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Tuning the Rate of Molecular Translocation

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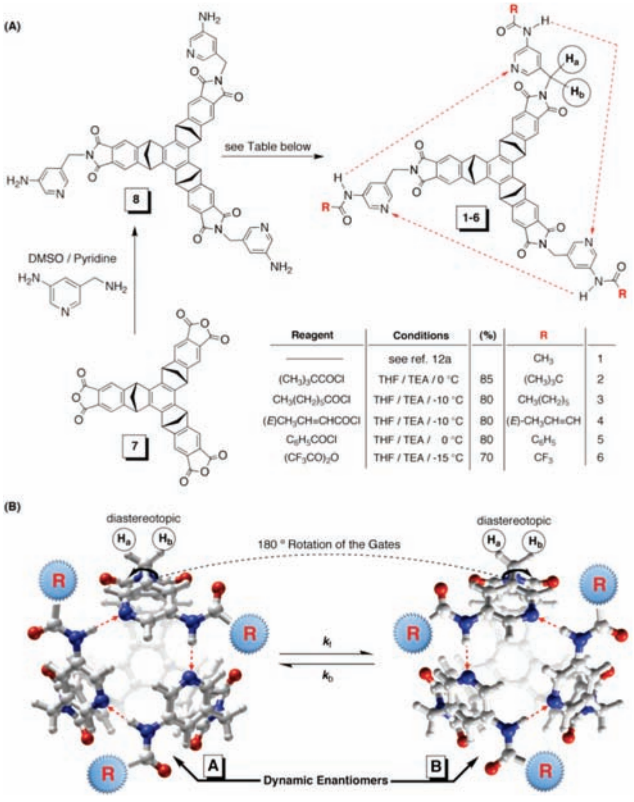
Biological molecules contain dynamic and functional interiors capable of directing chemical operations such as gating, translational/rotational movement, and covalent bond formation/cleavage.[1] These natural systems have their working components synchronized[2] and well-ordered by the hierarchical constitution.[3] Abiotic molecules/assemblies, adept at mediating encapsulation or chemical reactions,[4] are less sophisticated but nonetheless designed to operate with intricate mechanisms.[5] Self-folding cavitands[6] have, for instance, been made to entrap/release molecules via folding, and (hemi)carcerands are known to prolong the lifetime and modulate the reactivity of "fleeting" intermediates.[7] Transition metal assembled cages, additionally, facilitate chemical transformations by virtue of their discrete inner-space characteristics.[8] Alongside these accomplishments in the field, gating has been recognized[9] as an important element affecting the kinetic lability (dissociation)[10] of encapsulation complexes. Full control of the gating presents an opportunity for controlling the kinetic reactivity in abiotic hosts; however, this control still poses a challenge.[11] This study, consequently, focuses on examining the in/out rate of guest's encapsulation as a function of the dynamics of gates revolving at the rim of gated molecular baskets (Figure 1).[12] Quantitative relationships have been established to allow for predicting and controlling the time that guest molecules spend inside the basket's interior.

Molecular baskets have been designed[12a] to contain three pyridine-based gates, linked via intramolecular hydrogen bonding (HB) from *meta* amido groups, to occlude space and thus form a dynamic and gated environment (Figure 1). The "hinge" $H_{a/b}$ signals 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, **A** and **B**, each containing hydrogen bonds displayed in a clockwise or counterclockwise orientation (Figure 1B).[12,14] In fact, the **A**/**B** interconversion necessitates that each of the gates revolves 180° about the "vertical" axis. This conformational change has additionally been shown to correlate with the exchange (departure/entrance) of guest molecules.[12a] To quantitatively examine the structure−activity relationship[13] in this supramolecular environment, we chose to alter the electronic (inductive and field) and steric (bulkiness) characteristics of the R amido units (see **1**−**6**, Figure 1). The hypothesis was that the perturbation imposed by R groups would, in **1**−**6**, affect the host's conformational dynamics and thereby allow a precise and predictable fine-tuning of the guest's kinetic lability.

