Encapsulation and Reactivity

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Molecular Recognition of a Transition State**

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Self-assembled or covalent hosts capable of enclosing space offer a confined environment for accommodating small to medium-sized molecules.[1] When the isotropic solvent shell around a molecule is substituted by the framework of the host, unique properties can arise, including the stabilization of transient intermediates[2] and catalysis of chemical reactions.[3] The research groups of Cram and Sherman[4a–c] were among the first to observe and characterize the limited rotational mobility[4d–j] of smaller molecules residing in carceplexes, and these seminal studies invoked steric interactions as a source of the retardation. Subsequently, Rebek and co-workers characterized encapsulation complexes with guests having limited translational mobility, thereby establishing the phenomenon of social isomerism and revealing new types of supramolecular chirality.[5] The conformational interconversion of encapsulated guest(s) has also been studied in artificial hosts,[4c,6,7] 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} ($\Delta\Delta G^{\neq}$) within the restrictive interior of carcerands.[4c] The chair–chair interconversion process for cyclohexane was noted to occur slower in "jelly doughnut" ($\Delta\Delta G^{\neq} \approx 0.3$ kcal mol^{-1})[6] and resorcin[4]arene ($\Delta\Delta G^{\neq} = 0.25 \pm 0.10$ kcal mol^{-1}) based cavitands.[7] 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[8] than in polar or nonpolar ($\Delta\Delta G^{\neq} \approx 1$–$3$ kcal mol^{-1}) solvents, respectively.

In light of such discoveries, we report a rather unusual case of accelerated ring flipping of cyclohexane inside newly developed hosts—gated molecular baskets.[9] We measured the kinetics of the conformational interconversion of [D_{11}]cyclohexane ($C_6D_{11}H$) by quantitative NMR spectroscopy and used electronic structure methods to identify the origin of the observed acceleration.

Gated molecular baskets (Figure 1) were designed[9] as models for examining the kinetics of molecular encapsulation.[10] These dynamic hosts comprise a bowl-shaped platform with three pyridine-based gates at its rim. The gates are transiently connected through a seam of intramolecular hydrogen bonds for controlling the in/out trafficking of guests (Figure 1). As a prelude to studies on the relationship

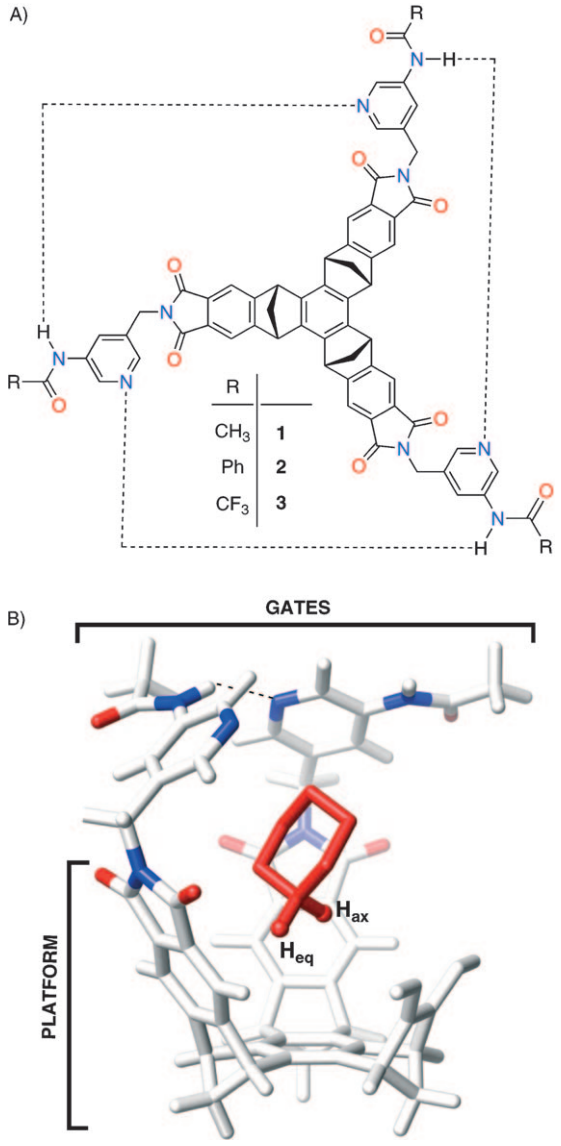

Figure 1. A) Structure of gated molecular baskets **1**–**3**. B) Energy-minimized structure of basket **1** containing cyclohexane (M06-2X/6-31G(d)). Please note that a side of the basket is omitted for clarity.

