

How Alkali-Metal Cations Affect the Inclusion of Decanoic Acid in β -Cyclodextrin

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An equimolar mixture of decanoic acid (Dec) with a concentration approximately 18 times above its critical micellar concentration (cmc) and β -cyclodextrin (β CD) in deuterated water have been studied by ^1H NMR, and the β CD CH protons (H_3 , H_4 , H_5 , H_6) have been used as probes for assessing the effects of varying the concentration of various alkali-metal chlorides (LiCl , NaCl , KCl , CsCl) on guest inclusion and aggregation processes. The observed chemical shift variations are consistent with the progressive aggregation of decanoic acid induced by an increase in $[\text{NaCl}]$ which, in turn, caused a progressive decrease in the amount of included decanoic acid and an increase in the deshielding of β CD H_5 and H_3 protons, as decanoic acid was replaced by water in the β CD cavity. When the different salts were considered and their concentrations varied, Na^+ , K^+ , and Cs^+ displayed a similar and common slope while Li^+ showed a smaller gradient. On the whole, the observed chemical shift variations point to a competition between the aggregation of decanoic acid and its inclusion in β CD. In particular, the self-association of decanoic acid induced by an increase in electrolyte concentration produces a variation in the observed chemical shift value. Apart from a global medium effect, the electrolyte is found to produce β CD-site and ion specific effects in the observed chemical shift variations.

1. Introduction

β -Cyclodextrin (cyclomaltoheptaose, β CD) is a cyclic oligosaccharide composed of seven $\alpha(1-4)$ -linked glucopyranose residues (Figure 1). Its ability to form inclusion complexes by accommodating guest molecules of suitable size in its cavity derives mainly from its gross geometrical shape in the form of a hollow truncated cone^{1,2} and has been extensively used in diverse areas such as medicine, catalysis, food chemistry, and separation technology.

When the guest displays amphiphilic behavior, the β CD cavity has a tendency to host the hydrophobic fragment or part of it, leaving the hydrophilic moiety to interact mainly with hydroxyl groups of the β CD rims and with the solvent. Since the guest may exhibit surfactant behavior in these cases, aggregates/micelles of varying dimensions, whose sizes may depend critically on the medium and, in particular, on the presence and concentration of electrolytes,³ can thus be formed.

The mode and extent of host–guest interactions can be probed effectively by ^1H NMR. Of particular use are the chemical shifts of the β CD CH protons H_3 and H_5 , since they form two inner crowns of hydrogen atoms, near the wider and narrower rim, respectively, of β CD (see Figure 1). In general, no distinct resonances for the free host and the host–guest species can be observed, and the chemical shifts change monotonically as the host:guest molar ratio is varied. Hence, the host–guest complexation system is considered to be in the NMR fast exchange chemical shift limit, and the observed chemical shifts of the host and guest resonances are averages of the chemical shifts for the free and complexed states, weighted by the fractions of molecules in each state.⁴ In principle, the experimental observation of H_3 and H_5 shifts enable us to infer on the type of the host–guest association, namely, of the inclusion type, since the corresponding CH bonds point toward the inside of the β CD cavity.

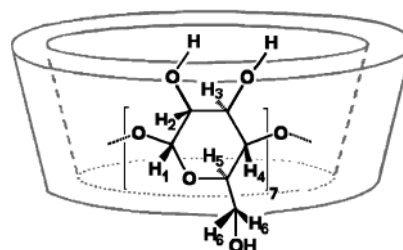


Figure 1. β CD macrocycle with a glucopyranose unit highlighted.

Decanoic acid is herein considered both as a guest molecule for inclusion in β CD and a surfactant with a reasonable critical micellar concentration ($\text{cmc} = 0.141 \text{ mM}$).⁵ When decanoic acid aggregates are formed in the presence of β CD, a competition is set up between decanoic acid inclusion in β CD and its self-association in the dispersion medium.⁶ In general, the number and strength of the β CD–alkylic fragment interactions increase with the length of the alkylic chain.⁷ Considering the large diameter of the β CD cavity and the conformational flexibility of the alkylic fragment, it has been suggested that the hydrocarbon chain coils inside the cavity.⁸

In real systems, the ionic strength of the medium cannot be ignored. The use of β CD as a drug solubilization/release system is an extensive current area of research⁹ and the concentration and type of ions present in the medium may affect the guest–host interactions. Salts are known to affect the solubilities of proteins in water, an effect known as the Hofmeister effect.¹⁰ Since it was later found that the increase in the concentration of salts reduces the solubilities in aqueous solutions of hydrophobic solutes such as benzene,^{11,12} the Hofmeister effect has been associated with the modulation of the hydrophobic effect by salts, whose ions are rank-ordered in the Hofmeister or lyotropic series by the extent to which they modulate hydrophobicity (reduction of hydrophobic solubilities in water has been dubbed as “salting-out” whereas increase of hydrophobic

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solubilities has been dubbed as “salting-in”). The relationship between the Hofmeister effect (measured by the ratio between the molar solubilities of the hydrophobe in a salt solution and in water, c_{hs}/c_{hw}) and the salt concentration, c_s , can be modeled by the equation¹³

$$\ln(c_{hs}/c_{hw}) = -k_s c_s$$

where k_s is the ion's salting-out coefficient. A positive value of this coefficient reflects a salting-out effect. When the hydrophobe is substituted by an amphiphile, the salting-out effect will eventually turn into the aggregation/micellization of the amphiphile.

In this work, an equimolar mixture in deuterated water of β -cyclodextrin (β CD) and decanoic acid with concentration approximately 18 times its cmc was studied by ^1H NMR. The β CD CH protons (H3, H4, H5, H6) and the decanoic acid protons were used as probes for assessing the effects of varying the concentration of various alkali-metal chlorides (LiCl, NaCl, KCl, CsCl) on guest inclusion and self-association processes. Since these are interdependent processes, one may expect variations in the chemical shifts of the observed CH protons that might lead to a better understanding of the influence of the electrolyte on both the guest encapsulation and self-association processes.

