Proton NMR Study of α-Cyclodextrin Inclusion of Short-Chain Surfactants

Noriaki Funasaki,*,† Seiji Ishikawa,† and Saburo Neya‡

Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan and Graduate School of Pharmaceutical Sciences, Chiba University, Inage-Yayoi, Chiba 263-8522, Japan

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Proton NMR spectroscopy was applied to determine the binding constants and the solution structures of 1:1 α-cyclodextrin (α-CD) complexes with hexyltrimethylammonium (HTAB) and octyltrimethylammonium (OTAB) bromides. Chemical shift data of all protons, referred to an internal standard, were used to determine reliable binding constants and chemical shift variations $\Delta\delta_{complex}$ induced by complex formation. The ROESY spectra of aqueous solutions containing α-CD and HTAB or OTAB provide information about rough structures of the complexes. The alkyl chains of HTAB and OTAB are incorporated from the wide rim of the α-CD cavity. The ROE intensities of intermolecular cross-peaks are plotted against the effective interproton distances for many structures different in the penetration depth of the alkyl chain. Detailed structures of the α-CD complexes with HTAB and OTAB are determined from the best correlations between the ROE intensities and the interproton distances. The $\Delta\delta_{complex}$ values for the protons of propanol, HTAB, and OTAB depend on the position located in the α-CD cavity. For instance, the proton near the proton H3 of α-CD exhibits the largest variation (ca. 0.2 ppm). The present data on single- and short-chain surfactants will provide the basis for determining the stoichiometry, the binding constants, and the structures of CD complexes with long-chain surfactants and double-chain surfactants.

Introduction

Cycloamyloses (cyclodextrins, CDs) are doughnut-shaped molecules, formed from D(+)-glucose units linked in a cycle. Cyclohexaamylose (α-CD), cycloheptaamylose (β-CD), and cyclooctaamylose (γ-CD) have diameters of approximately 0.45, 0.70, and 0.85 nm, respectively. The interior of the doughnut predominantly contains CH groups and it provides, therefore, a relatively hydrophobic environment into which polar molecules can be trapped.[1,2] This CD cavity, therefore, can accommodate surfactants very well. Complex formation between surfactants and CDs have been extensively investigated by spectroscopic, thermodynamic, surface chemical, computational, and crystallographic methods.[3,4]

Irrespective of these extensive studies, the binding constants and stoichiometries of the surfactant-CD complexes reported in the literature up to 1992 were frequently conflicting or exhibited serious deviations.[3,5] Recently, there seems to be a general agreement: electromotive force measurements, fluorescence or visible-light probe method, and surface tension method provide reliable binding constants.[5−7] These are essentially methods for determining the concentration of a surfactant in the free state. NMR will be the most powerful method for various investigations of solutions. The NMR chemical shift method has been employed for binding constant determination of surfactants and CDs.[8−10] Very recently, it has been demonstrated that applications of this method require a special attention to references of chemical shifts.[11−13] The internal reference method is superior to the external one in several points, but it is often difficult to find any inert reference.[14,15] The volume magnetic susceptibility of solvent containing an external reference is usually different from that of a sample solution. Because the volume magnetic susceptibility of the sample solution depends on the concentration of an added substance, this effect on the chemical shift must be corrected.[10−13]

NMR data, such as NOE cross-peaks, vicinal spin−spin coupling constants, and chemical shifts generally provide information on rather detailed solution structures. The relationship between chemical shifts and structures remains almost unexplored for CD inclusion complexes.[16] Rough solution structures of complexes of surfactants and related compounds with CDs are estimated from ROESY spectra and chemical shifts as well as molecular mechanics calculations; the direction and depth of surfactant penetration in the CD cavity were inferred.[8,9,17]

Recently, we determined rather detailed solution structures of complexes of propyl compounds with α-CD, mainly on the basis of ROESY intensity data.[18] In the present work, we aimed at the determination of solution structures and binding constants for α-CD complexes with hexyltrimethylammonium (HTAB) and octyltrimethylammonium (OTAB) bromides by ^{1}H NMR. These short-chain surfactants were chosen, because their chain lengths are close to the depth of α-CD. This reduces the number of plausible structures of the complexes. On the basis of rather accurate structures and chemical shift variations, the relationship between the structure of the complex and the chemical shift variation will be estimated.

