Journal of Inclusion Phenomena and Macrocyclic Chemistry **50**: 173–181, 2004.

^{1}H-NMR Studies of the Inclusion Complexes between α-Cyclodextrin and Adamantane Derivatives Using Both Exchangeable Hydroxy Protons and Non-Exchangeable Aliphatic Protons

BIRGIT BENDEBY, LENNART KENNE and CORINE SANDSTRÖM*
Department of Chemistry, Swedish University of Agricultural Sciences, P.O. Box 7015, SE-750 07 Uppsala, Sweden

(Received: 17 September 2003; in final form: 29 April 2004)

Key words: adamantane analogues, α-cyclodextrin, conformation, hydration, hydrogen bond, hydroxy protons, inclusion, ^{1}H-NMR, water

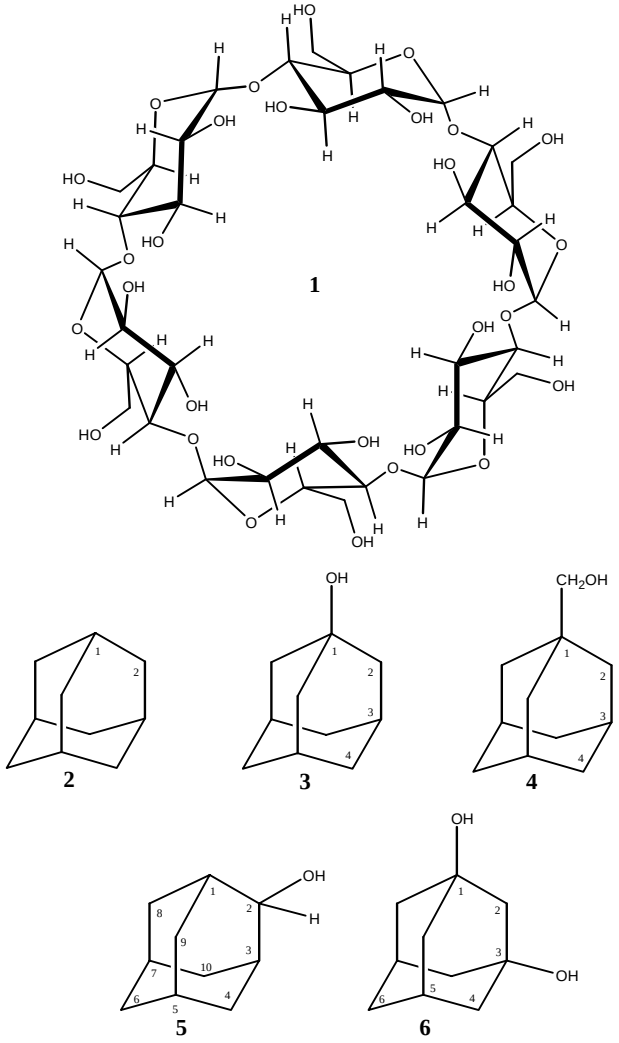
Abstract

The inclusion complexes between α-cyclodextrin (α-CD) and adamantane, 1-adamantanol, 1-(hydroxymethyl)-adamantane, 2-adamantanol, and 1,3-adamantanediol in aqueous solution have been studied by ^{1}H-NMR spectroscopy using both non-exchangeable and exchangeable protons. The complexation-induced ^{1}H-NMR shifts (CIS) and NOEs of non-exchangeable protons, as well as the CIS, NOEs, temperature coefficients, and linewidth of signals from exchangeable hydroxy protons have been determined. The stoichiometry of the adamantane/α-CD complex could not be determined due to the low solubility of adamantane. However, for 0.11 equivalent of adamantane added, two sets of separate ^{1}H signals for the free and bound α-CD were observed. The signal from O(3)H in the complexed form appeared narrow and upfield shifted with a low-temperature coefficient indicating reduced hydration inside the hydrophobic cavity of α-CD. Both 1-adamantanol, and 1-(hydroxymethyl)-adamantane formed 1:1 inclusion complexes with α-CD and only one set of NMR signals was observed. The CIS and NOEs suggested that both complexes had similar structures. The O(2)H signal of α-CD was broadened at low temperature and became narrower as the temperature raised. The broadening increased with higher concentration of guest suggesting interaction between O(2)H of α-CD and the guest molecules. The stoichiometry of the α-CD/2-adamantanol complex could not be determined with certainty, but the NMR data suggested equilibrium between 2:1 and 1:1 complex. As with adamantane, a sharp and upfield shifted O(3)H signal with a very low-temperature coefficient was observed. No inclusion complex was formed between 1,3-adamantanediol and α-CD. This study showed how the hydroxy protons of α-CD could be used to obtain complementary information on the geometry and stability of inclusion complexes of α-CD.

