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Chemistry in Confined Spaces: High-Energy Conformer of a Piperidine Derivative is Favored Within a Water-Soluble Capsuleplex

Mintu Porel,[†] Nithyanandhan Jayaraj,[†] S. Raghothama,[‡] and V. Ramamurthy*,[†]

Department of Chemistry, University of Miami, Coral Gables, Florida 33124, United States, and NMR Research Centre, Indian Institute of Science, Bangalore, 560 012, India

murthy1@miami.edu

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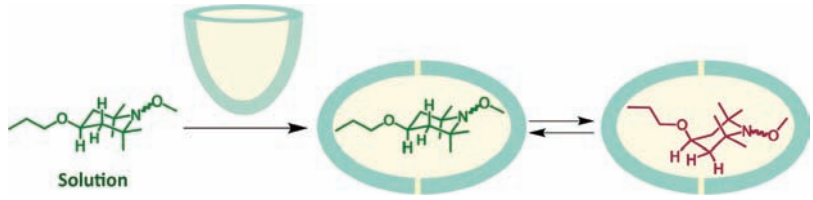
ABSTRACT



Propyloxy-substituted piperidine in solution adopts a conformation in which its alkoxy group is equatorially positioned. Surprisingly, two conformers of it that do not interconvert in the NMR time scale at room temperature have been found within an octa-acid capsule. The serendipitous finding of the axial conformer of propyloxy-substituted piperidine within a supramolecular capsule highlights the value of confined spaces in physical organic chemistry.

Confined spaces offer a unique opportunity to examine and manipulate the properties of small molecules and reactive intermediates.[1,2] Pioneers Cram and co-workers established in 1991 the storage of the highly reactive cyclobutadiene in solution within a hemicarcerand at room temperature.[3] Their predicted possibility of synthesis and examination of a number of reactive species within the inner phases of appropriate hemicarcerands have been realized during the last two decades; persistency when generated within a hemicarcerand in solution of transient species such as benzyne, cycloheptatetraene, enol, carbene, and nitrene has been demonstrated.[4] However, conformational isomers of cyclohexanes trapped within the confined spaces of synthetic cavitands at room temperature remain elusive.[5,6] In this context, it must be noted that within solid thiourea channels the preferred conformation of a few monohalocyclohexanes has the halogen axially positioned and differs from their equatorial position in solution.[7,8] This communication is concerned with stabilization of a high-energy conformer of a piperidine derivative within the confined space of a capsule made of two octa-acid molecules (OA, Scheme 1), at room temperature in aqueous solution.[9−11] We have carried out ^{1}H NMR experiments on capsuleplexes of piperidine derivatives **2a**−**e** (Scheme 1) within OA in aqueous solution.[12]

[†] University of Miami.
[‡] Indian Institute of Science.

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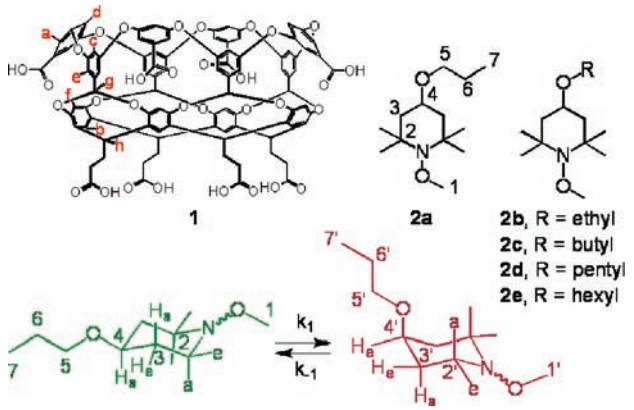
Scheme 1. Chemical Structures of Octa-Acid (**1**) and Piperidine Derivatives **2a**−**e** Examined in This Study[a]



[a] Two possible conformations of **2a** with respect to the C−O−alkyl substitution are also shown. These two conformations are color coded in accordance with the NMR spectra displayed in Figures 2 and 3.

These spectra revealed that **2a** exists in two distinctly different noninterconverting conformations at room temperature within the OA capsule, while **2b**−**e** adopt the same conformation both in the OA capsule and in solution.