Experimental Section

Materials. Commercial samples of α-CD (Ensuiko Research Laboratories, Yokohama), propanol (PrOH), tetramethylammonium chloride (TMA, Nacalai Tesque, Kyoto), HTAB, OTAB

* Corresponding author. E-mail: funasaki@mb.kyoto-phu.ac.jp.
† Kyoto Pharmaceutical University.
‡ Chiba University.

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(Tokyo Kasei), and 99.9 at. % D deuterium oxide (Aldrich) were used as received.

NMR Measurements. All ^{1}H NMR experiments were carried out in deuterium oxide at 298.2 ± 0.1 K. The NMR spectra were obtained with a JEOL Lambda 500 spectrometer. The proton chemical shift and spin−spin coupling constant were determined by Nuts data processing software. The proton chemical shifts of OTAB and α-CD were determined as a function of the α-CD concentration, up to 14.5 mmol dm^{-3} (mM), in the presence of 3.568 mM OTAB. The chemical shifts of HTAB and α-CD were determined as a function of the α-CD concentration, up to 22 mM, in the presence of 3.568 mM HTAB. These chemical shifts were referenced to the internal 0.5 mM TMA signal at 3.176 ppm.[18] The chemical shifts of PrOH were determined as a function of the α-CD concentration, up to 70 mM in the presence of 5.695 mM PrOH.

Two-dimensional rotating frame nuclear Overhauser effect spectroscopy (ROESY) for a solution containing 10 mM OTAB and 10 mM α-CD was performed at 500 MHz with the JEOL standard pulse sequences; data consisted of 8 transients collected over 2048 complex points. A mixing time of 250 ms, a repetition delay of 1.2 s, and a 90° pulse width of 11.0 μs were used. The ROESY data set was processed by applying an exponential function in both dimensions and zero-filling to 2048 × 2048 real data points prior to the Fourier transformation. The ROESY spectrum for a solution containing 3.1 mM HTAB and 30.5 mM α-CD was also performed under the same conditions as those for the OTAB and α-CD system. All ROESY spectra were symmetrized about the diagonal. Small cross-peaks were neglected, because their magnitude was close to that of noise. The volume of a ROESY cross-peak was measured by summation of spectrum intensities with a certain region around the cross-peak and slightly depended on the region of integration, peak overlap, and the signal-to-noise ratio. The critical micelle concentration (cmc) of OTAB is 130 mM, and that of HTAB has not been reported, probably because HTAB has an alkyl chain too short to form micelles.[19] Therefore, all NMR measurements were carried out below the cmc.

The assignment of internal methylene groups of OTAB was established on the basis of the ^{1}H-^{13}C shift correlated (C−H COSY) spectrum of a 3 mM OTAB solution, obtained with the JEOL standard pulse sequences. However, the signals of the C4 and C5 atoms were indistinguishable from each other at 3 mM. In the INADEQUATE spectrum of a 900 mM OTAB solution, the C5 signal appeared at lower field than the C4 signal. On the basis of this finding, the signal of the ϵ-methylene protons bonded to the C5 atom was assigned from the C−H COSY spectrum of the 900 mM OTAB solution.

Molecular Modeling. The solution structure of α-CD in the complex of PrOH-α-CD was used to construct those of the complexes of α-CD with HTAB and OTAB.[18] The α-CD molecule is almost symmetric around the *x* axis, where the O4 plane is at $x = 0$. The side of primary hydroxyl groups has a negative *x* value, whereas that of secondary hydroxyl groups has a positive *x* value.

Calculations and molecular graphics were carried out simultaneously using our own software with a personal computer running on Microsoft Windows 2000. The relative position of α-CD and guest can be easily varied and be shown digitally on the display.[20]

Results

Chemical Shifts and Binding Constants. Figure 1 displays the 500 MHz ^{1}H NMR spectra of a deuterium oxide solution containing 3.568 mM OTAB at four concentrations of α-CD. The Hα and Hβ methylene protons, αCH_2 and βCH_2, of OTAB exhibit complicated multiplet signals around 3.3 and 1.8 ppm, respectively. By computer simulations, vicinal spin−spin coupling constants were determined to be $^3J_{\alpha R\beta} = 4.8$ and $^3J_{\alpha S\beta} = 12.5$ Hz regardless of the presence and absence of 19.5 mM α-CD. These coupling constants indicate that the nitrogen and γ-carbon atoms are fixed around the trans position about the Cα−Cβ bond, regardless of the presence and absence of α-CD. The ω-trimethyl proton of OTAB exhibits a sharp triplet signal at 0.9 ppm. Intermediate five methylene groups consist of three major signals partially overlapping with each other. In the absence of α-CD, the signals at high, intermediate, and low field were assigned to the ς- and η-methylene groups, the ϵ-methylene group, and the γ- and δ-methylene groups, respectively, on the basis of the C−H COSY and INADEQUATE spectra. In the presence of 19.5 mM α-CD, the peaks at high and low fields contain two methylene groups. As the concentration of α-CD is increased, the ϵ-methylene signal moves from the high-field signal to the low-field signal.

