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Guest Mobility Increases Hemicarceplex Kinetic Stability.

David Place, Joshua Brown and Kurt Deshayes*
Department of Chemistry
Bowling Green State University
Bowling Green, OH 43403

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Abstract: When acetophenone is incarcerated within hemicarcerand **1**, constructed with *o*-xylyl linker units, the guest resides exclusively along the long axis of the host. In contrast, the unsymmetric guests incarcerated within the more flexible hemicarcerand constructed with butylene linker units, **2**, show clear evidence of exchange between the hemispheres. The barriers of rotation proceed as: acetophenone > quinoline > indole. Host **2** retains acetophenone more strongly within its interior than **1**. The difference in stability is primarily due to an increased enthalpic component to the activation free energy for acetophenone egress from **2**.

Interest in non-covalent interactions between molecules dates back into the last century and remains a topic of intense interest. Methodology developed by the Cram group for the entrapment of molecules within closed surface hosts has added a new area of research to this field.[1,2,3] The hosts that are of particular interest to us are the hemicarcerands. The large kinetic barrier to egress allows hemicarcerands to retain guests within their interiors at room temperature, but permits irreversible guest release at elevated temperatures. It has been reported that incarcerated acetophenone spins rapidly around the long axis of the hemicarcerand **1**, constructed with o-xylyl linker units, Figure 1.[4] However, the acetyl group and the para-hydrogen occupy different hemispheres of the host, and do not interchange positions within the complex ("hindered guest rotation") at temperatures up to 125°C, above which measurements cannot be made because of rapid guest egress.

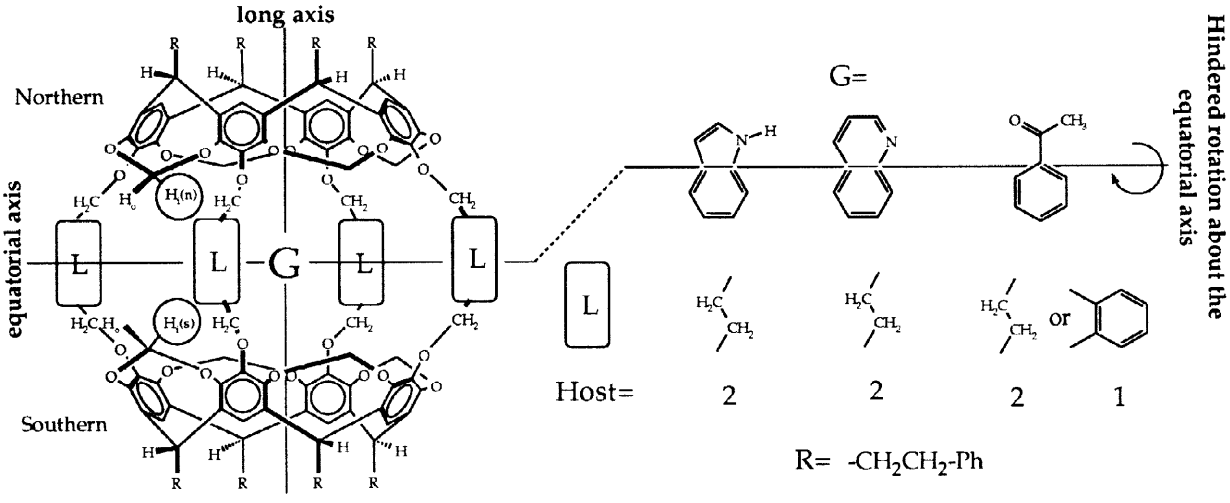

Figure 1: Structure of Hosts **1** and **2** and guests investigated in this study.

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In order to expand upon this observation, work was carried out with a more flexible host, **2**, constructed with butylene linker units. Hemicarceplexes of **2** containing acetophenone and carceplexes of **2** of the other guests having similar dimensions, shown in Table 1, were prepared. Using the principle of mass action, acetophenone was placed into the interior of **2** by exchange with the N,N-dimethylacetamide (DMA) guest in **2**·DMA by stirring at elevated temperature in a solution containing a large excess of acetophenone.[5] Quinoline and indole could not be introduced into **1** or **2** by this same method (i.e., driving these guests through the host portals) so a previously reported two step procedure was used.[2]

In all cases, the four fold symmetry evidenced in the NMR spectra indicates that the guest is spinning rapidly about the long axis of the host (data not shown). In contrast, the unsymmetric guest residing along the long axis of the host causes the interior hydrogens of the two hemispheres, marked as $H_i(n)$ and $H_i(s)$ in Figure 1, to be nonequivalent, and therefore exhibit unique chemical shifts. Portions of the variable temperature NMR spectra containing the $H_i(n)$ and $H_i(s)$ signals for **2**·acetophenone, **2**·quinoline and **2**·indole are shown in Figure 2.[6]

