Complexation in Pseudorotaxanes Based on α-Cyclodextrin and Different α,ω-Diaminoalkanes by NMR Diffusion Measurements

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The interactions of 1,4-diaminobutane (**1**), 1,6-diaminohexane (**2**), 1,8-diaminooctane (**3**), 1,10-diaminodecane (**4**), and 1,12-diaminododecane (**5**) with α-cyclodextrin (α-CD) were studied in aqueous solutions by NMR diffusion measurements before and after protonation. The correlation between the association constant and the length of the alkyl chain of the diamine unit was studied. The assumption that protonation on the amino groups can be used as a stopper and, as a result, to convert the pseudorotaxanes into rotaxanes was tested. In addition, other factors that can affect the pseudorotaxane stability, such as the effects of temperature, were tested. On the basis of these measurements, the following conclusions could be reached: (1) The association constant increases with the increase in the alkyl chain length. (2) For the salts (**2b**−**5b**), both in neutral and in acidic solutions, the binding constants increase as the number of CH_2 units increases. (3) The association constants of the complexes of the diaminoalkane salts and α-CD are lower than those of the corresponding neutral diaminoalkanes. (4) This difference between the binding constants of the diaminoalkanes and their respective salts decreases as the chain length increases. (5) By examining the effects of temperature on the ^{1}H NMR spectra, it was found that after addition of DCl the energy barrier for the threading−dethreading process of the salt of **5a** is larger than that for the salt of **4a**.

Introduction

Cyclodextrins (CDs) are cyclic compounds consisting of glucose units attached at the 1,4 position. The most commonly used CDs are the α-, *β*-, and *γ*-cyclodextrins, having six to eight glucose units, respectively. Because of their water solubility, nontoxicity, relative low price, and complexation ability, they are suitable for a wide range of applications in the food industry, in medicaments, as drug delivery systems and as chemical sensors.[1,2] These characteristics of CDs made them also good models of enzyme mimics.[2f]

Cyclodextrins may be used as cyclic components of supramolecular assemblies because they have a rigid, well-defined ring structure and an ability to bind various guests. The ability of organic compounds to bind to the cyclodextrin cavity in aqueous solution is due to its hydrophobic nature. Cyclodextrins can, and have been, used as a ring component for the construction of pseudorotaxanes and rotaxanes.[3] Pseudorotaxanes are formed when linear molecules penetrate the cavities of cyclic molecules, thus forming stable complexes.[3] Linear long-chain molecules bearing terminal amino or carboxylic functional groups have been used to construct cyclodextrins pseudorotaxanes.[3,4] However, it has been noted that the stability of these complexes is not high, and hence, it is difficult to characterize such pseudorotaxanes.[3] It was also stated that, until recently, relatively little attention has been paid to the true nature of the species in aqueous solution.[4d]

Recently, it was suggested that protonation on the amino groups can be used as a stopper and as a result may convert the pseudorotaxanes into rotaxanes.[5]

NMR parameters, such as chemical shift and relaxation times, have been used to study inclusion complexes in general[6a,b] and that of cyclodextrin in particular.[6c] Since the changes in chemical shift upon the formation of complexes between α,ω-diaminoalkanes and α-CD are relatively small, we decided to study these complexes using NMR diffusion measurements. NMR diffusion measurements, as obtained by the pulsed gradient spin−echo (PGSE) technique,[7] have been used to probe complexation[8] and are now becoming more and more popular in organic supramolecular chemistry.[9] It has been shown that this method is suitable for determining the association constants of organic complexes in different solutions.[8,9b,c,e−g]

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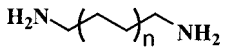
Chart 1



1a: n = 1 **1b**: **1a**·2HCl
2a: n = 2 **2b**: **2a**·2HCl
3a: n = 3 **3b**: **3a**·2HCl
4a: n = 4 **4b**: **4a**·2HCl
5a: n = 5 **5b**: **5a**·2HCl

Here, we report the association constants of pseudorotaxanes based on different α,ω-diaminoalkanes (Chart 1) and α-CD.

The correlation between the association constant and the length of the alkyl chain of the diaminoalkanes was investigated. As we wanted to test the assumption that protonation can act as a stopper and transform pseudorotaxanes to rotaxanes, we also studied the influence of protonation on the stability of the different pseudorotaxanes, both in neutral and in acidic conditions. This was done by following the changes in the ^{1}H NMR spectra and in the diffusion coefficients of different components in the solutions. We also examined the influence of temperature on the spectra of two of these pseudorotaxanes. Total line shape analysis was used to determine the energetic barrier for the threading−dethreading process of the α,ω-diaminoalkanes' chains from the α-CD.

