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Translational motion inside self-assembled encapsulation complexes

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Dedicated to the memory of Dmitry M. Rudkevich

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ABSTRACT

The motion of guests inside a cylindrical self-assembled host is studied through NMR techniques. Small molecules encapsulated alone, such as the gas molecules cyclopropane and butane, are found to exchange locations slowly but measurably on the NMR time scale using 2D techniques. These molecules can move past one another while still inside the capsule. When gases are coencapsulated with longer flexible molecules such as alkanes, less motion is apparent yet these can still slip by one another and folding of the alkanes also can be detected. Activation barriers for these processes are in the range of 15–17 kcal/mol.

1. Introduction

Reversible encapsulation complexes have become a tool of modern physical organic chemistry; recent reviews by Fujita,[1] Raymond[2] and this group[3] describe their applications and some of the unique phenomena that can be exposed by these complexes. Most of the capsules have roughly spherical spaces inside. These include tennis balls,[4] calixarene dimers,[5] and resorcinarene dimers,[6] whereas among the metal/ligand systems the spaces inside are, if not spherical, 'non-directional'. By this we mean that guests can freely spin, rotate, tumble, and translate within the host in all directions. With larger capsules such as softballs,[7] resorcinarene hexamers,[8,9] pyrogallolarene hexamers,[10,11] and some ligand/metal assemblies,[12] two or more molecules can be confined, yet the exchange of their positions in these spaces is also very rapid on the time scales available to study the motions such as NMR spectroscopy. The exceptions are the cylindrical capsules **1.1** (Fig. 1) introduced in 1998[13] and related structures.[14] In these, long molecules with different ends spin rapidly along the cylinder's axis but cannot tumble freely. The capsular assemblies show two different ends. Here we discuss the situation with two or more molecules inside.

The coencapsulation of two guests in the space can lead to a number of new forms of isomerism,[15] caused by the limited motion of the guests. A specific example, known as social isomerism[16] is shown in Figure 2 and involves the coencapsulation of chloroform with *p*-ethyl-toluene. The upfield regions of the NMR spectra (shown) reveal that two isomeric complexes are present: their signals are sharp and widely separated and speak for large energetic barriers between the two isomeric forms. They cannot interconvert while inside the capsule; chloroform is too large to slip past the aromatic while the *p*-disubstituted aromatic is too long to tumble readily within the capsule. Either of these motions could convert one isomer to the other. Instead, the interconversion involves the dissipation of one complex and reassembly in the new isomeric arrangement. Accordingly, exchange is slow on the NMR time scale but still fast on the human time scale, and this research was undertaken to get a measure of the dynamics of interconversion of such isomers.

We first observed such interconversions through the encapsulation of 1,2-dichloroethane in the cylindrical capsule (Fig. 3). Here, a single resonance for the guest was observed somewhat broadened in the NMR spectrum and 2D spectroscopy showed that the broadness was due to some extent because of the positional exchange of the terminal guests with the one in the center. The resonance for the latter was obscured by the alkyl groups on the periphery of the capsule so it was difficult to locate and accurately measure the cross-peaks.[17] Apparently, the long and narrow dihaloethane was able to slip past itself inside the capsule, perhaps aided by breathing motions that widen the center of the capsule. Such motions are energetically not costly as they distort only the hydrogen bonds of the capsule.

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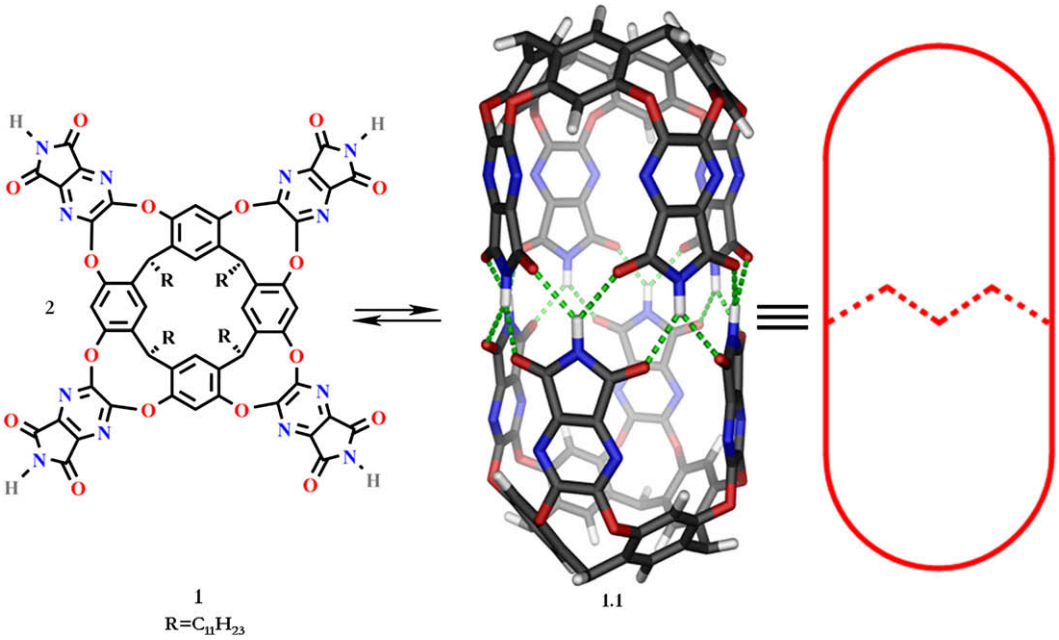