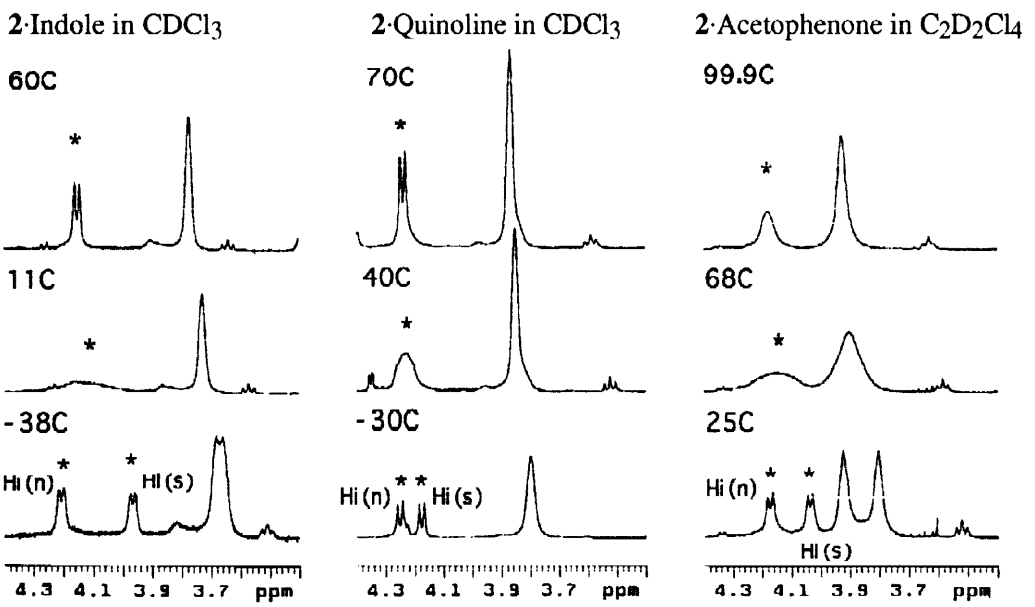

Figure 2: Host protons H_i are marked with (*).

As seen in Figure 2 all three complexes formed with host **2** show clear coalescence of the interior methylene (H_i) NMR signals. The guest in these complexes can be envisioned as behaving like a gyroscope that spins rapidly around the long axis while rotating more slowly about the equatorial axis.

The barrier to rotation can be calculated from the difference in chemical shift and the temperature of coalescence.[6] It is not possible to drive either quinoline or indole from the interior of **2**; however, slow irreversible acetophenone egress is observed above 100°C from which an activation free energy of egress can be calculated. Guest length, barrier to hindered rotation about the equatorial axis, and activation energy for acetophenone egress into DMSO solution are given in Table 1.

Table 1: Activation free energy for guest flipping about the equatorial axis in host **2** and thermodynamic parameters for guest egress.

		Hindered Rotation				Guest egress (25°C) in DMSO-*d6*		
Complex	Guest Size[a]	$\Delta\nu$ Hz	k_c Hz	T_c	$\Delta G^{\ddagger}_c$ kcal/mol	$\Delta H^{\ddagger}$ kcal/mol	$\Delta S^{\ddagger}$ cal /K mol	$\Delta G^{\ddagger}$ kcal/mol
2·Indole[b]	6.54	96	213.3	11°C	13.3	-	-	-
2·Quinoline[b]	7.18	29	64.4	40°C	15.7	-	-	-
2·Acetophenone	7.38	52	118.4	68°C	16.8	28.0	-3.5	29.0
1·Acetophenone[c]	7.38	-	-	-	-	19.7	-18.3	25.3

(a) Longest distance reported. (b) Guest egress not detected. (c) Coalescence not reached due to rapid guest egress at elevated temperatures, ref. 4.

Differences in shape, size and adaptability of the host portals have been shown to mediate activation energy of guest release,[7] and these factors are certainly important in this case. The structure of the two hosts provides evidence for the differences in the properties of their respective acetophenone complexes. The long axis of the cavity of **1** is 9.7 Å while the long axis of host **2** is 11.1 Å as determined by X-ray crystal structure analysis.[1] The larger and more flexible **2** can adapt to different guest orientations so that movement of the guest within host **2** is possible. In contrast, the smaller **1**, with its more rigid *o*-xylyl linker units, cannot adjust to guest motion, therefore acetophenone is frozen along the long axis of host **1** even at elevated temperatures.

Even though both indole and quinoline can rotate within the interior of host **2**, these guests cannot be driven through the host portals. The transition state for guest egress can be modeled as the guest moving into the portal of an extended host structure. It appears that the rigid polyaromatic guests cannot sustain the correct orientation needed to move into the portal of **2**. Examination of CPK molecular models suggests that rotation of the acetyl group of acetophenone out of the plane of the aromatic ring helps orient acetophenone within the host portal, which facilitates acetophenone egress.

The entropic contribution to the barrier for guest egress at 25°C for **2**·acetophenone is just 1 kcal/mol. The modest entropic cost for guest egress from **2**·acetophenone indicates the system becomes only slightly more ordered as it approaches the transition state. In contrast, under the same conditions the

entropic barrier for acetophenone egress from **1** is 5.6 kcal/mol. The more rigid structure of **1** creates a larger entropic barrier by limiting the possible geometries of the transition state. The entropic barrier is not crucial since the majority of the barrier to guest egress is found in the enthalpic component of the activation free energy, Table 1.

The enthalpic barrier to acetophenone egress from **2** at 25°C is 28 kcal/mol while the enthalpic barrier for acetophenone egress from **1** under the same conditions is 19.7 kcal/mol. There is an apparent contradiction in that host **2** appears to grasp acetophenone within its interior with the looser grip, yet retains acetophenone more tenaciously. However, host **2** can continually endeavor to maximize favorable host-guest interactions, and minimize disfavorable ones, as acetophenone rotates within its interior. The rigidity of **1** prevents optimization of the interactions between host and guest, and therefore retains the guest with strict orientation, but less strongly. The adaptive nature of host **2** may be part of the reason neither indole nor quinoline can sustain a geometry within **2** that permits guest egress, although without a comparison with data obtained using host **1** this hypothesis remains speculative.

In conclusion, a system in which a "perfect" fit is achieved between host and guest would not require structural adaptation of the components to maximize the decomplexation barrier. However, in the absence of optimum complementarity it appears that a dynamic receptor can have an advantage in thermal stability over a static receptor of similar structure and dimension.

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