J|A|C|S ARTICLES

Published on Web 12/28/2009

Gated Molecular Recognition and Dynamic Discrimination of Guests

Stephen Rieth, Xiaoguang Bao, Bao-Yu Wang, Christopher M. Hadad, and Jovica D. Badjić*

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210

Received October 4, 2009; E-mail: badjic@chemistry.ohio-state.edu

Abstract: Some highly efficient enzymes, e.g., acetylcholinesterase, use gating as a tool for controlling the rate by which substrates access their active site to direct product formation. Mastering gated molecular encapsulation could therefore be important for manipulating reactivity in artificial environments, albeit quantitative relationships that describe these processes are unknown. In this work, we examined the interdependence between the thermodynamics (ΔG°) and the kinetics ($\Delta G_{in}^\ddagger$ and $\Delta G_{out}^\ddagger$) of encapsulation as mediated by gated molecular basket **1**. For a series of isosteric guests (**2**−**6**, 106−107 Å^3) entering/exiting **1**, we found a linear correlation between the host−guest affinities (ΔG°) and the free energies of the activation ($\Delta G_{in}^\ddagger$ and $\Delta G_{out}^\ddagger$), which was fit to the following equation: $\Delta G^\ddagger = \rho\Delta G^\circ + \delta$. Markedly, the kinetics for the entrapment of smaller guest **7** (93 Å^3) and bigger guest **8** (121 Å^3) did not follow the free energy trends observed for **2**−**6**. Thus, it appears that the kinetics of the gated encapsulation mediated by **1** is a function of the encapsulation's favorability (ΔG°) and the guest's profile. When the size/shape of guests is kept constant, a linear dependence between the encapsulation potential (ΔG°) and the rate of guests' entering/departing basket ($\Delta G_{in/out}^\ddagger$) holds. However, when the potential (ΔG°) is fixed, the basket discriminates guests on the basis of their size/shape via dynamic modulation of the binding site's access.

Introduction

Mechanistic details about the formation of host−guest encapsulation complexes are obtained from kinetic measurements[1] and are critical for designing synthetic receptors[2] with a mode of action resembling biological molecules. The exchange of guests has thus been found to occur via: (a) a full or partial dissociation of the host's subunits;[3] (b) an "expansion" of the host's apertures;[4] and (c) a conformational change in the host's shell.[5] All of these insightful findings, however, do not disclose *quantitative relationships*[6] that guide the recognition's kinetics. A high thermodynamic bias (ΔG°) for a chemical process, e.g., molecular recognition, can lead to a low activation barrier ($\Delta G^\ddagger$) and an early transition state (according to Hammond's postulate), although the relationship does depend upon context.[7] Precise control over the kinetics of the encapsulation[5,8] presents a challenge, thereby providing an opportunity for directing chemical reactivity[9,10] and sequestration.[11] Interestingly, some very efficient enzymes, such as acetylcholinesterase, promote a dynamic selection of guests via stochastic motion of aromatic residues (gates) located along a pathway leading to the active

(1) (a) Detellier, C. Complexation Mechanisms. In *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Elsevier: Oxford, UK 1996, *35* 7−375. (b) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2529–2586. (c) Macartney, D. H. Kinetics of Complexation. In *Encyclopedia of Supramolecular Chemistry*; Atwood, J. L., Steed, J. W., Eds; Marcel-Dekker, Inc: New York, 2004. (d) Palmer, L. C.; Rebek, J., Jr. *Org. Biomol. Chem.* **2004**, *2*, 3051–3059. (e) Marquez, C.; Hudgins, R. R.; Nau, W. M. *J. Am. Chem. Soc.* **2004**, *126*, 5806–5816. (f) Pluth, M. D.; Raymond, K. N. *Chem. Soc. Rev.* **2007**, *36*, 161–171.