Figure 1. Formula of the resorcinarene-derived module **1** and its dimeric capsule **1.1**. The capsule is shown without peripheral alkyl groups and the cartoon used elsewhere in this publication is shown on the right.

We coencapsulated small gases such as ethane with longer alkane guests such as heptane. The NMR spectrum is shown in Figure 4 with 2D data given. The cross-peaks observed make it clear that C_1 and C_7 of the alkane exchange their chemical environments, but how is this accomplished?

One mechanism for exchange would involve movement of only the alkane, as shown in the cartoons (folding, Fig. 5), moving from **A** in the counterclockwise direction to **B**. End-over-end tumbling of the alkane would also result in the interconversion but this would require serious coiling of the alkane in order to shorten it enough to be able to move in the roughly 7 Å space. In cavitands, where 'breathing' near the open-ends takes place, tumbling of coiled octane has been observed.[18] A second and very different mechanism involves the exchange of positions of the two guests from their respective halves of the capsules (slipping, Fig. 5). Do the alkane and gas move past one another while still in the capsule? The two types of motion have different consequences. In the first, the capsule maintains its identity at both ends. In the second, these ends exchange environments. In those cases where the N–H signals are sufficiently separated in the NMR spectra, it may be possible to distinguish between the two mechanisms, i.e., to detect the exchange through N–H cross-peaks. The difference in chemical shifts is not easily predicted, particularly if both ends of the capsule are occupied by alkane guests.

A similar behavior was shown by the coencapsulation of cyclopropane with heptane. The latter gives a sharp spectrum that reveals something of the mobility of guests within **1.1** (Fig. 6). The volume of space taken up by the two different guest 'phases' is consistent with earlier experience. [14] The cross-peaks indicate that heptane 'folds' inside: C_1 exchanges with C_7, C_2 with C_6, etc., and the

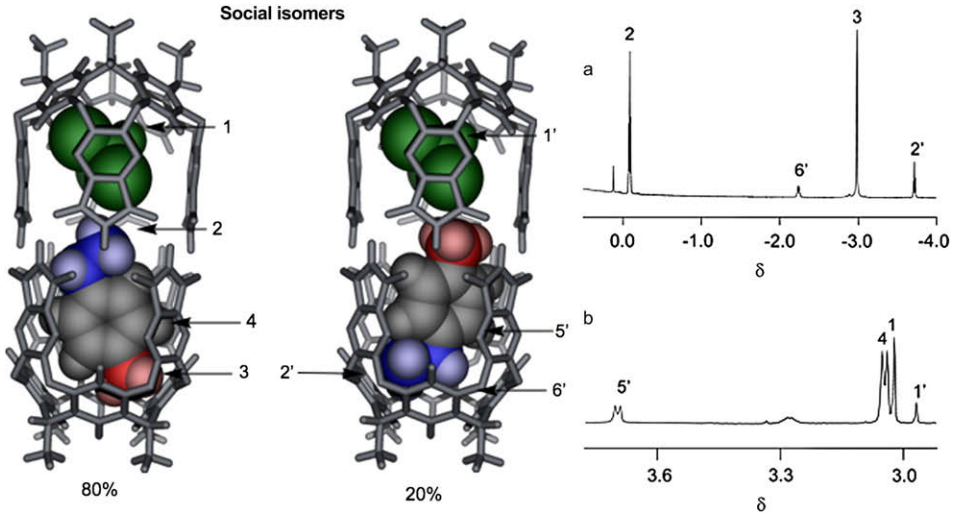

Figure 2. Isomeric coencapsulation complexes of chloroform (top) and *p*-ethyl-toluene (bottom). The guests are too large to exchange positions while inside the capsules, and separate sets of NMR signals are seen for the isomers. The ethyl group is shown in blue, methyl in red.