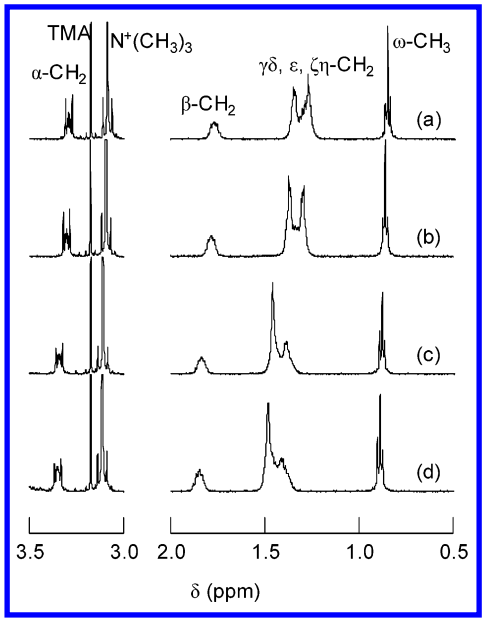

Figure 1. Proton NMR spectra (the OTAB region) of 3.568 mM OTAB solutions at different α-CD concentrations (mM): a, 0; b, 0.45; c, 4.5; d, 19.5.

Though the α-CD region is not shown in Figure 1, the H1 proton of α-CD appeared near 5.1 ppm, the protons of H3, H5, and H6 resonated around 3.85 ppm, and those of H2 and H4 were assigned to the peaks centered at 3.6 ppm. Because two protons, H6*R* and H6*S* of H6, are distinguishable from each other, we dealt with them separately. The H1, H2, and H4 protons are located on the outer surface of the CD cavity, whereas those of H3 and H5 are on the inner surface. The spectra of the HTAB-α-CD systems are similar to those of the OTAB-α-CD systems (data not shown). The major difference is that the intermediate methylene groups of HTAB exhibit a single peak, regardless of the presence and absence of α-CD. All vicinal spin−spin coupling constants of HTAB, OTAB, and α-CD remained almost unchanged with the addition of α-CD (data not shown): no major conformational change for these molecules occurs with addition of α-CD.

We presume that the complex (AT−CD) formation of alkyltrimethylammonium bromide (AT) and α-CD (CD) is rapid on the NMR time scale. Under this condition, the chemical shift of AT can be written as

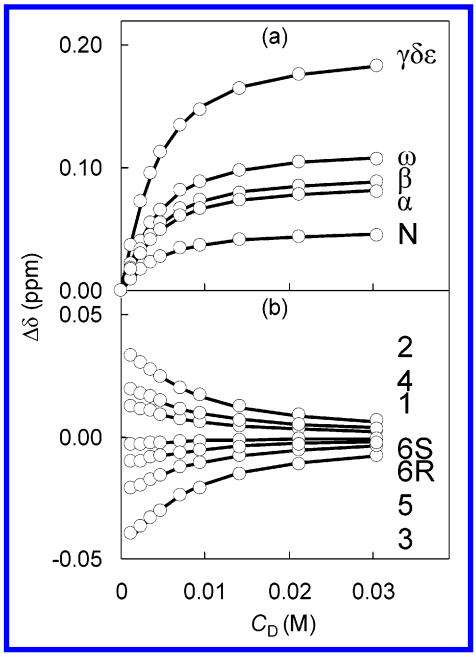

Figure 2. Chemical shift variations of all protons of (a) 10 mM HTAB and (b) α-CD as a function of the α-CD concentration. The solid lines are calculated using the values of K_1 and $\Delta\delta_{AT-CD}$ given in Table 1.

$$\delta = ([AT]\delta_{AT} + [AT{-}CD]\delta_{AT-CD})/C_{AT}$$
$$= ([AT]\delta_{AT} + K_1[AT][CD]\delta_{AT-CD})/C_{AT} \quad (1)$$

