 (Si(CH\(_3\))\(_4\)) in a 2.36 mM solution of 27 containing 3.05 molar equivalents of 10 (7.20 mM) in CD\(_2\)Cl\(_2\). The concentration of free basket, [basket], was determined to be 1.92 \pm 0.19 mM by NMR integration.
Figure 126: 2-D $^1$H EXSY Spectrum (400 MHz, 250.0 ± 0.1 K) of a 0.69 mM solution of basket 27 containing 0.93 molar equivalents of 50 (C(CH$_3$)Br$_2$Cl, 0.64 mM) in CD$_2$Cl$_2$. The sample spectrum shown has been symmetrized for clarity. The concentration of free basket, [basket], was determined to be 0.38 ± 0.04 mM by NMR integration. Please note $k^*_{\text{out}} = k^*_{\text{d}}$ and $k^*_{\text{in}} = k^*_{\text{r}}$.

$^1$H NMR Line-Shape Analysis of the A/B Interconversion

First-order rate constants $k_A$ and $k_B$, for the A/B interconversion of baskets 46 and 45 were obtained by simulating the line-shapes of diastereotopic H$_{ef}$ signals at various temperatures (WINDNMR-Pro).$^{53}$ First-order rate constant $k_{\text{rac}} = k_A = k_B$ was, for each system, calculated from an Eyring plot (250 K).
$184.0 \pm 0.1 \, \text{K}$

$186.3 \pm 0.1 \, \text{K}$

$188.5 \pm 0.1 \, \text{K}$

$190.7 \pm 0.1 \, \text{K}$

$192.9 \pm 0.1 \, \text{K}$

$195.1 \pm 0.1 \, \text{K}$

$197.3 \pm 0.1 \, \text{K}$

$199.6 \pm 0.1 \, \text{K}$
201.8 ± 0.1 K

205.1 ± 0.1 K

Figure 127: Simulated (WinDNMR-Pro)\textsuperscript{53} and experimental $^1$H NMR (400 MHz) resonances for the H$_{ef}$ protons in 45 (2.0 mM) in CD$_2$Cl$_2$; please note that $k_{AB} = k_{rac}$.

$k_{rac,250K} \approx 2.95 \times 10^3$ s$^{-1}$

Figure 128: Eyring plot describing the temperature dependence of $k_{rac}$ of a 1.1 mM solution of 46 in CD$_2$Cl$_2$. 
Figure 129: Eyring plot describing the temperature dependence of $k_{\text{rac}}$ of a 2.0 mM solution of 45 in CD$_2$Cl$_2$.

$k_{\text{rac,250K}} \sim 4.85 \times 10^4 \text{ s}^{-1}$

A.4 Supplementary Data for Chapter 3.5

Sample Preparation for 2-D EXSY Experiments

All NMR solutions and standards were prepared under nitrogen in a glove box. All NMR samples were prepared in J. Young NMR tubes purchased from Norell. CD$_2$Cl$_2$ and C$_6$D$_5$CD$_3$ were degassed using the freeze-thaw method and stored under nitrogen in a glove box.
Procedure for 2-D $^1$H EXSY Experiment

The sample solution (J. Young NMR tube) was cooled to $188.8 \pm 0.1$ K inside the NMR probe and allowed to equilibrate for 1.0 h. The $^1$H spin-lattice relaxation times ($T_1$) for the free and encapsulated guest molecules were determined by a standard inversion-recovery pulse sequence with a relaxation delay ($\tau_d$) of at least $5*T_1$. Following, a series of gradient NOESY experiments were run with a relaxation delay of $5*T_1$ and mixing times ($\tau_m$) of 0 ms and 100 ms. Each of the 128 F1 increments was the accumulation of 2 scans. The peak integrals were determined using XWinNMR software from Bruker, after the phase and baseline corrections in both dimensions. The magnetization exchange rate constants ($k^{*}_{obs}$) between the axial and equatorial protons of cyclohexane-d$_{11}$ residing outside ($k^{*}_{outside}$) and inside ($k^{*}_{inside}$) the cavity were calculated using the EXSYCalc program (Mestrelab Research). The chair-to-chair interconversion rate constants ($k$) were calculated as $k = (2)(k^{*}_{outside})$ for cyclohexane residing outside the cavity and $k = (2)(k^{*}_{inside})$ for cyclohexane residing inside the cavity. The mean value was reported with standard deviation as an experimental error. The quantitative NOESY experiments were repeated twice.
Figure 130: 2-D $^1$H EXSY Spectrum (400 MHz, 188.8 ± 0.1 K) of a 1.4 mM solution of basket 27 containing 10.6 molar equivalents of cyclohexane-d$_{11}$ (14.8 mM) in CD$_2$Cl$_2$.

