ORGANIC LETTERS

2004
Vol. 6, No. 12
1967−1970

Supramolecular Recognition and Structural Elucidation of Inclusion Complexes of an Achiral Carbene Precursor in β- and Permethylated β-Cyclodextrin

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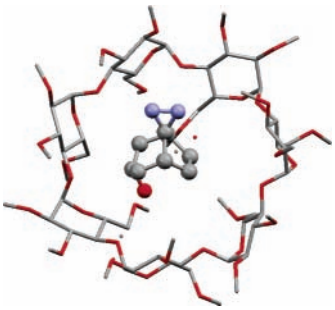
Received March 19, 2004

ABSTRACT



Inclusion of achiral carbene precursor *endo*-8-azibicyclo[3.2.1]octan-3-ol (1) in chiral β-cyclodextrin (7-Cy) and tri-*O*-methyl-β-cyclodextrin (TRIMEB) leads to 1:1 complexes 1@7-Cy and 1@TRIMEB, respectively. The combined methods of induced circular dichroism, NMR spectroscopy, and X-ray structure determination were employed for the first time for structural elucidation of the complexes in solution and the solid state. Significantly different orientations of 1 were observed. Compared with 1@7-Cy, 1@TRIMEB exhibits a different guest orientation and an association constant one-twentieth lower.

Cyclodextrins (Cy) have successfully been used in supramolecular carbene chemistry to modify the course of the reaction of included guests.[1] One aim of our research is to find new reaction pathways inside host molecules, for example to enhance the intra- and innermolecular selectivity of C−H insertions of carbenes. Since, in a confined space, reactive species cannot react indiscriminately, we expected to reach this goal by complexation of the carbene precursor. As a guest, we used *endo*-8-azibicyclo[3.2.1]octan-3-ol (**1**) because of its size and the known chemistry of the parent carbene.[2]

During the investigation of aziadamantane complexes, we recognized that the generated carbenes, among other reactions, tend to attack the hydroxy groups of the cyclodextrins employed.[1,3] Therefore, heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB) was used as a host with an anticipated reduced inner reactivity toward carbenes. TRIMEB was prepared from β-cyclodextrin (**7-Cy**) with methyl iodide and NaH in DMSO.[4] Its purity was established by careful

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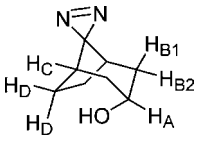
10.1021/ol049478o CCC: $27.50
Published on Web 05/18/2004

integration of the signals for the methyl groups in the ^{1}H NMR spectrum and by ESI-MS. As a model guest compound, symmetrical *endo*-8-azibicyclo[3.2.1]octan-3-ol (**1**) was synthesized from bicyclo[3.2.1]oct-2-en-8-one ethylene acetal, which was prepared by condensation of an enamine derived from cyclopentanone with acrolein.[5] After regioselective oxymercuration[6] (71%) and Schmitz diazirine synthesis,[7] **1** was obtained in 61% yield. The complexes were formed by mixing guest and host together in the solvent used for the measurements (vide infra). Next, information was gathered about the geometry of the obtained complexes. Here, the results of our structural investigation of the complex between **1** and **7-Cy** and TRIMEB, respectively, are presented. In this study, both induced circular dichroism (ICD) and NMR spectroscopy (ROESY, Job's diagram) were employed.[8]



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First, the interaction between **1** and **7-Cy** was investigated. For this purpose, the stoichiometry was determined by the method of continuous variations (Job's method).[9] Nine samples of a mixture of host and guest were prepared, and the total concentration was kept constant at 8.81 mM. As a consequence of the lack of solubility of the diazirine **1** in pure water, this measurement was performed in the presence of 10% methanol. The position of the maximum at a mole fraction of 0.5 indicates a 1:1 stoichiometry (Figure 1).[9] In

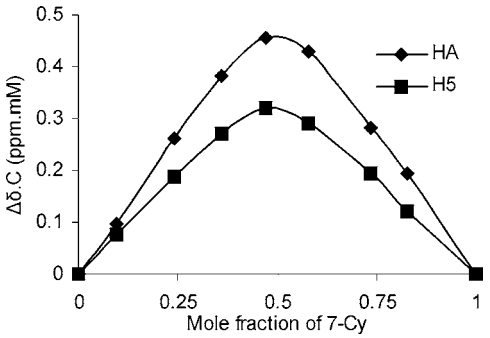

Figure 1. Job's diagram for **1@7-Cy** in D_2O/MeOD 90/10, with $[\mathbf{1}]_o + [\mathbf{7\text{-}Cy}]_o = 8.81$ mM for a proton of the guest and of the host.