First, we present the results on **2b**−**e** that set the stage to understanding the unique behavior of **2a**. ^{1}H NMR titration experiments of **2b**−**e** with OA established that they form 1:2 (guest:host) complexes in water at pH 8.5 (sodium tetraborate buffer). Inclusion of the guest is revealed by the significant upfield shift of the C−O−alkyl hydrogen signals, especially the CH_3 group of the alkyl chain (Figures S1 and S2 in Supporting Information, [SI]).[13] 2D DQF COSY ^{1}H NMR correlation spectra of **2b**−**e**@OA_2 helped us identify the conformation of guest molecules within the capsule (Figures S3−S6 in SI). Strong cross peaks between diaxial and geminal-hydrogens and weak or negligible cross peaks between axial−equatorial hydrogens are expected in DQF-COSY spectra.[14,15] In Figures S3−S6 (SI), strong cross peaks between geminal hydrogens at C-3 (marked as 3a and 3e) and between vicinal hydrogens at C-4 (marked 4) and one of the two hydrogens at C-3 (marked 3a) are observed. The absence of a cross peak between C-4 and C-3e hydrogens is noteworthy. These data suggest that the conformation adopted by **2b**−**e** within the OA capsule has the O−alkyl group placed equatorially (Scheme 1). By examining Figures S7 and S8 (SI), we came to the conclusion that in D_2O both **2b** and **2c** adopt the same conformation as in a capsule.

The single set of H-d and H-f hydrogens in each of the four symmetrical panels of the OA cavitand results in an identical chemical shift of all these hydrogens. When the capsuleplex of two OAs and a guest is symmetrical, only a single signal each for all eight H-d and all eight H-f hydrogens is expected. However, the host NMR signals of capsuleplexes of **2b**−**e**@OA_2 reveal the presence of independent signals for some of the identical OA hydrogens present on the top and bottom halves of the capsule (e.g., signals due to H_e in **2b** and signals due to H_{a-f} for **2c**−**e** in Figure S2, SI). This suggests that **2b**−**e** do not tumble freely within the capsule, which makes the two halves of the capsule identical, in the NMR time scale at room temperature.

Although **2a**, similar to **2b**−**e** discussed above, formed a 1:2 capsuleplex (Figure S9, SI), it exhibited a distinctly different behavior. Examination of ^{1}H NMR spectra of OA, **2a**, and **2a**@OA_2 displayed in Figure 1 reveals that for the

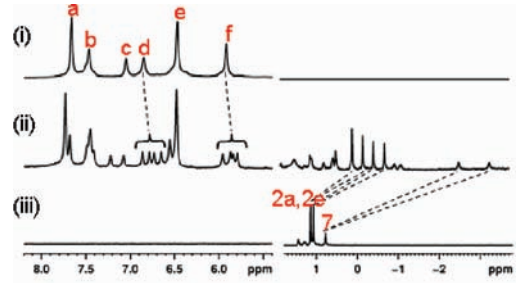


Figure 1. Partial ^{1}H NMR spectra (500 MHz, D_2O) of (i) OA, (ii) **2a**@OA_2 ([OA] = 1 mM; [**2a**] = 0.5 mM; 10 mM sodium tetraborate buffer), and (iii) **2a**. Host resonances are labeled in letters "a−f", and guest resonances are labeled in numbers.

capsuleplex **2a**@OA_2 four signals for each of the H-d and H-f of OA and two signals for each of the guest methyl groups marked 2a, 2e, and CH_3-7 are present. Note that for **2b**−**e**@OA_2 only two signals for each of H-d and H-f of OA and one signal each for 2a, 2e, and the terminal alkyl methyl group were present (Figures S1 and S2, SI). This difference suggested that **2a** forms two types of complexes with OA. The presence of four distinct signals for H-d and H-f of OA is consistent with the existence of "two independent unsymmetrical complexes in solution" with one set of signals (two H-d, two H-f, and one CH_3-7) belonging to one complex and the other set to the second complex.

One possibility for the above hypothesis of "two independent unsymmetrical complexes" is that the guest **2a** is captured in two different conformations within the capsule (Scheme 1). The 2D DQF COSY NMR spectrum of **2a** in D_2O confirmed that this molecule exists in only one conformation in solution similar to **2b**−**e** (Figure S10, SI). Given the existence of **2a** in a single conformation in solution (C−O−alkyl at equatorial position), the possibility of trapping an alternate conformer with the C−O−alkyl group at the axial position seemed exciting. The observed two distinct signals suggested that there may indeed be two conformers trapped within the OA capsule and that they do not interconvert between the two conformers in the NMR time scale at room temperature. To examine if the two conformers interconvert at a longer time scale, we recorded

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a 2D ROESY spectrum with 300 ms mixing time at room temperature; partial spectra are displayed in Figure 2 and