Introduction

The α-, β- and γ-cyclodextrins are cyclic oligosaccharides that are used for instance in pharmaceutical chemistry to bring hydrophobic compounds into aqueous solution. They have the ability to form complexes with water-insoluble substances and thus enable distribution in aqueous media. The driving forces to form inclusion complexes of CDs are electrostatic, van der Waals and hydrophobic interactions and hydrogen bonding [1, 2]. The α-cyclodextrin (α-CD) is constituted of six gluco-pyranose units linked together by α-1,4-glycosidic bonds, while β-, and γ-CD are made of seven and eight residues, respectively (Scheme 1). α-CD, as well as β-, and γ-CD have been structurally determined by X-ray crystallography to have a conical shape with the C(6) hydroxy groups at the narrow rim and the C(2) and C(3) hydroxy groups at the wider rim forming a hydrophobic cavity. The secondary hydroxy groups, O(2)H and O(3)H, form a circle of consecutive inter-residue hydrogen bonds. These hydrogen bonds are found in the crystal structure [1], in dimethyl sulfoxide (DMSO) solutions [3–5] and in aqueous solutions [6]. Often when NMR studies are performed on inclusion complexes of α-CD, the complexation-induced ^{1}H-NMR shifts (CIS) and NOEs of the C(3)H and C(5)H signals are used to determine the stoichiometry and geometry of the complex because of the positions of these protons in the α-CD structure. But the hydroxy protons, that should also be affected by even a partial inclusion of a guest into the hydrophobic cavity and thereby give additional structural information, are not much used for NMR studies in aqueous solution. This is partly due to the difficulties in observing these protons because of fast exchange with water. However, by lowering the temperature it is possible to reduce the exchange enough to

* Author for correspondence. E-mail: corine.sandstrom@kemi.slu.se



Scheme 1. Structure of α-CD (**1**), adamantane (**2**), 1-adamantanol (**3**), 1-(hydroxymethyl)-adamantane (**4**), 2-adamantanol (**5**) and 1,3-adamantanediol (**6**).

observe the hydroxy proton signals by NMR. It has been shown that much information can be obtained from analysis of the NMR data obtained for hydroxy protons of carbohydrates in aqueous solution [7–15].

In the last few years, we have studied the use of hydroxy protons in conformational analysis of carbohydrates in aqueous solution [6, 16–20], and the work has now extended to intermolecular interactions [6]. In the present work, we would like to get a better understanding of the effects of inclusion complex formation on α-CD hydroxy protons. For this, water solutions of α-CD (**1**) and adamantane (**2**), 1-adamantanol (**3**), 1-(hydroxymethyl)-adamantane (**4**), 2-adamantanol (**5**) and 1,3-adamantanediol (**6**), respectively (Scheme 1) were studied. The hydrophobic cavity of the cyclodextrin, which can host an adamantane molecule and the low water solubility of the adamantane derivatives make inclusion complexes favourable for stabilisation in aqueous solutions. Along with the CIS and NOEs of aliphatic protons, the temperature coefficients, CIS, NOEs and line shape of hydroxy protons of α-CD were determined. We aim to show that additional information about the structure of the inclusion complexes can be obtained from analysis of NMR data of hydroxy protons.

Experimental

Sample and buffer preparation

All chemicals were obtained from SIGMA–ALDRICH. The NMR experiments were performed on a 600 MHz NMR spectrometer equipped with a 5 mm QXI H/P/C/N probe. The NMR solvent mixture was 15% acetone-d_6/85% aqueous 10 mM sodium phosphate buffer to retain pH 6.0. Calibration of NMR spectra was performed by setting the residual acetone-d_5 signal to δ_H 2.204 ppm. To avoid contamination of the samples by borate salts, which would cause difficulties in observation of the hydroxy protons, the NMR sample tubes were placed in

aqueous 100 mM sodium phosphate buffer of pH 7 [7] for at least 2 h and then rinsed with Milli-Q® purified water and air dried before use. The stoichiometry of the complex between α-CD and the five different adamantane derivatives was determined from NMR spectra run on samples prepared by making stock solutions of α-CD and adamantane derivatives (10 or 5 mM depending on solubility) and by mixing them in different ratios. The molar equivalent of guest molecules added was accurately determined from the intensities of the signals of the aliphatic ring protons of α-CD and of an aliphatic proton of each adamantane derivative. In these experiments, the water presaturation pulse sequence was used. The temperature coefficients of the hydroxy protons of α-CD were determined by running a series of one-dimensional NMR spectra for every five degrees between 30 and −10 °C using the WATERGATE pulse sequence [21, 22] for water suppression. All 2D spectra were recorded at −10 °C using the States-TPPI [23] method and the WATERGATE sequence for water suppression. DQF-COSY and TOCSY spectra were acquired with 2K data points in t_2 and 256 points in t_1, the data were zero-filled to 2K × 1K. For TOCSY, mixing times (τ_m) of 30 and 60 ms were used and a $\pi/4$ shifted sine-bell square window function was applied in both dimensions prior to Fourier transformation. For NOESY, two different mixing times (τ_m) of 400 and 800 ms were used and for processing a $\pi/6$ shifted sine-bell square window function was used in both dimensions. In the case of 2-adamantanol, a series of ROESY experiments with spin lock pulse width of 50, 80, 150, 300 and 500 ms were also recorded. The 256 spectra of 2K data points were zero-filled in t_1 to 1K data points prior to Fourier transformation and a $\pi/6$ shifted sine-bell square window was used.