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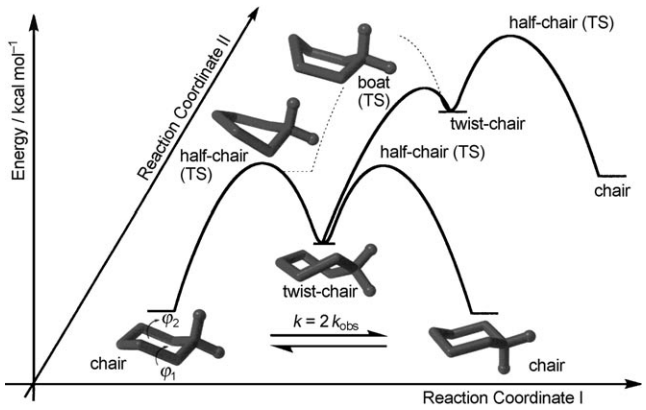

Figure 2. An energy diagram for the conformational interconversion of cyclohexane.[11b] The interconversion of ground- and transition-state conformers can be described with two degrees of freedom ϕ_1 and ϕ_2.[11a] Note that only one cycle of the pseudorotation is shown.

between the gating and reactivity, we decided to examine the conformational dynamics of a well-characterized system inside the molecular cage provided by gated baskets **1**–**3**: the chair-to-chair interconversion of cyclohexane (Figure 1). The potential energy surface (PES) for the interconversion of cyclohexane, which has been intensively studied both theoretically and computationally,[11] is described with two degrees of freedom (ϕ_1 and ϕ_2, Figure 2)[11] 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 2). 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}.[12] By using NMR spectroscopy, Anet et al. measured the interconversion of $C_6D_{11}H$ in CS_2 as a solvent and found that it occurs with an activation enthalpy ($\Delta H^{\neq}$) of (10.71 ± 0.04) kcal mol^{-1} and an activation entropy ($\Delta S^{\neq}$) of (2.2 ± 0.2) eu (Table 1).[13] Importantly, the activation energy ($\Delta G^{\neq}$) for the process is barely a function of the liquid phase (methylcyclohexane, acetone, and CS_2);[14] although the value of $\Delta G^{\neq}$ is somewhat higher in the gas phase[15] (Table 1).

There is moderate thermodynamic affinity for [D_{11}]cyclohexane occupying the interior of baskets **1**–**3**

Table 1: Activation parameters $\Delta H^{\neq}$, $\Delta S^{\neq}$, and $\Delta G^{\neq}$ (188.8 K) for the conformational interconversion of [D_{11}]cyclohexane (2D EXSY NMR, 400 MHz, CD_2Cl_2, 188.8 ± 0.1 K) inside baskets **1**–**3** in CS_2, the gas phase, CD_2Cl_2, and $C_6D_5CD_3$.

Solvent	$\Delta H^{\neq}$ [kcal mol^{-1}]	$\Delta S^{\neq}$ [eu]	$\Delta G^{\neq}$ [kcal mol^{-1}]	k [s^{-1}]
CS_2[a]	10.71 ± 0.04	2.2 ± 0.2	10.29 ± 0.06	4.7 ± 0.7
gas phase[b]	12.1 ± 0.5	5.7 ± 0.5	10.6 ± 0.5	2.1 ± 1.5
basket **1**	–	–	9.43 ± 0.03	43 ± 3
basket **2**	–	–	9.45 ± 0.02	41 ± 2
basket **3**	–	–	9.56 ± 0.04	30 ± 3
CH_2Cl_2[c]	10.2 ± 0.1	0.4 ± 0.4	10.1 ± 0.1	6.9 ± 2.2
$C_6D_5CD_3$[c]	10.3 ± 0.2	1.2 ± 0.7	10.1 ± 0.2	7.9 ± 4.3

[a] See Ref. [13]. [b] See Ref. [15]. [c] Obtained from Eyring plots and lineshape analysis of ^{1}H NMR signals (197 to 236 K).[17]

