ORGANIC
LETTERS

2008
Vol. 10, No. 23
5361−5364

Encapsulation of Guests within a Gated Molecular Basket: Thermodynamics and Selectivity

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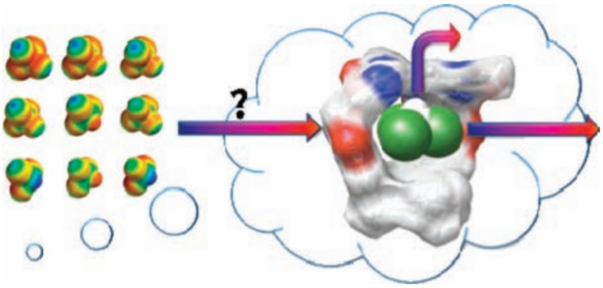
Received September 19, 2008

ABSTRACT



Molecular basket 1 has been designed to contain a set of aromatic gates, each with rotational mobility restricted via intramolecular hydrogen bonding. This structural, yet dynamic, feature of the host has been revealed to permit the formation of a *transient* enclosed space capable of containing haloalkanes, whose size/shape, electronic and entropic attributes contributed to the thermodynamics of binding. Markedly, the basket is capable of mediating the trafficking of a broad range of molecules.

There has been considerable interest in ascertaining details about regulating the kinetics and thermodynamics of molecular encapsulation.[1] The motivation comes from the prospect of understanding the relationship between molecular transport, translocation, and reactivity in artificial environments.[2] Accordingly, the first and foremost element in forecasting the action of any receptor, that is, molecular baskets (Figure 1), is related to identifying potential guests. For such an exercise, theoretical approaches are available,[3] allowing us to forecast the host/guest complexation thermodynamics; in reality, however, the solvation and molecular dynamics (entropy) contribute to the recognition events and complicate the interpretation of theory. Respectively, Rebek and co-workers have noted that for encapsulations guided by nonspecific host/guest intermolecular contacts, a guest would occupy 55.0 ± 0.8% of the host cavity.[4] Such an empirical, but useful, guide for predicting the encapsulation selectivity in liquids can be severely restricted by difficulties in defining the host's inner space; often, receptors contain apertures with poorly defined physical boundaries. Houk and co-workers have, accordingly, suggested that the aperture characteristics at the "skin" of a (hemi)carcerand play an important role in delineating the kinetic as well as the

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(1) For selected examples, see: (a) Kerckhoffs, J. M. C. A.; van Leeuwen, F. W. B.; Spek, A. L.; Kooijman, K.; Crego-Calama, M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5717–5722. (b) Davis, A. V.; Fiedler, D.; Seeber, G.; Zahl, A.; Van Eldik, R.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 1324–1333. (c) Vatsouro, I.; Alt, E.; Vysotsky, M.; Boehmer, V. *Org. Biomol. Chem.* **2008**, *6*, 998–1003. (d) Barrett, E. S.; Dale, T. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 2344–2350.

(2) See, for example: Fiedler, D.; Leung, D. H.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2005**, *38*, 349–358.

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(4) (a) Mecozzi, S.; Rebek, J., Jr. *Chem.−Eur. J.* **1998**, *4*, 1016–1022. (b) Hamann, B. C.; Shimizu, K. D.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326–1329.

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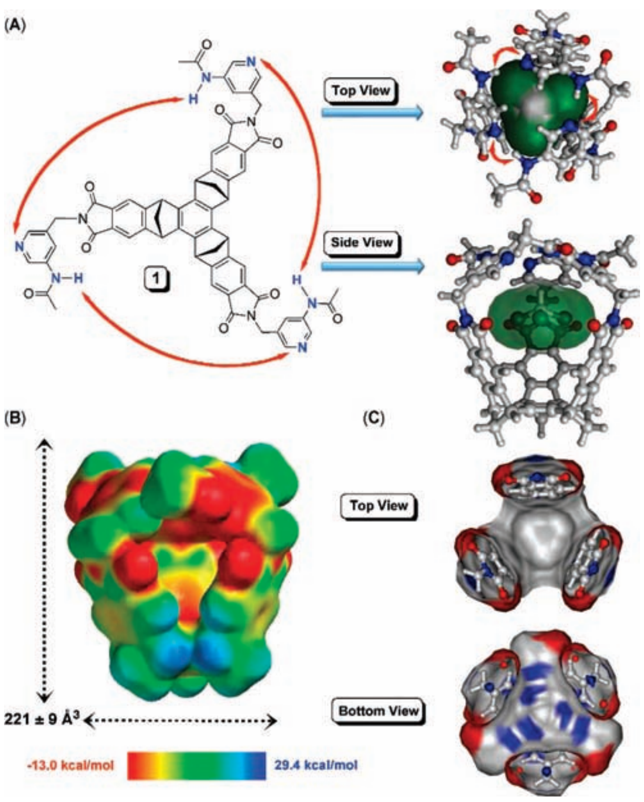

