# Direct Observation and Rate of Interconversion of the 1:2 Complex between 1,4-Dimethylbicyclo[2.2.2]octane and α-Cyclodextrin by NMR

Ulf Berg,* Magnus Gustavsson, and Nina Åström

*Organic Chemistry 1, Chemical Center, P.O. Box 124 University of Lund, S-22100 Lund, Sweden*

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Cyclodextrins (CDs) act as hosts for many small molecules in water solution and have been recognized as potential artificial enzymes with both catalytic and selective properties[1−3] and as building blocks in supramolecular chemistry.[2] Considerable attention has been devoted to the driving force of the inclusion,[2,5−8] but much less to the kinetics[9−11] and its dependence upon variations in solvent, concentration, salt addition, etc. We became interested in the dynamic behavior of such complexes and have investigated a system designed for this purpose. Model studies indicate that bicyclo[2.2.2]octane is size consistent with the cavity of α-CD and also meets criteria in terms of hydrophobicity, structural rigidity, and suitability for dynamic NMR probing. We describe here an investigation of the complexation of 1,4-dimethylbicyclo[2.2.2]octane (**1**) with α-CD. We also present evidence for the coexistence of three species of **1** assigned as substrate in two different phases and a 1:2 guest−host complex. Free and complexed **1** exchange with a remarkably high barrier.

A solution of **1**[12] in methanol was added to α-CD dissolved in $H_2O$. A voluminous precipitate was formed, which dissolved on the addition of DMF and gentle warming.[13] The $^1$H NMR spectra[14] exhibited broad singlets at room temperature for the methyl and methylene protons at $\delta$ 0.78 and 1.37, respectively. On lowering of the temperature, the signals broadened further and at ca. 10 °C decoalesced to three sets of signals (called A, B, and C for methylene and A′, B′, and C′ for methyl; see Figure 1a). A closer look at the spectra revealed that one set, B and B′, emerged as sharp signals without showing exchange broadening. A striking feature was the substantial differences in line width among the three sets of signals. The relative intensities varied with the concentration ratio [**1**]:[α-CD] such that the signals $A^{(\prime)}$ increased at the expense of the $B^{(\prime)}$ and $C^{(\prime)}$ signals when the relative amount of α-CD increased (Figure 1b). When [**1**]:[α-CD] < 1:2.5, essentially only $A^{(\prime)}$ was present. The $A^{(\prime)}$ to $C^{(\prime)}$ equilibrium shifted to $C^{(\prime)}$ at higher temperatures, and the coalesced $A^{(\prime)}$ and $C^{(\prime)}$ signals at $\delta$ 1.37 and 0.78 showed increased intensity at the expense of that of $B^{(\prime)}$ at higher temperatures. The α-CD spectrum went through parallel broadening and partial decoalescence, leading to the appearance of a strongly downfield-shifted $H_3$ signal at $\delta$ 4.2 *with the same integral as A*. When α-CD was excluded, both signals $B^{(\prime)}$ and $C^{(\prime)}$ were still present and had the same chemical shifts. When the concentration of **1** was increased, the same NMR pattern was found but with a higher intensity of $B^{(\prime)}$. When the solution was left overnight, a new phase appeared, which was isolated and identified as essentially pure **1**. The two phases were not macroscopically observable at the original concentration.

The $A^{(\prime)}$ to $C^{(\prime)}$ exchange was examined by both band shape analysis and saturation transfer experiments. Strong saturation transfer at −10 °C was obtained from $A^{(\prime)}$ to $C^{(\prime)}$. The signals $B^{(\prime)}$ and $C^{(\prime)}$ were too close for meaningful saturation transfer experiments. Band shape analysis[15] gave $\Delta G^{\ddagger}_{282\,K} = 13.4 \pm 0.1$ kcal/mol for the $A^{(\prime)}$ to $C^{(\prime)}$ exchange. Notably, the $B^{(\prime)}$ signals remain sharp but decrease in intensity at higher temperatures, indicating an even higher barrier for $B^{(\prime)}$ to $C^{(\prime)}$ exchange. Increasing the amount of DMF from 0.3 to 0.4 mL lowered the barrier to 13.0 kcal/mol and changed the equilibrium in favor of $C^{(\prime)}$. Addition of 0.1−0.3 mL of methanol-$d_4$ to the solution affected both relative complex stability and dynamics: first the $A^{(\prime)}$ disappeared, and after further addition the remaining two signals merged, whereas addition of LiCl (0.5 M) had no noticeable effect.