Results and discussion

α-CD and adamantane ***(2)***

Due to the low solubility in water of adamantane, only a molar equivalent of 0.11 adamantane could be obtained. The NMR spectra showed one set of resonances at 30 °C, but two sets of resonances for α-CD below 10 °C (Figure 1), indicating that at this temperature the exchange between bound and free form was slow on the NMR time scale. In the set of α-CD signals with low intensity and similar integration values as those of the adamantane signals, C(1)H and C(3)H were deshielded by 0.229 and 0.088 ppm, respectively, while C(4)H and C(5)H were shielded by 0.050 and 0.086 ppm, respectively. The C(6)H signals had the same chemical shifts in both sets. The major set of signals had the same chemical shifts as the signals from a solution only containing α-CD confirming that the set of smaller signals were from α-CD in complexation with the guest molecule (Figure 1). For the complex, a strong NOE was observed between C(3)H of **1** and H2 of **2**, while weaker NOEs were observed between C(3)H of **1** and H1 of **2** and between C(5)H and H2 of **2**. The O(2)H and O(6)H signals in the complex had the same chemical shifts as those in the free form (Table 1) whereas O(3)H was shielded by 0.33 ppm compared to the same proton in the free form (Figure 1). An NOE was observed between O(3)H and H2 of adamantane. The temperature coefficient ($d\delta/dT$) for O(3)H in the complex was lower, −4.7 ppb/°C, than for O(3)H in the free form, −8.9 ppb/°C (Table 1, Figure 2a and b). This small $d\delta/dT$-value and the narrow line indicate reduced exchange with water. We have previously shown [19, 20] that hydroxy protons with reduced hydration are shielded. Thus, these data together with the upfield shift experienced by the O(3)H signal indicate lower solvation of O(3)H due to expulsion of water from the cavity upon inclusion of adamantane. The intramolecular hydrogen bond between O(3)H and O(2) might be strengthened due to exclusion of water from the cavity of the α-CD and thereby less competition for hydrogen bonding to water. However no direct experimental data could be obtained to support this hypothesis.

α-CD and 1-adamantanol ***(3)***

Only one set of NMR signals was observed for α-CD and 1-adamantanol **(3)**, in the temperature range −10 to 30 °C. The plot of the chemical shifts of the C(3)H and C(5)H signals of α-CD as a function of the molar equivalent of added 1-adamantanol (Figure 3a) showed that the major changes occurred up to 1 equivalent of added guest molecule. The C(3)H was deshielded by 7 ppb while C(5)H was shielded by 4 ppb. Further addition of guest molecule had only a minor effect on these chemical shifts suggesting that one host molecule was complexed with one guest molecule. In the NOESY spectra, the intermolecular NOEs between α-CD and **3** had the same signs as the intramolecular α-CD NOEs, while the intramolecular NOEs within **3** had opposite signs, confirming the partial inclusion of **3** into **1**. Strong NOEs were observed between C(3)H of **1** and H2, H3 and H4 of **3**, while weak NOEs were found between C(5)H of **1** and H3 and H4 of **3**.

The O(3)H and O(6)H hydroxy protons had temperature coefficients and linewidths similar to those of α-CD alone (Table 1, Figure 2). As the amount of 1-adamantanol (**3**), was increased, the O(2)H signal was broadened up to a 1:1 stoichiometric ratio (Figure 4). Small upfield shifts of 0.045 and 0.028 ppm were measured for the O(2)H and O(3)H signals, respectively. However, when more 1-adamantanol was added, both signals were slightly shifted back to the values measured for α-CD alone and the O(3)H signal was more similar in intensity to that for α-CD alone. As usually observed for hydroxy protons, the O(3)H and O(6)H signals were broader at higher temperature due to faster exchange with water. The O(2)H signal of **1** was on the other hand

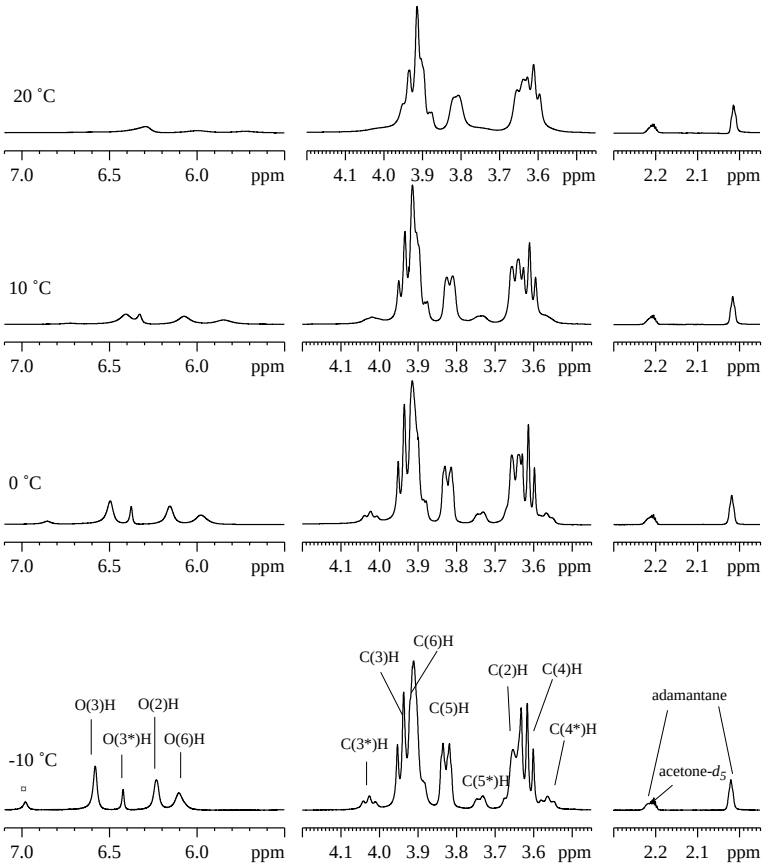


Figure 1. One-dimensional ^{1}H-NMR spectra for solution of α-CD (**1**)/adamantane (**2**) (ratio 8:1). Below 10 °C two set of α-CD resonances can be observed. ¤ Hemiacetal of acetone-d_6 * Proton signals of α-CD in complex.