Figure 1. (A) Chemical structure of gated molecular basket **1** (left), and the energy optimized (DFT, B3LYP) top and side views of its conformer folded via hydrogen bonding (right).[8] (B) Electrostatic potential surface map of **1** calculated using AM1 method with Spartan. (C) Computer generated images of the inner van der Waals surface of **1** (UCSF Chimera Software).

thermodynamic stability of the encapsulation complex.[5] In the prospect of exploring and understanding the action of dynamic abiotic receptors, molecular baskets have been designed to enclose a semirigid platform with a set of rotatable aromatic gates for regulating the in/out transport of molecules (Figure 1).[6] When folded with a transition metal,[7] their tenacity for encapsulating linearly shaped guests has been identified. The gates are, thereby, restrained at one "point", via coordinating to the metal cation, to undergo an energetically inexpensive rotation (<5 kcal/mol),[7] each about its axis; this rather facile gearing process reduces the effective volume of the basket's interior to dominate the selectivity for guest encapsulation. When operated via intramolecular hydrogen bonding,[8] however, the gates are held to each other at two "points" (Figure 1A), with the barrier for the rotation of about 10 kcal/mol. *With less dynamic "doors" controlling the basket's entrance, the guest selectivity and the encapsulation thermodynamics have not been investigated, and are a subject of the present study.*

Gated basket **1** has previously been shown[8] to regulate the in/out transport of CCl_4 via a mechanism where the flaps revolve, each about its axis, to form a corridor for guests to pass (Figure 1A). To approximate the internal volume of **1**, we first optimized its folded structure[8] using density functional theory (DFT, B3LYP/6−31G(d))[8] and then computed the volume limited by the inner van der Waals surface (Spartan).[4b] In this way, the cavity size was estimated to 221 ± 9 Å^3, with the error margin corresponding to standard deviation of six independent computations. Indeed, the energetically inexpensive breathing dynamics of the host must also be contributing to the volume fluctuation, adding to the uncertainty (c.a. 10%).[4a] The calculated electrostatic potential surface (AM1, Spartan) of the concave interior of **1** (Figure 1B) presents domains with the negative potential at the center of its bottom −17, side −5, and top −10 kcal/mol faces.[10] Apparently, a prospective guest is to be "soaked" within π clouds constituted by the seven aromatic rings. The inner space of **1** comprises a complex surface loosely resembling an elongated triangular pyramid (Figure 1C).

The folded form of **1**, therefore, provides a sufficiently spacious inner space to accommodate a guest; the sizable apertures, however, make the selectivity, kinetics and thermodynamics of the encapsulation difficult to predict. Halomethane derivatives **2-12** (Figure 2) possess size, shape, and the electrostatic potential surface that qualitatively complement the basket's interior. Their capacity for occupying this dynamic host was, therefore, examined first. In a typical experiment, a halomethane compound was added to **1**,[9] dissolved in CD_2Cl_2, and the solution was subjected to variable temperature (VT) ^{1}H NMR study. When a guest occupied the inner space of **1**, two sets of resonances

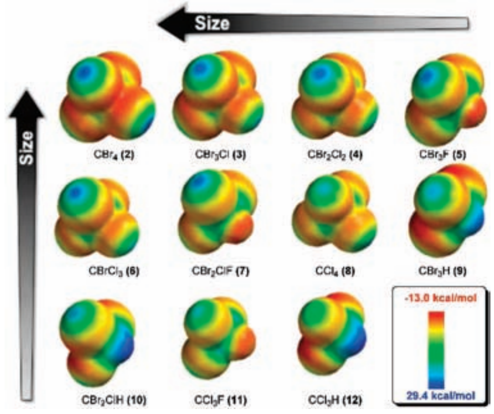

Figure 2. Electrostatic potential surfaces (AM1, Spartan) of halomethanes **2**−**12**.

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Table 1. Thermodynamic Parameters for the Entrapment of Halomethanes **2**−**12** Inside Gated Molecular Basket **1**

