Ring Inversion Dynamics of Encapsulated Cyclohexane

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Received May 8, 1997

Molecules completely surrounded by other molecules provide physical organic chemistry with the means to study reactive intermediates,[1] intermolecular forces,[2,3] and new forms of stereoisomerism.[4] The latter is a result of the considerable crowding that guest molecules can experience when their container hosts are held together with covalent bonds.[5,6] Assemblies held together by only hydrogen bonds—molecular capsules—can also form molecule within molecule complexes and are more dynamic. They assemble reversibly on time scales that range from hours to milliseconds,[7] and the following question arises: Are the capsules sufficiently rigid to constrain motions of molecules trapped inside? A study by Sherman[8] concludes that rotation of pyrazine within an unsymmetrical capsule is constrained and is slow on the NMR time scale. Here the ring inversion of encapsulated cyclohexane is used as a reporter of the conditions inside two capsules.

Cyclohexane can be encapsulated in a synthetic receptor having a flattened spherical shape: the "Jelly Doughnut" (Figure 1). At room temperature in a *p*-xylene-d_{10} solution, a slightly broadened NMR signal at −0.87 ppm for bound cyclohexane is evident.[9] On cooling, this signal further broadens and flattens into the baseline at 283 K (10 °C). [The solution freezes at lower temperatures.] The use of methylene chloride-d_2 allowed for studies at lower temperatures. When the Jelly Doughnut is dissolved in a mixture of cyclohexane-d_{11} and CD_2Cl_2 (15%, v:v), roughly half the complexes contain the cyclohexane derivative at room temperature.

Figure 2 shows the appropriate region of the proton NMR spectra (600 MHz) of the encapsulated cyclohexane-d_{11} at different temperatures. The low temperature extreme (Figure 2a) is reached at 203 K where a spacing ($\delta\nu$) of almost 600 Hz (∼1 ppm) is observed between the axial and equatorial positions of the lone proton.[10] Given that the $\delta\nu$ value for the "free" cyclohexane-d_{11} is less than 0.5 ppm, the environment inside the Jelly Doughnut produces a magnetic field corresponding to a spectrometer operating at 1.2 GHz! (The larger chemical shift difference between axial and equatorial hydrogens on the cyclohexane results from the anisotropy created by the host's triphenylene floor and ceiling.)

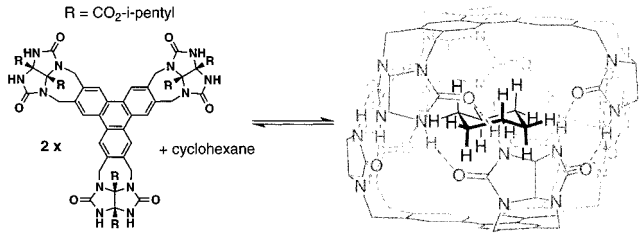

Figure 1. A triphenylene spacer adorned with three functionalized glycolurils dimerizes to form the Jelly Doughnut. The dimer, held together with 12 hydrogen bonds, readily encapsulates cyclohexane under a variety of conditions. (Note: Some groups have been removed for clarity.)

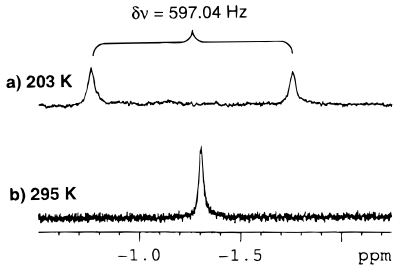

Figure 2. Portions of 600 MHz proton NMR spectra showing the resonance(s) of cyclohexane-d_{11} encapsulated within the Jelly Doughnut.

Given the $\delta\nu$ value and assuming a similar ring-inversion barrier for free[11] and encapsulated cyclohexane-d_{11}, a coalescence temperature (T_c) of about 241 K was predicted for the guest by the Eyring equation.[12] Surprisingly, an even higher T_c was found (248 ± 0.5 K). This corresponds to a free energy of activation at coalescence (ΔG^*) of 10.55 ± 0.05 kcal/mol. For the free cyclohexane derivative we observed a ΔG^* of 10.25 ± 0.05 kcal/mol at T_c = 233.5 ± 0.5 K, a value in excellent agreement with those (10.1−10.3 kcal/mol) found in a number of other studies.[11]

What causes the increased barrier for the guest's ring inversion process? Perhaps "cramped quarters" restrict cyclohexane's internal motions, thus raising the transition state for inversion. Molecular modeling[13] indicates that the volume of space inside the empty jelly doughnut (243 Å^3) shrinks slightly upon placing cyclohexane inside (229 Å^3). This appears to be driven by favorable van der Waals contacts between the six axial hydrogens and the π systems above and below.[14]

Since the transition state (the "half-chair" conformer) involves a partial planarization of the cyclohexane,[15] we doubt steric effects are responsible for the modest increase observed in activation energy. Another possibility is that encapsulation lowers the ground state of cyclohexane through favorable