(2) (a) Gibb, C. L. D.; Gibb, B. C. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 4857–4862. (b) Zuccaccia, D.; Pirondini, L.; Pinalli, R.; Dalcanale, E.; Macchioni, A. *J. Am. Chem. Soc.* **2005**, *127*, 7025–7032. (c) Gottschalk, T.; Jaun, B.; Diederich, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 260–264. (d) Podkoscielny, D.; Philip, I.; Gibb, C. L. D.; Gibb, B. C.; Kaifer, A. E. *Chem.—Eur. J.* **2008**, *14*, 4704–4710. (e) Isaacs, L. *Chem. Commun.* **2009**, *6*, 619–629. (f) Stanisky, C. M. R.; Cross, J.; Saunders, M. *J. Am. Chem. Soc.* **2009**, *131*, 3392–3395. (g) Brotin, T.; Dutasta, J.-P. *Chem. Rev.* **2009**, *109*, 88–130. (h) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418–3438. (i) Tartaggia, S.; Scarso, A.; Padovan, P.; De Lucchi, O.; Fabris, F. *Org. Lett.* **2009**, *11*, 3926–3929. (j) Clever, G. H.; Tashiro, S.; Shionoya, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7010–7012.

(3) (a) Craig, S. L.; Lin, S.; Chen, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 8780–8781. (b) Barrett, E. S.; Dale, T. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 2344–2350.

(4) (a) Fyfe, M. C. T.; Raymo, F. M.; Stoddart, J. F. *Slippage and constrictive binding, in Stimulating Concepts in Chemistry*; Voegtle, F., Stoddart, J. F., Shibasaki, M., Eds.;Wiley-VCH: Weinheim, Germany, 2000. (b) Davis, A. V.; Raymond, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 7912–7919.

(5) (a) Ihm, C.; Kim, M.; Ihm, H.; Paek, K. *J. Chem. Soc., Perkin Trans. 2* **1999**, *8*, 1569–1575. (b) Houk, K. N.; Nakamura, K.; Sheu, C.; Keating, A. E. *Science* **1996**, *273*, 627–629. (c) Liu, Y.; Warmuth, R. *Org. Lett.* **2007**, *9*, 2883–2886.

(6) (a) Cox, B. G.; Garcia-Rosas, J.; Schneider, H. *J. Am. Chem. Soc.* **1981**, *103*, 1054–1059. (b) Cram, D. J.; Lein, G. M. *J. Am. Chem. Soc.* **1985**, *107*, 3567–3668. (c) Houk, K. N.; Leach, A. G.; Kim, S. P.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 4872–4897. (d) Hunter, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5310–5324.

(7) Herbert, M.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1844–1854.

(8) (a) Piatnitski, E. L.; Deshayes, K. D. *Angew. Chem., Int. Ed.* **1998**, *37*, 970–973. (b) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 1264–1267. (c) Sherman, J. *Chem. Commun.* **2003**, *14*, 1617–1623. (d) Mough, S. T.; Goeltz, J. C.; Holman, K. T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5631–5635. (e) Giles, M. D.; Liu, S.; Emanuel, R. L.; Gibb, B. C.; Grayson, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 14430–14431. (f) Nishimura, N.; Kobayashi, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6255–6258.