<table>
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</tr>
<tr>
<td></td>
<td>20.3</td>
<td>3.7</td>
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</table>

Figure 131: 2-D $^1$H EXSY Spectrum (400 MHz, 188.8 ± 0.1 K) of a 1.4 mM solution of basket 45 containing 10.0 molar equivalents of cyclohexane-d$_{11}$ (14.0 mM) in CD$_2$Cl$_2$.

<table>
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<th>Mixing Time</th>
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<th>$k^*$ outside</th>
</tr>
</thead>
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<td>3.5</td>
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<tr>
<td></td>
<td>21.7</td>
<td>3.9</td>
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<tr>
<td>100 ms</td>
<td>19.3</td>
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<td>20.8</td>
<td>4.0</td>
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</table>
Figure 132: 2-D $^1$H EXSY Spectrum (400 MHz, 188.8 ± 0.1 K) of a 1.1 mM solution of basket 46 containing 35.0 molar equivalents of cyclohexane-d$_{11}$ (38.5 mM) in CD$_2$Cl$_2$. 
Figure 133: 2-D $^1$H EXSY Spectrum (400 MHz, 188.8 ± 0.1 K) of a 200.1 mM solution of cyclohexane-$d_{11}$ in C$_6$D$_5$CD$_3$. Please note $k^\text{flip} = k^\text{obs}$.

Van’t Hoff Analysis of Baskets Encapsulating Cyclohexane-$d_{11}$
Figure 134: A series of 1H NMR (400 MHz) spectra of a 1.4 mM solution of basket 27 containing 10.6 molar equivalents of cyclohexane-d_{11} (14.8 mM) in CD_{2}Cl_{2}.

\[ K_{188.8K} = 313.6 \pm 29.0 \text{ M}^{-1} \]

Figure 135: Van’t Hoff plot describing the temperature dependence of the natural logarithm of equilibrium constant \( K \), for the encapsulation of cyclohexane-d_{11}. The 'H
NMR integration of the amide N-H signals of basket 27 ($\delta = 11.6$ and 11.3 ppm) was used to obtain the value for $K$. The error was calculated as the 95% prediction interval.

Figure 136: A series of 1H NMR (400 MHz) spectra of a 1.7 mM solution of basket 45 containing 10.0 molar equivalents of cyclohexane-d$_{11}$ (16.7 mM) in CD$_2$Cl$_2$. 

221
\[ K_{188.8K} = 191.4 \pm 12.6 \, \text{M}^{-1} \]

Figure 137: Van’t Hoff plot describing the temperature dependence of the natural logarithm of equilibrium constant \( K \), for the encapsulation of cyclohexane-d_{11}. The \(^1\)H NMR integration of the amide N-H signals of basket \( 45 (\delta = 11.6 \text{ and } 11.3 \, \text{ppm}) \) was used to obtain the value for \( K \). The error was calculated as the 95% prediction interval.
Figure 138: A series of $^1$H NMR (400 MHz) spectra of a 1.1 mM solution of basket 46 containing 35.0 molar equivalents of cyclohexane-$d_{11}$ (38.5 mM) in CD$_2$Cl$_2$.

$K_{188.8K} = 51.8 \pm 5.2 \text{ M}^{-1}$

Figure 139: Van’t Hoff plot describing the temperature dependence of the natural logarithm of equilibrium constant $K$, for the encapsulation of cyclohexane-$d_{11}$. The $^1$H
NMR integration of the amide N-H signals of basket 46 (δ = 11.6 and 11.3 ppm) was used to obtain the value for $K$. The error was calculated as the 95% prediction interval.