Table 2: Thermodynamic parameters $\Delta H°$, $\Delta S°$, and $\Delta G°$ for the binding of [D_{11}]cyclohexane to baskets **1**–**3** ($\Delta G°$ and K at 188.8 K) in CD_2Cl_2 obtained from variable-temperature ^{1}H NMR data (186–228 K) and van't Hoff plots.[17]

Basket (R)	$\Delta H°$ [kcal mol^{-1}]	$\Delta S°$ [eu]	$\Delta G°$ [kcal mol^{-1}]	K[a] [M^{-1}]
1 (CH_3)	-3.88 ± 0.07	-9.2 ± 0.3	-2.15 ± 0.03	314 ± 29
2 (Ph)	-3.92 ± 0.04	-10.3 ± 0.2	-1.96 ± 0.02	191 ± 13
3 (CF_3)	-3.31 ± 0.05	-9.7 ± 0.2	-1.48 ± 0.04	52 ± 5

[a] Obtained from ln$K$ versus $1/T$ linear functions at 188.8 K.[17]

(Table 2). The binding free energy $\Delta G°$ is less favorable as more electron-withdrawing R groups (EWGs) are installed at the amide position (Figure 1). 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 $\Delta G°$ values.

The rate coefficient k for [D_{11}]cyclohexane undergoing a chair flipping motion inside **1**–**3** was determined by using ^{1}H-^{1}H NMR EXSY spectroscopy[16] at (188.8 ± 0.1) K (Table 1): the first-order magnetization rate constant k^*_{obs} ($k^*_{obs} = k_{obs} = {}^1/_2\,k$) was obtained for the chemical exchange of the proton residing at the axial and the equatorial positions (Figure 3).[17] 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 3). The interconversion kinetics of [D_{11}]cyclohexane in bulk dichloromethane (CD_2Cl_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[12,13] (Table 1). On the basis of the measurements (Table 1), it was determined that the interconversion of cyclohexane occurs roughly five times faster inside baskets **1**–**3** than in the reference bulk solvents CD_2Cl_2 and $C_6D_5CD_3$. What is the origin of the acceleration?

An elevated pressure was earlier demonstrated to facilitate the interconversion of cyclohexane.[14] Originally, the

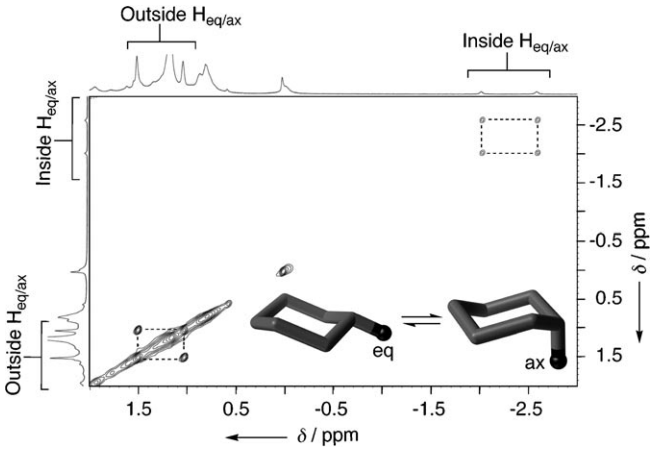

Figure 3. A 2D NMR EXSY spectrum (400 MHz, 188.8 ± 0.1 K) of a 14.0 mM solution (CD_2Cl_2) of [D_{11}]cyclohexane and basket **2** (1.40 mM). The volumes of the diagonal and cross-signals were used to extract the magnetization rate constant k^*_{obs} that characterized the conformational interconversion.[17]

stochastic model for isomerization reactions[11g,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 κ (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[11c] in the liquid phase conflicts with statistical RRKM theory, and the transmission coefficient κ 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[18] to affect the interconversion and thereby control the isomerization rate. Our computational results, 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 κ.[11b] The basket could contribute energetically in two ways: the destabilization of the chair conformer and the stabilization of the half-chair transition state (Figure 4).