entry	guests	volume (Å^3)[a]	PC[b] (%)	$\Delta H°$ (kcal/mol)[c]	$\Delta S°$ (cal/mol-K)[c]	$\Delta G°$ (kcal/mol)[c,d]
2	CBr_4	106.2	48	−4.85 ± 0.09	−0.2 ± 0.4	−4.8 ± 0.1
3	CBr_3Cl	101.9	46	−6.8 ± 0.2	−7.6 ± 0.8	−4.5 ± 0.1
4	CBr_2Cl_2	97.5	44	−5.42 ± 0.06	−5.8 ± 0.2	−3.7 ± 0.1
5	CBr_3F	94.3	43	−5.3 ± 0.1	−7.3 ± 0.4	−3.1 ± 0.2
6	CCl_3Br	92.9	42	−5.5 ± 0.1	−7.2 ± 0.4	−3.4 ± 0.2
7	CBr_2ClF	89.6	41	−4.1 ± 0.4	−5 ± 2	−2.6 ± 0.9
8	CCl_4	88.3	40	−3.1 ± 0.2	−1.2 ± 0.8	−3 ± 1
9	CBr_3H	87.8	40	−1.73 ± 0.08	2.3 ± 0.4	−1.0 ± 0.1
10	CBr_2ClH	83.5	38	n/a	n/a	n/a
11	CCl_3F	80.8	37	n/a	n/a	n/a
12	CCl_3H	74.4	34	n/a	n/a	n/a

[a] Calculated with Spartan. [b] Packing coefficients were computed following published procedure.[4a] [c] Obtained from the corresponding van't Hoff plots. The error margins in $\Delta H°$ and $\Delta S°$ 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.

appeared (Figure 3): one corresponded to the "empty" and another to the filled basket. Integration of the resonances afforded the binding constant (K), and from a Van't Hoff plot (Figure 4A), thermodynamic parameters ($\Delta H°$, $\Delta S°$) for the encapsulation were obtained (Table 1).[9]

Notably, the propensity of the basket for sequestering halomethanes is a function of their size (Figure 4A).[11] Thus, the largest guest, CBr_4 (**2**), showed the highest affinity for occupying **1** (Table 1). The enthalpic contribution ($\Delta H°$) for CBr_4 binding was, however, found to be less favorable −4.85 ± 0.09 kcal/mol, Table 1). In fact, when the binding enthalpies ($\Delta H°$) for **2**−**9**, were plotted against the guest volumes, an apparent bell-shaped dependence was obtained (Figure 4B).[2] Evidently, molecules with a "distorted" spherical shape present a better match for the egg-shaped pocket of the basket, affording more favorable noncovalent contacts. Using ^{1}H NMR spectroscopy, the encapsulation was observed for guests 84−110 Å^3 in volume. Importantly, this size-based selectivity is in good agreement with Rebek's "55% rule" (Table 1)![4] The enthalpic and entropic changes for the binding of **2**−**9**, moreover, fluctuate in a way that the two parameters compensate one another (Table 1).[12] The uncertainity in the estimate of $\Delta H°$ and $\Delta S°$, obtained from the same data set, is correlated[13] so that different statistical treatments have been developed to quantify the compensa-

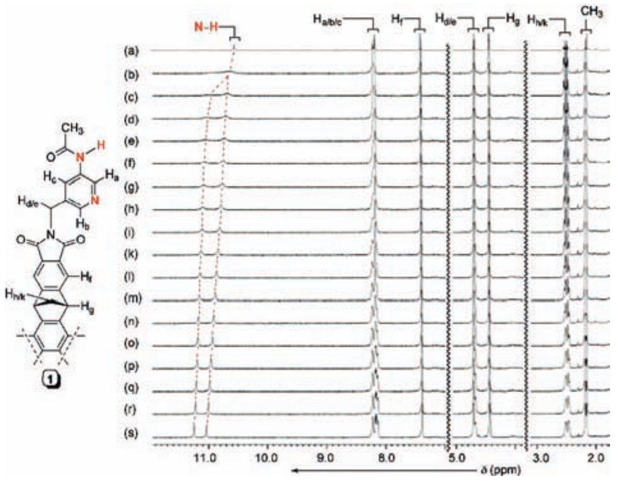

Figure 3. Variable temperature (VT) ^{1}H NMR spectra (400 MHz, CD_2Cl_2) of a solution of **1** (2.56 mM) before (a, 298 K) and after addition of **3** (1.35 mM) at: 301.8 (b), 296.3 (c), 292.9 (d), 290.6 (e), 288.4 (f), 286.1 (g), 283.9 (h), 281.6 (i), 278.8 (k), 276.0 (l), 273.2 (m), 270.3 (n), 267.5 (o), 264.7 (p), 261.9 (q), 259.1 (r), and 254.6 K (s).