2. Materials and Methods

Decanoic acid (Fluka, 99%), hexanoic acid (Aldrich, 99%), β -cyclodextrin (Fluka, $\geq 99\%$), LiCl (Riedel-de Haën, $\geq 98\%$), NaCl (Panreac, $\geq 99.5\%$), KCl (Merck, $\geq 99.5\%$), CsCl (Aldrich, 99%) and D_2O (Aldrich, 99.9%) were used as received without further purification.

Solutions for NMR were prepared from a 2.5 mM stock solution of β CD in D_2O , obtained by heating an appropriate weight of β CD in D_2O at approximately 50 °C for 1 h. This solution was divided in two equal parts: one was used to prepare solutions of β CD with the alkali cations salts; the other to prepare β CD–aliphatic acid mixtures with the salts. The concentration of hexanoic acid was 2.5 mM while that of decanoic acid was either 2.5 mM (above cmc) or 1 mM (below cmc). The concentrations of the salts were varied between 50 and 250 mM. A standard procedure was used for all solutions which included heating at approximately 50 °C for 1 h followed by ultrasonification for three periods of 15 min.

The ^1H NMR spectra were recorded at either 300 or 500 MHz, on Bruker DRX spectrometers. The chemical shift of TSP was used as a reference. ROESY spectra were recorded at 500 MHz using a 3 kHz mixing field applied for 300 ms.

The NMR spectra were always recorded using freshly prepared solutions. This precaution was carried out due to the fact that we had chosen to deal with unbuffered solutions, to avoid any interference between the buffer and the β CD inclusion process. Phosphate anions from the buffer are known to induce small, yet significant, NMR shifts in the inside β CD protons and to discriminate to some extent between the inside and outside β CD protons.¹⁴

Molecular modeling was carried out for the inclusion complexes using the Gaussian 98 system of programs.¹⁵ Full geometry optimizations were performed at the semiempirical level PM3. Energies were subsequently calculated for the geometry optimized structures by single point calculations at the Hartree–Fock level with the 6-31G basis set. GaussView was used to visualize the geometry optimized structures.¹⁶ Aimed at determining a likely inclusion mode for the guest

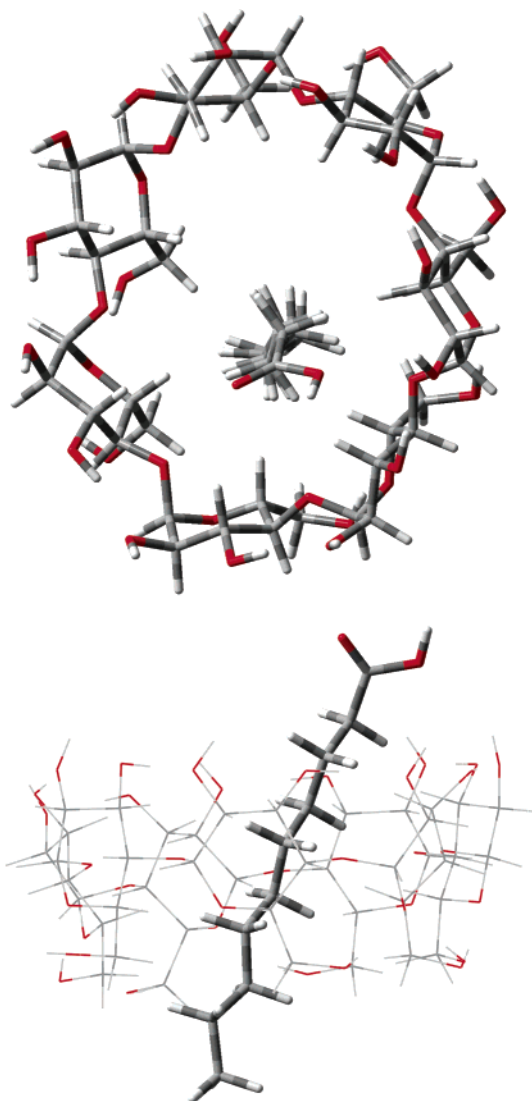


Figure 2. Calculated inclusion mode for the β CD•Dec complex. While the hydrocarbon chain of decanoic remains all-trans, the top view reveals that a slight twisting occurs near the methyl end of the hydrocarbon chain, when the decanoic acid is inside the β CD cavity.

molecule in the β CD cavity (Figure 2), these calculations also revealed that the hydrocarbon chain of the decanoic acid molecule, while still keeping the all-trans conformation, tends to slightly twist inside the β CD cavity, near its methyl end, thus increasing the number of $\text{H}\cdots\text{H}$ close contacts and enhancing the host–guest interactions.

Given the large dimension of the β CD molecule and the minimum requirements for reliable predictions of nuclear magnetic shielding constants (RHF/6-311+G(2d,p)),¹⁷ we had to resort to small model systems whose geometry had been previously optimized with the B3LYP method and the 6-31G(d) basis set. The considered model systems were 1,4-*O,O*-dimethyl-D-(+)-glucopyranose (Glc) in a vacuum and in interaction with one ethane molecule, with one or two water molecules in different relative positions, or with the hydronium ion. These model systems were solely considered for the single purpose of obtaining some guidance in the interpretation of the observed chemical shifts variations for the β CD protons. In these calculations, the Glc–ethane interactions were modeled by $\text{CH}_{\text{(Glc)}}\cdots\text{HC}_{\text{(ethane)}}$, $\text{CH}_{\text{(Glc)}}\cdots\text{O}_{\text{water}}$, and $\text{CH}_{\text{(Glc)}}\cdots\text{O}_{\text{hydronium ion}}$ contacts, whose distances were kept at 2.40–2.45 Å. The latter model contacts with the oxygen atoms of a water molecule and