Six R groups were deliberately chosen and installed to give baskets **1**−**6** (Figure 1A). The syntheses proceeded via methodology whereby *tris*-anhydride **7** was reacted with 5-(aminomethyl)pyridin-3-amine to yield modular *tris*-amine **8**.[14] Subsequently, an alkanoylation of **8** gave desired **2**−**6** in satisfactory yields (70−85%).



Reagent	Conditions	(%)	R	
———	see ref. 12a		CH_3	1
$(CH_3)_3CCOCl$	THF / TEA / 0 °C	85	$(CH_3)_3C$	2
$CH_3(CH_2)_5COCl$	THF / TEA / -10 °C	80	$CH_3(CH_2)_5$	3
(*E*)$CH_3CH{=}CHCOCl$	THF / TEA / -10 °C	80	(*E*)-$CH_3CH{=}CH$	4
C_6H_5COCl	THF / TEA / 0 °C	80	C_6H_5	5
$(CF_3CO)_2O$	THF / TEA / -15 °C	70	CF_3	6

Figure 1. Chemical structures of molecular baskets **1**−**6** (A). Top view of **A** and **B** dynamic enantiomers of **1**−**6** that interconvert by simultaneous 180° rotation of the gates (B). The diastereotopic nature of $H_{a/b}$ protons permitted a thermal dependence of the ^{1}H NMR line shapes, which upon simulation analysis gave the interconversion rate constants ($k_{f/b}$).[14]

Table 1. Calculated Electrostatic Potential Energies (AM1/HF (6-31G**)) at the N−**H** and Pyr−**N** Sites in Model Compounds[14] and ^{1}H NMR (400 MHz, CD_2Cl_2) Chemical Shifts of the N−**H** Resonance of **1**−**6** Containing an Excess (> 60 mol equiv) of *t*-BuBr

R	N−**H**[a] (kcal/mol)	Pyr−**N**[a] (kcal/mol)	δ (N−**H**)[b] (ppm)	δ (N−**H**)[c] (ppm)
$(CH_3)_3C$	58	−49	9.7	10.4
CH_3	62	−48	10.8	11.4
$CH_3CH{=}CH$	61	−49	10.8	11.4
$CH_3(CH_2)_5$	62	−49	10.7	11.3
C_6H_5	59	−49	11.2	11.8
CF_3	69	−44	12.2	12.6

[a] Model compounds[14] consist of one phthalimide "arm". [b] 298 K. [c] 213 K.

The electron density perturbation in **1**−**6**, caused by substituents R, ought to anisotropically impact the electrostatic N−**H**···**N** contacts and thereby have an effect on the intramolecular hydrogen bonding.[15] 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

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Table 2. Kinetic Parameters for the Revolving of Gates (k_b, ^{1}H NMR Line-Shape Analysis) and the Translocation of *t*-BuBr (k_{in}, k_{out}, 2D EXSY NMR) in Molecular Baskets **1**−**6** (CD_2Cl_2), at 226.0 ± 0.1 K. Thermodynamic Stabilities ($\Delta G°$, 226.0 K) of the Encapsulation Complexes

basket	R	k_b (s^{-1})^{a,b}	k_{in} (M^{-1} s^{-1})^b	k_{out} (s^{-1})^b	$\Delta G_b^‡$ (kcal/mol)	$\Delta G_{out}^‡$ (kcal/mol)	$\Delta G°$ (kcal/mol)
1	CH_3	108 ± 22	524 ± 110	4.7 ± 0.7	11.0 ± 0.1	12.4 ± 0.1	−2.1 ± 0.1
2	$(CH_3)_3C$	78 ± 16	1964 ± 392	11.5 ± 0.9	11.1 ± 0.1	12.0 ± 0.1	−2.3 ± 0.1
3	$CH_3(CH_2)_5$	97 ± 20	407 ± 73	4.3 ± 0.4	11.0 ± 0.1	12.4 ± 0.1	−2.0 ± 0.1
4	(*E*)-$CH_3CH{=}CH$	83 ± 17	239 ± 68	2.8 ± 0.1	11.1 ± 0.1	12.6 ± 0.1	−2.0 ± 0.1
5	C_6H_5	20 ± 4	38 ± 12	0.4 ± 0.1	11.7 ± 0.1	13.5 ± 0.1	−2.0 ± 0.2
6	CF_3	4 ± 1	0.7 ± 0.1	0.07 ± 0.02	12.4 ± 0.1	14.2 ± 0.2	−1.0 ± 0.2