The 500 MHz $^1$H NMR spectrum at −10 °C revealed additional selective broadening of signal A and a tendency toward further fine structure, which was not observed for the A′ signal. This behavior is consistent with a symmetrical complex in which the geminal methylene protons are rendered diastereotopic, giving rise to an AA′BB′ pattern. A ROESY spectrum at −10 °C shows strong positive cross peaks between A and $H_3$ and between A′ and $H_5$ and negative cross peaks between $A^{(\prime)}$ and $C^{(\prime)}$ (Figure 1c).

This behavior suggested the assignment of the different sets of signals in the following way: signals $B^{(\prime)}$ arise from dispersed **1** and $C^{(\prime)}$ from dissolved **1**. The concentration dependence, integration of the $H_3$/A peaks, and the shape of the A and A′ peaks indicate that set $A^{(\prime)}$ originates from a symmetrical 1:2 **1**:α-CD complex. The 1:1 complex may exist in very low concentration or in rapid equilibrium with free **1** or the 1:2 complex.

Further information about the structures of the species was gained from complexes of **1** with α-CD 2-monotosylate.[16] A sample of **1**:α-CD 2-monotosylate (1:0.8) in the same solvent mixture showed two sets of signals corresponding to $B^{(\prime)}$ and $C^{(\prime)}$ below 25 °C with the same shifts as for unsubstituted α-CD. Also in this case the $C^{(\prime)}$ signals increased and the $B^{(\prime)}$ signals decreased at higher temperatures without coalescence, and they eventually disappeared at 25 °C. Apparently, a single substituent at the wide rim of α-CD is enough to prevent formation of a 1:2 complex.

Molecular modeling[17] of a 1:1 complex with the MM2 force field gives the minimized structure shown in Figure 2. The

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(14) Solutions were 6.5 mM in **1** and 3.5−30.0 mM in α-CD, and the solvent mixture had the composition 0.5 mL of $D_2O$, 0.3 mL of methanol-$d_4$, and 0.3 mL of DMF-$d_7$.
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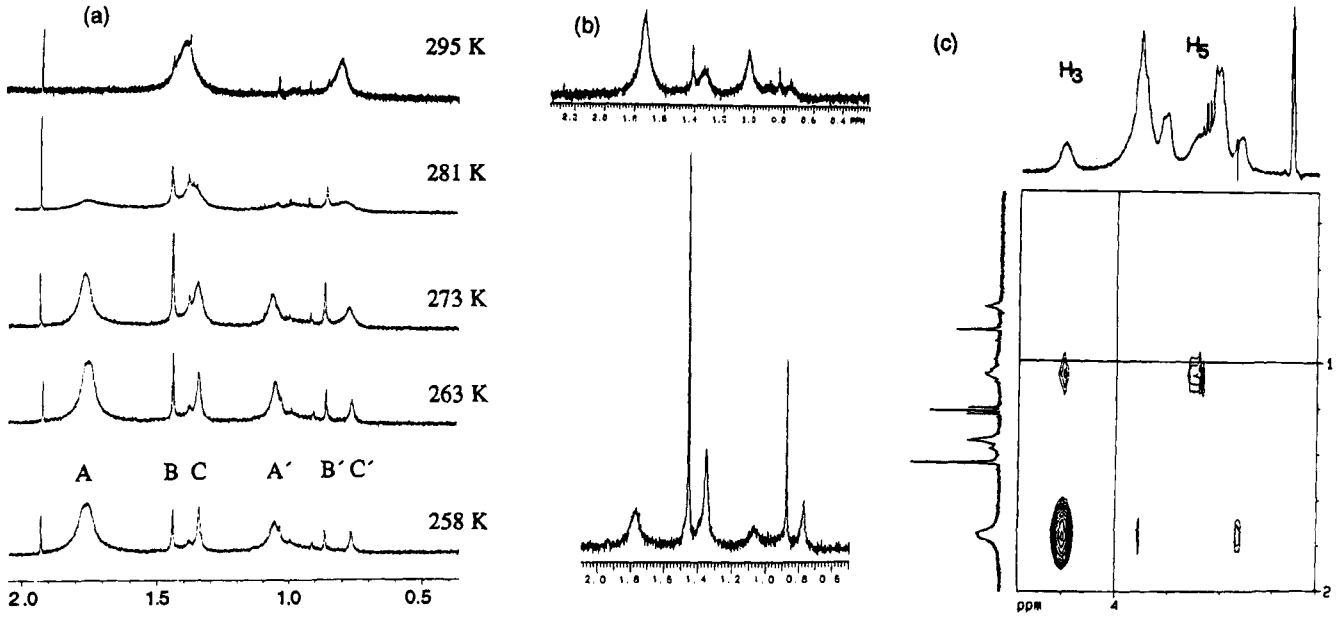