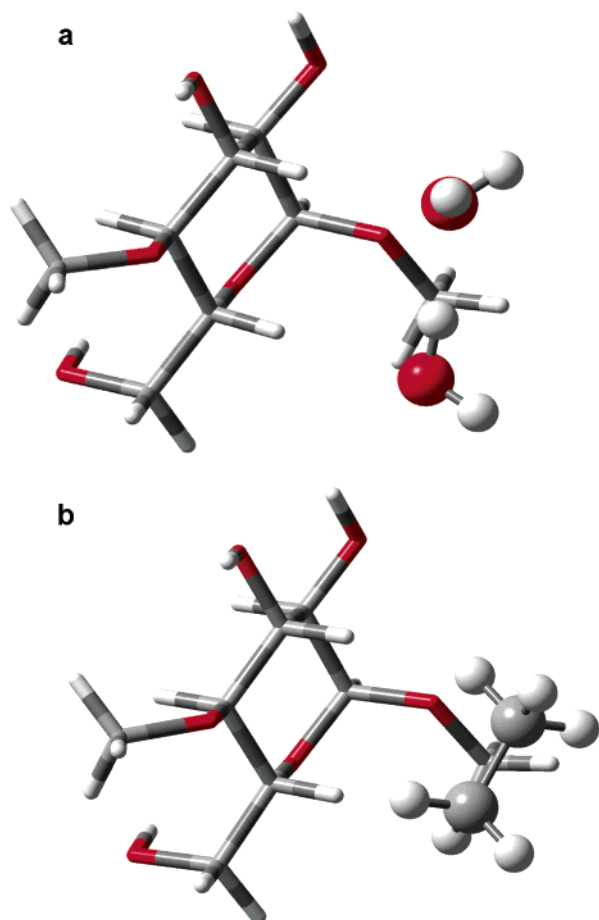


Figure 3. Model systems for the interaction of Glc with (a) two water molecules or with (b) one ethane molecule. See text for details.

of a hydronium ion try to reflect the relatively hydrophobic nature of the β CD cavity. In fact, the water molecules in the β CD cavity tend to form a cluster of molecules rather than favoring hydrogen bonding interactions with the β CD ether oxygen atoms.¹⁸

3. Results and Discussion

In general, the addition of an amphiphile to an aqueous β CD solution leads to a shielding of the H3 and H5 protons located inside the β CD cavity. This effect, ascribed to the interaction between the β CD CH bonds and the amphiphile's hydrocarbon moiety, is generally considered as a clear indication of the guest inclusion in β CD. Either for decanoic or hexanoic acid in 2.5 mM equimolar solutions in β CD, the shielding of protons H3 and H5 were confirmed. In addition, our calculations of the nuclear magnetic shielding constants for the model systems (see Methods) revealed qualitative agreement with the experimental results. In particular, the substitution of two water molecules in close interaction with Glc (Figure 3a) by an ethane molecule (Figure 3b) is accompanied by the shielding of H3 and H5, as experimentally observed.

As shown in Figure 4a, the chemical shift changes of various β CD protons (H3, H4, H5, and H6), for the β CD(2.5 mM)/Dec(2.5 mM) mixture in D_2O at different NaCl concentrations (50, 100, 150, 200, and 250 mM), are approximately linear over this concentration range. Since the plotted values are the chemical shift differences with respect to the no-salt situation (i.e., zero concentration of electrolyte), all the straight lines pass through the origin. Positive slopes indicate proton deshielding caused by adding electrolyte. In particular, the chemical shift

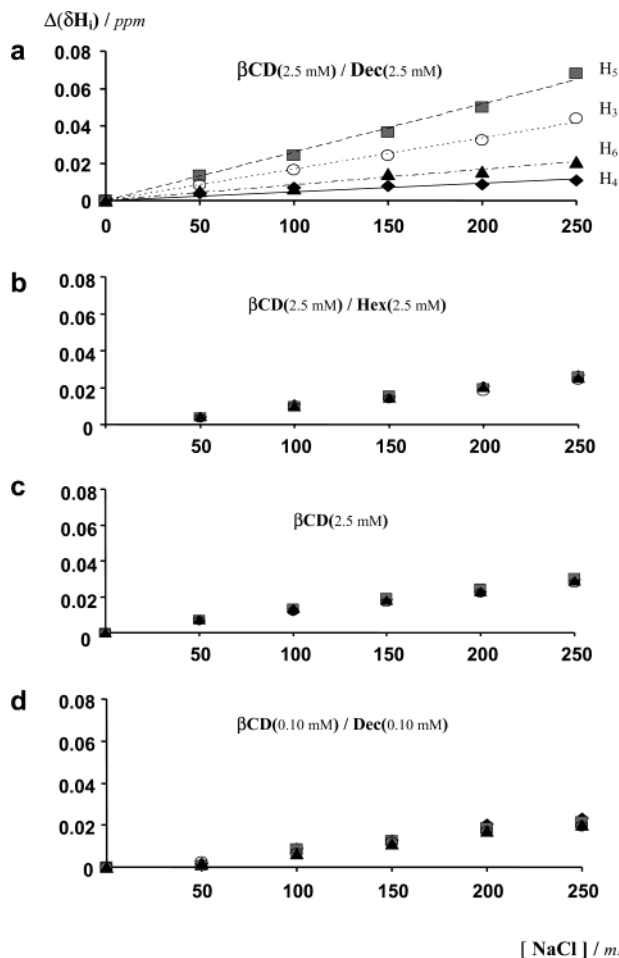


Figure 4. Chemical shifts variations for β CD protons, at different concentrations of NaCl in D_2O : (a) β CD(2.5 mM)/Dec(2.5 mM); (b) β CD(2.5 mM)/Hex(2.5 mM); (c) β CD(2.5 mM); (d) β CD(0.10 mM)/Dec(0.10 mM).

changes for H5 and H3 (gradients 2.7×10^{-4} and 1.8×10^{-4} ppm mM^{-1} , respectively), both located inside the β CD cavity, are much greater than for H6 and H4 (gradients 0.8×10^{-4} and 0.4×10^{-4} ppm mM^{-1} , respectively). By contrast, the chemical shift variations for all the observed protons in the β CD(2.5 mM)/Hex(2.5 mM) and β CD(2.5 mM) systems fall on straight lines with very similar gradients (1.0×10^{-4} and 1.1×10^{-4} ppm mM^{-1} , respectively; see Figure 4, parts b and c). Unlike the β CD/Dec mixture, no distinction between β CD protons was found for the β CD/Hex and β CD systems.

