Complex of 4-Fluorophenol with α-Cyclodextrin: Binding Mode in Solution Is Opposite to That in the Solid State

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Despite the important role X-ray crystallography plays in the studies of supramolecular complexes,[1] it is apparent that intermolecular interactions in solution may be influenced by driving forces other than those operating in the solid state. In many cases, however, it is believed that the geometry of inclusion complexes in the crystal lattice reflects their solution structure reasonably well. We report here an example of a distinctly different mode of complexation observed for the same interacting molecules in solution and in the solid state.

Previously reported X-ray studies on the inclusion complex of 4-fluorophenol (4-FP) with α-cyclodextrin (α-CyD)[2] revealed an unusual inclusion mode in which the hydrophilic OH group of phenol was hidden inside the hydrophobic cyclodextrin cavity (Figure 1a). Such orientation was attributed to the stabilizing effect of a C−F--HO hydrogen bond in the crystal structure. NMR studies on the interactions of *para*-substituted phenols with cyclodextrins suggest that the opposite inclusion mode (hydroxyl group in contact with the water environment, Figure 1b) is routinely observed in aqueous solutions.[3] The latter inclusion mode was also proposed, but not proven, for the 4-FP−α-CyD complex in the aqueous environment.[4]

To determine the solution structure of the 4-FP−α-CyD complex by ^{1}H NMR, we have performed a series of the rotating-frame NOE experiments (ROESY) that provide the most reliable information about the relative interproton distances in compounds/complexes of intermediate molecular weight, such as cyclodextrins.[5] The spectra were collected from the solutions of 4-FP and α-CyD in a 1:1 ratio in D_2O at two different pD values, 8.3, where 4-FP exists in a protonated form, and 11.4, where 4-FP is ionized,[6] and two temperatures, 10 and 30 °C.

In all cases, the obtained ROESY spectra contained cross-peaks between aromatic signals of the 4-FP and the signals of the CyD protons located inside the macrocycle cavity (H3 and H5 in Figure 3), indicating the formation of inclusion complexes (Figure 2). The structure of the complexes can be derived from the relative intensities of the cross-peaks given in Table 1. Besides the intermolecular cross-peaks, we also observed strong *intra*molecular signals from the interaction of the H1 and H4 CyD protons that are held closely in the adjacent glucose units. These signals, which are relatively condition-independent, were used as volume references for the evaluation of relative intensities of the intermolecular cross-peaks (Table 1).[7]

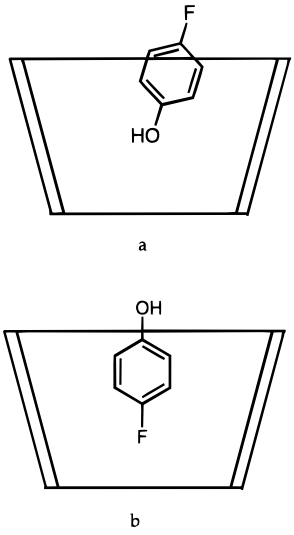

Figure 1. Inclusion modes of 4-FP in the complex with α-CyD.

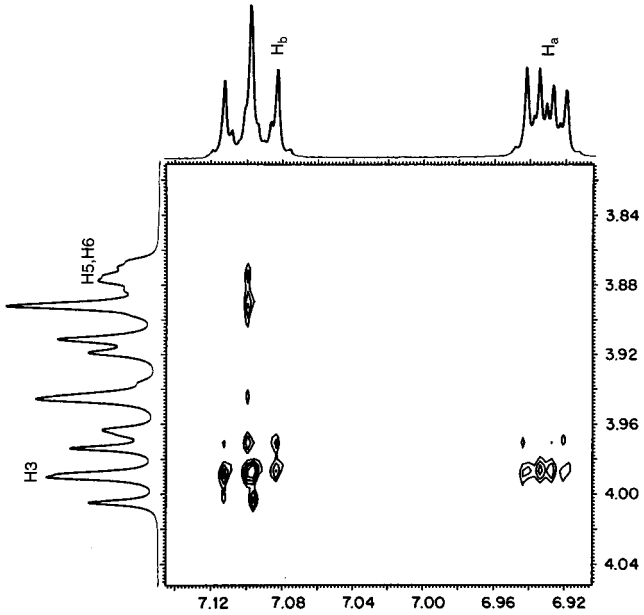

Figure 2. Intermolecular cross-peak area of the 4-FP/a-CyD ROESY spectrum (pD 8.3, 10 °C).

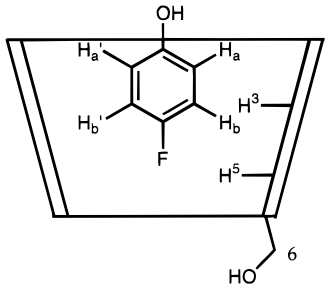

Figure 3. Cross-peak-generating protons in the 4-FP−α-CyD complex.