Table 1. ^{1}H-NMR chemical shifts (δ, ppm), CIS, and temperature coefficients (ppb/°C) for the hydroxy protons of α-CD (**1**) alone and in the presence of adamantane analogues (**2**–**6**)

	α-CD	O(2)H	O(3)H	O(6)H	O(3c)H
α-CD (**1**)	δ	6.222	6.570	6.090	
	dδ/dT	−8.0	−8.6	−12.5	
Adamantane (**1** + **2**)	δ	6.233	6.582	6.104	6.423
	CIS	0.011	0.012	0.014	−0.333
	dδ/dT	−8.2	−8.9	−13.1	−4.7
1-Adamantanol (**1** + **3**)	δ	6.177	6.542	6.080	
	CIS	−0.045	−0.028	−0.010	
	dδ/dT	−12.7[a]/−5.5[b]	−7.3	−11.7	
1-(Hydroxymethyl)-adamantane (**1** + **4**)	δ	6.183	6.539	6.080	
	CIS	−0.039	−0.031	−0.010	
	dδ/dT	−9.7[a]/−5.7[b]	−7.7	−12.6	
2-Adamantanol (**1** + **5**)	δ	6.222	6.569	6.085	6.428
	CIS	0.000	−0.001	−0.005	−0.206
	dδ/dT	−10.0	−8.1	−12.1	−1.2
1,3-Adamantanol (**1** + **6**)	δ	6.219	6.567	6.083	
	CIS	−0.003	−0.003	−0.007	
	dδ/dT	−7.7	−8.1	−12.2	

[a]Calculated for temperatures below 0°C.
[b]Calculated for temperatures above 0°C.

narrower when the temperature raised. At −10 °C, the O(2)H signal was broader than the O(3)H and O(6)H signals, but upon an increase in temperature, it became sharper until it reached a line shape similar to those of the O(3)H and O(6)H signals. Figure 2c shows the temperature dependence of the chemical shift of the

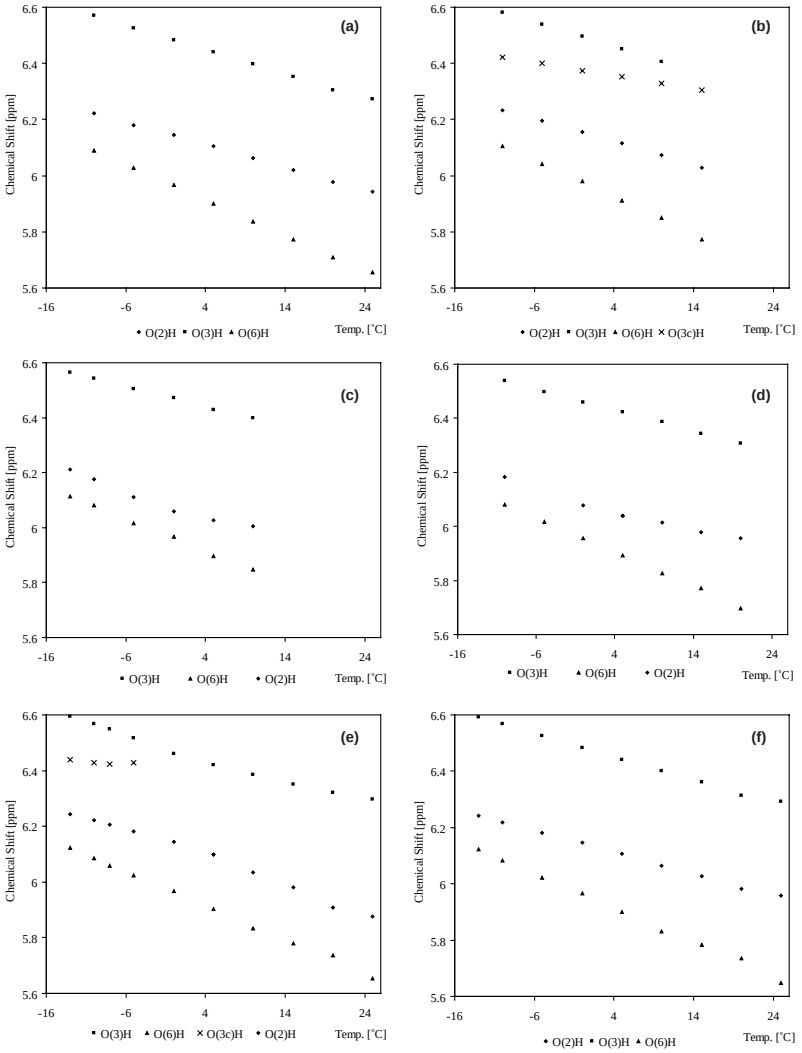


Figure 2. Temperature dependence of hydroxy proton resonances of (a) α-CD (**1**) and α-CD in mixtures with (b) adamantane (**2**), (c) 1-adamantanol (**3**), (d) 1-(hydroxymethyl)-adamantane (**4**), (e) 2-adamantanol (**5**), (f) 1,3-adamantanediol (**6**).