Two relevant features emerge from each of these plots: the signs and the relative magnitudes of the slopes. A positive slope indicates a deshielding effect, whereas a negative slope points to proton shielding. When the increase of electrolyte concentration does not discriminate among β CD protons, as is the case for the β CD/Hex and β CD systems, then one is observing a global medium effect associated with the addition of electrolyte.¹⁹ When, for a particular electrolyte concentration, the observed protons change their chemical shifts by the same amount, then one can infer that specific interactions, which would otherwise distinguish the protons, are absent. On the other hand, for the β CD/Dec mixture, each defined electrolyte concentration leads to a different chemical shift change (Figure 4a). In particular, the increase in electrolyte concentration induces a distinction between those β CD protons which are inside and those which are outside the β CD cavity.

The cmc of decanoic acid in water (0.141 mM)⁵ is about 18 times lower than the initial decanoic acid concentration used in

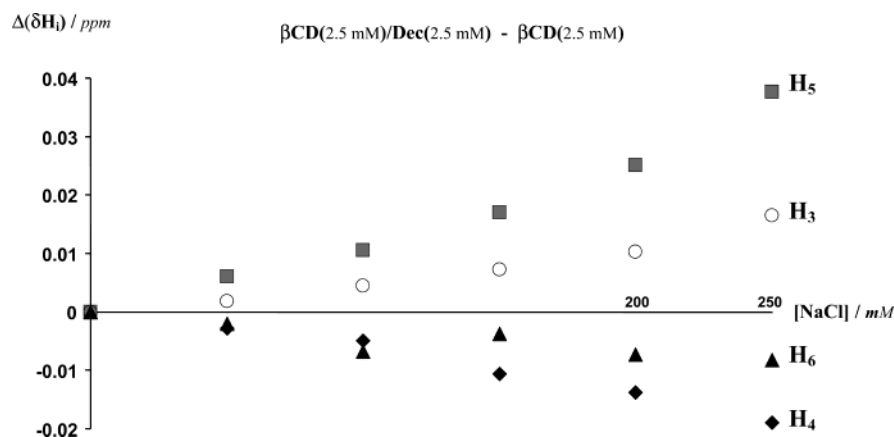


Figure 5. Chemical shifts variations for β CD protons, at different concentrations of NaCl in D_2O , for the difference β CD(2.5 mM)/Dec(2.5 mM) – β CD(2.5 mM).

the above experiments. While the presence of β CD is known to increase the decanoic acid cmc by reducing the amount of nonencapsulated guest,²⁰ an appreciable extent of aggregation might still occur in the β CD/Dec mixture, as suggested by comparison of the results for the β CD/Dec and β CD/Hex systems (Figure 4, parts a and b). To confirm this suspicion, a β CD/Dec experiment was carried out using an initial decanoic acid concentration well below its cmc in water ($[Dec]_0 = 0.10$ mM). The resulting plot (Figure 4d) showed the pattern obtained for the β CD/Hex and β CD systems (Figure 4, parts b and c) with all the observed β CD protons falling in a single straight line with a gradient (ca. 0.9×10^{-4} ppm mM^{-1}) not significantly different from that obtained for β CD/Hex and β CD. This result suggests that the distinct chemical shift changes caused by the electrolyte addition to the β CD/Dec aqueous mixture might be associated with the aggregation process of decanoic acid. While decanoic and hexanoic acids have association constants with β CD which differ by approximately 1.5 orders of magnitude ($\log K_{\beta CD_Dec} = 4.01$, $\log K_{\beta CD_Hex} = 2.47$),²¹ their respective cmcs differ by approximately 3 orders of magnitude, being smaller for decanoic acid.⁵

To subtract out the global medium effect due to the presence of the electrolyte, one should consider the β CD/Dec– β CD difference (Figure 5). In this plot, H5 and H3 have positive gradient differences (Δ gradients 1.6×10^{-4} and 0.7×10^{-4} ppm mM^{-1} , respectively) and so deshield with respect to the β CD solution due to the increase in the NaCl concentration, whereas H6 and H4 undergo relative shielding, though with smaller gradient differences (Δ gradients -0.3×10^{-4} and -0.7×10^{-4} ppm mM^{-1} , respectively). By contrast, the difference β CD/Hex– β CD yields almost negligible gradient differences (values are between $+3 \times 10^{-6}$ and -4×10^{-5}), for all the probed β CD protons, indicating that in this system the increase in [NaCl] does not induce any significant effect.

Since no distinct β CD proton resonances are observed for free β CD and the β CD_{Dec} inclusion complex, the host–guest complexation system is considered to be in the NMR fast exchange chemical shift limit, and the observed chemical shifts of the host resonances are averages of the chemical shifts for the free and complexed states, weighted by the fractions of molecules in each state⁴

$$\delta = x_{\beta CD} \delta_{\beta CD} + x_{\beta CD_Dec} \delta_{\beta CD_Dec}$$

where x and δ stand for molar fraction and chemical shift, respectively, and the subscripts indicate the free and complexed states of β CD. By drawing attention to this well-known

dependence of the chemical shift in the fast exchange regime, we would like to stress that a variation in the observed chemical shift (the left-hand side δ) does not necessarily require a variation in any of the right-hand side chemical shift values, since a variation in the molar fractions is enough to bring about a variation in the resulting chemical shift value. In particular, a decrease in $x_{\beta CD_Dec}$ due to self-association of decanoic acid and, consequently, an increase in $x_{\beta CD}$ will bring about an increase in the resulting δ value (deshielding), since the decanoic acid inclusion in β CD causes the shielding of H3 and H5 ($\delta_{\beta CD_Dec} < \delta_{\beta CD}$).