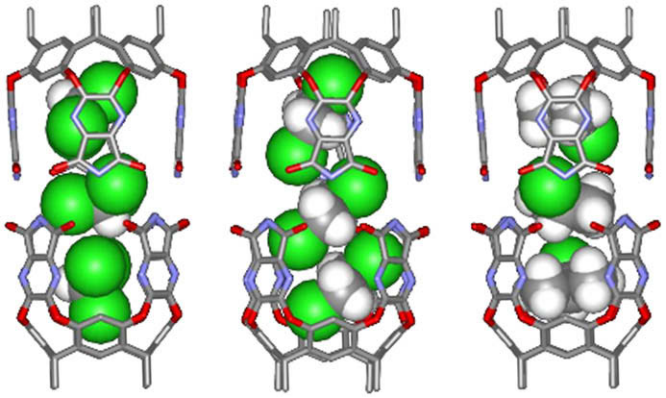

Figure 3. Capsules with three guests: chloroform (left), 1,2-dichloroethane (center), and isopropyl chloride (right). Only the dichloro guests can slowly exchange positions while inside the capsule.

NMR signals reveal the nature of the motion. The methyl group moves past the methylenes through a folded intermediate. Also, intermolecular NOE's are seen between both methyl groups and cyclopropane. But there is no exchange observed between the two imide N–H signals. *The two halves of the capsule remain distinct*. This indicates that the two guests do not slip past each other but stay in their respective halves of the capsule.

We were able to observe exchange of the slipping kind in the coencapsulation of ethane and 1,5-dichloropentane. Here, the spectra showed N–H exchange Figure 7. As mentioned earlier, 1,2-dichloroethane revealed that molecules of this size and flexible shape are able to slip past each other at rates that are detected on the NMR chemical shift time scale. The Cl atoms at the ends of the C_2 or C_5 chains are smaller than the methyl 'knobs' on the respective alkanes and this may aid the slipping mechanism. We also saw slipping in cases where all the coguests were gases.

The exchange of gas molecules in and out of the capsule on this time scale adds another complication that needs to be considered and thwarts a unique interpretation. If the gas leaves and the coguest slips to capsule's center, the ends of the capsule have exchanged environments, i.e., the return of a gas molecule to the capsule can occur at either end. We cannot exclude this mechanism at the present time for Figure 7. While it is available for all the cases discussed here, it can be excluded for those of Figures 4 and 6.

When **1** is dissolved in cyclopropane-saturated mesitylene-d_{12}, sharp signals appear in the NMR spectra and three cyclopropane guests can be seen inside (Fig. 8a). Separate resonances are seen for the cyclopropane at the middle of the capsule (−1.1 ppm) and the two at the ends (−4.2 ppm). To our knowledge, this was the first observation of more than one gas molecule in a self-assembled capsule. Initially the integration showed a nonintegral number of guests, but this was an artifact of the delay times in spectrum acquisition: the spin-lattice relaxation time (T_1) for cyclopropane guests located at the ends of cavity is 14 s and the one at the center of the capsule shows T_1 of 12 s. Accordingly, accurate integration requires delay times of unusual length (40 s), because there are few hydrogens on the inner surface of the capsule (or outside in the deuterated solvent). Two butane guests are observed in the capsule **1.1** under comparable conditions (see Fig. 8b). The chemical shifts of the methyl and methylene hydrogens indicate rapid tumbling within the space.

These guests exchange positions while within the capsule and exchange with external cyclopropane at detectable rates on the NMR time scale. Cross-peaks are seen in the 2D spectrum (Fig. 9) and integration allows an activation barrier to be calculated as 17.5 kcal/mol for the exchange inside the capsule.