Here δ_{AT} and δ_{AT-CD} stand for the chemical shifts of AT in the free and bound states, K_1 is the binding constant, [AT] and [CD] are the molarities of AT and CD in the free state, and C_{AT} denotes the total molarity of AT. The corresponding equation holds for the chemical shift of α-CD. Figure 2 shows the chemical shifts of all protons of (a) OTAB and (b) α-CD as a function of the α-CD concentration, where the HTAB concentration was kept constant at 10 mM. These data were employed to determine the best fit binding constant (K) and chemical shift variations ($\Delta\delta_{AT-CD}$) using eq 1. It is noted that the agreement between theory and experiment is slightly worse for the internal methylene protons than that for the other protons, because the former protons are composed of nonequivalent protons exhibiting different chemical shifts.

Table 1 summarizes the binding constants and chemical shift variations for three systems of α-CD with PrOH, HTAB, and OTAB. The binding constants for HTAB and OTAB are not available in the literature. As a first approximation, the binding constant for the surfactant-α-CD system is determined by the number of carbon atoms in the surfactant. For instance, the binding constants for hexanol and octanol were determined to be 0.891 and 6.31 mM^{-1} by dye method.[21] The binding constants for hexanesulfonate and octanesulfonate ions were determined to be 0.51 mM^{-1} by NMR[22] and 3.03 mM^{-1} by reaction kinetics,[23] respectively. In comparison with these literature values, the present binding constants for HTAB and OTAB are reasonable.

ROESY Spectra and Structures of Complexes. A partial ROESY spectrum of a solution containing 3.1 mM HTAB and 30.5 mM α-CD is shown in Figure 3. Under this condition, the concentration of the complex HTAB−CD is 2.88 mM. The ROESY spectrum of a solution containing 10.0 mM OTAB and 10.0 mM α-CD was also recorded (spectrum not shown). Under this condition, the concentration of the complex OTAB−CD is 8.47 mM.

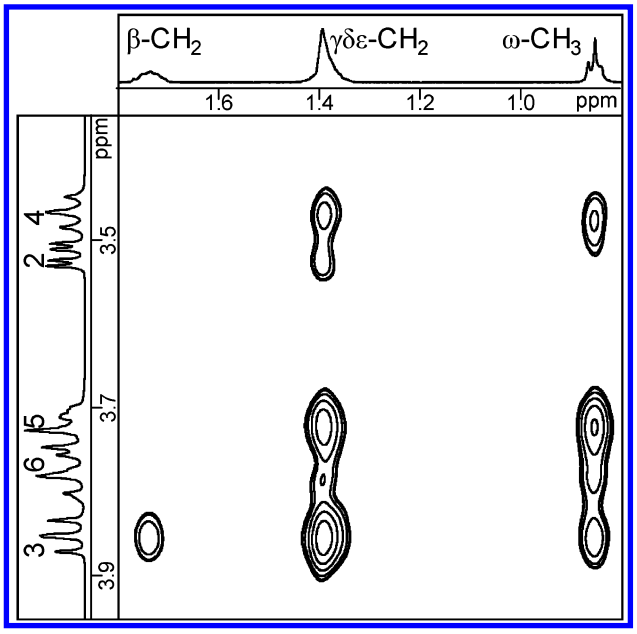

Figure 3. Partial ROESY spectrum of a solution containing 3.1 mM HTAB and 30.5 mM α-CD.

TABLE 1: Binding Constants and Chemical Shift Variations (ppm) for Three Binary Systems of α-CD with PrOH, HTAB, and OTAB

	PrOH	HTAB	OTAB
K (mM^{-1})	0.020	0.436	3.61
$\Delta\delta(NCH_3)$		0.049	0.027
$\Delta\delta(\alpha CH_2)$	0.089	0.088	0.060
$\Delta\delta(\beta CH_2)$	0.200	0.096	0.079
$\Delta\delta(\gamma$-$\epsilon CH_2)$		0.198	
$\Delta\delta(\gamma\delta CH_2)$			0.133
$\Delta\delta(\epsilon CH_2)$			0.158
$\Delta\delta(\varsigma\eta CH_2)$			0.143
$\Delta\delta(\omega CH_3)$	0.130	0.117	0.036
$\Delta\delta$(H1)	0.008	0.025	0.025
$\Delta\delta$(H2)	0.009	0.066	0.044
$\Delta\delta$(H3)	−0.039	−0.079	−0.045
$\Delta\delta$(H4)	0.016	0.038	0.048
$\Delta\delta$(H5)	−0.046	−0.042	−0.010
$\Delta\delta$(H6*S*)	−0.006	−0.006	−0.020
$\Delta\delta$(H6*R*)	−0.006	−0.021	−0.005