this experiment, no new peaks appeared; only the signals were shifted. This means that the complex is in fast exchange with the free components. Next, an NMR titration[10] was performed to determine the association constant *K*. To avoid a large excess of one of the components required by the traditional linearization methods, a curve-fitting procedure[11,12] was chosen using the following equation[13] that describes fast exchange systems ($\Delta\delta$ represents the changes in the shifts of the observed compound B. A and B are the concentrations of the two components):

$$\Delta\delta = 0.5\Delta\delta_{max}[(A + B + (1/K)) - [(A + B + (1/K))^2 - 4AB]^{1/2}]/B$$

A binding constant of 11 200 ± 3000 M^{-1} was obtained observing the shift of H_5 in D_2O. The relatively large deviation is due to the fact that *K* is large, and at the concentrations needed for NMR measurements, full complexation almost always prevails. Therefore, this experiment was repeated in D_2O/MeOD 90/10 in order to obtain a more accurate value. As expected, in this solvent mixture the complex is weakened and gives rise to a *K* of 2900 ± 600 M^{-1}.

These measurements also provide information about the geometry of the complex: in the presence of **7-Cy**, all signals of **1** are shifted, especially H_D and H_{B2}, whereas H_{B1} produces the smallest changes (less than 0.03 ppm). The guest too causes changes in the chemical shift of the host, but only for H_3 and H_5. Changes in the shift of the **7-Cy** protons H_1, H_2, and H_4 which are located on the outside of the cavity (Figure 2), are not observed. These results show that **1** is totally entrapped in the cavity and that no other association complexes are formed.

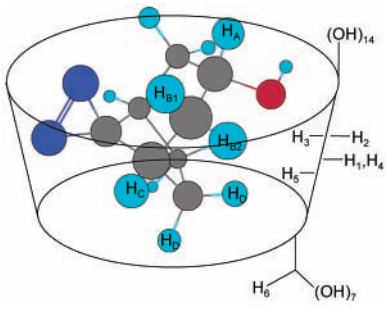

Figure 2. Proposed geometry for **1@7-Cy** in solution according to NMR experiments.

2D ROESY experiments offer a second possibility to investigate the complex by NMR spectroscopy. For **1@7-Cy**, no intense intermolecular cross-peaks with H_A were observed. H_3 shows cross-peaks with all other guest protons, whereas H_5 gives only one strong signal with H_D. Hence, H_A is close enough to the cyclodextrin inner wall to undergo changes in the chemical shift. However, its intermolecular

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NOE is only 25−35% of the NOE of the other guest protons to H_3 and H_5 of **7-Cy**. These observations imply that the hydroxy group of **1** is located on the wider rim of **7-Cy** and the diazirine group is not very deeply submerged into the cavity, but close to the secondary OH-groups as shown in Figure 2. This is also corroborated by the ICD spectrum of **1@7-Cy**, which is quite typical for a diazirine in a polar solvent.

1@7-Cy was also analyzed by induced circular dichroism (ICD) to support the previous results. The investigation of the complex was performed in water and in H_2O/EtOH 70/30 as well. A positive Cotton effect and a linear Scatchard plot[14] were observed for both solvents. This also confirms the formation of a 1:1 complex. The data were then treated by the curve fitting method using the ICD version of the general equation (B is the concentration of the compound bearing the chromophore):

$$\Delta\epsilon = 0.5\Delta\epsilon_\infty[(A + B + (1/K)) - ((A + B + (1/K)^2 - 4AB))^{1/2}]/B$$

The calculated points were fitted to the experimental points by minimizing the sum of the squares of their difference using the quasi-Newton method from the Solver Add-in of Excel.[11] An association constant of 760 ± 100 M^{-1} was obtained in water/ethanol 70/30 ($\Delta\epsilon_\infty = 0.099$) and of 10 700 ± 2000 M^{-1} in water ($\Delta\epsilon_\infty = 0.0815$), respectively. $\Delta\epsilon_\infty$ is larger than the one observed with aziadamantane in **7-Cy** ($\Delta\epsilon_\infty = 0.057$),[15] but the complex **1**@**7-Cy** is considerably weaker (aziadamantane@**7-Cy**: $K = 6150 \pm 300$ M^{-1} in water/ethanol 70/30).[15] This is probably due to the hydroxy group of diazirine **1** that enhances the solubility of **1** in polar solvents.