Experimental Section

General Methods. Diffusion experiments were carried out at 400 MHz with a Great 1/10 pulsed gradient unit capable of producing magnetic field pulse gradients in the *z*-direction of about 50 G cm^{-1}. All experiments were carried out using a 5 mm inverse probe. The pulsed gradients were incremented from 0 to 40.2 G cm^{-1} in 10 steps, and their duration in all cases was 2 ms. The pulse gradient separation was 62 ms. All measurements were performed at least three times, and the reported diffusion coefficients are the mean ± standard deviation of three experiments. Only data where the correlation coefficients of $\ln(I/I_0)$ versus $\gamma^2\delta^2g^2(\Delta - \delta/3)$ were higher than 0.999 are reported. The measurements were all preformed at 298.0 K. The experiments were performed on solutions in which the concentration of the diaminoalkanes was 2.8 mM.

Materials. α-CD, diaminoalkanes **1a**−**5a**, and the deuterated solvents (D_2O and DCl) were purchased from Aldrich (USA) and were used as supplied. The pseudorotaxane of α-CD and **4a** was prepared as follows: 1.9 mg of **4a** was dissolved in 4 mL of D_2O (2.8 mM), and 1 mL of this solution was added to 5.5 mg of α-CD (**4a**/α-CD ratio of 1:2). After heating to 40 °C for a few minutes, a clear solution was formed. All the other pseudorotaxanes were prepared in a similar way. The salts **3b**−**5b** were prepared by bubbling HCl through $CHCl_3$ solutions of the corresponding diaminoalkanes. The salts were precipitated and filtered. Compound **2b** was purchased from Aldrich (USA).

Determination of Association Constants. Association constants were determined by evaluating the changes in the diffusion coefficients of the guests upon the addition of α-CD.

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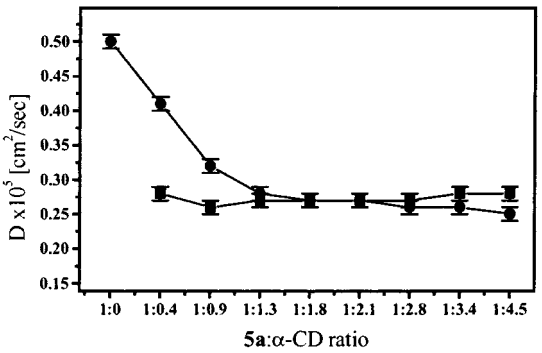

Figure 1. Plot of the diffusion coefficients of α-CD (■) and **5a** (●) as a function of the ratio between **5a** and α-CD in D_2O solutions at 298 K.

The diffusion coefficients were determined by the PGSE technique, according to which the ratio between the echo intensity in the presence (I), and in the absence (I_0), of a pulsed gradient is given by eq 1[7]

$$\ln(I/I_0) = -\gamma^2g^2\delta^2(\Delta - \delta/3)D = -bD \qquad (1)$$

In eq 1, γ is the gyromagnetic ratio (rad·s/gauss), g is the pulsed gradients' strength (gauss/cm), Δ and δ are the time separation between the pulsed-gradients and their duration, respectively (s), and D is the diffusion coefficient (cm^2 s^{-1}). For an isotropic solution, a plot of $\ln(I/I_0)$ vs the diffusion weighting expressed as the b value should give a straight line, whose slope is equal to $-D$. The difference in the diffusion coefficients of the guest in the free state and in the host/guest solution was used to calculate the bound molar fraction (X). The rationale for this calculation is that if the host and the guest are bound tightly, they should have an identical diffusion coefficient since they diffuse together as one supramolecular entity. However, if the guest binds very weakly to the host, its diffusion coefficient should not be affected by the presence of the host. For any other case, assuming fast exchange on the NMR time scale between the free and bound guests, the measured diffusion coefficient (D_{obs}) should be a weighted average of the diffusion coefficient of the free (D_{free}) and the bound guest (D_{comp}), thus allowing evaluation of the bound fraction (X), according to eq 2.

$$X = [D_{free} - D_{obs}]/[D_{free} - D_{comp}] \qquad (2)$$

As a last step, the bound fraction and the known molecular concentrations of the host/guest solutions are used to compute the association constants. Total line shape analysis was performed by the gNMR 4.1 program (Adept Scientific, U.K).