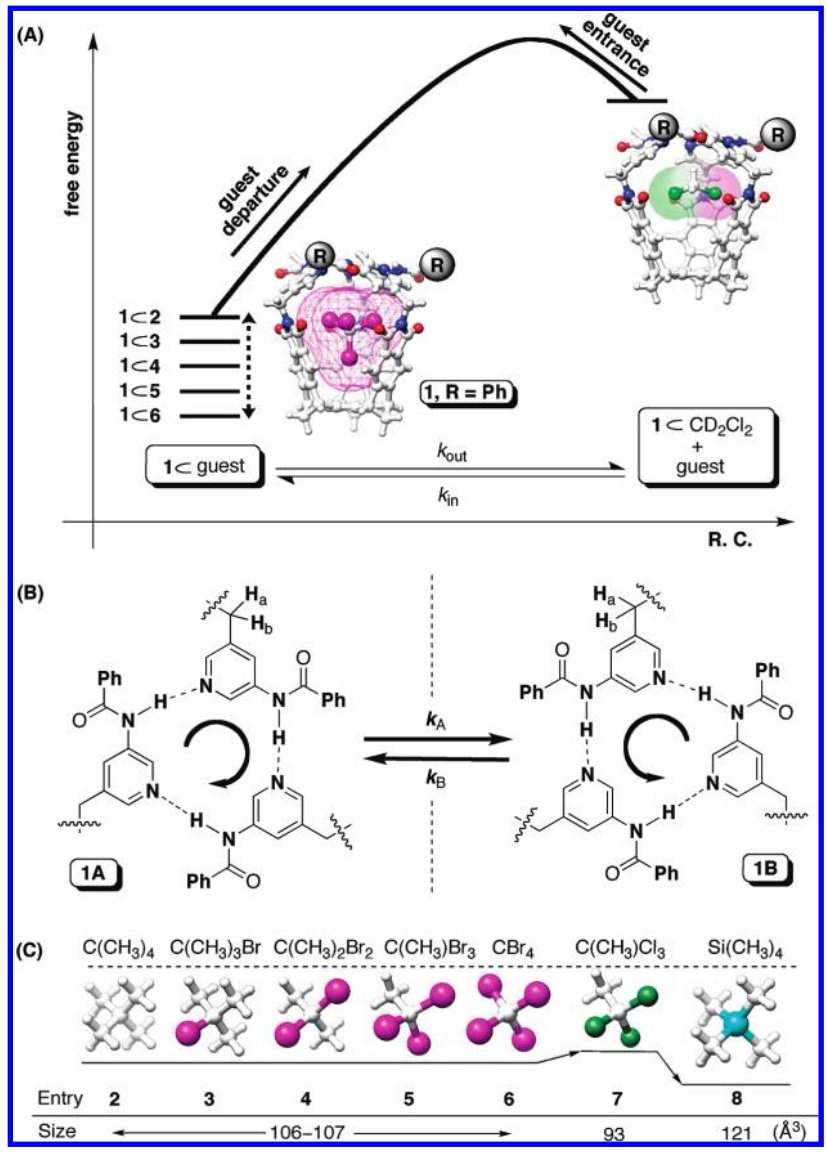

Figure 1. (A) Reaction coordinate diagram showing an equilibrium with guests **2**−**6** (CBr_4 is displayed) entering (k_{in}) and departing (k_{out}) gated molecular basket **1** (internal volume: 220 Å^3). Solvent molecules (CD_2Cl_2, right) occupy basket **1** devoid of external guests. (B) Top view of **1A** and **1B** enantiomeric baskets that interconvert by 180° rotation of their gates. (C) Energy minimized structures (B3LYP/3-21G) of guests **2**−**8** and their corresponding volumes (Å^3).

site: the rate of trafficking of a bigger guest is hindered as compared to a slightly smaller analogue.[9a] Accordingly, the present study addresses the potential of synthetic baskets (Figure 1) to dynamically distinguish guests on the basis of gating. The encapsulation kinetics has been found to follow a free-energy relationship, suggesting important principles that might govern recognition in artificial and gated environments.[12]

Results and Discussion

Gated molecular baskets[13] were originally designed and synthesized in our laboratory. These hosts have a bowl-shaped platform with three pyridine-based gates, linked via a seam of intramolecular hydrogen bonds (HBs) to occlude space and form a dynamic and gated environment (Figure 1). The interconversion of two C_3 symmetric enantiomers, **1A** and **1B**, each

(9) (a) McCammon, J. A.; Northrup, S. H. *Nature* **1981**, *293*, 316–317. (b) Zhou, H.-X.; Wlodek, S. T.; McCammon, J. A. *Proc. Nat. Acad. Sci. U.S.A.* **1998**, *95*, 9280–9283. (c) Winn, P. J.; Ludemann, S. K.; Gauges, R.; Lounnas, V.; Wade, R. C. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 5361–5366.

(10) For selected examples, see: (a) Heemstra, J. M.; Moore, J. S. *J. Org. Chem.* **2004**, *69*, 9234–9237. (b) Ryu, E.-H.; Cho, H.; Zhao, Y. *Org. Lett.* **2007**, *9*, 5147–5150. (c) *Supramolecular Catalysis*; van Leeuwen, P. W. N.; Wiley-VCH, Weinheim, Germany, 2008. (d) Skouta, R.; Wei, S.; Breslow, R. *J. Am. Chem. Soc.* **2009**, *131*, 15604–15605. (e) Atkinson, M. B. J.; Bucar, D.-K.; Sokolov, A. N.; Friscic, T.; Robinson, C. N.; Bilal, M. Y.; Sinada, N. G.; Chevannes, A.; MacGillivray, L. R. *Chem. Commun.* **2008**, *44*, 5713–5715. (f) Coquiere, D.; de la Lande, A.; Parisel, O.; Prange, T.; Reinaud, O. *Chem.—Eur. J.* **2009**, *15*, 11912–11917. (g) Mitsui, K.; Hyatt, Sarah, A.; Turner, D. A.; Hadad, C. M.; Parquette, J. R. *Chem. Commun.* **2009**, *22*, 3261–3263.