Of even more interest was the question of whether the permethylated β-cyclodextrin (TRIMEB) also could be used as a host for **1**. Therefore, the corresponding complex was prepared and the experiments repeated as described before with **1@7-Cy**. When compared with **1**@**7-Cy** the ICD spectrum displayed a more detailed fine structure (Figure 3) and the major band was bathochromically shifted by 6 nm. This shows that the diazirine nitrogen atoms are placed in a more apolar environment[15] and are shielded from the solvent

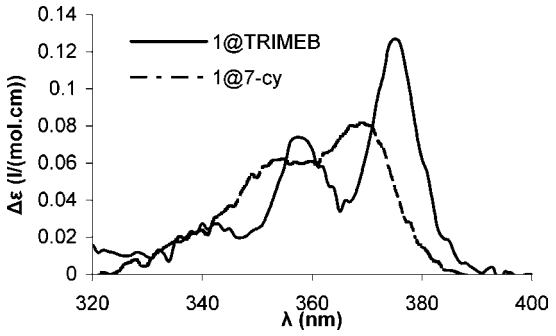

Figure 3. ICD of **1** by complex formation with **7-Cy** and TRIMEB (extrapolated) in water.

when included in TRIMEB, whereas they are more exposed to the hydroxy groups in the **7-Cy** complex. The association constant was calculated from the concentration dependence of $\Delta\epsilon$ (Figure 4) ($K = 550 \pm 60$ M^{-1}, $\Delta\epsilon_\infty = 0.127$, $T =$ 293 K). This proved that TRIMEB is still able to include **1** but that the complex is strongly weakened by a factor of 20, when compared with **1@7-Cy**. The value for K is confirmed by NMR experiments (Figure 5) ($K = 460 \pm 60$ M^{-1}, $\Delta\delta_{max} = 0.236$ ppm for H_3, $T = 300$ K). This means that under the reaction conditions applied (1 mM of a 1:1 mixture of host and guest in water), only 26% of the diazirines are complexed, while 74% are directly exposed to water molecules. In contrast to the results obtained with **7-Cy**, where only H_3 and H_5 showed changes in the chemical shift (0.11 and 0.12 ppm, respectively), the outer protons (H_1, H_2, and H_4) also experience a significant chemical shift change in the range of 0.09−0.11 ppm. This is in the same range that was observed for H_5 (0.113 ppm) and is probably due to conformational changes upon complexation.[16]

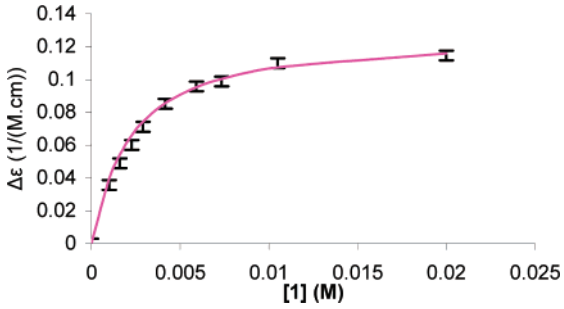

Figure 4. Curve fitting of the ICD data for the complex formation of **1** with TRIMEB in water at 293 K ($[\mathbf{1}]_o = 0.59$ mM).

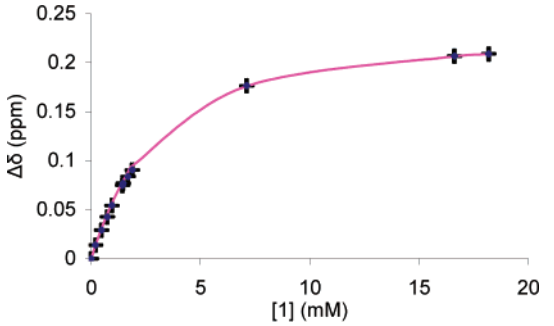

Figure 5. Association constant determination for **1@TRIMEB** in D_2O for H_3 at 300 K ($[\text{TRIMEB}]_o = 1.26$ mM).