Results and Discussion

Of the three commercial CDs, addition of α-CD induced the maximal change in the diffusion coefficient of **4a**, implying that the highest association constant to this diaminoalkanes is obtained when α-CD serves as the ring of the pseudorotaxane. This is an expected result since the cavities of both β-CD (7.8 Å) and γ-CD (9.5 Å) are larger than needed to accommodate the alkyl chain, thus reducing the hydrophobic interactions. The association constants were determined by evaluating the changes in the diffusion coefficients of the guests upon addition of α-CD. In these calculations, we assumed that the diffusion coefficient of the complex is similar to the diffusion coefficient of α-CD in the solution containing α,ω-diaminoalkanes (**1**−**5**) and α-CD. Figure 1 shows the changes in the diffusion coefficients of α-CD and **5a** upon varying the **5a**/α-CD ratios.

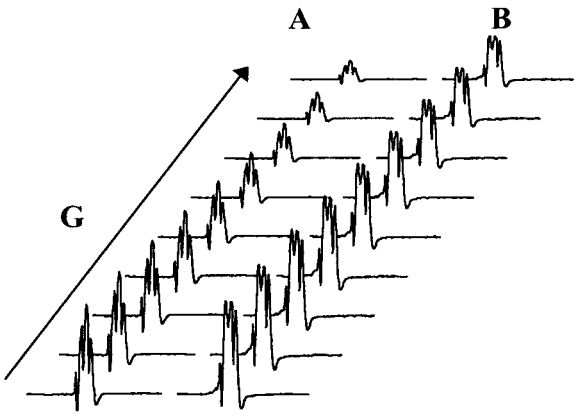

Figure 2. Signal intensity of the triplet of **4a** in D_2O, as a function of the pulse gradient strength (G) for (A) **4a** in the free state, and (B) a 1:5 solution of **4a**/α-CD.

Figure 1 shows that the changes in the diffusion coefficients of α-CD throughout the titration are marginal. In addition, it was found that the diffusion coefficient of the α-CD in the aqueous solution having a **5a**/α-CD of 1:0.9, where most of α-CD molecules are in the bound state, is similar to the diffusion coefficient of **5a** in the 1:4.5 solution, where practically all the **5a** molecules are in the bound state. These results indicate that in the present systems, the assumption that the diffusion coefficient of the complex is, to a first approximation, the diffusion coefficient of the α-CD in the mixture is valid. This is in contrast to a recent report in which a more significant effect of the diffusion coefficient of the host α-CD was found upon the addition of cholic acid.[10]

Figure 2 shows the decay of the signal intensity of the triplet of **4a** as a function of the pulsed-gradient strength for a solution of **4a** (Figure 2A) and for a solution of **4a**/α-CD in a ratio of 1:5.

The signal intensity of **4a** decays faster in the free state (Figure 2A) than in the 1:5 solution of **4a**/α-CD (Figure 2B), demonstrating that there is a significant interaction between the two molecules under these experimental conditions.

Effect of the Length of the Alkyl Chains. Figure 3 shows the natural log of the normalized signal attenuation (ln I/I_0) as a function of the b values for the D_2O solutions of the free guests **1a**, **2a**, and **4a** and their D_2O solution with α-CD (Figure 3A, B, and C, respectively).

From Figure 3A, it is clear that the signal attenuation, and hence, the diffusion coefficients of **1a** in the free state and in the D_2O solution of α-CD, are very similar and differ considerably from that of α-CD, implying the existence of very weak interactions between α-CD and **1a**. However, the opposite is true for **4a**. Here (Figure 3C), the signal attenuations of **4a** and α-CD in their D_2O solution are almost identical and very different from that of **4a** in the free state, indicating that most of the **4a** molecules are bound to the α-CD under these experimental conditions. For **2a**, as shown in Figure 3B, the signal decay, and hence the diffusion coefficient, implies that some of the diaminoalkane molecules are bound to α-CD, while others are not. Table 1 depicts the diffusion coefficients of the host α-CD and the guests **1a**−**5a** in the free state and in their D_2O solutions with α-CD, along with the association constants (K_a's) computed from these values.

