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Note

Complexation of single- and double-chain surfactants by cyclomalto-oligosaccharides

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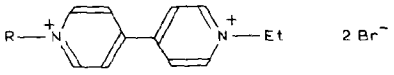
The cyclomalto-oligosaccharides (cyclodextrins, CDs) constitute one of the best known types of host molecules. Their ability to form inclusion complexes with organic compounds in aqueous solution results from their toroidal shape and the hydrophobic character of their inner surface[1–3]. While the practical applications of CD complexes in the cosmetic, food, and pharmaceutical industries are increasing[4], there have been few reports on the interactions of CDs and amphiphilic molecules[5–11]. This situation is relatively surprising because amphiphilic compounds (surfactants) usually contain hydrophobic groups, the complexation of which by CDs in aqueous environments should be a rather favorable process. For instance, such anionic and cationic surfactants as sodium dodecyl sulfate and cetyltrimethylammonium bromide interact[5,6] with cyclomaltohexaose (αCD) and cyclomaltoheptaose (βCD), and it was concluded that the surfactant alkyl chain is included in the cavity of the CD.

We have previously studied surfactant–CD interactions, using amphiphilic molecules with a covalently attached, redox-active group[10,11]. The redox-active group confers electroactivity to the free surfactant and its complexes with CD so that electrochemical techniques can be utilized to assess their properties. This approach is exemplified by the surfactant derivatives **1** and **2** which contain the 4,4′-bipyridinium (viologen) group.



1 R = n-$C_{16}H_{33}$
2 R = n-$C_{18}H_{37}$

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Electrochemical studies with **1** and **2** in the presence of αCD and βCD indicated that the CD interacts strongly with the alkyl tail of the surfactants[10,11]. For αCD, the heterogeneous rate of electron transfer between the viologens and the electrode surface was essentially unaltered by complexation; however, βCD seemed to decrease the kinetics of the electron transfer process and was less effective than αCD in solubilizing the reduced forms of the surfactant viologens or preventing their dimerization[10,11]. The interpretation of these results was based on a better fit of the alkyl chain inside the cavity of αCD. CPK models reveal that the cavity of αCD is ideally suited to form an inclusion complex with an "all-*gauche*" alkyl chain. By contrast, βCD has a cavity with a larger diameter, and direct interactions with the viologen sub-unit appear feasible.

We now report high-field ^{1}H-n.m.r. data that support this interpretation and also preliminary observations on the interactions of CDs with double-chain, vesicle-forming surfactants.

Fig. 1A shows the aliphatic region of the 400-MHz ^{1}H-n.m.r. of a solution of αCD in D_2O. The sole signal (1.12 p.p.m., t) must correspond to a trace impurity in the cyclodextrin sample since αCD has no signals in this region. Fig. 1B shows the absorptions in the aliphatic region of a solution of **1** in D_2O. The signals at 0.82 (t), 1.2, 1.3, and 2.02 p.p.m. correspond to protons on C-16, C-4/15, C-3, and C-2, respectively, of the hexadecyl chain, and that at 1.64 p.p.m. (t) to Me of the Et group. These assignments were verified using COSY 2D-n.m.r. spectroscopy.

The aliphatic region of the ^{1}H-n.m.r. spectrum of a solution containing **1** and a 10-fold excess of αCD is shown in Fig. 1C. Comparison with Fig. 1B reveals some remarkable differences, namely, the splitting of the large absorption for methylene

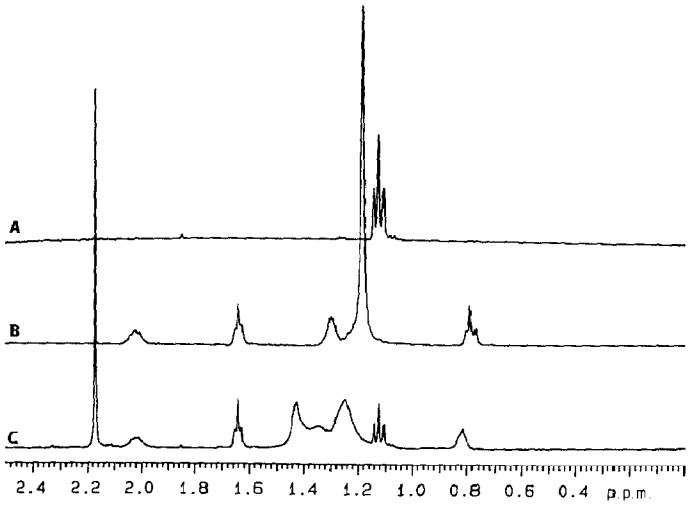
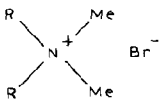