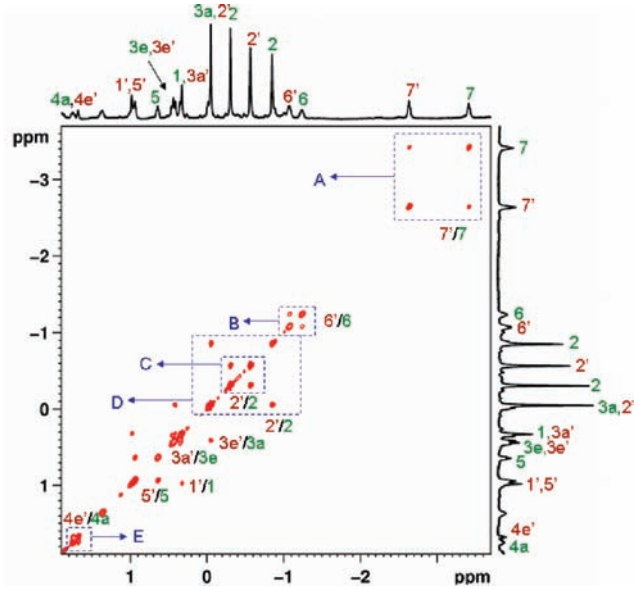

Figure 2. Partial 2D ROESY spectrum (500 MHz, mixing time = 300 ms) of **2a**@OA_2 ([OA] = 5 mM; [**2a**] = 2.5 mM in 50 mM sodium tetraborate buffer). The color represents the proton of the conformer of the same color in Scheme 1 (bottom) for **2a**. In these spectra, we are unable to unequivocally assign the four signals seen for the four methyl groups at 2,2′ positions to the exact conformer. The color codes shown for the methyl groups should be taken as tentative assignments.

Figure S11 (SI), respectively. Since the diagonal and cross peaks have different signs, the exchange peaks (EXSY) and NOESY peaks are easily distinguished in the ROESY spectrum (see boxes Y and X in Figure S11; SI).[16−18] Importantly, the EXSY cross-peaks have the same sign as the diagonal. Examination of Figure 2 showing the signals due to methyl groups of the guest (marked CH_3-7, CH_3-7′, CH_3-2, and CH_3-2′) as well as others (see boxes A, B, C, D, and E) suggests that the corresponding signals exchange in the time scale (300 ms) of the ROESY experiment. The two sets of peaks have thus been identified based on 2D ROESY cross peaks to be due to two species (possibly conformers) that exchange in 300 ms and accordingly are color coded green and red in Figure 2.

In Figure S12 (SI), a partial 2D ROESY spectrum displaying the NOESY interaction between the host and guest signals is displayed. From this, it is clear that H-g signals of the two halves of the capsule interact with the CH_3-7 and OCH_3 signals of both isomers of the guest suggesting that the two ends of the two conformers are anchored at the two tapered ends of the capsule. Very important information is gained from examination of the correlation between H-d signals of the host and 2,2′ CH_3 signals of the guest. Examination of Figures S12 and S13 (SI) reveals that the methyl groups at the 2-positions of both isomers interact with the H-d signal of the host that is split into four, one set for the axial and one for the equatorial isomer complex. This suggests that the relative locations of the two isomers are similar within the capsule.

Confirmation that the above two sets of signals to be indeed due to two conformers of **2a** whose C−O−alkyl groups are positioned axially and equatorially, respectively, came from DQF COSY ^{1}H NMR spectrum of **2a**@OA_2 (Figure 3 and Figure S14 in SI). Cross peaks between vicinal

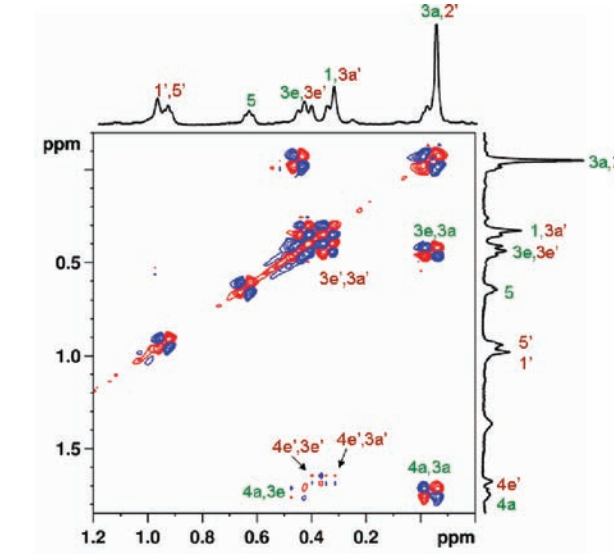

Figure 3. Partial 2D DQF COSY NMR spectrum (500 MHz, mixing time = 300 ms) of **2a**@OA_2 ([OA] = 5 mM, [**2a**] = 2.5 mM in 50 mM sodium tetraborate buffer). Chemical structures of two conformers are represented in two different colors. The color of the assigned protons in the 2D DQF COSY NMR spectrum represents the proton of the conformer with that particular color.

hydrogens H-4 and H-3 (axial) and H-3 (equatorial) of the guest in the DQF COSY NMR spectrum provided the most important information. In the green set of signals, H-4 correlates strongly with one of the two H-3 hydrogens (marked 3a) and poorly with the other H-3 (marked 3e). Such a correlation is consistent with the hypothesis that the green and red signals correspond to the guest with the C−O−alkyl group positioned equatorially and axially, respectively. It is important to note that according to the DQF COSY ^{1}H NMR spectrum of **2a** in D_2O only one conformer with the C−O−alkyl group at the equatorial position is present in solution (Figure S10 in SI).