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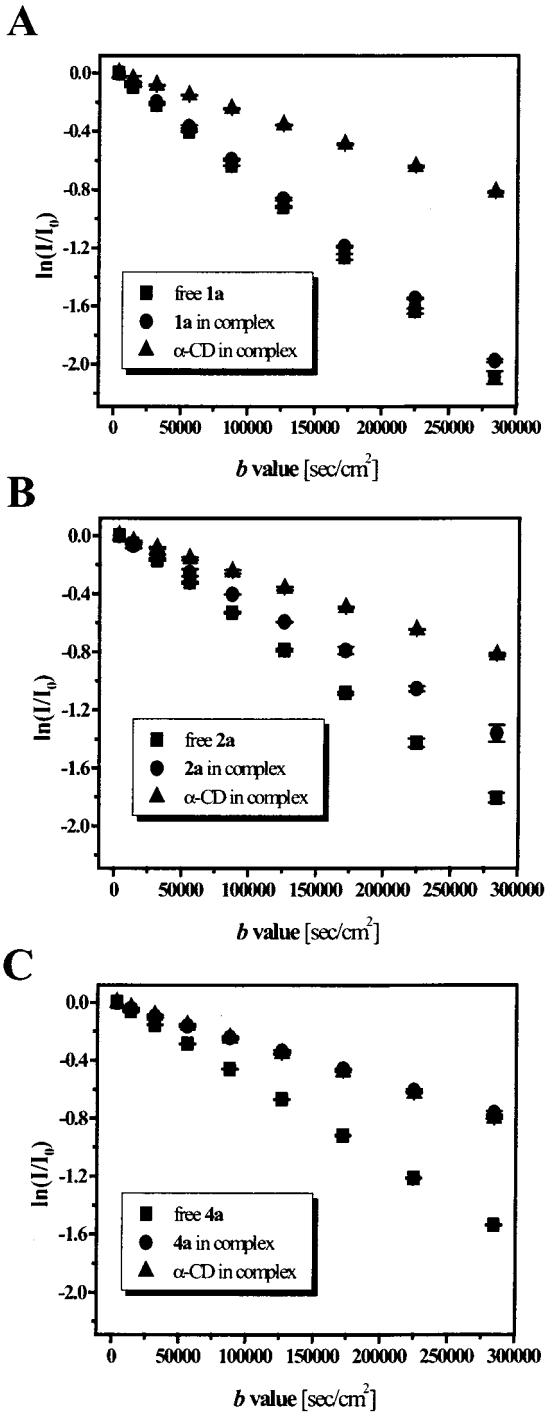

Figure 3. Natural log of the normalized signal attenuation (ln I/I_0) as a function of the b values for three different diaminoalkanes in the free state (■) and for α-CD (▲) and the diaminoalkanes (●) in (A) a 1:2.9 solution of **1a**/α-CD, (B) a 1:5.1 solution of **2a**/α-CD, and (C) a 1:3.7 solution of **4a**/α-CD.

These data show that the association constant is affected dramatically by the length of the alkyl chain of the diaminoalkane. It was found that when the alkyl chain is too short, there is almost no complexation (as in the case of **1a**). It was also found that the association constant (K_a) between the α-CD and the diaminoalkane increases as the chain length increases. This is to be expected, since as the hydrophobic part in the diaminoalkanes becomes larger with the increase in the chain length, the hydrophobic interactions with the cyclodextrin cavity become more pronounced. Surprisingly, we found

Table 1. Diffusion Coefficients ($\times 10^5$ in $cm^2\ s^{-1}$) and the Computed Association Constants log K_a of Host α-CD and Guests 1a, 2a, 3a, 4a, and 5a in D_2O at 298 K

system	*D* amine	*D* CD	*D* water	*X*[a]	log K_a
α-CD [2.8 mM]		0.30 ± 0.01	1.96 ± 0.01		
1a	0.76 ± 0.01		1.97 ± 0.01		
1a/α-CD (1:2.9)	0.71 ± 0.01	0.29 ± 0.01	1.97 ± 0.01	0.11 ± 0.03	1.18 ± 0.14
2a	0.65 ± 0.01		1.96 ± 0.01		
2a/α-CD (1:5.1)	0.49 ± 0.02	0.30 ± 0.01	1.96 ± 0.01	0.46 ± 0.04	1.81 ± 0.07
3a	0.60 ± 0.01		1.96 ± 0.01		
3a/α-CD (1:0.8)	0.47 ± 0.01	0.29 ± 0.01	1.95 ± 0.01	0.42 ± 0.05	2.83 ± 0.21
4a	0.55 ± 0.01		1.96 ± 0.01		
4a/α-CD (1:0.7)	0.38 ± 0.01	0.29 ± 0.01	1.96 ± 0.01	0.65 ± 0.06	4.13 ± 0.30
5a	0.50 ± 0.01		1.94 ± 0.01		
5a/α-CD (1:0.9)	0.32 ± 0.01	0.26 ± 0.01	1.94 ± 0.01	0.75 ± 0.10	3.85 ± 0.27

[a] The bound molar fraction.