hydroxy proton signals. In the temperature range −13 to 10 °C, O(3)H and O(6)H had a linear temperature dependence with temperature coefficients similar to those of α-CD alone. The temperature coefficient for O(2)H was not linear but showed instead two regions, with different slopes. A change in slope was found around 0 °C. A $d\delta/dT$-value of −12.7 ppb/°C was measured between −10 and 0 °C, while for the highest temperatures a value of −5.5 ppb/°C was measured (Table 1, Figure 2c). The broadening of the O(2)H signal of α-CD upon addition of 1-adamantanol might be due to exchange processes or limited mobility (T_2 changes) upon the formation of an inclusion complex. The exchange processes can include exchange of O(2)H within the α-CD, with the neighbouring water molecules, or the OH of the guest molecules. When the temperature raises, the mobility will increase leading to a sharpening while the increase in exchange rate will lead to a broadening of the NMR signal. Since a decrease in linewidth was observed when the temperature raised, it suggested that the contribution of mobility to the linewidth was stronger than that of exchange processes. The values of the $d\delta/dT$ indicated that O(2)H is more solvated at the lowest temperatures. A possible explanation is that at low temperature, the inclusion complex is more stable, the hydrophobic part of 1-adamantanol is inside the α-CD cavity and O(2)H is mainly surrounded by water. At higher temperature, the stability of the inclusion complex decreases, and O(2)H has a closer contact with the more hydrophobic part of 1-adamantanol.

α-CD and 1-(hydroxymethyl)-adamantane ***(4)***

The NMR data showed that the complex formed between α-CD and 1-(hydroxymethyl)-adamantane was similar to that formed between α-CD and 1-adamantanol. The CIS determined for C(3)H and C(5)H of α-CD in the presence of **4** (Figure 3d) were similar to those determined with **3** (Figure 3c), and suggested the formation of a 1:1 complex. Strong intermolecular NOEs were observed from C(3)H to the H4 of

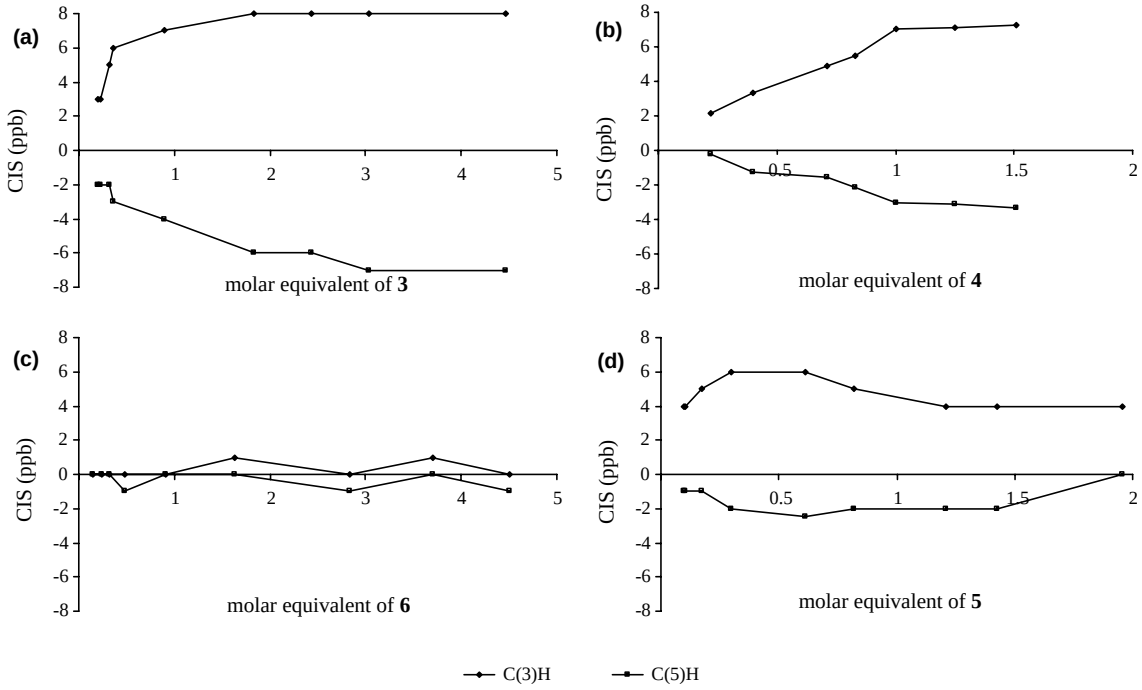


Figure 3. Plot of complexation-induced ^{1}H-NMR shifts (CIS, ppb) of C(3)H and C(5)H of α-CD (**1**) as a function of molar equivalent of the guest molecule (a) 1-adamantanol (**3**), (b) 1-(hydroxymethyl)-adamantane (**4**), (c) 1,3-adamantanediol (**6**) and (d) 2-adamantanol (**5**).

1-(hydroxymethyl)-adamantane as well as to H2 and H3. Further NOEs from O(2)H of α-CD to H2 and H3 of **4** were observed in 1D NOE experiments. The fact that the strongest NOEs were found between C(3)H and H4 indicates that 1-(hydroxymethyl)-adamantane **4** was not completely immersed into the α-CD cavity. The formation of an inclusion complex was supported by the observation that signals of C(3)H of α-CD and H3 and CH_2 of 1-(hydroxymethyl)-adamantane were also broadened. The behaviour of the hydroxy proton signals of α-CD was similar to that observed for the α-CD/1-adamantanol complex (Table 1, Figure 2c and d). The