The ONIOM[19a] (MP2/6-31G(d):AM1) method was employed 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. 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 (see Tables S1 and S2 in the Supporting Information).[17] Unfortunately, we were unable to evaluate the system with the MP2 level of theory because of its size.[19b] Thus, we employed density functional theory (DFT) calculations using the M06-2X functional,[22] as this method has been optimized for studying noncovalent interactions between organic molecules (see the Supporting Information). To assess the role of the basket as a host, we 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 4B). Further inspection of the interatomic distances (Figure 4A) reveal three (cyclohexane) C–H···π (basket) contacts (<2.7 Å from hydrogen to the π centroid)[21] 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 **1**. Examination of the encapsulated half-chair conformation (Figure 4C) 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 (see Table S3 in the Supporting Information). 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. Our 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 3), 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 4B) is consistent with the experimental finding ($\Delta\Delta G^{\ddagger} \approx 0.5$ kcal mol^{-1}).

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 4A). This result is in agreement with a greater difference in the chemical shift $\Delta\delta_{ax/eq}$ of the axial/equatorial protons of $C_6D_{11}H$ inside baskets **1**–**3** (227 Hz) than in bulk solvent (190 Hz, Figure 3). Moreover, the splitting pattern of the ^{1}H NMR signals of the entrapped $C_6D_{11}H$ did not alter at lower temperatures, thus suggesting a low activation barrier for this compound tumbling in the interior of **1**–**3**. The results of molecular dynamics (MD) simulations[17] are consistent with this observation, disclosing a random fluctua-

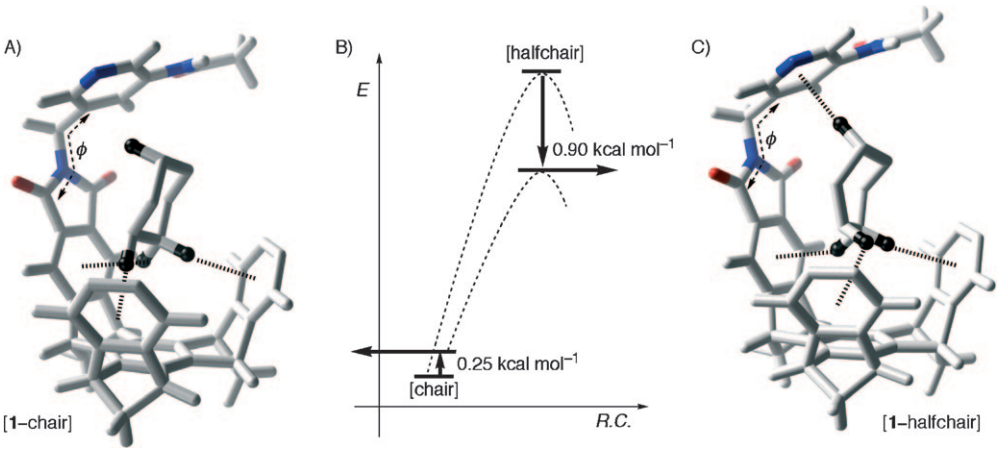

Figure 4. Energy-optimized structures of chair (left) and half-chair (right) conformers inside gated molecular basket **1** (M06-2X/6-31G(d)); note that some structural features are omitted for clarity. Host–guest C–H···π contacts and the dihedral angle ϕ ($\Delta\phi = 4.1°$) are also shown.

Table 3: 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 **1**.[a]

Conformation	Vacuum [kcal mol^{-1}]	Basket **1** [kcal mol^{-1}]
chair	0	0
half-chair	12.02	10.87
twist-boat	6.19	6.05
boat	7.51	–

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

tion of cyclohexane (111 Å^3) inside closed **1**–**3** (ca. 221 Å^3) over a period of 10 ns.

The molecular framework of gated baskets was herein shown to promote the conformational interconversion of cyclohexane by more favorable noncovalent binding, thereby stabilizing the transition state.[22] The result is in line with the Pauling paradigm explaining the proficiency of enzymes, and recent suggestions by Zhang and Houk that address a greater benefit of covalent over noncovalent catalysis.[23] Nonetheless, the incorporation of proper elements of design into artificial hosts is necessary to facilitate chemical conversions through a differential binding change, but is challenging to implement given the subtlety of weak noncovalent contacts that one needs to take into an account. For the time being, serendipitous discoveries provide us with necessary information for enhancing our understanding of the fine details pertaining to the rational design of encapsulation-based catalysts.

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