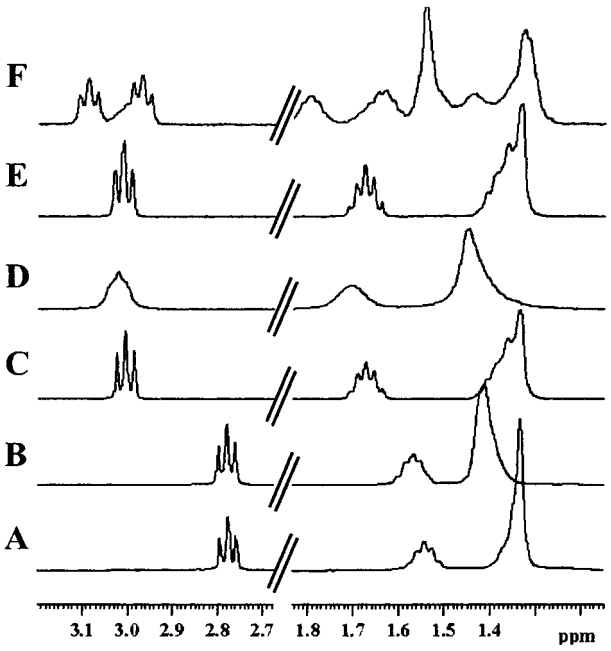

Figure 4. Sections of the 400 MHz ^1H NMR spectra in D_2O at 298 K of (A) **4a**, (B) **4a** in a 1:1.9 solution of **4a**/α-CD (C) **4b**, (D) **4b** in a 1:1.8 solution of **4b**/α-CD, (E) **4a** solution after the addition of DCl, and (F) **4a** in a 1:1.9 solution of **4a**/α-CD after the addition of DCl.

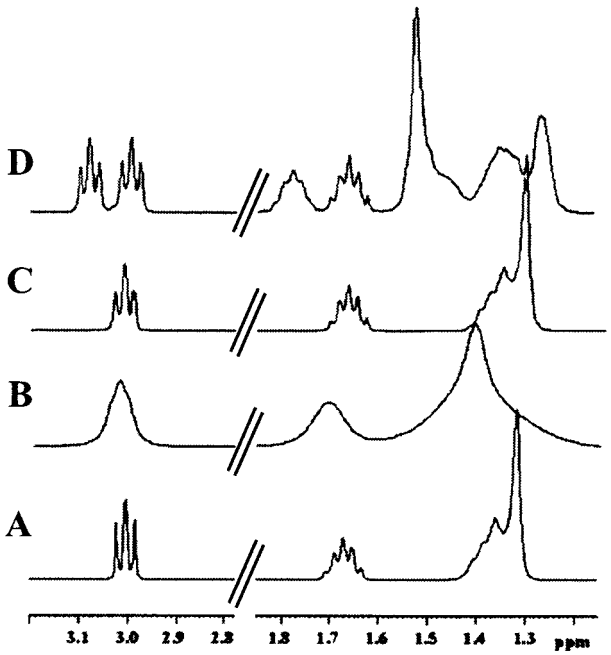

Figure 5. Sections of the 400 MHz ^1H NMR spectra in D_2O at 298 K of (A) **5b**, (B) **5b** in a 1:2 solution of **5b**/α-CD, (C) **5a** after the addition of DCl, and (D) **5a** in a 1:1.7 solution of **5a**/α-CD after the addition of DCl.

that the K_a of **4a** with α-CD is a little higher than that of **5a** (Table 1). The reason might be further interactions between the terminal amine groups and the hydroxy group of the α-CD, which may stabilize the complex further. Such an interaction may be weaker in **5a**, where the amino groups are relatively remote from the α-CD ring. It should be noted that under our experimental conditions, we found no indication for the formation of a 2:1 type complex of α-CD and **5a**, although such complexes have been suggested recently.[4d]

Protonation Effect. As protonation was recently suggested as a potential stopper,[5] the influence of protonation on the stability of the different pseudorotaxanes was also studied, both in neutral and in acidic conditions, by simultaneously following the changes in the ^1H NMR spectra and in the diffusion coefficients of the various species in the solution. The changes in the ^1H NMR spectra of **4a** and **4b** upon the addition of α-CD, with and without the addition of DCl, are shown in Figure 4.

The addition of α-CD to a neutral solution of **4a** (Figure 4A) or **4b** (Figure 4C) results in small changes in the chemical shifts and in significant signals broadening, as shown in parts B and D, respectively, of Figure 4. However, when α-CD is added to an acidic solution of **4a** (Figure 4E), several sets of signals are observed (Figure 4F). When DCl was added to the solution of **4b** and α-CD (Figure 4D), the resulting spectrum was similar to the spectrum shown in Figure 4F (data not shown). These sets of peaks indicate a slow exchange on the NMR time scale between the threaded and unthreaded diaminoalkanes. The same behavior was observed for **5a** and **5b**, as can be seen in Figure 5. Here again, there is a significant broadening of the signals upon addition of the α-CD to **5b** (Figure 5B). Upon the addition of DCl to the **5a**/α-CD solution, two sets of signals are observed (compare Figure 5C with Figure 5D).

