pH Dependent In−Out Isomerism of an Amino-β-cyclodextrin Derivative

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An amino derivative of β-cyclodextrin [6-(6-aminehexanamide)-6-deoxy)-β-cyclodextrin (6-βCD)] was synthesized, and the formation of an intramolecular inclusion complex was studied by NMR techniques. The deprotonation/protonation of the amino group stimulates an in/out movement of the pendant group toward/from the cyclodextrin cavity, the protonated species lying outside the hydrophobic cyclodextrin cavity but the unprotonated one residing inside and outside the cavity. The protonation of the amino group is a fast exchange rate NMR time-scale process, but the chain movement is a slow one. The equilibrium constants of both processes were determined from ^{1}H NMR experiments and the kinetic constants for the slow process were determined from exchange spectroscopy (EXSY) experiments.

Introduction

Chemical exchange refers to any chemical or physical process which causes a perturbation of the magnetic environment of atoms resulting in differences in their NMR parameters (chemical shift, scalar coupling, or relaxation). Measurements of such processes by NMR are widely used to obtain valuable information about the molecular dynamics and structure of many systems (unfolding of proteins, helix−coil transitions of nucleic acids, conformational equilibria, etc.) and, in particular, on supramolecular complexes. The body of literature about supramolecular chemistry that makes use of NMR is extremely large,[1] and recompilations of kinetic and thermodynamic data for macrocyclic hosts and guests obtained by NMR (and other methods) have been published.[2] This is particularly true for the formation of inclusion compounds by cyclodextrin hosts.[3−5]

Most cyclodextrin complexing systems obey to the fast exchange condition. Under these circumstances, the observed chemical shift is a weighted average of the chemical shifts in both free and complexed states, allowing the determination of the equilibrium constants for the formation of the complex by varying the host/guest concentration ratio.[6−8] When the host−guest complexation has a slow exchange rate compared to the NMR time scale, the signals of host and guest nuclei in the complex and in the free state appear at different chemical shifts. Only a few intermolecular cyclodextrin complexes[9,10] obeying the slow exchange rate regime have been observed.

To study intramolecular processes, a modified cyclodextrin incorporating a pendant group must be synthesized. This can lead to two different inclusion processes (Figure 1). First, if intermolecular interactions are dominant, the modified cyclodextrin can form supramolecular entities in which the unimers are interlocked forming linear supramolecular polymers.[11−19] Second, if intramolecular interactions predominate, the self-inclusion of the hydrophobic residue inside the cavity of its supporting cyclodextrin originates an intramolecular inclusion complex. This process has also been named inside−outside isomerism.[20] Examples of this kind of complex have been published.[20−42] These complexes have important applications since when the pendant group is a fluorophore, they can be used as chemosensors.[26−30,43−49] The two processes (inter/intra) compete with each other, and one of them must be avoided if the other one is desired.

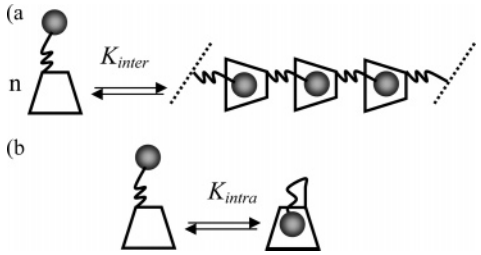

Figure 1. (a) Self-assembling of unimers by inclusion of the chain into the cavity of an adjacent cyclodextrin unimer, forming supramolecular polymers. (b) Self-inclusion of the chain, forming an intramolecular complex.

The measurement of the equilibrium constant for the formation of intramolecular complexes has been achieved in a few cases, from fluorescence[21,29,47] or NMR (under slow rate conditions)[22,38,40] measurements. The first method is only valid when the pendant group is a fluorophore and the second one is a priori of universal application. However, it has only been applied in a few cases.[22,38,40] The equilibrium constant has not been determined even when the typical split of signals (first reported by Boger et al.[50]) is noticed.[42] The slow exchange regime is ideal for the determination of the intramolecular equilibrium between the two conformers since the chemical shifts (and other NMR parameters) of nuclei in both free and complexed states are determined individually in the same NMR spectrum.

In an aqueous solvent, the equilibrium between the two conformers will be a compromise between the relative interactions of the pendant group with the hydrophobic environment inside the cavity of the cyclodextrin and the hydrophilic

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environment outside it. Consequently, a strong modification of the polarity of the pendant group should have a high effect on the in−out isomerism, even leading to its suppression. To explore this hypothesis, the 6-(6-aminehexanamide)-6-deoxy)-β-cyclodextrin (6-βCD) was synthesized and the equilibrium of the intramolecular process was studied by NMR techniques. This compound has been chosen since the hydrophobic/hydrophilic nature of amine derivatives can be easily modified by changing the pH of the solution. Thus, the ammonium species will probably lye outside the hydrophobic cavity of βCD, but the unprotonated amine species, less hydrophilic, could reside inside the cavity. This is a simple in−out system in which its position is pH dependent. This can be useful for understanding and designing more complex molecular devices.