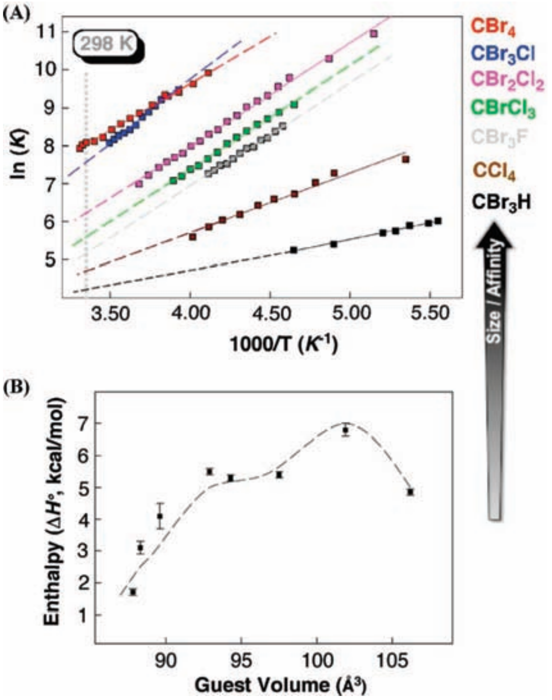

Figure 4. (A) Van't Hoff plot(s) for the encapsulation of guests **2**−**9** inside molecular basket **1**. (B) Experimental enthalpic changes for the encapsulation of halomethanes **2**−**9** (Table 1), as a function of their volumes (the dashed line serves to guide the eye).

tion effect.[14,15] Regardless, a higher enthalpy is, in our case, qualitatively offset with an adverse entropy to indirectly contribute to the stabilities of the complexes (ΔG°, 298 K).

Interestingly, guests **5** and **7** were encapsulated, but the apparent stabilities were somewhat lower than expected on the basis of the guest size (Table 1). Notably, the two molecules contain a fluorine atom, each with a negative potential at its northern pole (Figure 2). We reason that the adverse electrostatic forces disfavored the host/guest interaction.[16]

Subsequently, we examined the thermodynamics of **1** interacting with bromoalkanes **2**,**13**−**14** and tetramethylsilane **15** (Figure 5). The guests were deliberately chosen to encompass comparable volumes and shapes, albeit each with a different number of methyl (Me) groups. The thermodynamics of the encapsulations was, as before, studied with variable temperature ^{1}H NMR spectroscopy.[9] Notably, the stabilities of the complexes (ΔG°, 298 K) changed radically along the series (Figure 5). At first, this finding was surprising since the investigated guests had similar volumes. Thus, the observed enthalpies, were found to be fairly consistent ($\Delta H^\circ \approx -4$ kcal/mol). The entropies, however, exhibited considerable and uniform changes: the greater the number of the Me groups, the more negative the entropic contribution was ($\Delta S^\circ = 0$ to -11 e.u.). Evidently, swapping the bromines in **2**, with methyl groups in **13**−**15** 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 5) calculations[9] verified this experimental observation. With the assistance of the hybrid exchange-correlation density functional (M05−2X), which has been optimized for dispersive interactions,[17] the binding energies (ΔE) were computed to parallel the experimental enthalpies.[9] 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 the methyl groups.[18]

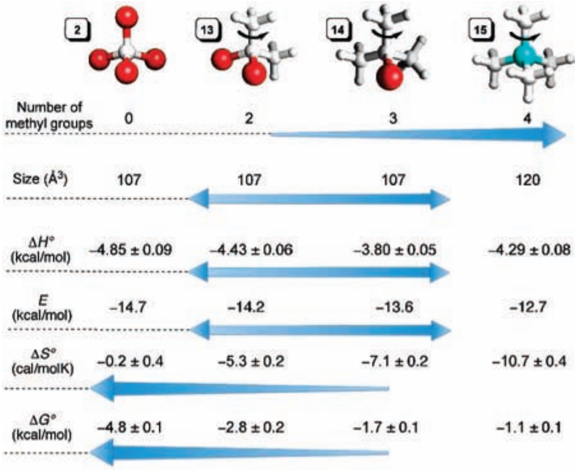

Figure 5. Chemical structures of **2** and **13-15**, and the corresponding thermodynamic parameters for the encapsulation. Computed binding energies (ΔE, kcal/mol),[9] at the M05−2X/6−31+G(d,p)//M05-2X/6-31G(d) level of theory.[17]

In summary, gated molecular baskets (Figure 1) are capable of enclosing a range of guests varying in size, shape and electronic characteristics. This property can be related to the considerable volume of the "dynamic" inner space that is created by revolving "doors" at the entrance: *the motion of the gates is restricted via intramolecular hydrogen bonding to allow for guests "spending" more time inside the host*! The packing coefficients are for **1** difficult to delineate precisely (Table 1), yet the entrapment can be observed for molecules 84−120 Å^3 in size: one, though, has to take into account both enthalpy (dictated by complementarity in volume, shape, and electrostatics) and entropy (internal mobility) to approximate the assembly thermodynamics. The kinetics of the encapsulation of molecules, presented here, is controlled via gating.[8] In view of that, the relationship between the trafficking of a range of guests and their reactivity can now be investigated in this modular setting.

Acknowledgment. This work was financially supported with funds obtained 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 methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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