**Figure 1.** (a) $^1$H NMR spectra (500 MHz) of a solution of **1** (6 mM) and α-CD (7 mM) at various temperatures. Solvent: methanol-$d_4$/$D_2O$/DMF-$d_7$ (3:5:3). Signals from impurities at $\delta$ ca. 1.0, 1.38, and 1.92. (b) $^1$H NMR spectra (300 MHz) in the same solvent at the **1**:α-CD concentration ratios 1:0.5 (lower spectrum) and 1:1.2 (upper spectrum). Temperature: 258 K. (c) Part of ROESY contour map of the same solution as in Figure 1a. The α-CD protons $H_3$ and $H_5$ in the complex, identified by a COSY spectrum, are indicated. Residual protons from $CD_3OD$ give a signal at $\delta$ 3.32, and an impurity has peaks at $\delta$ 1.20 and 3.63.

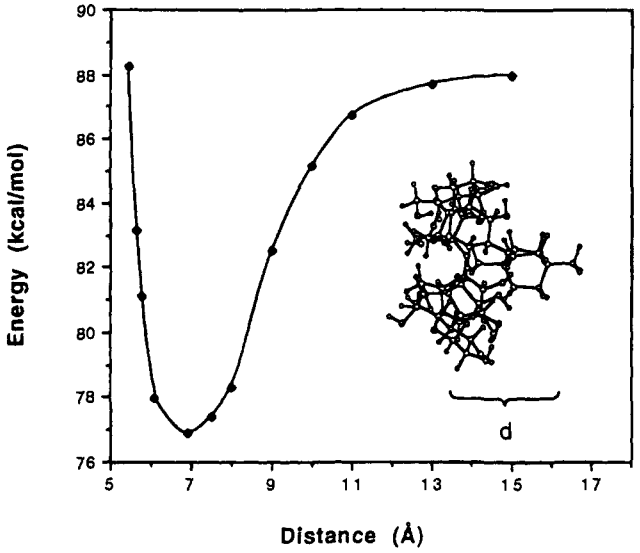


**Figure 2.** MM2 steric energy of the interaction between **1** and α-CD as a function of the distance between the center of the cavity of α-CD and **1**, and MM2 minimum energy structure of the 1:1 complex of **1** and α-CD. The minimum energy structure is obtained after relaxation of all degrees of freedom. The other structures are given by the following constrained minimization. The center of the cavity is defined by the geometrical center of the six glycosidic oxygens. The distance is defined as the distance from this point to the rear methyl carbon atom. This distance is the only constrained parameter in the minimization. The light horizontal line represents the sum of the energies of optimized **1** and α-CD.

modeled complex has neither $C_6$ nor $C_3$ symmetry of the α-CD residue,[18] and the van der Waals surface indicates that there is room for a second α-CD at the free half of **1** to give a 1:2 complex. Figure 2 also shows the steric energy of the interaction as a function of the distance between **1** and the interior of the cavity. The calculated enthalpy of reaction in the gas phase is −11.3 kcal/mol and is due entirely to the London dispersion term, which is calculated to be −14.6 kcal/mol. The difference, 3.3 kcal/mol, is the deformation energy ("induced fit")[19] of α-CD in order to accommodate **1** in the complex.

The observation of separate NMR signals from free and complexed guest molecules and their exchange rate is unprecedented (to our knowledge) for small nonionic guest molecules and affords a possibility to study the effect of changes of various parameters on kinetics and equilibrium. The stability of the 1:2 compared to the 1:1 guest−host complex[20] and the high barrier are the result of several cooperative effects: (i) size and symmetry relations are optimal between guest and host; (ii) destabilization of the 1:1 complex occurs due to the large hydrophobic surface exposed to the solvent in the 1:1 complex visualized in Figure 2; and (iii) the solvent effects are probably extremely important and, because of the composite mixture, difficult to understand in detail. Although DMF was used primarily for improving solubility, it probably has a powerful influence on both equilibria and kinetics.[21]

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