In summary, both folding and slipping can be observed in coencapsulated guests. Cyclopropane can get past another of its kind

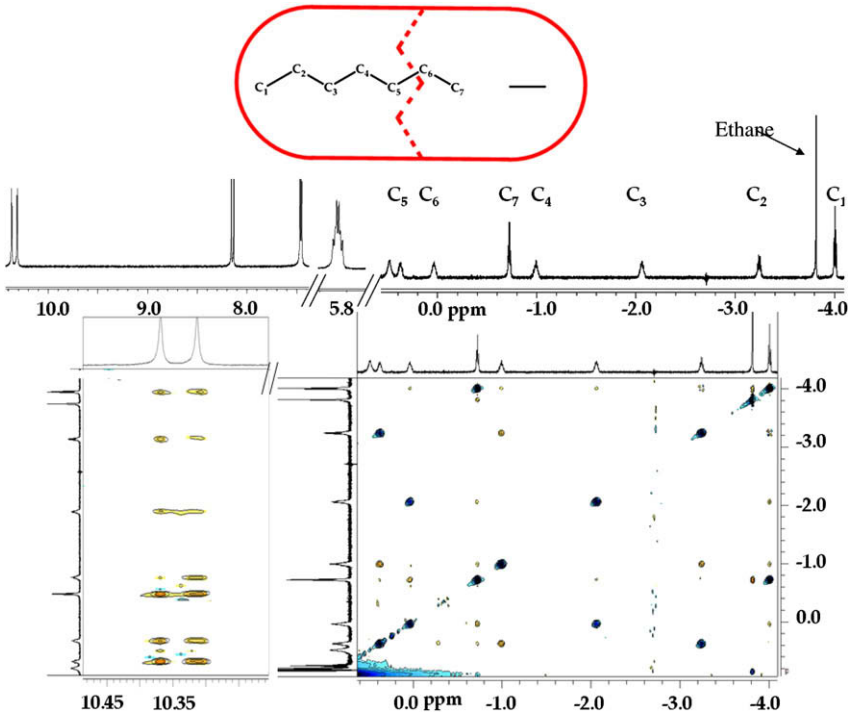

Figure 4. Coencapsulation of ethane and heptane. Top: portions of ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}). Center: 2D EXSY NMR spectrum (mixing time 300 ms); cross-peaks show exchange between C_1 and C_7, C_2 and C_6, etc. NOE's show that the methyl groups of heptane move near all the methylenes. Lower left: NOE's show that all hydrogens of the heptane pass near the imide N–H's at the center of the assembly, but ethane stays near the end of the capsule. Ethane moves in and out of the capsule on this time scale.

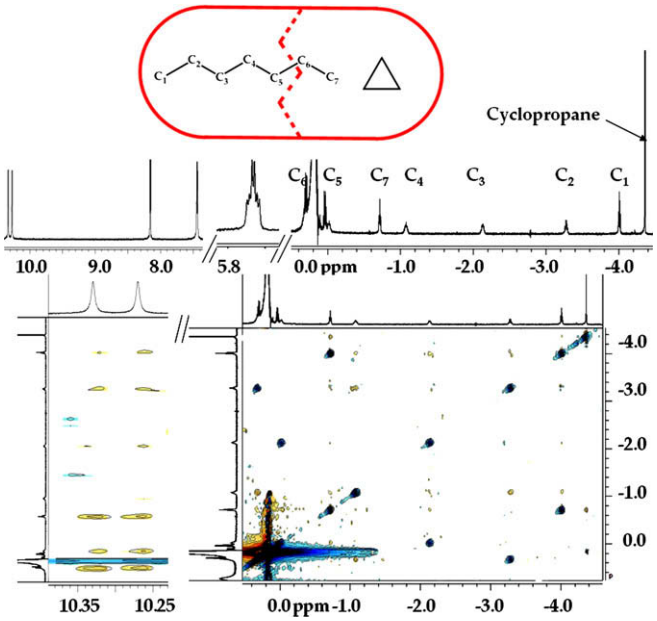

Figure 5. Cartoon depictions of exchange mechanisms: in folding the ends of the capsule remain different; in slipping the ends exchange environments. The circled C represents any coguest of the alkane.

inside and so can *n*-butane, but cyclpropane does not slip past heptane. It is tempting to conclude that small gases (if these terms are applicable to single molecules) can exchange positions, but coencapsulation with a liquid or solid slows the translational motions.