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The ROESY spectrum confirms the presence of an inclusion complex and the absence of an association complex, since no signals are observed with the outer protons H_1 and H_2. It also shows that **1** is oriented differently in TRIMEB than in **7-Cy**. In **1@TRIMEB**, not only H_3 but also H_5 are in the neighborhood of several guest protons, with the resonances for H_3 exhibiting higher intensities. H_C seems to be the deepest embedded proton, since it gives rise to a weak signal with H_{Me6}. And H_6 produces a small signal with H_C and H_{B1}. An interesting observation is also that in contrast to the geometry of **1@7-Cy** in solution, even H_A produces strong cross-peaks with H_3 and H_5. This suggests that tri-*O*-methyl-β-cyclodextrin protects the alcohol function of **1** from water better than the underivatized **7-Cy**. The guest proton with the smallest cross-peaks is H_{B2}, which is located close to the upper rim of the cyclodextrin cavity. Thus, in this case it is suggested that the diazirine ring is located at the bottom of the cyclodextrin near the narrower rim. In the TRIMEB complex, cross-peaks were also observed with H_4. This is likely caused by ROE-TOCSY[17] from H_3 and H_5 as it was observed earlier.[16,18] Figure 6 shows the suggested orientation of **1@TRIMEB** derived from the NMR data.

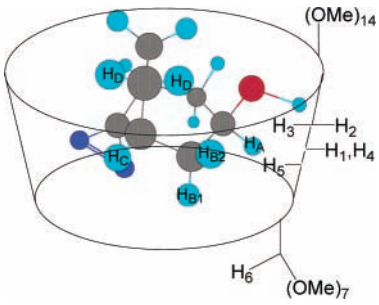

Figure 6. Proposed geometry for **1@TRIMEB** in solution according to NMR experiments.

1@TRIMEB has been found to crystallize in a 1:1 stoichiometry (Figure 7). This is only the second time that the complex of a diazirine in a cyclodextrin has been examined by a single-crystal X-ray structure.[19] A single-crystal was grown in D_2O at a concentration of 14 mM at 30 °C. Its structure (orthorhombic, space group $P2_12_12_1$, a = 11.188(2) Å, b = 25.291(2) Å, c = 29.152(5) Å, R_1 = 0.0517) is isomorphous to the Ub phase described by Cardinael et al.,[20] a type of packing also found for the complex of TRIMEB with other molecules.[20,21,22] The guest's OH-hydrogen binds to an oxygen atom of one of the glycosylidic bonds. None of the guests atoms exhibits disorder. Compound **1** takes only one position in the TRIMEB cavity. The whole guest molecule lies above the plane formed by the intersaccharidic atoms (O_4), near the wider rim. Both nitrogen atoms of the diazirine group display short contacts with the neighboring complex, one with a methyl group of the narrower rim and two others with H_6. The hydrophilic part of **1** is included in the cavity, whereas the more hydrophobic diazirine group is located near the lipophilic methyl groups. This structure is confirmed by molecular models which find for TRIMEB an *inverse* hydrophobicity when compared with the underivatized cyclodextrins.[23] The tilt angles between the glucose units belong to the same structural group[24] as the corresponding methylcyclohexane@TRIMEB complex. This means that **1** does not induce a particular fit with the host. TRIMEB simply embeds the guest in the most adapted of the possible conformations.[25]

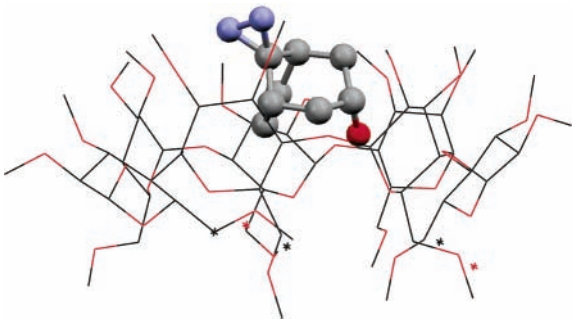

Figure 7. Single-crystal X-ray structure of **1@TRIMEB** showing the orientation of **1**.

It has been shown that **1** forms a 1:1 inclusion complex with **7-Cy** and TRIMEB. In the TRIMEB complex in the solid state, the orientation of the diazirine and the hydroxy group of **1** is in the opposite direction when compared with the results for the major structure of the complex in solution. Moreover, when compared with **7-Cy,** the permethylation of the host also causes reorientation of the guest molecule and a strong weakening of the complex by a factor of 20.

Acknowledgment. Dedicated to Professor Karl Schlögl on the occasion of his 80th birthday. This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung in Österreich (Project P12533-CHE).

Supporting Information Available: CIF file for the crystallographic data, ROESY spectra of **1@7-Cy** and **1@TRIMEB**, *K* for **1@7-Cy**, a spreadsheet for the nonlinear curve fitting of the NMR, and the ICD titration experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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