Experimental Section

Synthesis of 6-βCD was carried out according to the literature procedures.[51] NMR spectroscopy has been used for determining thermodynamic and structural parameters involved in the formation of intramolecular complexes. ^{1}H, ^{13}C, correlation spectroscopy (COSY), ^{1}H-^{13}C heterocorrelated, and ROESY experiments were recorded using a Bruker AMX-500 NMR spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Exchange spectroscopy (EXSY) experiments were recorded using a Varian Inova 750 operating at 750 MHz for ^{1}H (the mixing time, τ_m, was 100 ms). The temperature was 298.1 K. Measurements at pH 5.93 were carried out in phosphate buffer, 0.2 M, and those at pH 11.10, in carbonate buffer, 0.2 M. Intermediate pH values were obtained by adding small amounts of KOD in D_2O without buffer.

The basic theories of static and dynamic light scattering techniques are very well-known and can be found elsewhere.[52,53] Light scattering measurements were carried out in a Brookhaven instrument constituted by a BI2030AT digital correlator with 136 channels and a BI200SM goniometer. The light source was a Uniphase solid-state laser system model 4601 operating at 532 nm (Brookhaven). Dust was eliminated by filtering the samples with Nuclepore filters with a pore size of 0.2 μm. The samples were placed in the cell for at least 30 min prior the measurement to allow for thermal equilibration. Their temperature was kept constant within 0.5 °C by a circulating water bath. To prevent mold growth, these experiments were carried out in the presence of sodium azide (10 mg mL^{-1}).

Results and Discussion

The amine group of 6-βCD will be in its protonated form at low pH values and in the unprotonated one at high basicity. Consequently, NMR spectra were obtained at pH values of 5.93 and 11.10, the concentration of 6-βCD being 10 mM in both cases. The full assignment of the ^{1}H NMR spectra of 6-βCD, at both pH values, is required to elucidate the existence of two conformers. These spectra are complex, but it is possible to assign all resonances by the combination of various mono- and bidimensional (^{1}H-^{1}H COSY and ^{1}H-^{13}C heterocorrelated) NMR techniques. Here, we will only comment on some illustrative examples.

^{1}H NMR Spectrum at pH 5.93. The ^{1}H resonances (Figure 2A) for the side chain moiety were assigned by the use of ^{1}H-^{1}H COSY spectrum. The assignment starts from the H*a* signal (δ 2.09 ppm), and the remaining chain protons were successively determined by observing the corresponding consecutive cross-peaks—H*a* with H*b* (δ 1.41 ppm), H*b* with H*c* (δ 1.20 ppm), and so on (Table 1). Integration of the signals is in full