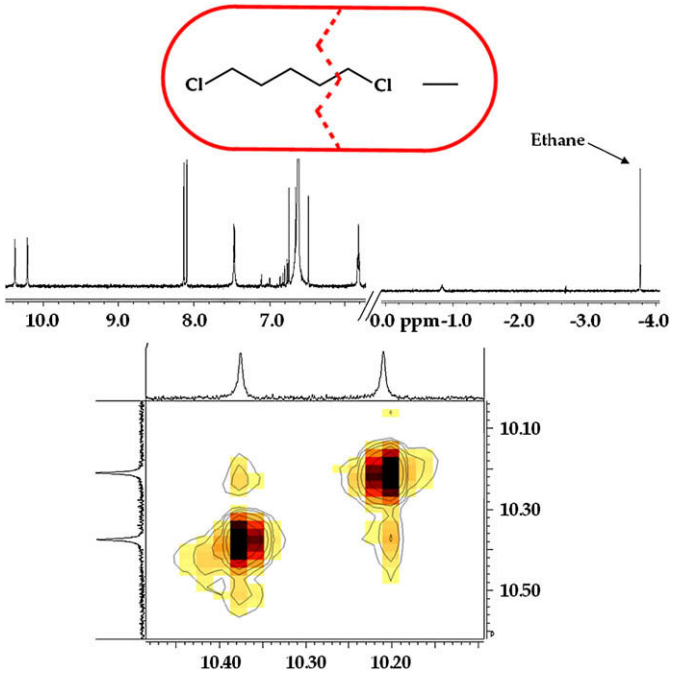

Figure 6. Coencapsulation of cyclopropane and heptane. Top: portions of ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}). Center: 2D EXSY NMR spectrum (mixing time 300 ms);Cross-peaks show exchange between C_1 and C_7, C_2 and C_6, etc. NOE's show that only the methyl groups of heptane are near the coguest. Lower left: NOE's show that all hydrogens of the heptane pass near the imide N–H's at the center of the assembly, but cyclopropane does not. Cyclopropane moves in and out of the capsule on this time scale.

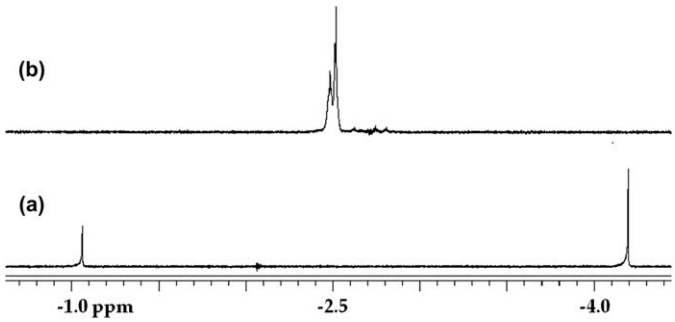

Figure 7. Coencapsulation of ethane and dichloropentane. Top: portions of ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}). Bottom: 2D EXSY NMR spectrum (600 MHz, mesitylene-d_{12}, mixing time 300 ms).Cross-peaks show exchange between the two halves of the capsule, consistent with the slipping mechanism of Figure 5.

2. Experimental section

2.1. General considerations

^{1}H NMR and 2D spectra were recorded on a Bruker DRX-600 spectrometer with a 5 mmQNP probe. Proton (^{1}H) chemical shifts are reported in parts per million (δ) with respect to tetramethylsilane (TMS, δ=0) and referenced internally with respect to the protio solvent impurity. Deuterated mesitylene (d_{12}) was obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA) and used without further purification.

2.2. Procedure for NOESY/EXSY experiments

The NOESY spectra were recorded at 300 K at 600 MHz with the phase-sensitive NOESY pulse sequence supplied with the Bruker software. Each of the 512 F1 increments was the accumulation of 40