The volume (ROE intensity) of the cross-peak was determined by integration and was normalized for that for the cross-peak between H1 and H3 of α-CD. The ROE intensity of the cross-peak is proportional to the number of equivalent protons. When internal rotations of a molecule are slower than overall tumbling, we can expect eq 2.[24,25]

$$\mathrm{ROE} = k\sum_{i=1}^{n_{CD}}\sum_{j=1}^{n_{AT}} d_{CDiATj}^{-6} \quad (2)$$

Here d_{CDiATj} denotes the distance between a proton (CDi) of CD and a proton (ATj) of AT and n_{CD} and n_{AT} stand for the number of equivalent protons of α-CD and AT group, respectively. For simplicity the effective distance, d_{eff}, is defined as

$$(d_{eff})^{-6} = (1/n_{CD}n_{AT})\sum_{i=1}^{n_{CD}}\sum_{j=1}^{n_{AT}} d_{CDiATj}^{-6} \quad (3)$$

From eq 2 and 3 we can expect that $\mathrm{ROE}/n_{CD}n_{AT}$ increases, as two protons become closer. For the intramolecular cross-peak between H1 and H3 of α-CD, ROE = 100, $n_{H1} = 6$, $n_{H3} = 6$ and $d_{eff} = 0.25$ nm.

TABLE 2: Intensities, ROE/$n_{AT}n_{CD}$, of ROESY Cross-Peaks for the Complexes of HTAB and OTAB with α-CD

	HTAB−α-CD					OTAB−α-CD				
	H2	H3	H4	H5	H6	H2	H3	H4	H5	H6
Hα	0	0	0	0	0	0	0.4	0	0	0
Hβ	0	1.4	0	0	0	0	0.6	0	0	0
H$\gamma\delta\epsilon$	0.4	5.2	0.8	1.7	0.6	0.3	6.0	1.1	3.3	0.6
H$\zeta\eta$						0.2	5.3	1.2	4.8	0.8
Hω	0	2.2	1.2	4.2	1.7	0	1.2	1.1	5.6	1.7

In Table 2, $ROE/n_{CD}n_{AT}$ is shown for intermolecular cross-peaks. Because there is no cross-peak between H1 and the protons of ATAB, the H1 region was omitted from Figure 3 and Table 2. In Table 2 the methyl group exhibits larger cross-peaks with H5 than those with H3 and neither the α-methylene group nor β-methylene group has any cross peak with H5 and H6. These findings indicate that the alkyl groups of HTAB and OTAB are incorporated in the cavity of α-CD from the secondary alcohol side.

We constructed initial structures of the α-CD complexes of HTAB and OTAB by substituting the alkyl chain on the basis of the solution structure of the α-CD complex of PrOH.[18] The PrOH molecule was substituted by the HTAB and OTAB molecules. Then, these molecules were moved along the symmetry axis of α-CD so that better structures are found. We assumed that the best structure has the largest correlation coefficient R in an empirical equation

$$\mathrm{ROE}/n_{CD}n_{AT} = k{d_{eff}}^{-a} \quad (4)$$

According to eq 2 and 3, the exponent a in eq 4 should be 6. The values for d_{eff} and R were calculated as a function of the penetration depth of the alkyl chain. At the largest R values ($R^2 = 0.91$ for HTAB and $R^2 = 0.60$ for OTAB), the values for k and a were 0.17 and 2.8 for HTAB and 0.024 and 4.3 for OTAB. For these best fit structures, the observed $ROE/n_{CD}n_{AT}$ values are plotted against the d_{eff} values, calculated for the complexes with HTAB (a) and OTAB (b), in Figure 4.

Figure 5 shows the most probable solution structures of α-CD complexes with HTAB and OTAB. As expected, these structures are consistent with the ROE intensities shown in Table 2.