$^1{H}$ NMR Line-Shape Analysis of Cyclohexane-d$_{11}$

First order rate constants, $k$, describing the interconversion between the two chair conformers of cyclohexane-d$_{11}$ were obtained by simulating the line-shapes at various temperatures (WINDNMR-Pro) in C$_5$H$_6$CD$_3$ and CD$_2$Cl$_2$. $k$ at 188.8 K was, for each solvent, calculated from an Eyring plot.
224.5 ± 0.1 K
221.7 ± 0.1 K
218.9 ± 0.1 K
216.2 ± 0.1 K
213.4 ± 0.1 K
210.6 ± 0.1 K
207.9 ± 0.1 K
205.1 ± 0.1 K
Figure 140: Simulated (WINDNMR-Pro)\textsuperscript{53} and experimental $^1\text{H}$ NMR (400 MHz) resonances of cyclohexane-$d_{11}$ (200.1 mM) in $\text{C}_6\text{D}_5\text{CD}_3$.

$k_{\text{188.8K}} = 7.9 \pm 4.3 \text{ s}^{-1}$
Figure 141: Eyring plot describing the temperature dependence of $k$ of a 200.1 mM solution of cyclohexane-d$_{11}$ in C$_6$D$_5$CD$_3$. The reported error margins are the standard errors from the linear least-squares analysis.

238.3 ± 0.1 K

232.8 ± 0.1 K

227.2 ± 0.1 K

224.5 ± 0.1 K

221.7 ± 0.1 K

218.9 ± 0.1 K
Figure 142: Simulated (WINDNMR-Pro) and experimental $^1$H NMR (400 MHz) resonances of cyclohexane-$d_{11}$ (200.1 mM) in CD$_2$Cl$_2$. 

$216.2 \pm 0.1 \text{ K}$  
$213.4 \pm 0.1 \text{ K}$  
$210.6 \pm 0.1 \text{ K}$  
$207.9 \pm 0.1 \text{ K}$  
$205.1 \pm 0.1 \text{ K}$
Figure 143: Eyring plot describing the temperature dependence of $k$ of a 100 mM solution of cyclohexane-d$_{11}$ in CD$_2$Cl$_2$. The reported error margins are the standard errors from the linear least-squares analysis.

\[ k_{\text{flip}, 188.8K} = 6.9 \pm 2.2 \text{ s}^{-1} \]

**A.5 Supplementary Data for Chapter 4.1**

*Sample Preparation for NMR Studies Involving Cu(I)*

All NMR solutions and standards were prepared and handled under nitrogen in a glove box. All NMR samples were prepared in J. Young Valve NMR Tubes purchased from Norell. CD$_2$Cl$_2$, C$_6$D$_6$, and C$_6$D$_5$CD$_3$ were degassed using the freeze-thaw method and stored under nitrogen in a glove box.
Figure 144: $^1$H–$^1$H COSY NMR spectrum (400 MHz, 300 K) of a 1.9 mM solution (CD$_2$Cl$_2$:C$_6$D$_6$ = 2:1) of 27:Cu(I).
Figure 145: $^1$H-$^1$H NOESY NMR spectrum (400 MHz, 200 ms mixing time, 300 K) of a 1.9 mM solution ($\text{CD}_2\text{Cl}_2$:C$_6$D$_6$ = 2:1) of 27:Cu(I).
Figure 146: A selected $^1$H DOSY NMR (500 MHz, 300 ± 1 K) spectrum of a 1.9 mM solution (CD$_2$Cl$_2$:C$_6$D$_6$ = 2:1) of 27:Cu(I). The resulting mean average diffusion coefficient (average of three experiments) is shown below.
Figure 147: Low Resolution MALDI-TOF mass spectrum of 27 containing 0.75 equiv. of (CuOTf)$_2$PhMe.