How does the increase in [NaCl] promote the aggregation of decanoic acid in solution, and why does the same induced process does not occur for the corresponding β CD/Hex mixture? Before dealing with these questions, additional remarks should be made on the above experiments and results. As previously mentioned, the NMR spectra were always recorded using freshly prepared unbuffered solutions. This precaution was taken in order to avoid any effect between the buffer anions and the β CD protons, in particular, discrimination between inside and outside β CD protons by the phosphate buffer anions.¹⁴ At the time of recording the spectra, the β CD/Dec mixture had a pH of 4.56. At this pH, the decanoate fraction amounts to 34% (the pK_a of decanoic acid is 4.84). The decanoate anions in the formed aggregates are likely to be stabilized by the Na^+ counterions, since these have the effect of reducing the repulsion between the carboxylate headgroups, thus lowering the cmc.²² Hence, the extent of the aggregation process increases and the β CD inclusion complex subsequently dissociates to some extent, thus causing the replacement of decanoic molecules in the β CD cavity by water molecules. This decanoic-by-water substitution in the β CD cavity deshields both H5 and H3, as observed. For the low salt concentrations used in this work, the salt operates directly on the aggregation process. Hence, the effect on the inclusion process is an indirect or secondary effect operating through the interdependence between the inclusion and the aggregation processes. This reasoning explains why the β CD proton discrimination is not observed for the hexanoic and decanoic acid mixtures below their respective cmcs.

To obtain some insight into the aggregation of decanoic acid molecules, the variation of the chemical shifts of the decanoic acid protons were also investigated, as the NaCl concentration was increased over the range 50–250 mM. It can be seen from Figure 6 that the carbon chain protons, except those linked to the α -carbon atom, present approximate linear chemical shift variations with a similar positive slope (average gradient 0.5×10^{-4} ppm mM^{-1}). On the other hand, the protons linked to the

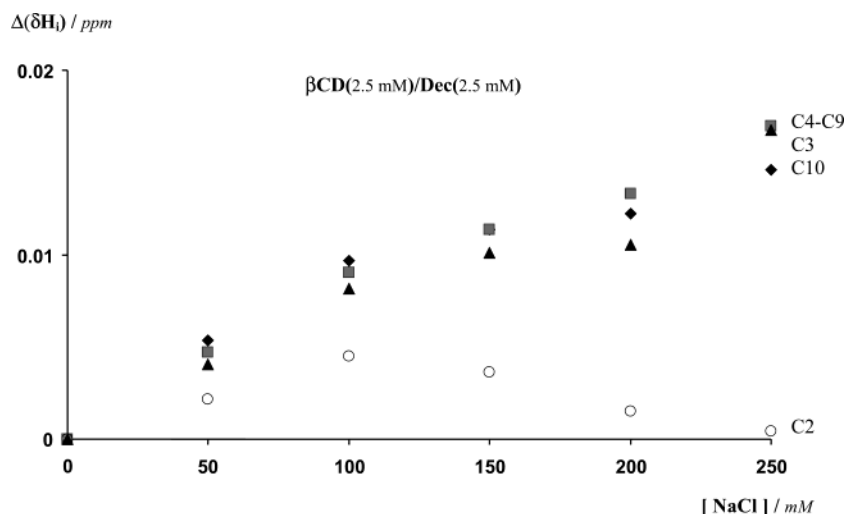


Figure 6. Chemical shifts variations for the decanoic acid protons (indicated by the carbon atom they are attached to), at different concentrations of NaCl in D₂O, for β CD(2.5 mM)/Dec(2.5 mM).

α -carbon atom show minor positive chemical shift variations (below 0.005 ppm) with a maximum about 100 mM.

Various inferences can be drawn from the results shown in Figure 6. First, since the chemical shift variations are positive for all the carbon chain protons, one might infer that the carbon chains are exposed to the solvent whose polarity increases due to the increase of electrolyte concentration. Second, with the single exception of the α -carbon atom protons, which are likely to be influenced by the electrostatic interactions with the headgroups, the chemical shifts variations of the remaining carbon chain protons share almost the same gradient, thus suggesting that the hydrocarbon chains in the aggregates should present an appreciable dispersion of conformations (chain disorder). In fact, this is expected, considering the length of the carbon chain of decanoic acid in the all-trans conformation and the size of the carboxylate headgroup.

It is well-known that the behavior of amphiphilic molecules in water reflects the balance between two opposing tendencies, namely, that of their polar headgroups, which tend to stay in solution, and that of their hydrocarbon tails, which tend to separate out as a distinct phase. The factors which determine the result of this balance (the hydrophilic–hydrophobic balance) include (i) the solvation of the headgroups, (ii) the interaction between headgroups eventually mediated by ions in solution, (iii) the interaction of hydrocarbon chains with water, and (iv) the interaction of hydrocarbon chains with themselves.²³ In addition, due to the packing requirements imposed by steric constraints among chain molecules at interfaces,²⁴ the relative sizes of the hydrophilic and hydrophobic parts of the amphiphilic molecules and, eventually, the conformational flexibility of the hydrocarbon chain play an important role in establishing this balance. In particular, a decrease in the number of carbon atoms in the hydrocarbon chain leads to an increase in the cmc,²² very much in consonance with the experimental finding that no distinct chemical shift changes result from electrolyte addition for β CD(2.5 mM)/Hex(2.5 mM), thus suggesting that, unlike for decanoic acid, no appreciable aggregation of hexanoic acid is taking place (its initial concentration was below the corresponding cmc value in the presence of β CD).