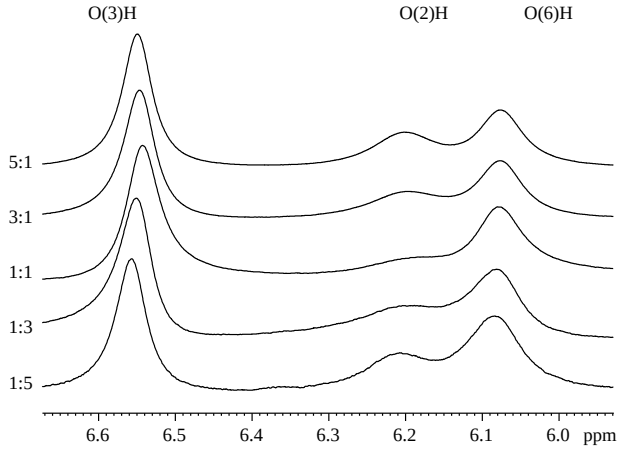


Figure 4. One-dimensional ^{1}H-NMR spectrum of α-CD (**1**)/1-adamantanol (**3**) at different molar ratio (5:1 (**1**–**3**), 3:1, 1:1, 1:3, 1:5) showing the hydroxy proton region with the change in shape of the O(2)H of α-CD upon increasing the amount of guest molecule.

O(3)H and O(6)H had δ, $d\delta/dT$ and linewidths similar to those of α-CD alone. The O(2)H signal was, as observed with 1-adamantanol, broader as the concentration of guest increased. Upon increasing the temperature, the O(2)H signal of **1** was sharper, and its temperature coefficients showed two regions, with different slopes. Below 0 °C, the temperature coefficient of −9.7 ppb/ °C was slightly larger than for that of α-CD alone, and above 0 °C, the temperature coefficient of −5.7 ppb/°C was lower than that of α-CD alone. The fact that the O(2)H and C(3)H signals of α-CD were broadened when complexed with **3** and **4** while the O(3)H signal was not, might be tentatively explained by inspection of the space-filling model of α-CD (Figure 5). O(3)H is acting as donor in the intramolecular hydrogen bond with O(2) and is pointing more toward the edge of the hydrophobic cavity. The O(2)H and C(3)H protons have positions allowing close contact with the guest molecule and are thus directly affected when the guest molecule is entering the hydrophobic cavity.

α-CD and 2-adamantanol (5)

The chemical shift of the C(5)H signal of α-CD was little affected (< 3 ppb, Figure 3) by addition of 2-adamantanol (**5**) while the curve for the CIS of C(3)H changed direction after addition of 0.5 molar equivalent of **5**. This would imply that two cyclodextrin molecules surrounded each molecule of 2-adamantanol. However, since only small CIS could be measured leading to ambiguity in the determination of the stoichiometry of

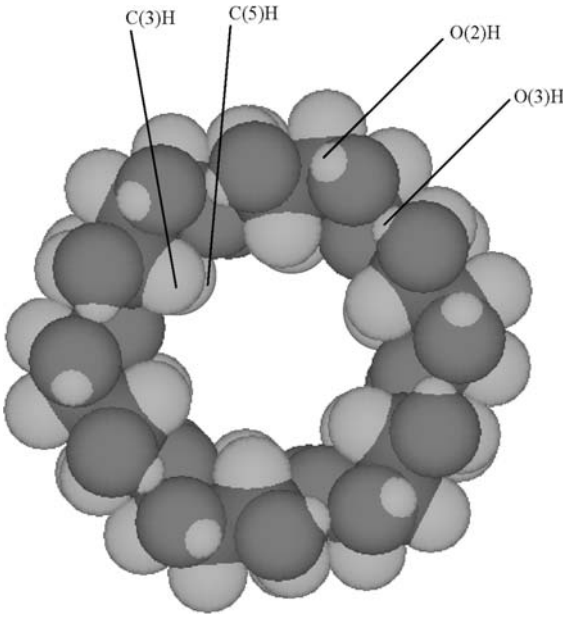


Figure 5. Space-filling model of α-CD, **1**. The O(2)H pointing outward the hydrophobic cavity is more exposed to interaction with hydrophilic groups than O(3)H which is located at the edge of the hydrophobic cavity.

the complex, the 2D NOESY and ROESY experiments as well as the study of hydroxy protons were performed on samples of α-CD and 2-adamantanol with a 1:1 and 2:1 ratio. At 30 °C, one set of sharp and well-resolved NMR signals were observed for the protons of α-CD and 2-adamantanol. As the temperature decreased to 5 °C, two sets of resonances were visible for 2-adamantanol. (It should be noted that at a ratio α-CD/2-adamantanol of 1:2, the NMR signals of 2-adamantanol were sharp even at −10 °C, while at a ratio of 5:1, the signals of α-CD were still broad). In ROESY, exchange cross-peaks could be observed between the two sets of signals of 2-adamantanol. One set of signals was only slightly downfield shifted (<0.10 ppm, set A, Table 2) compared to the signals of 2-adamantanol alone while the other set was much more downfield shifted (up to 0.45 ppm, set B, Table 2). At temperatures below 5 °C, the signals for C(3)H and C(5)H of α-CD were very broad, and no indication of the existence of two sets of signals for the CH protons of α-CD could be obtained. NOEs from C(3)H of α-CD to H4, H6 and H9 of 2-adamantanol, Set A were observed. No intermolecular NOE involving C(5)H of α-CD or H5, H7, H8 and H10 of **5** was found, suggesting only partial inclusion. Due to spectral overlap in the 2D NOESY and ROESY spectra, it was not possible to determine if H1 and H3 had NOE to C(3)H of **1**. It is also unclear why NOEs were observed only to protons of Set A of **5** and not to Set B where the largest deshielding was observed.