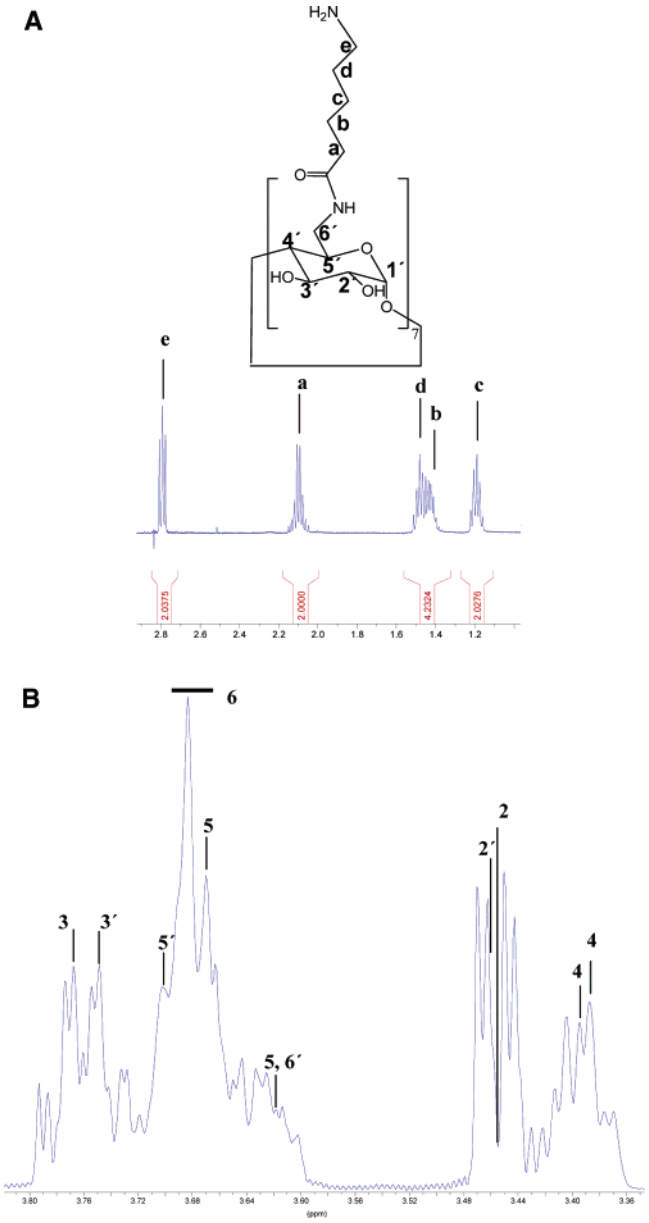

Figure 2. ^{1}H NMR spectrum of 6-βCD in D_2O at pH 5.93; $T = 298$ K. (A) Pendant chain moiety. (B) Protons of the glucose residues.

agreement with the assignment of the resonances. Protons on the same atom carbon are equivalent.

The remaining resonances observed in the ^{1}H NMR spectrum were assigned to the protons of the glucose residues (Figure 2B). The methodology was the same as above. Now, the starting signals were those of the six H-1 protons and the H-1′ proton (doublet, δ 4.89 ppm), the apostrophe indicating the glucose residue with the pendant group. The assignments are shown in Table 1. The ^{1}H-^{1}H COSY spectrum evidences that the glucose residues are not equivalent and that a pseudosymmetrical C_2 axis through the substituted glucose residue exists. The difference between the glucose residues vanishes with the distance to the substituted glucose residue.

^{1}H NMR Spectrum at pH 11.10. The resonances were assigned as before. Figure 3 (^{1}H-^{1}H COSY spectrum) shows that, at this pH, the H*a* resonance appears as two signals at δ 2.06 (a_C) and δ 2.08 (a_L) ppm. All other signals of the protons of the alkyl chain (*b*−*e*) are also split (see values in Table 1; signals are denoted with the subscripts "C" or "L"). It is remarkable that the COSY spectrum only evidences interactions

TABLE 1: Chemical Shift Values of 6-βCD (10 mM) in D_2O at pH 5.93 and 11.10 (750 MHz)[a]

δ (ppm), pH 5.93				δ (ppm), pH 11.10			
H-1	H-1'		4.89 (d)	H-1	H-1'		4.90
H-2	H-2'		3.45 (dd)	H-2	3.46	H-2'	3.45
H-3	3.77 (dd)	H-3'	3.75 (dd)	H-3	3.77	H-3'	3.75
H-4	3.40−3.39 (t)	H-4' (t)	3.25	H-4	3.40−3.42	H-4'	3.24
H-5	3.62−3.67	H-5'	3.70	H-5	3.66−3.59	H-5'	3.67
H-6	3.69	H-6'	3.16 and 3.62	H-6	3.71−3.68	H-6'	3.13−3.64
	H-*a*		2.09	H-a_L	2.08	H-a_C	2.06
	H-*b*		1.41	H-b_L	1.39	H-b_C	1.38
	H-*c*		1.20	H-c_L	1.14	H-c_C	1.12
	H-*d*		1.49	H-d_L	1.40	H-d_C	1.28
	H-*e*		2.78	H-e_L	2.64	H-e_C	2.83

[a] The following abbreviations are used in this table: (d) doublet; (dd) double doublet; (t) triplet.

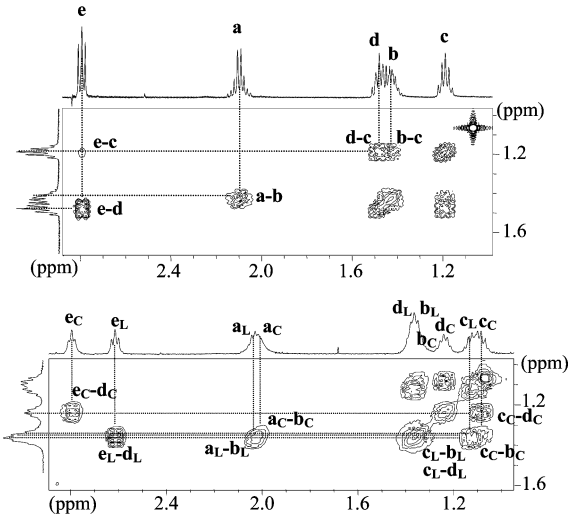

Figure 3. Comparison between ^{1}H-^{1}H COSY spectra (alkyl chain region) at pH values of 5.93 (upper figure) and 11.10 (lower figure).