To assess the effect of varying the concentration of the hydronium ion, the concentration of deuterated hydrochloric acid was increased from 50 up to 250 mM. For these DCl concentrations, at room temperature (20 °C), the extent of acid hydrolysis of β CD is considered to be insignificant.²⁵ As can be seen from

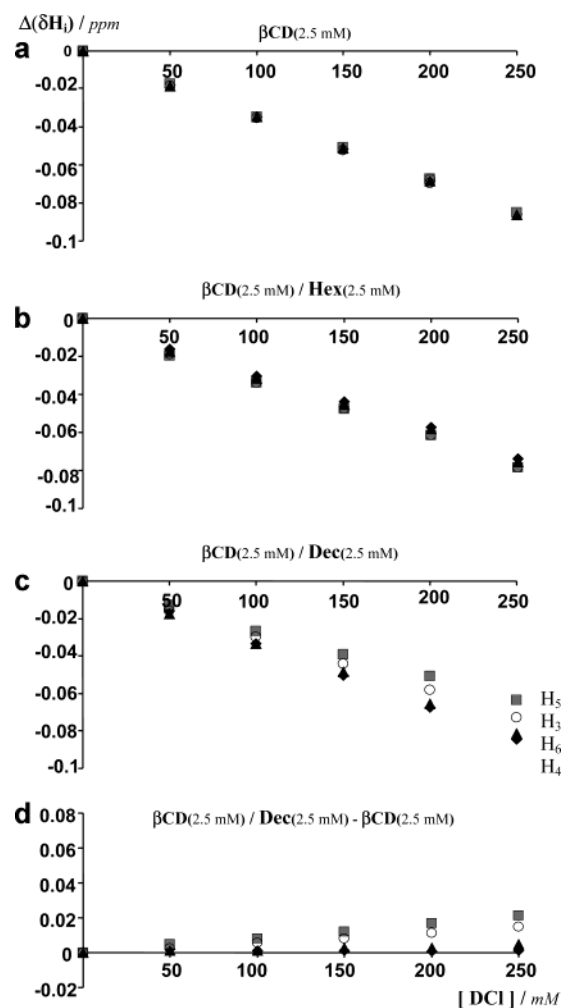


Figure 7. Chemical shifts variations for the various β CD protons, at different concentrations of DCl in D₂O: (a) β CD(2.5 mM); (b) β CD(2.5 mM)/Hex(2.5 mM); (c) β CD(2.5 mM)/Dec(2.5 mM); (d) β CD(2.5 mM)/Dec(2.5 mM) – β CD(2.5 mM).

Figure 7, for both β CD (Figure 7a) and β CD/Hex (Figure 7b) solutions, all the observed β CD protons give similar negative slopes (gradients -3.4×10^{-4} ppm mM⁻¹ and -3.0×10^{-4} ppm mM⁻¹, respectively). On the other hand, for the β CD/Dec mixture (Figure 7c), the β CD protons have distinct slopes (H5, -2.5×10^{-4} ppm mM⁻¹; H3, -2.9×10^{-4} ppm mM⁻¹; H6,

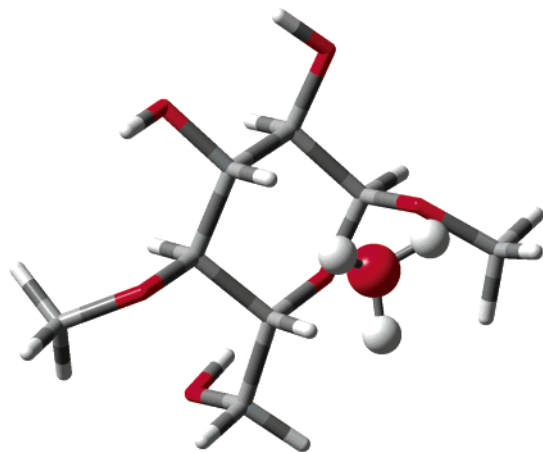


Figure 8. Glc-hydronium ion model system. See text for details.

H4, -3.3×10^{-4} ppm mM^{-1}). Hence, the same picture occurs again, with the β CD/Dec mixture showing discrimination of the observed β CD protons. However, in this case, all the gradients are negative, i.e., all the observed β CD protons display a shielding effect. Unlike the other cations which are not able to penetrate into the β CD cavity carrying their first hydration shells, the hydrogen ion has easy access to the β CD cavity since its main diffusion process uses the hydrogen bonded network of water molecules (the so-called Grotthuss mechanism). The global medium effect caused by the hydronium ion can be seen in the β CD solution (Figure 7a) and corresponds to a nonspecific shielding effect. This effect is in qualitative agreement with the calculated nuclear magnetic shielding constants for the Glc-hydronium ion model system (Figure 8) which show that the interaction between Glc and a hydronium ion, with close contacts between H3, H5, and the oxygen atom of the hydronium ion (distances around 2.4 Å), leads to the shielding of these β CD CH protons. Since all the initial concentrations of DCl used in this work are far larger than that of the decanoic acid in the β CD/Dec solution, all the carboxylate ions are converted to carboxylic acid. Hence, the aggregates are not so strongly stabilized by the electrolyte ions and the process of aggregation is less extensive. On the other hand, the increase in electrolyte concentration leads to an increase in the inclusion of decanoic acid in β CD since this is the single way the hydrocarbon chains of decanoic acid molecules have of avoiding an exclusively polar environment (hydrophobic effect). In turn, this inclusion process leads to the shielding of the observed β CD protons, as observed (see Figure 7).