The behaviour of the hydroxy protons of α-CD confirmed that the complex was different than that formed with 1-adamantanol and 1-(hydroxymethyl)-adamantane. An additional α-CD O(3)H signal whose intensity increased with concentration of 2-adamantanol appeared at low temperature and coalesced with the other O(3)H signal of α-CD at 5 °C. This new O(3)H signal was shifted upfield by 0.21 ppm relative to the other O(3)H signal and had a very small $d\delta/dT$-value of −1.2 ppb/°C (Table 1, Figure 2e). The linewidth, temperature coefficient, and chemical shift of this new O(3)H signal indicate, as in the case of adamantane, that the water in the vicinity of this proton has been excluded because of inclusion of 2-adamantanol into the hydrophobic cavity. From the NOE data it is however difficult to conclude on the geometry of the complex. For high temperature, the NMR data suggest a partial inclusion of 2-adamantanol in α-CD as shown in Figure 6a. As the temperature decreased, the existence of an equilibrium between a 1:1 and a 2:1 complex (Figure 6b) might be considered.

Inclusion complexes of the 2:1 α-CD-guest type have been reported for complexes of α-CD with 1-bromoadamantane [24] and with adamantane-1-carboxylic acid [25]. The possible geometry of the inclusion complex with 1-bromoadamantane has been proposed to be two CDs encapsulating the guest with the Br atom not penetrating the hydrophobic cavities [24]. This structure was deduced from ROESY experiments and molecular models. With adamantane-1-carboxylic acid, a geometry in which the COOH group is inserted into the second α-CD cavity has been proposed [25]. It has been suggested

Table 2. ^{1}H-NMR chemical shifts of 2-adamantanol (**5**) alone and with α-CD (**1**) at −10 °C

Protons[a]	**5** alone	**5** with **1**		
	e/a	Set A	Set B	CIS[b]
1, 3	1.863	1.876	2.189	0.326
2	3.918	3.985	4.176	0.258
4, 9	1.704/1.978	1.717/1.871	1.926/2.048	0.222/0.070
5, 7	1.780	1.812	2.076	0.296
6	1.716	1.735	1.921	0.205
8, 10	1.540/1.991	1.562/1.997	1.771/2.437	0.231/0.446

[a] The numbering is shown on Scheme 1.
[b] Difference in chemical shift between Set B and **5** alone.

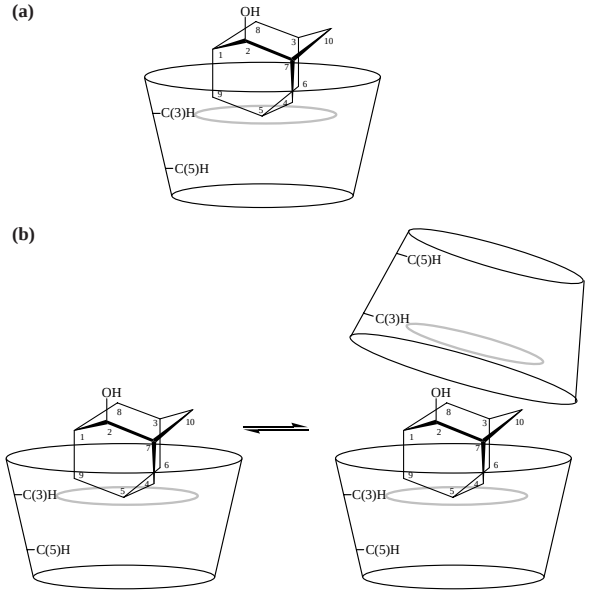


Figure 6. Representation of proposed (a) 1:1 complex between α-CD, **1**, and 2-adamantanol, **5** and (b) a 2:1 complex. The grey line represents the cavity lined by C(3)H of α-CD.

[26] that when the guest is asymmetric, the high affinity part of the guest binds into an α-CD cavity, leaving the low affinity part for a second α-CD.

*α-CD and 1,3-adamantanediol **(6)***

The CIS for C(3)H and C(5)H of α-CD from 0 to 1 equivalent 1,3-adamantanediol (6), was <1 ppb (Figure 3). This suggested that the environment of C(3)H and C(5)H inside the α-CD hydrophobic cavity was not affected by increased amounts of 1,3-adamantanediol (**6**). Since the CIS indicated no complex formation, the following NMR experiments were performed on the sample with one equivalent of guest. No intermolecular NOEs were observed between α-CD and 1,3-adamantanediol. The chemical shifts of the hydroxy proton signals of α-CD and 1,3-adamantanediol were very similar to those measured for the two compounds alone (Table 1). The temperature coefficients of the α-CD hydroxy protons were similar to those measured on a sample containing only α-CD. The NMR spectra showed no line broadening for the hydroxy proton signals. The hydroxy proton signal of 1,3-adamantanediol was visible because of its abundance. These data indicated that no inclusion complex was formed between α-CD and 1,3-adamantanediol.

Conclusion

The goal of this work was to determine whether the hydroxy protons could be used to study the structure of the inclusion complexes between α-CD and adamantane derivatives. We have shown that intermolecular NOEs can be observed between hydroxy protons of α-CD and the protons of the guest molecules. The sensitivity of the chemical shifts, temperature coefficients and linewidth of hydroxy proton signals to intermolecular interaction and hydration changes makes them suitable for studies of inclusion complexes. Since the hydroxy proton chemical shifts, temperature coefficients and linewidths were not affected when no complexation occurred (e.g. 1,3-adamantanediol), it also indicated that the changes found for the hydroxy protons can be used as probes for studying the formation and the structure of inclusion complexes.