Chemical Formula: $C_{63}H_{42}CuN_9O_5$
Calculated: 1134.26
Found: 1134.20
Figure 148: Variable Temperature (VT) $^1$H NMR (400 MHz) spectra of a 0.71 mM (CD$_2$Cl$_2$:C$_6$D$_5$CD$_3$ = 2:1) solution of 27.
Figure 149: The simulated (WINDNMR-Pro) and the experimental signals for the exchange of spins corresponding to $\text{H}_{\text{de}}$ nuclei in 27. The apparent first-order rate constants $k_1/k_{-1}$ are shown on the right.
Figure 150: A series of $^1\text{H}$ NMR (400 MHz, 243 K) spectra of a 2.2 mM solution of 27 (CD$_2$Cl$_2$:C$_6$D$_5$CD$_3$ = 2:1), containing 0.5 molar equivalents of (CuOTF)$_2$PhMe, 10.0 molar equivalents of CH$_3$CBr$_2$CH$_3$, and 1.5 molar equivalents of CH$_3$NC, and recorded after an addition of 18.6 molar equivalents of Na$_2$S·9H$_2$O. The heterogenous mixture was shaken in between the measurements.
Figure 151: A series of $^1$H NMR (400 MHz, 243 K) spectra of a 0.71 mM solution of 27 (CD$_2$Cl$_2$:C$_6$D$_5$CD$_3$ = 2:1) containing 1.0 molar equivalent of (CuOTF)$_2$PhMe and recorded after addition of (A) 0.0, (B) 4.0, (C) 8.0, and (D) 12.0 molar equivalents of CH$_3$CBr$_2$CH$_3$. 
Figure 152: $^1$H-$^1$H COSY NMR (400 MHz, 300 K) spectrum of a 1.0 mM solution (CD$_2$Cl$_2$) of [27=H]$^+$. 
Figure 153: $^1$H-$^1$H NOESY NMR (400 MHz, 200 ms mixing time, 300 K) spectrum of a 1.0 mM solution (CD$_2$Cl$_2$) of [27cH]$^+$. 
Figure 154: Variable Temperature (VT) $^1$H NMR (400 MHz) spectra of a 1.0 mM solution (CD$_2$Cl$_2$) of [27cH]$^+$. 
Figure 155: $^{19}$F NMR (376 MHz, 300 K, CD$_2$Cl$_2$) spectra of 1.0 mM solution of (A) [27cH]$^+$ and (B) pyridinium trifluoroacetate, both containing α,α,α-trifluorotoluene (standard). Please note [1cH]$^+$ CF$_3$CO$_2^-$ = [27cH]$^+$ CF$_3$CO$_2^-$.

Figure 156: Variable Temperature $^1$H NMR (400 MHz) spectra of a 0.7 mM solution (CD$_2$Cl$_2$) of 27 containing 1.0 molar equivalent of CH$_3$SO$_3$H (inset: the singlet corresponds to unperturbed CH$_3$ in methanesulfonate anion).
Figure 157: $^1$H-$^1$H EXSY NMR (400 MHz, 200 ms mixing time, 300 K) spectrum of 1.6 mM solution of 27 (CD$_2$Cl$_2$) containing 3.2 molar equivalents of TFA.
Figure 158: $^1$H-$^1$H NOESY NMR (400 MHz, 250 ms mixing time, 243 K) spectrum of a 0.8 mM solution of 27 containing 50 molar equivalents of CH$_3$CBr$_2$CH$_3$ and 3.5 molar equivalents of TFA.
Figure 159: A series of $^1$H NMR (400 MHz, 243 K, CD$_2$Cl$_2$) spectra of a 1.3 mM solution of 27, containing 2.2 molar equivalents of CH$_3$CBr$_2$CH$_3$ and 3.4 molar equivalents of TFA, and recorded after addition of 140 molar equivalents of K$_2$CO$_3$. The mixture was shaken in between the measurements.
Figure 160: A selected $^1$H DOSY NMR (500 MHz, 300 ± 1K) spectrum of a 2.3 mM solution (CD$_2$Cl$_2$) of 27. The resulting mean average diffusion coefficient ($D$) and the hydrodynamic radius were calculated (from three independent measurements) to be $8.7 \pm 0.6 \times 10^{-10}$ m$^2$s$^{-1}$ and $6.1 \pm 0.4$ Å, respectively.
Figure 161: A selected $^1$H DOSY NMR (500 MHz, 300 ± 1K) spectrum of a 2.3 mM solution (CD$_2$Cl$_2$) of [27H$^+$. The resulting mean average diffusion coefficient ($D$) and hydrodynamic radius were calculated (from three independent measurements) to be $8.3 \pm 0.9 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ and $6.4 \pm 0.7 \text{ Å}$, respectively.
Figure 162: A selected $^1$H DOSY NMR (500 MHz, 300 ± 1K) spectrum of a 2.3 mM solution (CD$_2$Cl$_2$) of 27 containing 3.5 molar equivalents of TFA. The resulting mean average diffusion coefficient ($D$) and hydrodynamic radius was calculated (from three independent measurements) to be $5.7 \pm 0.5 \times 10^{-10}$ m$^2$s$^{-1}$ and $9.4 \pm 0.4$ Å, respectively.