Correlation between Chemical Shifts and Structures. Chemical shift variations $\Delta\delta_{AT-CD}$ provide some information about the structure of the CD complex. Although those values, quantitatively analyzed on the basis of ring current effects of benzene, were used to determine the solution structures of CD complexes of aromatic guests,[26] this is not the cases for aliphatic guests.[16] On the basis of the solution structures of α-CD complexes with PrOH, HTAB, and OTAB, we try to find an empirical relationship between the chemical shift variation and the structure of the α-CD complex. Figure 6 shows the $\Delta\delta_{AT-CD}$ values plotted against the positions of protons in the α-CD cavity, where the center of α-CD is located at $x = 0$. The x values for the intermediate methylene protons of HTAB and OTAB are their averages. The $\Delta\delta_{AT-CD}$ values for protons near H3 have a maximum of about 0.2 ppm.

Discussion

In the present work, the chemical shift was referred to internal 1 mM TMA. The advantage of an internal reference lies in the fact that the effective field experienced by the nuclei of both reference and sample molecules is exactly the same. However, the compounds used as internal references must be inert with respect to the sample as regards intermolecular effects. External referencing avoids the difficulty of dealing with the solute−solvent interactions, but the problem of differential shielding now arises.[13−15] For systems of α-CD and cationic guests, TMA is an excellent internal standard for chemical shifts, though

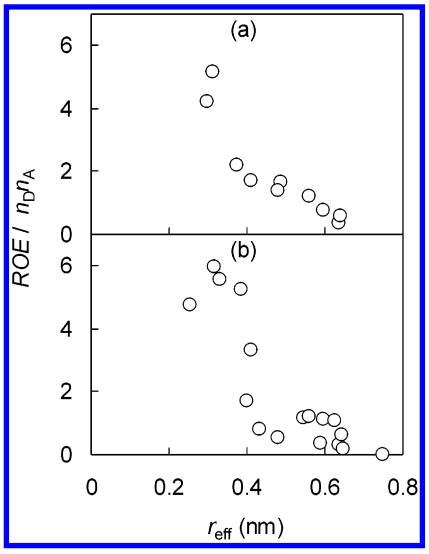

Figure 4. Plots of ROESY intensities against the effective interproton distances for the complexes of α-CD with (a) HTAB and (b) OTAB.

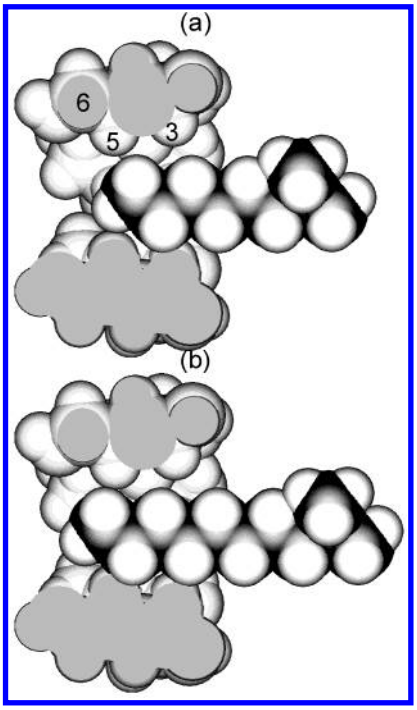

Figure 5. Cross-sections of the solution structures of α-CD complexes with (a) HTAB and (b) OTAB.

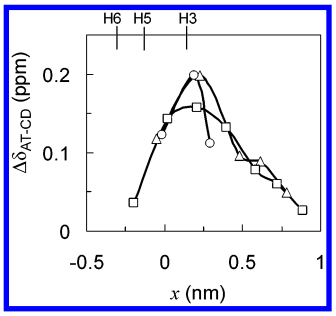

Figure 6. The $\Delta\delta_{AT-CD}$ values of methyl and methylene protons plotted against the penetration depth, x, of PrOH (circles), HTAB (triangles), and OTAB (squares) in the α-CD cavity. The primary alcohol side has a positive x value and the O4 plane of α-CD is located at $x = 0$.

sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) is an inadequate internal standard.[11−13]

A systematic ^{1}H NMR study using an external DSS standard has been reported on the systems of alkyl carboxylates and native and modified cyclodextrins by Wilson and Verrall.[9] They did not correct for the change in volume magnetic susceptibility of sample solutions that was induced by addition of these carboxylates and cyclodextrins.[11−13] This neglect could result in the dependence of binding constants on the kind of protons investigated. In a rare study, the difference in volume magnetic susceptibility between the solvents of reference and sample was corrected, but the change in volume magnetic susceptibility of the sample solution with addition of CD was not taken into consideration.[27] When the α-CD concentration is changed, the relationship between the chemical shifts (δ_{ext} and δ_{int}) referred to an external standard and to an internal inert standard is given as follows: $\delta_{ext} = \delta_{int} - 0.421C_{CD}$. This relationship holds true for all protons being contained in the α-CD solution.[11−13,22] Thus, NMR chemical shifts, determined under appropriate experimental conditions, afford reliable binding constants.