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(10) All spectra were recorded with simultaneous deuterium decoupling. Prior to acquisition, the instrument and samples were allowed to equilibrate at the various temperatures for at least 1 h, and thermostat values fluctuated by no more than 0.5 K.
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(12) All calculations and coalescence spectra may be found in the Supporting Information. For analogous calculations involving cyclohexane-d_{11}, see: Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; VCH Publishers: New York, 1991; pp 267−274.
(13) Modeling was performed on an SGI Indy R5000 using Macromodel with Amber* minimization. (See: Mohamadi, F.; Richards, N. G. J.; Guidia, W. C.; Liskamp, R.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.) Cavity volumes were calculated for minimized structures using GRASP. (See: Nicholls, A.; Sharp, K. A.; Honig, B. *Proteins* **1991**, *11*, 281.)
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(15) Volumes were calculated for three conformers of cyclohexane: Chair = 87.2 Å^3; twisted boat = 86.4 Å^3; and half-chair = 87.2 Å^3. See ref 13.

S0002-7863(97)01489-3 CCC: $14.00

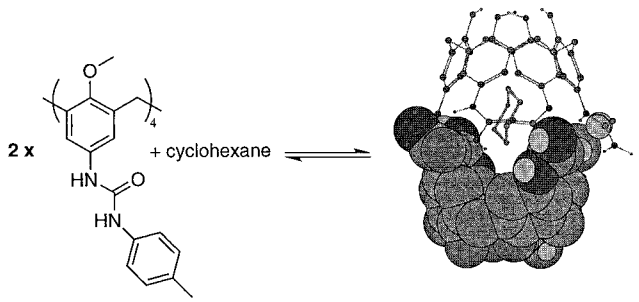

Figure 3. A functionalized calix[4]arene self-assembles forming a dimer capable of encapsulating cyclohexane. The split-view of the dimer shows one of the minimized structures for this system. (Note: Some of the groups have been removed from the dimer for clarity.)

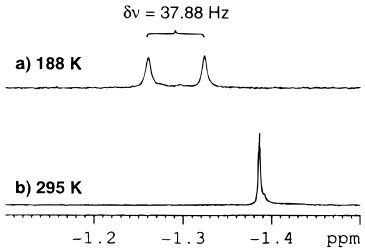

Figure 4. Portions of 600 MHz proton NMR spectra showing the resonance(s) of cyclohexane-d_{11} encapsulated within the calix[4]arene dimer.

contacts. The process leading from the chair-conformer to the transition state reduces the number and quality of favorable C−H (and C−D) to π contacts that *stabilize* the ground state. These contacts, worth a few hundred calories, are of the magnitude first measured by Wilcox with a molecular torsion balance.[16]

A second, smaller capsule is available from a functionalized calix[4]arene which dimerizes via hydrogen bonding (Figure 3).[17] Calculations and a recent crystal structure[18] converge on a value of 190 Å^3 for the cavity, large enough to accommodate cyclohexane. Indeed, a 1% solution of cyclohexane-d_{11} in toluene-d_8 (v:v) results in the encapsulation of cyclohexane in almost 50% of the dimers (Figure 4). Despite this relatively high affinity, no significant difference in activation energies was found for the ring inversions of free and encapsulated cyclohexane species ($\Delta G^* = 10.24$ and 10.27 ± 0.05 kcal/mol, respectively.[10,11]

This finding is in keeping with the differences between the cavities of the two hosts: the calixarene dimer boasts a much more spherical cavity. Several orientations corresponding to energy-minima are possible for the chair conformer within the dimer according to modeling. Each offers the possibility of CH to π interactions between the cyclohexane and the cavity's phenyl rings located in the "poles". However, there are a similar number of such contacts when the dimer is modeled while encapsulating the half-chair conformer of cyclohexane. There is no special stabilization of the ground state and, accordingly, no change in the activation energy.

Our original question asked if molecular capsules were rigid enough to constrain guest motion. For guests, the rigidity of capsules magnifies positive interactions with the host relative to the solvent and this leads to encapsulation. In some instances, these interactions may be favorable enough to restrict guest motions. Such should be the case in the contacts between the polarized C−H bonds of pyrazine and the electron rich phenoxide surfaces in Sherman's capsule.[8] In our case, C−H to π interactions likely raise the ring-inversion barrier of encapsulated cyclohexane.

In hydrogen bonded capsules, unfavorable interactions (i.e., sterics, coulombic repulsion) are not likely to be major contributors in the restriction of guest motion. Sizeable interactions of this nature probably would preclude encapsulation all together. In covalently sealed hosts, the possibility of guest expulsion is severely limited so guest motions may be hindered by other forces. Sterics, for example, are probably responsible for the hindered rotation of certain guests in Cram's carceplexes.[6] In contrast, gentle coercion is required to constrain guests of molecular capsules. Our current efforts are focused on teasing apart the subtle factors, at the subkilocalorie level, that describe these interactions of "molecules within molecules".[19]

Acknowledgment. We are grateful to the Skaggs Research Foundation and the National Institutes of Health for financial support. We also thank Ronald K. Castellano for the synthesis of the calix[4]arene dimer, Dr. Göran Hilmersson for experimental advice, and Dr. Sandro Mecozzi for computations.

Supporting Information Available: Coalescence spectra and a discussion of error analysis (1 page). See any current masthead page for ordering and Internet access instructions.

JA9714898

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