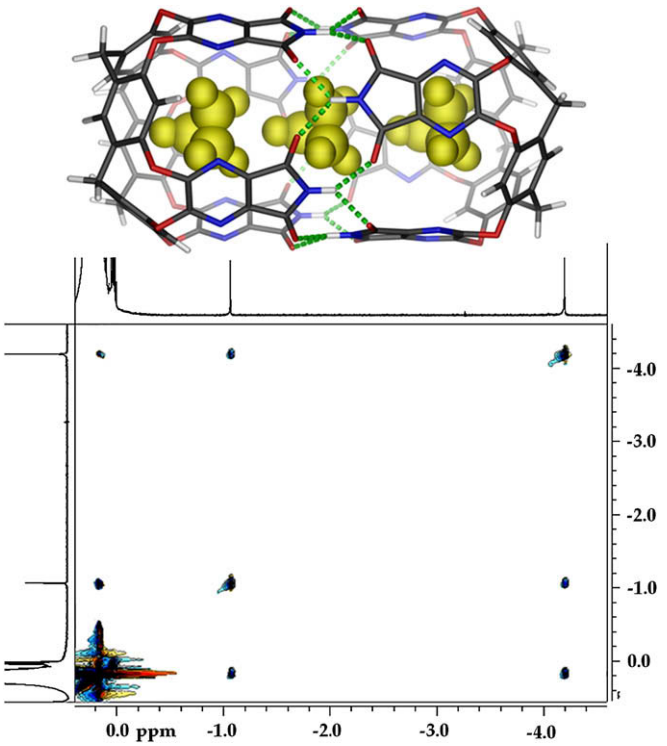

Figure 8. Upfield regions of the ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}) spectra of encapsulated cyclopropane and *n*-butane. Solutions of **1.1** (2 mM) in (gas-saturated) mesitylene-d_{12} were used to obtain the spectra: (a) cyclopropane (b) *n*-butane.

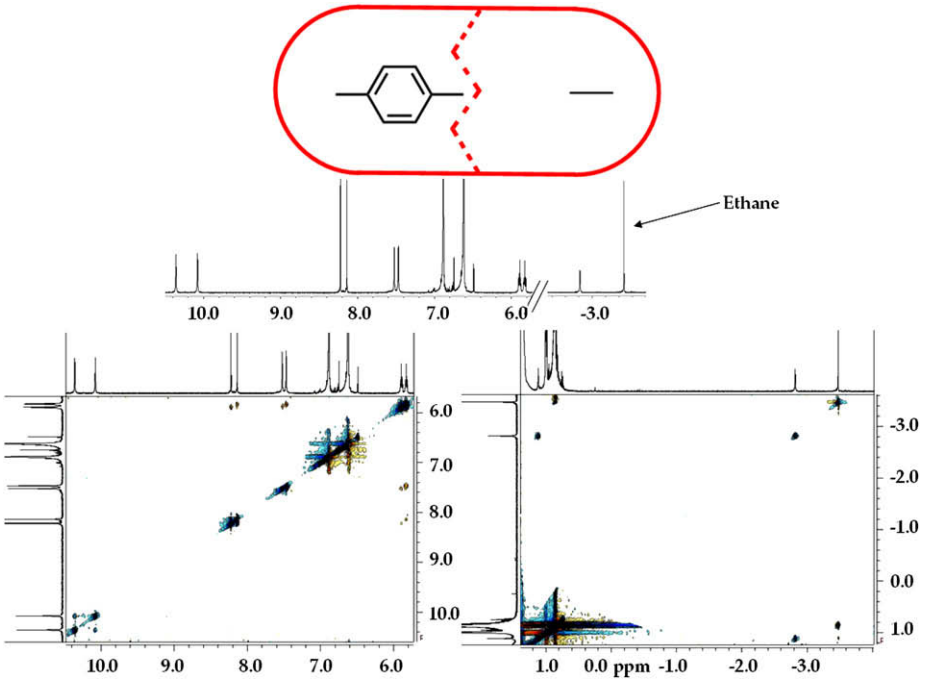

Figure 9. 2D EXSY NMR spectrum (600 MHz, mesitylene-d_{12}, mixing time 300 ms) of encapsulated cyclopropane; cross-peaks indicate the exchange of guest positions within the capsule and exchange from both positions with external cyclopropane.

scans with a 300 ms mixing time. The MestreC program (Mestrelab Research, Santiago de Compostela) was used to analyze the spectra. Before Fourier transformation, the FIDs were multiplied by a 90° sine square function in both the F2 and the F1 domains. 1K×1K real data points were used, with a resolution of 1 Hz/point. For EXSY analysis, two spectra were taken sequentially, first with 300 ms mixing time and then with 0 ms mixing time. The magnetization transfer rate constants, $k1$ and k-1, were calculated using the EXSYCALC program (Mestrelab Research). The rate constant k is the sum of the two dependent magnetization transfer rate constants $k1$ and k-1 obtained from the calculations, an approximation due to the system being in equilibrium. $\Delta G^{\#}$ was obtained using the Eyring equation with error of ±0.1 kcal/mol.

2.3. T_1 measurements

Longitudinal relaxation times (T_1) values were measured by the inversion recovery technique. A waiting time (T_W) of at least five times the longest relaxation time was used. All spectra were recorded at 300 K, and each run took 12–16 h. T_1 values were determined by a linear least squares, two parameter fit of the experimental data directly performed by XWINNMR program (Bruker). At least 14 points were included for each T_1 calculation.

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