The chemical shift variation $\Delta\delta_{complex}$ with complex formation has not fully used to estimate the structure of the CD complex with various guest molecules, except for aromatic molecules.[16,26,28] In the present work, the chemical shifts of α-CD, HTAB, and OTAB were investigated over a wide range of molar ratios of two components so that accurate $\Delta\delta_{complex}$ values for α-CD, HTAB, and OTAB can be determined (Figure 2). For HTAB, it is noted that the maximum of the observed $\Delta\delta$ value (Figure 2) is very close to $\Delta\delta_{AT-CD}$ (Table 1). As Table 1 shows, the protons H1, H2, and H4 located on the exterior of the α-CD cavity exhibit low-field shifts and the protons H3, H5, and H6 located on the interior exhibit high-field shifts. For HTAB and OTAB, the absolute variations of the outer protons are similar to those of the inner protons, although this finding may seem strange. Two systematic studies have been reported on the $\Delta\delta_{complex}$ values for aliphatic guest molecules.[9,17] A similar large variation of H4 has been reported on the nonanal-α-CD system.[17] The proton H4, an outer proton of α-CD, is not distant from some alkyl protons of HTAB and OTAB in the complexes, because ROESY cross-peaks between these protons are observed (Figure 2 and Table 2). This proximity can induce some chemical shift variations of H4. The macrocycle of α-CD in the free state is highly distorted, and this distortion is released by complex formation.[26] Six oxygen atoms 4 link two glucose units to form the macrocycle of α-CD. Therefore, the release of distortion induced by complex formation will change the magnetic environment around H4 and may lead to a large variation of the chemical shift of H4. Because at the present there are very few reports on the $\Delta\delta_{complex}$ values for the outer protons of α-CD, further investigations will be necessary to confirm this interpretation.

Because the signals of the intermediate methylene protons of HTAB (Figure 3) and OTAB (Figure 1) are not very well resolved, the average values of these protons are plotted in Figure 6. This proton seems to be between two large peaks of intermediate methylenes at 0 mM (Figure 1a) and 0.45 mM α-CD (Figure 1b) and to be fused into the low-field peak at high α-CD concentrations (Figure 1, parts c and d). This indicates that this signal has a large chemical shift variation of ca. 0.2 ppm. This is consistent with the result of Figure 6, because the ϵCH_2 proton is close to the H3 proton in the OTAB-α-CD complex (Figure 5b). The $\Delta\delta_{complex}$ values for either aliphatic or aromatic guest molecules provide useful information about the structure of the complex.

The structures of the complexes shown in Figure 5 will be time-averaged and should not be regarded as rigid bodies. In Figure 4, ROESY cross-peaks are found even for rather large distances, and the observed power coefficients *a* for HTAB (2.8) and OTAB (4.3) are smaller than a theoretical value of 6 (eq 2). These findings suggest that the α-CD molecule continues the shuttle motion on the alkyl chains of these molecules.

Generally, ROESY spectra are used to estimate rough structures of CD complexes.[16] In the present work, the numerical determination of ROE intensities allows us to estimate rather detailed structures of the complexes of α-CD with HTAB and OTAB. Our ROESY spectrum (Figure 3) of the HTAB-α-CD system indicates that exterior protons H2 and H4 exhibit cross-peaks with the incorporated HTAB molecule. This is the first report on such a finding, though these weak cross-peaks are not usually detected at high noise levels. Furthermore, the ROE data of these peaks are consistent with those of the interior protons (Figure 4).

Complex formation between long-chain surfactants and CDs has been extensively investigated by various techniques, though the number of structural studies is limited.[3−9] A long-chain surfactant molecule can bind two α-CD molecules. For double-chain surfactants, more stoichiometries must be taken into consideration.[20,29,30] The present work on single- and short-chain surfactants provides the basis for determining the stoichiometries, binding constants, and the structures of complexes for these more complicated systems.[5,20,29,30]

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