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Table 1. ROESY Cross-Peak Volumes[a] for the Complexes of 4-Fluorophenol with α-Cyclodextrin

	relative cross-peak areas				
condns	$H_b \leftrightarrow$ H5(H6)	$H_a \leftrightarrow$ H5(H6)	$H_b \leftrightarrow$ H3	$H_a \leftrightarrow$ H3	H1 ↔ H4
pD 8.3, 10 °C	<0.5	<0.5	3.15	1.17	100
pD 8.3, 30 °C	0.912	<0.5	1.17	1.07	100
pD 11.4, 10 °C	1.12	<0.5	3.89	1.60	100
pD 11.4, 30 °C	1.45	<0.5	2.65	0.844	100

[a] Integration was performed with a relative error not exceeding 10%.

The most intense *inter*molecular NOEs were observed between the H3 protons of the CyD (located inside the cavity closer to the upper rim of the macrocycle) and the aromatic protons of 4-FP adjacent to fluorine (H_b). The H_b signals also showed a medium-intensity cross-peak with the H5 of CyD (located closer to the lower rim). The other pair of guest protons (H_a) showed only moderate cross-peaks with the H3 of the host. This spectral pattern is consistent with the inclusion mode in which the fluorine atom is hidden inside the CyD cavity, and the hydroxyl group faces the aqueous environment (Figure 1b). Such a pattern was consistently reproduced at both 10 and 30 °C as well as for the ionized and deionized forms of the guest. Somewhat lower intensities of the cross-peaks at 30 °C may be attributed to the lower complex stability[8] at the higher temperature.

These results, combined with the previously published X-ray data, reveal that the 4-FP−α-CyD complex behaves as a peculiar "molecular switch" in which the inclusion mode inverts upon transition from solution into the crystal state.[9] While we are unaware of any other example of such behavior, it appears to be consistent with the different forces that govern complexation in solution and in the solid state. The association in solution is primarily driven by the dispersive and hydrophobic interactions.[10] The latter component, apparently determining the outside position of the hydroxyl group in the complex, is completely eliminated in the solid state. On the contrary, hydrogen bonding, suggested as a configuration-determining factor in the crystalline state,[2] becomes negligible in aqueous solution due to the competition with water molecules. Since the reversible host−guest complexation usually occurs with high on- and off-rates, and the guest possesses a high rotational mobility inside the cavity,[11] the inversion of the complex structure may readily occur during the slow crystallization process. These results demonstrate that some caution should be used in extrapolating the X-ray data to the solution structure in the cases where multiple configurations with similar energies are possible in a supramolecular complex.[12]

Experimental Section

All compounds were purchased from Aldrich. α-CyD was dried for 4 h at 110 °C under 0.1 mm. Working solutions (1.0×10^{-2} M of both 4-FP and α-CyD) were prepared in deuterium oxide of 99.96% deuterium enrichment. pD adjustments were made with the CF_3COOD/D_2O and $NaOD/D_2O$ solutions. Assignment of the NMR signals was made according to the previously reported spectra.[4,5]

NMR spectra were obtained on a Bruker AMX-600, using a hydrogen base observation frequency of 600.14 MHz. The ROESY experiments were acquired using a sweep width of 4 kHz and 4K real data points in the acquisition dimension. The second dimension consisted of 1K time increments of 16 scans each. Spinlock times of 225 and 400 ms were used. All spectra were acquired at either 10 or 30 °C in a phase-sensitive manner using time-proportional phase incrementation for quadrature detection in the second dimension. Data were processed on an SGI workstation using Sybyl/Triad or NMRZ software (Tripos, Inc.).

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(7) The intramolecular cross-peaks originate from the interactions of *six* proton pairs in each CyD molecule. Therefore, the magnitude of the H1 ↔ H4 cross-peaks is much higher than that for the *inter*molecular NOE, which is brought about by interaction of at most two proton pairs. Partial dissociation of the complex under the experimental conditions results in further decrease of the intermolecular cross-peak intensity.

(8) For the thermodynamics of CyD inclusion complexes, see: Rekharsky, M. V.; Goldberg, R. N.; Schwarz, F. P.; Tewari, Y. B.; Ross, P. D.; Yamashoji, Y.; Inoue, Y. *J. Am. Chem. Soc.* **1995**, *117*, 8830 and references therein.

(9) The NMR data reflect the predominant time-average position of the guest within the cavity, and a small fraction of the opposite-mode complex may also be present in solution. Therefore, the "switching" involves a transformation of the *most abundant* solution complex form to the *single*, and opposite, form in the solid state.

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(12) The reviewers of this paper have suggested that the NMR data as well as previous studies of CyD complexes with phenols may indicate an error in structure determination reported in ref 2, since the F and OH groups are isoelectronic and their assignment has been based primarily on thermal parameters. While the switch mechanism discussed above explains all available data reasonably well, further studies on the solid-state complex may be needed to check the validity of the reported structure.