With 1-adamantanol and 1-(hydroxymethyl)-adamantane, 1:1 inclusion complexes were formed with α-CD. The increase in the linewidth of the O(2)H signal of α-CD upon addition of guest molecules was attributed to limited mobility due to formation of inclusion complex and/or to exchange processes. With adamantane and 2-adamantanol, an additional O(3)H signal originating from the bound form of α-CD was observed. This signal was narrow, shifted upfield by more than 0.2 ppm, and had a very small temperature coefficient, indicative of the reduced hydration of O(3)H upon formation of the inclusion complex. The O(6)H of α-CD was not affected by addition of the guest molecules indicating that this proton was not involved in complex formation. The adamantane derivatives investigated in this study have relatively similar size but different solubility. The formation of stable inclusion complexes with adamantane and 2-adamantanol which are poorly soluble in water, is more favoured than with 1-adamantanol and 1-(hydroxymethyl)-adamantane which are more polar. This was reflected in the NMR spectra by the existence of two sets of resonances for the free and bound forms of α-CD in interaction with **2** and **5**, and by the reduced hydration of O(3)H of the bound

α-CD. One possible explanation for the different response of O(2)H and O(3)H signals to the formation of inclusion complexes might be that O(2)H and O(3)H have different positions on the α-CD cavity rim (Figure 5). The space-filling model of α-CD shows that O(3)H is somehow pointing toward the edge of the hydrophobic cavity and its hydration will be reduced due to expulsion of water when the guest is entering the cavity. In the inter-residual hydrogen bond interaction between the two secondary hydroxy groups in α-CD, O(2) is acting as the hydrogen bond acceptor. Thus O(2)H, which is more exposed to water, will also be more available for hydrogen bond interaction with the hydrophilic part of a guest molecule (Figure 5).

Acknowledgement

This work was supported by grants from the Swedish Research Council.

References

1. H.-J. Schneider, F. Hacket, V. Rüdiger, and H. Ikeda: *Chem. Rev.* **98**, 1755 (1998).
2. L. Liu and Q.X. Guo: *J. Inclusion Phenom. Macrocycl. Chem.* **42**, 1 (2002).
3. M. Onda, Y. Yamamoto, Y. Inoue, and R. Chûjô: *Bull. Chem. Soc. Jpn.* **61**, 4015 (1988).
4. J.C. Christofides and D.B. Davies: *J. Chem. Soc. Chem. Commun.* 560 (1982).
5. M. St-Jacques, P.R. Sundararajan, K. Taylor, and R.H. Marchessault: *J. Am. Chem. Soc.* **15**, 4386 (1976).
6. S. Bekiroglu, L. Kenne and C. Sandström: *J. Org. Chem.* **68**, 1671 (2003).
7. B. Adams and L. Lerner: *Magn. Reson. Chem.* **32**, 225 (1994).
8. B. Adams and L. Lerner: *J. Am. Chem. Soc.* **114**, 4827 (1992).
9. B.R. Leeflang, J.F.G. Vliegenthart, L.M.J. Kroon-Batenburg, B.P. Vaneijck, and J. Kroon: *Carbohydr. Res.* **230**, 41 (1992).
10. J. Kroon, L.M.J. Kroon-Batenburg, B.R. Leeflang, and J.F.G. Vliegenthart: *J. Mol. Struct.* **322**, 27 (1994).
11. L. Poppe and H. van Halbeek: *J. Am. Chem. Soc.* **113**, 363 (1991).
12. L. Poppe, R. Stuike-Prill, B. Meyer, and H. van Halbeek: *J. Biomol. NMR* **2**, 109 (1992).
13. H. van Halbeek and L. Poppe: *Magn. Reson. Chem.* **30**, S74 (1992).
14. L. Poppe and H. van Halbeek: *J. Am. Chem. Soc.* **114**, 1092 (1992).
15. L. Poppe and H. van Halbeek: *Nature Struct. Biol.* **1**, 215 (1994).
16. C. Sandström, H. Baumann, and L. Kenne: *J. Chem. Soc.-Perkin Trans.* **2**, 809 (1998).
17. C. Sandström, H. Baumann, and L. Kenne: *J. Chem. Soc.-Perkin Trans.* **2**, 2385 (1998).
18. I. Ivarsson, C. Sandström, A. Sandström, and L. Kenne: *J. Chem. Soc.-Perkin Trans.* **2**, 2147 (2000).
19. S. Bekiroglu, C. Sandström, T. Norberg, and L. Kenne: *Carbohydr. Res.* **328**, 409 (2000).
20. C. Sandström, G. Magnusson, U. Nilsson, and L. Kenne: *Carbohydr. Res.* **322**, 46 (1999).
21. M. Piotto, V. Saudek, and V. Sklenar: *J. Biomol. NMR* **2**, 661 (1992).
22. V. Sklenar, M. Piotto, R. Leppik, and V. Saudek: *J. Magn. Reson. Ser. A* **102**, 241 (1993).
23. D. Marion, M. Ikura, R. Tschudin, and A. Bax: *J. Magn. Reson.* **85**, 393 (1989).
24. P.M. Ivanov, D. Salvatierra, and C. Jaime: *J. Org. Chem.* **61**, 7012 (1996).
25. W.C. Cromwell, K. Byström, and M.R. Eftink: *J. Phys. Chem.* **89**, 326 (1985).
26. M.R. Eftink, M.L. Andy, K. Byström, H.D. Perlmutter, and D.S. Kristol: *J. Am. Chem. Soc.* **111**, 6765 (1989).