How do alkali-metal cations (Li^+ , Na^+ , K^+ , and Cs^+) affect the chemical shifts of the β CD CH protons in the β CD/Dec mixture? To address this question we increased the concentration of the corresponding chlorides up to 250 mM and recorded the chemical shift variations of the β CD protons (Figure 9). This figure shows that all the cations give approximately linear variations, with Na^+ , K^+ , and Cs^+ displaying a similar and common slope and Li^+ showing the smallest gradient. These trends are particularly clear for H5 and H3 whose positive chemical shift variations are the largest for the observed β CD protons, in consonance with the interpretation given above, according to which the cation induced aggregation of decanoic acid will inevitably cause dissociation of the inclusion complex, thus leading to the replacement of decanoic molecules in the β CD cavity by water molecules which, in turn, results in deshielding of the β CD protons. The reduction in the free decanoic acid concentration explains why protons H4 and H6 also suffer deshielding, although to a smaller extent.

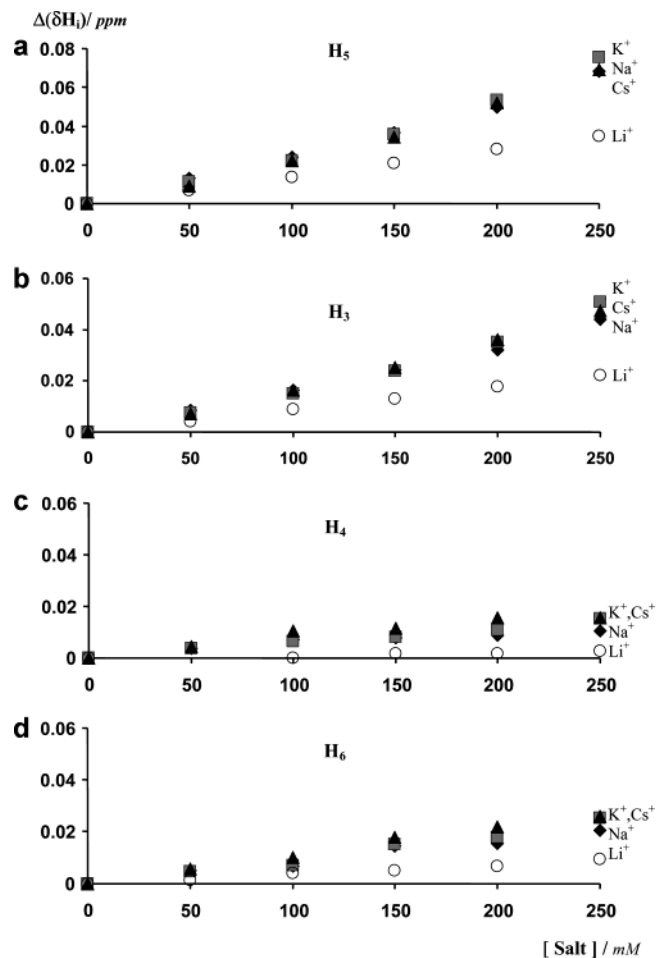


Figure 9. Chemical shifts variations for the β CD protons of β CD(2.5 mM)/Dec(2.5 mM), at different concentrations of the alkali-metal chlorides (LiCl , NaCl , KCl , and CsCl) in D_2O , for the following β CD protons: (a) H5; (b) H3; (c) H4; (d) H6.

A question still remains to be answered: why do Na^+ , K^+ , and Cs^+ display an almost common slope and Li^+ shows the smallest gradient? Before dealing with this question, one should consider the effects of these cations on the chemical shift variations of proton H5, for β CD(2.5 mM)/Dec(2.5 mM), β CD-(2.5 mM)/Hex(2.5 mM), and β CD(2.5 mM) solutions (Figure 10; please note that Figures 9a and 10a show the same results). Again, the same general pattern is observed; i.e., Li^+ gives the smallest chemical shift variations, although the slope for Cs^+ follows closely that for Li^+ , in the β CD solution.

For the cations considered in the present work, the experimental salting-out constants for benzene (k_s/M^{-1} : Li^+ , 0.141; Na^+ , 0.195; K^+ , 0.166; Cs^+ , 0.088)¹¹ follow the decreasing order $\text{Na}^+ > \text{K}^+ > \text{Li}^+ > \text{Cs}^+$, i.e., with Li^+ just above Cs^+ which has the smallest salting-out constant. Thus, the salting-out effect cannot be explained by a correlation with the ion charge density alone, since Li^+ has the highest charge density and yet does not show the highest salting-out effect among the alkali-metal cations. On the contrary, Li^+ shows the second smallest salting-out constant for benzene.

To explain the anomalous behavior of lithium seen in our chemical shift plots, we consider a molecular dynamics simulation study carried out for the hydration of ions in SPC/E water at 25°C.²⁶ The average coordination numbers of Li^+ , Na^+ , K^+ , Rb^+ , and Cs^+ were found to be approximately 4, 6, 7, 8, and 8, respectively.²⁷ In addition, the residence times of water in the first hydration shell of Li^+ , Na^+ , K^+ , Rb^+ , and Cs^+ (approximately 51, 22, 14, 12, and 14 ps, respectively) pass