To elucidate further the nature of the doubling of the peaks, a diffusion experiment was performed on the 1:2.7 solution of **5a**/α-CD with DCl. In this experiment, it was found that the two triplets at 3.01 and 3.09 ppm, which appeared at 1:1 ratio regardless of the **5a**/α-CD ratios, had the same diffusion coefficient ($(0.28 \pm 0.01) \times 10^{-5}$ $cm^2\ s^{-1}$), which is nearly identical to that of α-CD in the complex ($(0.27 \pm 0.01) \times 10^{-5}\ cm^2\ s^{-1}$). The above finding implies that these triplets should be attributed to the two $^+NH_3CH_2-$ groups of the threaded **5b**. The two $^+NH_3$-

Table 2. Diffusion Coefficients ($\times 10^5$ in $cm^2\ s^{-1}$) and the Computed Association Constants log K_a of Host α-CD and Different Guests in D_2O at 298 K

system	*D* salt	*D* CD	*D* water	X^a	log K_a
2b	0.64 ± 0.01		1.95 ± 0.01		
2a + DCl	0.65 ± 0.01		1.95 ± 0.01		
2b/α-CD (1:1.3)	0.63 ± 0.01	0.30 ± 0.01	1.95 ± 0.01	~0	
2a/α-CD + DCl (1:2.2)	0.63 ± 0.01	0.29 ± 0.01	1.95 ± 0.01	~0	
3b	0.57 ± 0.01		1.96 ± 0.01		
3a + DCl	0.58 ± 0.01		1.96 ± 0.01		
3b/α-CD (1:1.1)	0.52 ± 0.01	0.29 ± 0.01	1.96 ± 0.01	0.17 ± 0.05	1.87 ± 0.15
3a/α-CD+ DCl (1:1.2)	0.54 ± 0.01	0.30 ± 0.01	1.95 ± 0.01	0.14 ± 0.05	1.75 ± 0.18
4b	0.53 ± 0.01		1.96 ± 0.01		
4b/α-CD (1:1.7)	0.33 ± 0.01	0.29 ± 0.01	1.96 ± 0.01	0.83 ± 0.08	3.34 ± 0.19
4a/α-CD + DCl (1:1.6)				0.82 ± 0.01[b]	3.31 ± 0.05[b]
5b	0.49 ± 0.01		1.97 ± 0.01		
5a/α-CD + DCl (1:0.9)				0.76 ± 0.01[b]	3.86 ± 0.06[b]

[a] The bound molar fraction. [b] Bound fraction and association constant extracted from integration.

CH_2− groups in the free diaminoalkanes are chemically equivalent. However, in the case of slow exchange, they become chemically unequivalent when threaded through the asymmetric α-CD. In Figure 4F, however, an additional triplet is present under the triplet at the higher field and based on the higher diffusion coefficient of this signal, as compared to the other two triplets it was attributed to the $^+NH_3CH_2$− groups of the free **4b**. All these results show that, in our case, the doubling of the peaks is not related to the formation of a mixture of a 1:1 and 1:2 complexes of **4a** or **5a** with α-CD, in contrast to a recent report.[4d] In the DCl solutions, a simple integration of the peaks attributed to the free salts of **4a** and **5a** at 3.03 and 3.04 ppm, respectively, and their bound salts, which both appear at 3.09 ppm, enabled the determination of the K_a's of these salts with α-CD. The association constants of **4b** and **5b** with α-CD are shown in Table 2.

Table 2 also shows the diffusion coefficients of the guests **2b**−**4b** in the free state, both in neutral and acidic solutions and in their neutral and acidic D_2O solutions with α-CD. The association constants computed from these diffusion coefficients are also depicted in Table 2. For the case of **2b**, we found that there was no change in the diffusion coefficient of the salt upon the addition of α-CD in either the neutral and acidic conditions, indicating that no complex was formed under these experimental conditions. According to the small change in the diffusion coefficient observed for **3b**, we concluded that only a small amount of the pseudorotaxane complex was formed after the protonation of the amino groups of **3a**. From the changes in the diffusion coefficients for **4b**, both in the absence and presence of DCl, we concluded that in this case also there is a decrease of the K_a with α-CD after protonation. However, here the decrease in K_a was much smaller than in the cases of **2a** and **3a**. This behavior seems to occur due to the repulsion between the charged $NH_3^+Cl^-$ groups and the hydrophobic cavity of the α-CD. This repulsion increases as the length of the chain decreases. Indeed, for **5a** there was no decrease in the K_a, either before or after the addition of DCl. Apparently, the chain length of this salt (around 17 Å[4d]) is large enough to prevent any repulsion between the $NH_3^+Cl^-$ groups and the hydrophobic cavity of the α-CD. Figure 6 summarizes the log K_a as a function of the number of CH_2 units in the α,ω-diaminoalkanes and their respective salts in neutral and acidic solutions.