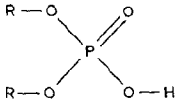
Fig. 1. 400-MHz ^{1}H-N.m.r. spectra of *A*, 20mM αCD in D_2O; *B*, 2mM **1** in D_2O; and *C*, 1mM **1** + 10mM αCD in D_2O. Internal acetone was used as the reference (2.17 p.p.m.). Presaturation removed the residual HDO peak.

groups at 1.2 p.p.m. into two different broad peaks and the broadening of the terminal methyl group (0.8 p.p.m.). In contrast, the triplet at 1.64 p.p.m. for Me of the Et group is not affected. These spectral changes clearly indicate that αCD forms an inclusion complex with **1** in which the hexadecyl chain is in the cavity. Thus, the methylene groups entrapped by the host are exposed to a microenvironment very different from that sensed by the unentrapped groups, which results in a split methylene-proton absorption. The broadened absorption of the terminal methyl protons is also consistent with this interpretation, as is the fact that the other methyl protons are unaffected, thus indicating the asymmetry of the interaction with the CD host. To the best of our knowledge, this constitutes the first direct spectroscopic evidence that the alkyl chain is the moiety involved in the complexation between CDs and surfactants in aqueous solution. The same conclusion has been reached on the basis of indirect evidence obtained by conductometric[5,6,9], surface tension[5,9], potentiometric[6], or voltammetric[10,11] measurements.

In extending this work, the interactions of CDs with double-chain surfactants have been explored. These surfactants are rather insoluble in aqueous media and can be utilized to build such complicated structures as lamellae and vesicles[12]. The commercially available surfactants dioctadecyldimethylammonium bromide (**3**, DODAB) and dicetyl phosphate (**4**, DCP) were studied.



3 (DODAB) R = n-$C_{18}H_{37}$



4 (DCP) R = n-$C_{16}H_{33}$

Ultrasonication of a dispersion of **3** in water decreases the turbidity substantially until a plateau is reached corresponding to the formation of small unilamellar vesicles (SUVs)[13]. The resulting dispersion is almost transparent, although its colloidal nature is still evidenced by a slight opalescence. Addition of excess of αCD to this dispersion causes a drastic increase in the turbidity (see Fig. 2) and the formation of a white precipitate, the induction period for which is highly dependent on the concentrations of **3** and αCD. The ^{1}H-n.m.r. spectrum of a solution of the precipitate in $(CD_3)_2SO$ indicated a mixture of αCD and **3** in the molar ratio ~5:1. This product can also be prepared by a procedure which does not involve sonication. In this procedure, a solution of **3** in chloroform is mixed with an aqueous solution of αCD. The two-phase mixture is heated to evaporate the chloroform. After the evaporation is complete, the dispersion is allowed to cool, yielding a white precipitate. The 400-MHz ^{1}H-n.m.r. spectrum of this solid (Fig. 3) shows all peaks expected for an αCD–**3** complex. The integrated intensities of the singlet at 4.8 p.p.m. (6 H-1 of αCD)[14] and the broad peak at 1.3 p.p.m. (32 CH_2 of **3**) give a value of ~5 for the molar ratio αCD/**3**.

Control experiments with tetramethylammonium bromide failed to produce

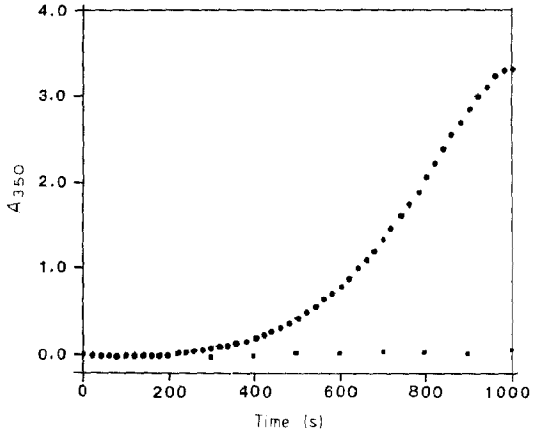


Fig. 2. Apparent absorbance (at 350 nm) as a function of time of a sonicated dispersion of vesicles of **3** upon the addition of CDs: ●, 0.5mM **3** and 6.6mM αCD; ■, 0.5mM **3** and 6.6mM βCD. These concentrations are those present intially. Optical pathway, 1.0 cm.