(11) Anslyn, E. V. *J. Org. Chem.* **2007**, *72*, 687–699.

(12) (a) Nakamura, K.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 1853–1854. (b) Sheu, C.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 8056–8070. (c) Wang, X.; Houk, K. N. *Org. Lett.* **1999**, *1*, 591–594. (d) Hooley, R. J.; Van, A. H. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 3894–3895. (e) Hooley, R. J.; Shenoy, S. R.; Rebek, J., Jr. *Org. Lett.* **2008**, *10*, 5397–5400.

(13) (a) Maslak, V.; Yan, Z.; Xia, S.; Gallucci, J.; Hadad, C. M.; Badjić, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 5887–5894. (b) Wang, B.-Y.; Bao, X.; Yan, Z.; Maslak, V.; Hadad, C. M.; Badjić, J. D. *J. Am. Chem. Soc.* **2008**, *130*, 15127–15133. (c) Wang, B.-Y.; Bao, X.; Stojanovic, S.; Hadad, C. M.; Badjić, J. D. *Org. Lett.* **2008**, *10*, 5361–5364.

Table 1. Activation Parameters for the Trafficking of Guests **2**−**8** (2D EXSY NMR, CD_2Cl_2, 250.0 ± 0.1 K) In (k_{in}, $\Delta G_{in}^{\ddagger}$) and Out (k_{out}, $\Delta G_{out}^{\ddagger}$) from Basket **1** and the **1A/B** Interconversion ($\Delta G_{A/B}^{\ddagger}$) as well as Thermodynamic Stabilities (ΔG°, 250.0 ± 0.1 K) of [**1** ⊂ **2**−**8**] Encapsulation Complexes

entry	guest	k_{in} ($M^{-1}s^{-1}$)[b]	k_{out} (s^{-1})[b]	$\Delta G_{in}^{\ddagger}$ (kcal/mol)	$\Delta G_{out}^{\ddagger}$ (kcal/mol)	$\Delta G_{A/B}^{\ddagger}$ (kcal/mol)[a]	ΔG° (kcal/mol)
2	$(CH_3)_4C$	1100 ± 115	30.3 ± 0.9	11.03 ± 0.05	12.81 ± 0.01	11.5 ± 0.1	−1.77 ± 0.05
3	$(CH_3)_3CBr$	1161 ± 134	16.2 ± 0.8	11.00 ± 0.06	13.12 ± 0.02	11.8 ± 0.1	−2.11 ± 0.06
4	$(CH_3)_2CBr_2$	1525 ± 200	3.41 ± 0.23	10.87 ± 0.07	13.89 ± 0.03	11.9 ± 0.1	−3.02 ± 0.07
5	$(CH_3)CBr_3$	2460 ± 251	0.48 ± 0.01	10.63 ± 0.05	14.86 ± 0.01	12.3 ± 0.1	−4.23 ± 0.05
6	CBr_4	8500 ± 3010	0.10 ± 0.03	10.02 ± 0.18	15.63 ± 0.15	12.6 ± 0.1	−5.6 ± 0.1
7	$(CH_3)CCl_3$	8040 ± 873	22.8 ± 0.8	10.04 ± 0.05	12.95 ± 0.02	11.6 ± 0.1	−2.90 ± 0.06
8	$(CH_3)_4Si$	480 ± 48	14.4 ± 0.5	11.44 ± 0.05	13.17 ± 0.02	12.5 ± 0.1	−1.73 ± 0.06

[a] Error margins were obtained on the basis of four independent measurements. [b] Each measurement was repeated twice.[16]

containing HBs displayed in a clockwise or counter-clockwise orientation, has been verified from the NMR exchange of the "hinge" $H_{a/b}$ resonances appearing as a singlet at high and an AB quartet at low temperatures (Figure 1B). Furthermore, the polar (inductive and field) and steric characteristics of the **R** amido units were shown[14] to have an effect on the in/out rate of the guest exchange: the guest trafficking was predominantly a function of the rate by which the gates revolve. For guests entering/exiting baskets, another question arises: is there a relationship between the thermodynamic potential (ΔG°) and the activation energy ($\Delta G^{\ddagger}$) for the encapsulation?