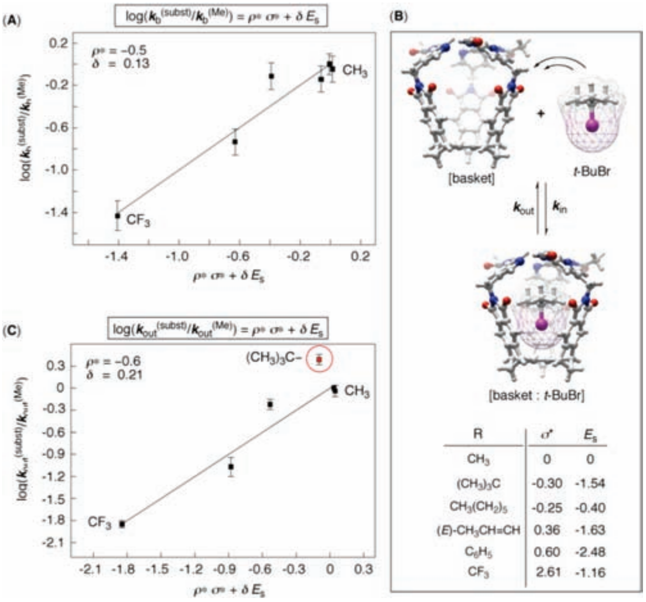
[a] Error margins (20%) were obtained on the basis of four independent measurements.[14] [b] Each measurement was repeated twice, and the error margins were propagated from the linear least-squares analysis of the experimental data.[14]

compounds[14] (AM1/HF(6-31G**), Spartan)[16] suggested a fluctuation in the charge density at the donor but rather consistent values at the acceptor atom (Table 1).

^{1}H NMR chemical shifts of the N−**H** signals in **1**−**6** are indicators for the strength and the proportion of the intramolecular hydrogen bonding (Table 1).[17] Markedly, bulky $(CH_3)_3C-$ groups enforced weaker ($\delta_{N-\mathbf{H}} = 9.7-10.4$ ppm) whereas all other substituents stronger ($\delta_{N-\mathbf{H}} = 10.8-12.6$ ppm) noncovalent contacts. FT-IR spectroscopic studies of **1**, **2**, and **6**, in addition, suggested the existence of a fully closed C_3 symmetric basket (as shown in Figure 1B) with other conformers populating the equilibrium to a lesser degree.[14] These findings are, importantly, supported by Schneider's suggestion[18] that ~2 kcal/mol of the free energy ($\Delta G°$, 298 K, $CDCl_3$) is to be attributed to a hydrogen bond lacking secondary electrostatic interactions; that is to say, $\Delta G°$ (298 K, $CDCl_3$) of ~6 kcal/mol can be expected to describe the formation of a "fully closed" basket.

First-order rate constants ($k_{f/b}$) for the interconversion of dynamic enantiomers **A** and **B** in **1**−**6** (Figure 1B) were determined by completing the line-shape analysis of the diastereotopic $H_{a/b}$ resonances at variable temperatures.[14] 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_b) for "averaging" the $H_{a/b}$ signals, i.e., revolving of the gates, were for **1**−**6** further incorporated into an Eyring plot to afford k_b's at 226.0 K (Table 2).[14] 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.

The dependence of the reaction's free energy ($\Delta G°$ or $\Delta G^‡$) on the reactant's substituents is described with substituent constants (σ) and accounted for by proportional free energy relationships (LFERs).[13] The concept has, interestingly, been used for examining noncovalent interactions, and typically, the electronic effects are solely evaluated.[19] In the case of baskets **1**−**6**, however, the gates' dynamics seems to be a function of not only electronic but also steric factors (Table 2). Moreover, the ground and the excited states for the **A/B** interconversion appear crowded when sizable R groups are introduced (Figure 1B). Taft's LFER scale, conveniently, defines polar (σ^*) and steric (E_s) substituent constants and has been recommended for studying aliphatic systems.[20] We used this two-parameter model to fit a plot of $\log(k_b^{(subs.)}/k_b^{(Me)})$ versus $\rho^*\sigma^* + \delta E_s$ (Figure 2A). 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 **2** with the sterically demanding $(CH_3)_3C-$ group, thus, underwent a rather "slow" **A/B** interconversion ($k_b = 78 \pm 16$ s^{-1}) despite its weak N−**H**···**N** hydrogen bonding contacts (Table 1).