To examine the possibility of interconversion between the two **2a**@OA_2 complexes, we recorded ^{1}H NMR spectra at different temperatures. As illustrated in Figure 4 (and Figure S15 in SI) at 70 °C, the four signals due to H-d and H-f of host OA coalesced into two, while the guest methyl signals remained unaffected. The change in only the host signals

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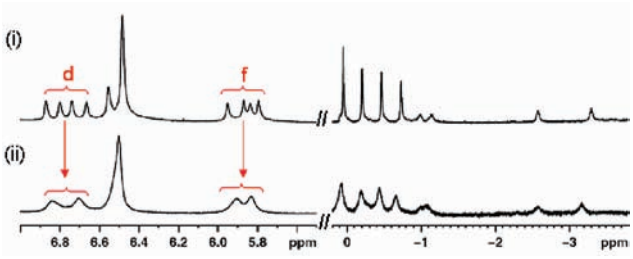

Figure 4. Partial ^{1}H NMR spectra (400 MHz, D_2O) of **2a**@OA_2 ([OA] = 1 mM, [**2a**] = 0.5 mM, in 10 mM sodium tetraborate buffer) at (i) 25 °C and (ii) 70 °C.

suggested that the capsule was becoming symmetrical at higher temperatures.

We interpret the absence of influence of temperature on the guest signals to indicate that at 70 °C it tumbles freely within the capsule without any interconversion between the two chair forms. To gain support to this thought, we recorded ^{1}H NMR spectra at various temperatures for **2b** and **2c** (smaller and larger molecules, respectively, than **2a**; i.e., R = CH_2CH_3 and $CH_2CH_2CH_2CH_3$). It is clear that coalescence of signals for **2b** occurred between 45 and 55 °C (Figure S16 in SI), while it was absent for **2c** even at 70 °C (notice the H-a, H-c, and H-f peaks in Figure S17, SI). From these observations, we conclude that the rate constants for the tumbling motion of the guest that would make the top and bottom halves of the capsule identical vary with the size of the guest molecule (**2b**@OA_2 > **2a**@OA_2 > **2c**@OA_2).

Although there was no change in the guest signals with respect to temperature, 2D ROESY experiments carried out at 300 ms and zero mixing times at various temperatures with **2a**@OA_2 enabled us to estimate the activation parameters for chair−chair interconversion of **2a**.[19] In these experiments, the areas under cross and diagonal peaks (Figure S18 (SI)) were integrated for a particular set of protons that exchanged. Examination of the data provided in Figure S18 (SI) reveals, as expected, the absence of cross peaks at zero mixing time suggesting the absence of magnetization transfer. Introduction of the integration values in the EXSY CALC program[20] provided the magnetization exchange rate constants that are related to the conformer exchange rate constants k_1 and k_{-1} (for definition see Scheme 1). The activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) calculated from the Eyring plot shown in Figure S19 (SI) for the forward process (k_1; Scheme 1) were 17.7 kcal mol^{-1} and 1.75 eu, respectively, and for the reverse process (k_{-1}; Scheme 1) were 18 kcal mol^{-1} and 2.52 eu, respectively. On the basis of integration of the ^{1}H NMR signals due to conformers, we conclude that the two isomers are present at a ratio of 53:47, indicative of a significant lowering of the energy of the axial conformer within the capsule. No signals due to free host and guest molecules were present in ^{1}H NMR spectra, both at 25 and 70 °C, suggesting that in the NMR time scale the complex is stable (Figures S15 and S20, SI). On the basis of this, we conclude that the kinetic parameters calculated above are not complicated by dissociation of the complex.

In this study, we have demonstrated the possibility of trapping a high-energy conformer of a piperidine derivative within a supramolecular assembly in aqueous solution. It is important to note that although only one of the five molecules we investigated exhibited the unusual behavior it was neither the smallest nor the largest in the series. Successful trapping of this molecule, albeit not an ideal or a general example, in a high-energy conformation within a capsule is suggestive of the possibility of yet to be discovered examples.

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Supporting Information Available: Experimental procedure and additional ^{1}H NMR, 2D DQF COSY NMR, 2D ROESY, variable-temperature ^{1}H NMR spectra, Eyring plot, and ^{1}H NMR of compounds **2a**−**e** as mentioned in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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