Without protonation, log K_a increases as the number of the CH_2 units increases. The optimal diaminoalkane is **4a**, and a small decrease in the binding constant is observed for **5a**. The binding constants extracted for the different salts (after protonation) in the neutral and in the acidic solutions were identical, within experimental error. Here, the binding constants increase as the number of the CH_2 units increases and the gap between the binding constants of the diaminoalkanes and their respective salts decreases as the chain length increases. For example, we found that **5a** and **5b** have the same binding constants with α-CD. Even the addition of DCl did not reduce the computed K_a for this system.

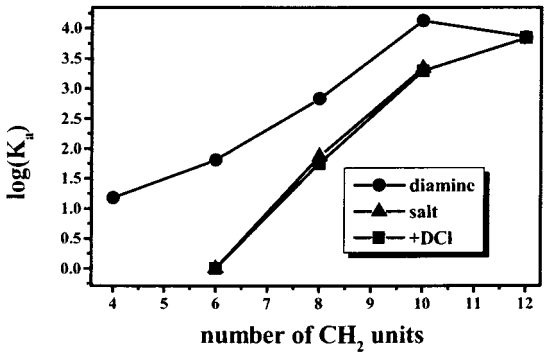

Figure 6. log K_a as a function of the number of CH_2 units in the α,ω-diaminoalkanes (●) and their respective disalts before (▲) and after the addition of DCl (■).

We also examined the influence of temperature on the spectra of the pseudorotaxanes of the salts of **4a** and **5a** with α-CD after addition of DCl, as shown in Figure 7.

At room temperature, in acidic conditions, several sets of peaks are observed for both salts, implying slow exchange on the NMR time scale. As the temperature is increased the exchange rate is accelerated, which causes broadening of the signals, which is then followed by coalescence. At higher temperatures, a narrowing of the signals is observed. The coalescence of the salt of **4a** under acidic condition occurs at 328 K and that of the salt of **5a** occurs at 348 K. Since, in the slow exchange, the differences in chemical shifts between the exchanging sites in each case are similar, this indicates that the energy barrier for the threading−dethreading process of the salt of **5a** is larger than that for the salt of **4a** after addition of DCl. In addition, the spectra in Figure 7A,B show that the coalescence peaks in both cases are shifted toward a higher field beyond their expected average values, i.e., toward the chemical shifts of the free diaminoalkanes. To determine more accurately the energetic

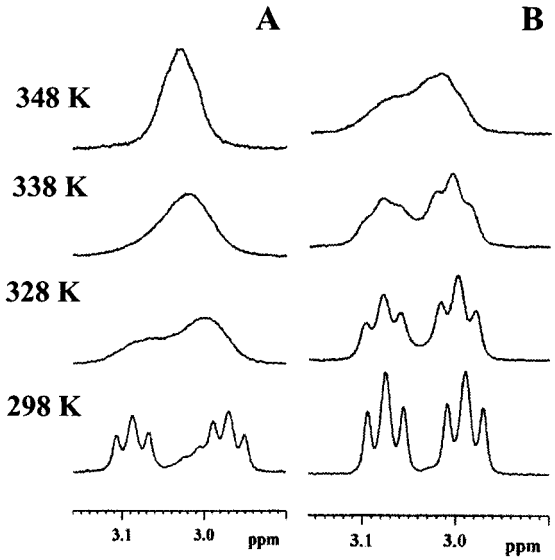

Figure 7. Sections of the 400 MHz ^{1}H NMR spectra in D_2O of (A) a 1:1.9 solution of **4a**/α-CD in the presence of DCl and (B) a 1:1.7 solution of **5a**/α-CD in the presence of DCl at different temperatures.