Neopentane **2** and four homologous haloalkanes **3**−**6** were chosen as guests (Figure 1C). These molecules have identical profiles with van der Waals volumes of Br and CH_3 groups contributing to uniform size (106−107 Å^3) and spherical shape across the series. Basket **1** (Figure 1) was used in the study, and its affinity (ΔG°) toward guests **2**−**6** was more favorable (more exoergic) as the number of CH_3 units decreased (Table 1). As elucidated in an earlier study,[13c] the encapsulation limits the rotational and vibrational degrees of freedom of CH_3 groups, which obstructs the binding via an unfavorable entropy ($\Delta S^{\circ} < 0$). Notably, the range of binding energies ΔG° (250 K, Table 1) spans ∼4 kcal/mol for these very similar guests, thereby allowing a critical evaluation of the possible linear free energy relationships (LFER).

Kinetics and LFERs. Two-dimensional $^1H-^1H$ and $^{13}C-^{13}C$ NMR magnetization transfer measurements (EXSY)[15] were completed to obtain the rate coefficients for guests **2**−**6** entering (k_{in}) and departing (k_{out}) basket **1** in CD_2Cl_2 at 250.0 ± 0.1 K (Table 1).[16] The encapsulation (Figure 1A) was in accord with an associative mechanism[1a] (Figure S10 of the Supporting Information) whereby the association was first order in the guest ($v_{in} = k_{in}$ [guest][basket]) while the dissociation process was zeroth order in the guest ($v_{out} = k_{out}$ [basket ⊂ guest]).[16]

After the host−guest affinities ($\Delta G^{\circ} = k_{in}/k_{out}$) were plotted against the corresponding free energies of activation ($\Delta G_{in/out}^{\ddagger}$), well-correlated linear relationships were observed (Figure 2); note that the binding energies ΔG° from the EXSY measurements match those obtained by the integration of ^1H NMR signals.[16] Evidently, there exists quantitative relationships between the thermodynamic potential for the encapsulation and the free energy of activation for guests **2**−**6** entering/exiting basket **1** in competition with the solvent (CD_2Cl_2). We analyzed these relationships with the following equation $\Delta G^{\ddagger} = \rho\Delta G^{\circ} + \delta$. The slopes of the fitted lines, which we

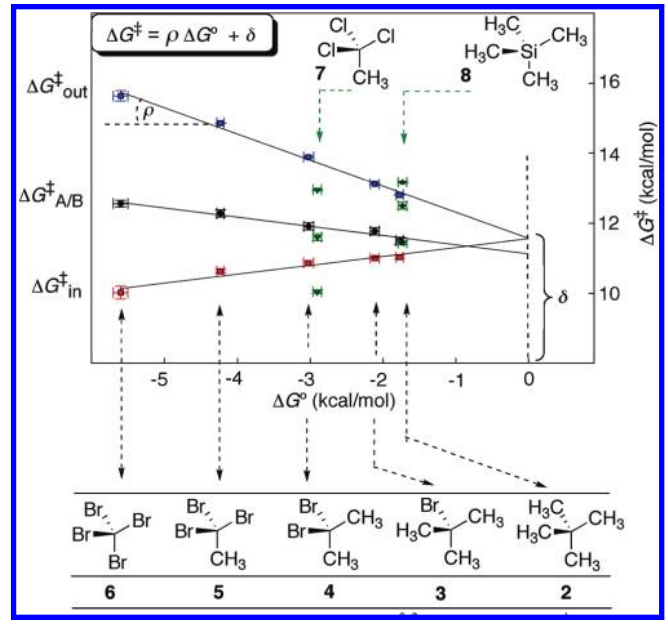

Figure 2. Activation energies for guests **2**−**6** (106−107 Å^3) entering ($\Delta G^{\ddagger}_{in}$) and departing ($\Delta G^{\ddagger}_{out}$) basket **1** were found to be a linear function of the corresponding binding energies (ΔG°, 250.0 ± 0.1 K). The kinetic behavior of smaller **7** (93 Å^3) and bigger **8** (121 Å^3) deviates from the observed linear free energy relationships ($\Delta G^{\ddagger} = \rho\Delta G^{\circ} + \delta$). The activation energies characterizing the revolving of gates ($\Delta G^{\circ}_{A/B}$) also exhibit a LFER.