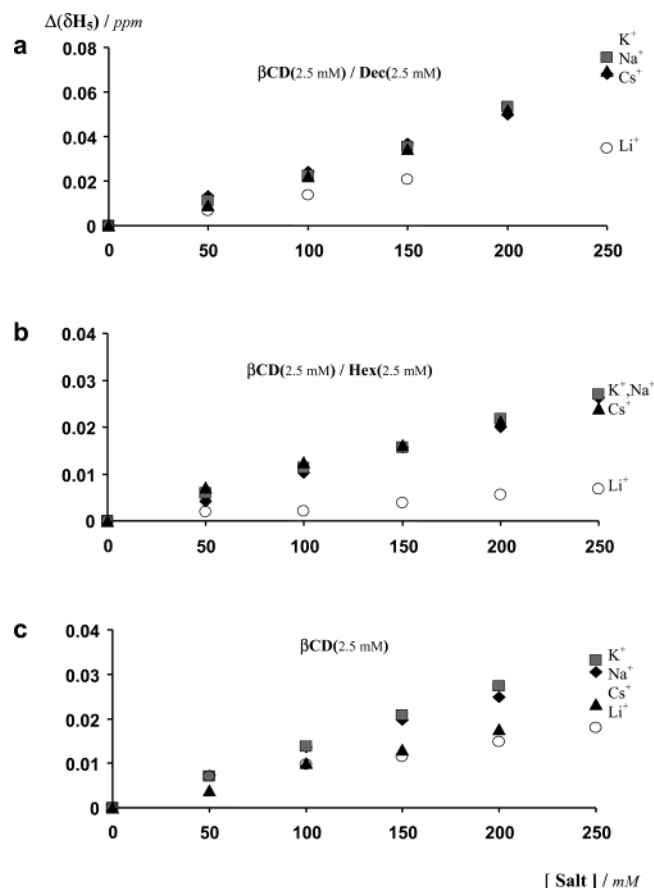


Figure 10. Chemical shifts variations for proton H5, at different concentrations of each of the alkali-metal chlorides (LiCl, NaCl, KCl, and CsCl) in D₂O, for the following solutions: (a) β CD(2.5 mM)/Dec(2.5 mM); (b) β CD(2.5 mM)/Hex(2.5 mM); (c) β CD(2.5 mM). Note that part a of this figure coincides with part a of Figure 9.

through a minimum as a function of size,²⁷ which in turn correlates with a maximum in the corresponding solvation entropy and points to different types of hydration, namely, electrostatic ion solvation (hydrophilic), for small cations, and cage formation (hydrophobic), for large cations.²⁶ The highest average residence time of water molecules in the first solvation shell of the lithium ion—approximately, 2.3 times that for Na⁺ and 3.6 times that of Cs⁺—leads both to a much slower exchange dynamics of the water molecules between the first and the second solvation shells²⁶ and to a presumably slower ion exchange with the bulk solution.²⁸

Because of its highest average residence time of water molecules in the first solvation shell, the solvated lithium ion has its charge more effectively distributed than the other alkali-metal cations, thus presumably causing less electrostriction (the effect of the local electric field on the volume occupied by the water molecules)¹¹ and leading to a molar volume larger than expected for its tetrahedral coordination.²⁹

The different behavior clearly seen for lithium in our chemical shift difference plots suggests that the effect of this cation on the solvent polarity, the aggregation process and on the guest–host interaction is much smaller than the other cations. Considering the above arguments, the reduced relative effect of Li⁺ on the overall solvent polarity (Figure 10c, β CD alone) may be a result of its more effective charge distribution which is tantamount to increasing its ionic radius, i.e., to reducing the effective charge density of the solvated Li⁺. In the β CD(2.5 mM)/Dec(2.5 mM) system, Li⁺ does not appear to stabilize the decanoic acid aggregates to any great extent (compared to the

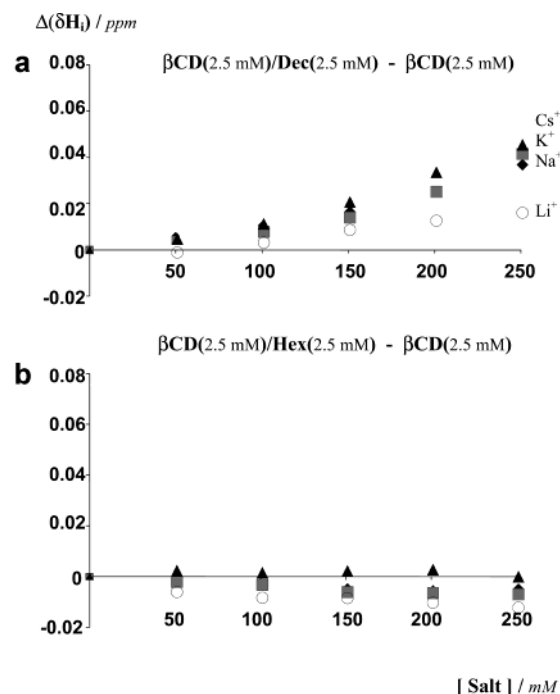


Figure 11. Chemical shifts variations for proton H5, at different concentrations of each of the alkali-metal chlorides (LiCl, NaCl, KCl and CsCl) in D₂O: (a) β CD(2.5 mM)/Dec(2.5 mM) – β CD(2.5 mM); (b) β CD(2.5 mM)/Hex(2.5 mM) – β CD(2.5 mM).

other cations) and thus the amount of decanoic acid included in the β CD cavity reduces only slightly (Figure 10a). Here the lithium ion cannot stabilize the decanoic acid polar headgroups due to its more effective charge distribution and larger than expected molar volume. The longer residence times of solvation water around the lithium cation may also impede the electrostatic interaction required for headgroup stabilization. In the β CD-(2.5 mM)/Hex(2.5 mM) system, all the cations introduce slight shielding for proton H5 (compare slopes in Figure 10, parts b and c), suggesting a small increase in hexanoic acid in the β CD cavity resulting from an increase in overall solvent polarity.

These effects are particularly clear in the plot for the β CD/Dec – β CD difference (Figure 11a) and the order observed for the different alkali-metal cations (Li⁺ < Na⁺, K⁺, Cs⁺) should reflect the experimental salting-out effects of the alkali-metal cations for decanoic acid in water.

4. Conclusions

In this work, we have used NMR to show that the alkali-metal cations cause β CD-site and ion specific effects in the β CD/Dec system due to the cation induced aggregation of decanoic acid that leads to the partial dissociation of the inclusion complex and to the replacement of decanoic molecules in the β CD cavity by water molecules. This, in turn, results in deshielding of the β CD protons.

The observed effect of alkali-metal cations on this process (Li⁺ < Na⁺, K⁺, Cs⁺) should reflect their relative salting-out potentials for aqueous decanoic acid. The average coordination numbers and residence times of water in the first hydration shell of these cations enable us to qualitatively explain the observed variations.

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