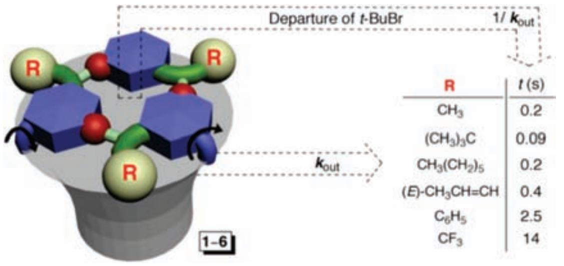


R	σ^*	E_s
CH_3	0	0
$(CH_3)_3C$	-0.30	-1.54
$CH_3(CH_2)_5$	-0.25	-0.40
(*E*)-$CH_3CH{=}CH$	0.36	-1.63
C_6H_5	0.60	-2.48
CF_3	2.61	-1.16

Figure 2. Linear free energy relationships (LFERs) for the revolving of gates (A) in baskets **1**−**6** and the dissociation of *t*-BuBr (B/C) from baskets **1**−**6**. Both correlations were 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_{in}) and departing (k_{out}) baskets **1**−**6** (Figure 2B) were ascertained by completing quantitative ^{1}H−^{1}H NOESY NMR (exchange spectroscopy, EXSY) measurements.[21] 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^*_{in} and k^*_{out}) for the exchange, at different mixing times (τ_m); τ_m's were originally estimated by measuring T_1 relaxations of *t*-BuBr protons.[10b,21,22] The association k_{in} and dissociation k_{out} rate constants (Figure 2B) were then obtained as $k_{in} = k^*_{in}$/[basket] and $k_{out} = k^*_{out}$ (Table 2).

Taft's linear free energy scale was used to correlate the kinetic data for the departure (k_{out}) of *t*-BuBr (Figure 2C). A plot of $\log(k_{out}^{(subs.)}/k_{out}^{(Me)})$ 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 baskets **1**−**6** 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 **2** containing bulky $(CH_3)_3C-$ units, however, did not follow the linear trend described in Figure 2C. The guest (*t*-BuBr) departed this



R	*t* (s)
CH_3	0.2
$(CH_3)_3C$	0.09
$CH_3(CH_2)_5$	0.2
(*E*)-$CH_3CH{=}CH$	0.4
C_6H_5	2.5
CF_3	14

Figure 3. Schematic representation of gated molecular baskets **1−6** capable of controlling time (*t*) that *t*-BuBr spends in their cavity (right). Choosing a proper R substituent, one can now tune this "residing" time to a desired value.

basket at a rate ($k_{out} = 11.5 \pm 0.9\ s^{-1}$) higher than expected considering the "slow" flipping of its gates ($k_b = 78 \pm 16\ s^{-1}$). It is, perhaps, that weaker hydrogen bonds at the seam of this basket (Table 1) 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.

The stability of *t*-BuBr complexes with **1−6** ($\Delta G°$, Table 2), apparently, decreased throughout the series. A notion that a more tightly closed basket has a "smaller" inner space, and thereby higher affinity toward solvent and lower toward *t*-BuBr, is appealing. The observed opposition of the thermodynamic stability and kinetic lability in the guest binding could, however, be important for catalytic applications.

The lifetime *t* ($1/k_{out}$) of the encapsulated *t*-BuBr is clearly a function of the basket's dynamics (Fugure 3) and can in this gated environment be controlled and predicted by choosing a proper R substituent. Considering the potential of encapsulating and stabilizing transient species[23] inside gated molecular baskets, this method of regulating the kinetic lability will now be extended toward directing the course of chemical reactions.

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Supporting Information Available: Detailed description of experimental methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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