denote as ρ,[17] correspond to the susceptibility by which the free energies of activation respond to the change in the thermodynamic affinity of guests **2**−**6** toward molecular basket **1**. For the values of ρ, the ingress of guests generates a smaller slope ($\rho_{in} = 0.25$), while the egress has a larger magnitude of its slope ($|\rho_{out}| = 0.74$, Figure 2). An early transition state would suggest that the guest entrapment ($\Delta G_{in}^{\ddagger}$) would be less responsive to ΔG° than $\Delta G_{out}^{\ddagger}$, as is observed. The intercept of the fitted lines, which we denote as δ, represents the activation barrier ($\Delta G^{\ddagger}$) for the encapsulation of a guest having a binding energy of $\Delta G^{\circ} = 0$; note that under this circumstance, $\delta = \Delta G_{in}^{\ddagger} = \Delta G_{out}^{\ddagger} = 11.56 \pm 0.14$ kcal/mol. One should note that the δ might also correlate to the binding energy of the solvent (CH_2Cl_2) as a competitive guest with basket **1**.

First-order rate constants ($k_{A/B}$, Figure 1B) for the interconversion of dynamic enantiomers **1A** and **1B** were obtained by completing NMR line-shape simulations of the coalescence of diastereotopic $H_{a/b}$ resonances at variable temperatures (220−270 K, Table 1).[16] After the data were placed into the free energy correlation plot (Figure 2), the activation energies for **1A/B** interconversion ($\Delta G_{A/B}^{\ddagger}$) were shown as well to be a linear

(14) Wang, B.-Y.; Rieth, S.; Badjić, J. D. *J. Am. Chem. Soc.* **2009**, *131*, 7250–7252.
(15) (a) Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546–4553. (b) Perrin, C. L.; Dwyer, T. J. *J. Chem. Rev.* **1990**, *90*, 935–967.
(16) See Supporting Information for more details.
(17) The slope ρ is akin to the Hammond-Leffler α value ($\alpha = \delta\Delta G^{\ddagger}/\delta\Delta G^{\circ}$). See: (a) Leffler, J. E. *Science* **1953**, *117*, 340–341. (b) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.

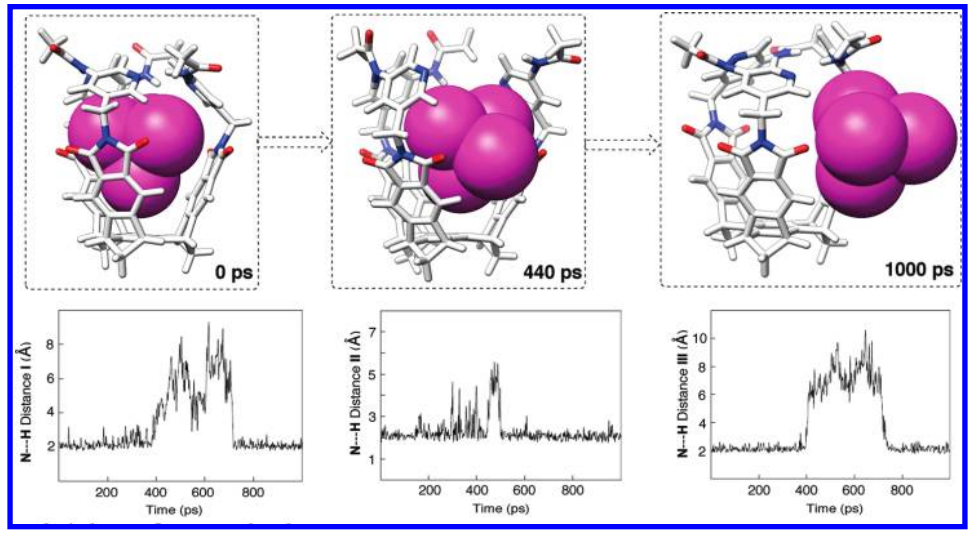

Figure 3. Snapshots of CBr_4 departing **1**, along a force vector aligned with the basket's side aperture, obtained from steered molecular dynamics (SMD) simulations of the process (0, 440, and 1000 ps; top). The variation of intramolecular N---H distances (assigned as I, II, and III) in basket **1** as a function of time during the SMD simulation (bottom).