any precipitates upon addition of similar excesses of αCD. Additions of βCD to dispersions containing sonicated vesicles of **3** did not cause any changes in turbidity during 20 min (see Fig. 2), but, after several hours, small amounts of white precipitates were formed that contained βCD and **3** in the molar ratio ~5:1. A similar reaction pattern with αCD and βCD was also exhibited by **4**.

In conclusion, the spectroscopic evidence presented here supports the common belief that cyclodextrins form inclusion complexes with surfactant

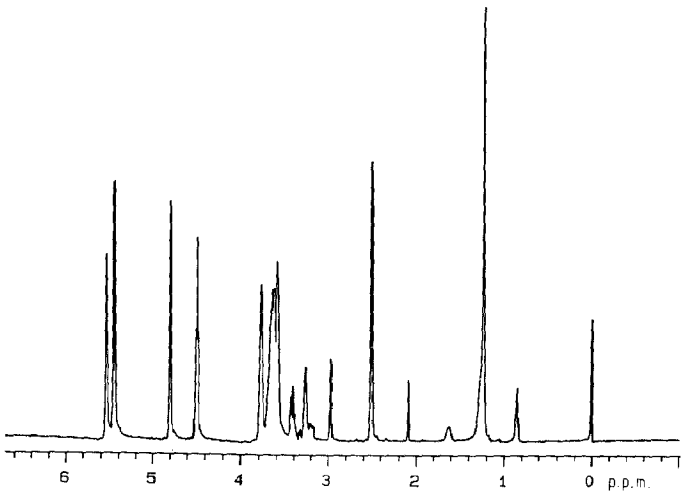


Fig. 3. 400-MHz ^{1}H-N.m.r. spectrum of a solution in $(CD_3)_2SO$ of the αCD–**3** complex. The large water peak was removed by presaturation to improve the observation of the peaks for αCD and **3**. Chemical shifts were measured against internal Me_4Si.

molecules in which the alkyl tails of the latter are partially engulfed by the cyclodextrin cavities. The preliminary results concerning the interactions of αCD and βCD with the double-chain surfactants **3** and **4** indicate their complexity, probably due to the complicated aggregation behavior of these surfactants. The data support the notion that several CD molecules (perhaps as many as 5–6) interact with one surfactant molecule. CPK models do not indicate any impossible steric features in these complexes, but the high CD/surfactant ratio merits a detailed structural study. At present, we are continuing to investigate their structures and properties and the potential application of these complexation phenomena to drug release systems.

EXPERIMENTAL

Materials. — The surfactant viologen **1** was synthesized and purified as reported[10]. αCD and βCD (Aldrich) were used without further purification; **3** (Kodak) and **4** (Sigma) were also commercial products. Aqueous solutions were prepared with distilled water and further purified by passage through a Barnstead Nanopure, four-cartridge system. D_2O (minimum 99.96 atom % D) or $(CD_3)_2SO$ (minimum 99.9 atom % D) were used for n.m.r. spectroscopy.

Equipment. 400-MHz ^{1}H-n.m.r. spectra were recorded with a Varian VXR-400-S spectrometer. Due to the low concentration of either **1** or αCD in the D_2O, presaturation was used to remove the residual HDO peak and facilitate the observation of the solute resonances.

Procedures. The preparation of the complex of αCD with **3**, without using sonication, was as follows. A solution of **3** (32 μmol) in $CHCl_3$ (3 mL) was mixed with a solution of αCD (320 μmol) in H_2O (20 mL). After boiling to evaporate the chloroform completely, the hazy dispersion was allowed to cool to room temperature, and the precipitate was collected, extensively washed with water, and dried in a vacuum oven at 70° for 3 h. N.m.r. analysis of the white powder indicated the presence of water hydration and the spectrum is shown in Fig. 3.

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