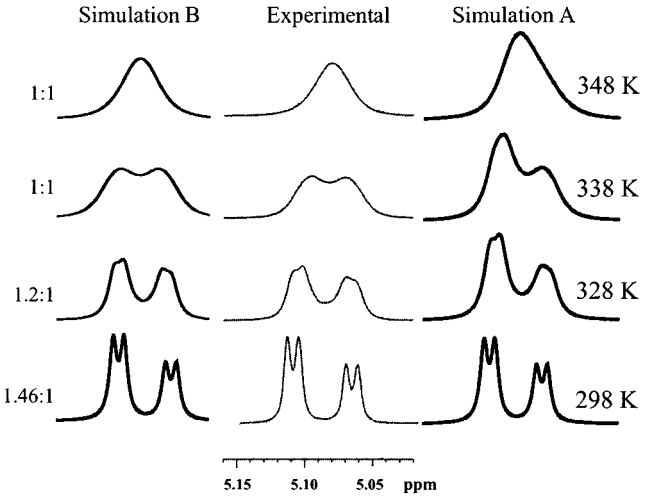

Figure 8. Comparison between a section of the experimental 400 MHz ^{1}H NMR spectra of the 1:1.7 solution of **5a**/α-CD after the addition of DCl and two simulations. In simulation A, the ratio between free and bound α-CD was kept constant (1:1.46), whereas in simulation B this ratio was changed in order to obtain a better fit between the simulations and the experimental spectra.

barriers for the threading−dethreading process, we performed a total line shape analysis of these spectra. The region of 5.02−5.16 ppm in the ^{1}H NMR spectrum of a 1:1.7 **5a**/α-CD D_2O solution with DCl, shown in the middle section of Figure 8, consists of two doublets at 5.07 and 5.11 ppm at 298 K. According to their diffusion coefficients ((0.30 ± 0.01) and (0.28 ± 0.01) × 10^{-5}cm^2 s^{-1}), the signals at 5.07 and 5.11 ppm could be attributed to a free α-CD and α-CD in the complex, respectively. This assignment was also supported by the fact that the addition of α-CD to this solution increases the peak at 5.07 ppm. Figure 8 shows this region of the experimental ^{1}H NMR spectrum in comparison to two simulated spectra, which were extracted from a total line shape analysis.

Simulation A is based on the assumption that the integration ratio between the two signals (free and bound α-CD) remains the same (1:1.46) during the temperature change. However, it is quite clear that this simulation is not consistent with the experimental spectra. Apparently, in addition to the change in the threading−dethreading rate, by increasing the temperature the equilibrium is shifted toward the free components of the pseudorotaxane. For that reason, another simulation was performed (simulation B) in which the ratio was altered. This simulation is almost identical to the experimental spectra, as can be seen in Figure 8. A similar analysis was performed for a 1:1.9 **4a**/α-CD D_2O solution with DCl. The free energies of activation ($\Delta G^{\ddagger}_{328K}$), which were calculated for the threading−dethreading processes of the salt of **4a** and the salt of **5a** from α-CD after addition of DCl, were 16.8 ± 0.3 and 17.8 ± 0.3 kcal/mol, respectively. This difference in $\Delta G^{\ddagger}$ between the two salts supports the previous assumption that the energy barrier for the threading−dethreading process of the salt of **5a** is larger than that of the salt of **4a** under this acidic condition. The data presented here demonstrate that the protonation of the amino groups of the diaminoalkanes reduces the stability of the pseudorotaxanes up to **4a**. For **5a**, there is no decrease in the K_a upon protonation, but even here the protonation is not sufficient to act as a stopper and transform the α-CD pseudorotaxanes into rotaxanes. The protonation seems to affect the exchange rate; however, only when the pH is rendered acidic can one observe two sets of signals that imply that the exchange between the free diaminoalkanes and the threaded diaminoalkanes is slow on the NMR time scale. The fact that protonation reduces the exchange rate for both **4a** and **5a** by increasing $\Delta G^{\ddagger}$ but affects only the association constant of system **4a** implies that in this case the protonation decreases more the association than the dissociation rates. In system **5a**, however, K_a remains unchanged after protonation, implying that the reduction of both the association and dissociation rates is the same. A plausible explanation for these observations is the fact that the pseudorotaxane obtained with the shorter amine, **4a**, is destabilized by the protonation while in the case of **5a** protonation has no effect on the stability of the obtained pseudorotaxane.

In conclusion, it was found that the association constant increases as the chain length of the diaminoalkane increases. The association constants of the complexes of the diaminoalkane salts and α-CD were found to be lower than those of the corresponding diaminoalkanes. This difference between the binding constants of the diaminoalkanes and their respective salts decreases with the increase of the chain length and disappears for **5a**. For **2a**, the protonation actually ejected the diaminoalkanes from the cavity of the α-CD and practically destroyed the pseudorotaxanes. The further acidification had no effect on the association constant but did affect the exchange rate of the threading−dethreading process. In none of our experiments could we obtain any evidence for the formation of a 2:1 α-CD/diaminoalkane complex. The total line shape analysis of the ^{1}H NMR spectra, taken at different temperatures, revealed that the energy barrier for the threading−dethreading process is higher for the salt of **5a** than for the salt of **4a** obtained after addition of DCl.

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