function ($R^2 = 0.972$) of the thermodynamic stability of **1/2−6** complexes. The slope of the fitted line is small ($|\rho_{A/B}| = 0.26$) while the intercept (11.13 ± 0.09 kcal/mol) is very similar to the δ value above (11.56 ± 0.14 kcal/mol, Figure 2). 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 **1**. Furthermore, the energy required for revolving the gates at $\Delta G^\circ = 0$ is almost equal to the constrictive binding ($\Delta G_{in}^{\ddagger} = \Delta G_{out}^{\ddagger} = 11.56 \pm 0.14$ kcal/mol)−physical barrier that a guest encounters in escaping the basket.[18] The host's conformational change, i.e., gating, is evidently controlling the uptake/release of guest molecules.

Mechanistic Considerations. The departure of sizable CBr_4 (or for that matter **2−5**), via a trajectory along the side aperture of the basket, was computed using steered molecular dynamics (SMD)[19] and the AMBER program.[16] 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 3).[16] Furthermore, the results of the SMD simulation indicated that smaller $CHCl_3$ (75 Å^3) can enter and exit **1**, without considerably perturbing the position of the gates.[16] If the trafficking of smaller guests does not require a considerable perturbation of the gates, then one could expect a faster **1A/B** interconversion (Figure 1B) 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 [**1**-CD_2Cl_2]: $\Delta G^{\ddagger} = 9.2 \pm 0.1$ kcal/mol at 250.0 K.[16]

On the Observed LFERs. The relationships described in Figure 2 pertain to guests (**2−6**) that have the same size and shape. Will guest molecules, having profiles slightly different from **2−6**, obey the $\Delta G^\circ/\Delta G^{\ddagger}$ linear correlations?

Guests **7** and **8** were chosen to examine this aspect (Figure 1C). 1,1,1-Trichloroethane **7** is a nonspherical compound and is smaller (93 Å^3) than guests **2−6** (~107 Å^3). Interestingly, **7** entered/departed basket **1** faster than one would predict on the basis of the LFER in Figure 2. Larger tetramethylsilane **8** (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 2. The results of the kinetic measurements for **7** and **8** can be interpreted by considering the mechanism of conformational gating in acetylcholinesterase (AChE).[9b] A guest will make repeated attempts to access the cavity of dynamic [**1**-CD_2Cl_2] via Brownian motion. The gates switch between open and closed states and when an attempt coincides with the open state, the encapsulation happens (Figure 3). The likelihood that the gates open wide enough to admit a substrate is evidently related to the substrate's size. Hence, larger substrate **8** has a lower probability while smaller substrate **7** has a higher probability for entering "the transient aperture" created by the gates.

Conclusions

Quantitative relationships that describe the kinetic discrimination of guests in artificial gated receptors have been studied. Our experimental results suggest that the encapsulation kinetics, mediated by gated basket **1**, is governed by the guest's profile and the host/guest interaction potential (ΔG°).[20] Thus, when the size/shape of guests is kept constant, the encapsulation potential (ΔG°) is a linear function of the rate by which they enter/depart basket **1** ($\Delta G_{in/out}^{\ddagger}$). However, when the potential is fixed (project a vertical line for **7** and **8** in Figure 2), basket **1** discriminates guests on the basis of their size/shape via dynamic modulation of the binding site's access, thereby resembling enzymes.[9] A more complete understanding of the kinetic selection will benefit from studying a broader scope of guest molecules and baskets, and such research is in progress.

Acknowledgment. This work was financially supported with funds from the Ohio State University and the National Science Foundation under CHE-0716355. Generous computational resources were provided by the Ohio Supercomputer Center.

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

JA908436C

(18) Cram, D. J.; Blanda, M. T.; Paek, K.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7765–7773.
(19) Izrailev, S.; Stepaniants, S.; Balsera, M.; Oono, Y.; Schulten, K. *Biophys. J.* **1997**, *72*, 1568–1581.
(20) Northrup, S. H.; Hynes, J. T. *J. Chem. Phys.* **1979**, *71*, 871–883.