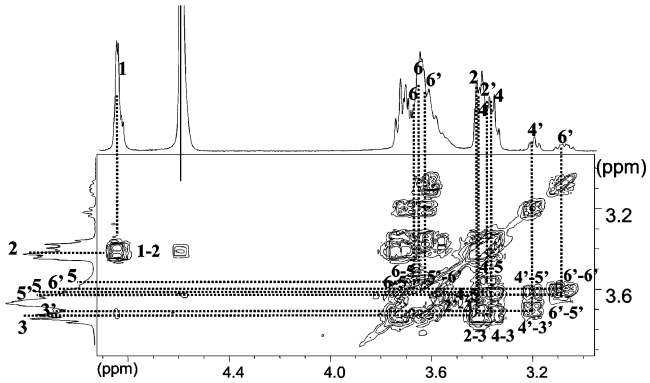

Figure 4. ^{1}H-^{1}H COSY spectrum of 6-βCD in D_2O; 10 mM at pH 11.10; region of the glucose moieties.

between signals named with the same subscript (i.e., C−C and L−L) but not with different subscripts (i.e., C−L). Furthermore, there are not cross-peaks between signals of protons bonded to the same carbon atom, i.e., *a*−*a*, *b*−*b*, and so on. It is to say, the sequence of interactions is either $a_C \rightarrow b_C \rightarrow c_C$ ... or $a_L \rightarrow b_L \rightarrow c_L$ ...

A similar split is observed for the βCD residue (Figure 4). For instance, the twelve protons H6 now appear at δ 3.71 and 3.68 ppm and H6′ protons are observed as two signals at δ 3.13 and 3.64 ppm (Table 1).

Further information is obtained from the analysis of spectra at different pH values ranging from 7.8 to 11.1 (Figure 5). This set of spectra shows that new signals appear (the spectrum at pH 7.83 can be used as reference) when pH increases. The areas of signals named "C" increase with pH, and simultaneously, the area of those named "L" diminish in the same proportion. These facts suggest that complexation equilibrium has a slow exchange rate-NMR time-scale.[22,40] Furthermore, the chemical shifts of "C" signals are pH independent, remaining constant over the entire series, but "L" signals evidence a continuous change with pH. The maximum displacement ($\Delta\delta$ 0.17 ppm) corresponds to the e_L signal (assigned to vicinal protons to the terminal amino group), and the minimum displacement is observed for a_L and b_L hydrogen atoms, the farthest ones from the amino group.

Thus, we have two unusual concomitant slow and fast exchange rate-NMR time-scale processes. Since it is well-known that the protonation of amines[54,55] is a fast exchange process, we accept that the chemical shift displacement of "L" signals corresponds to the acid−base equilibrium of the amino group of the alkyl chain, according to eq 1,

$$\mathrm{pH} = \mathrm{p}K_a + \log \frac{\delta - \delta_{RNH_3^+}}{\delta_{RNH_2} - \delta} \qquad (1)$$

$\delta_{RNH_3^+}$ and δ_{RNH_2} are the chemical shifts of pure protonated and unprotonated species, and δ is the chemical shift at a given pH. The dependence of δ for e_L proton with pH is shown in Figure 6, where the dashed line is the best-fit curve, drawn with values of $pK_a = 10.53 \pm 0.09$, $\delta_{RNH_3^+} = 2.865 \pm 0.005$, and $\delta_{RNH_2} = 2.65 \pm 0.02$. This pK_a value is in full agreement with the pK_a values of primary amines[56] and those obtained by May et al. for some protonated 6A-polyamine-substituted β-cyclodextrins.[51]

Since "C" signals appear at high pH values but their chemical shifts are not affected by pH, the involved nuclei have to be in two different environments. As shown above, one is the bulky solvent which affects the chemical shift through the protonation of the amino group, and the other one can only be the hydrophobic cavity of the cyclodextrin. There are two possibilities to insert the pendant chain into the cavity (Figure 1). The first one is the self-inclusion of the chain into the cavity of its cyclodextrin on which it is grafted (intramolecular process). This process does not modify the molecular weight of the complex. The second one is the inclusion of the chain into the cyclodextrin cavity of an adjacent molecule, forming a supramolecular linear conglomerate (either oligomer or polymer) by the self-assembling of unimers. In this case, the new entity will have a molecular weight which depends on the degree of polymerization and is a function of the intermolecular equilibrium constant.[57] Thus, the best way to distinguish both situations is to measure the molecular weight and the hydrodynamic radius of the complexes from static and dynamic light scattering (SLS and DLS) experiments. Recently, we have used these techniques to distinguish between the formation of a linear supramolecular polymer and the chelate complex. Any of the two supramo-

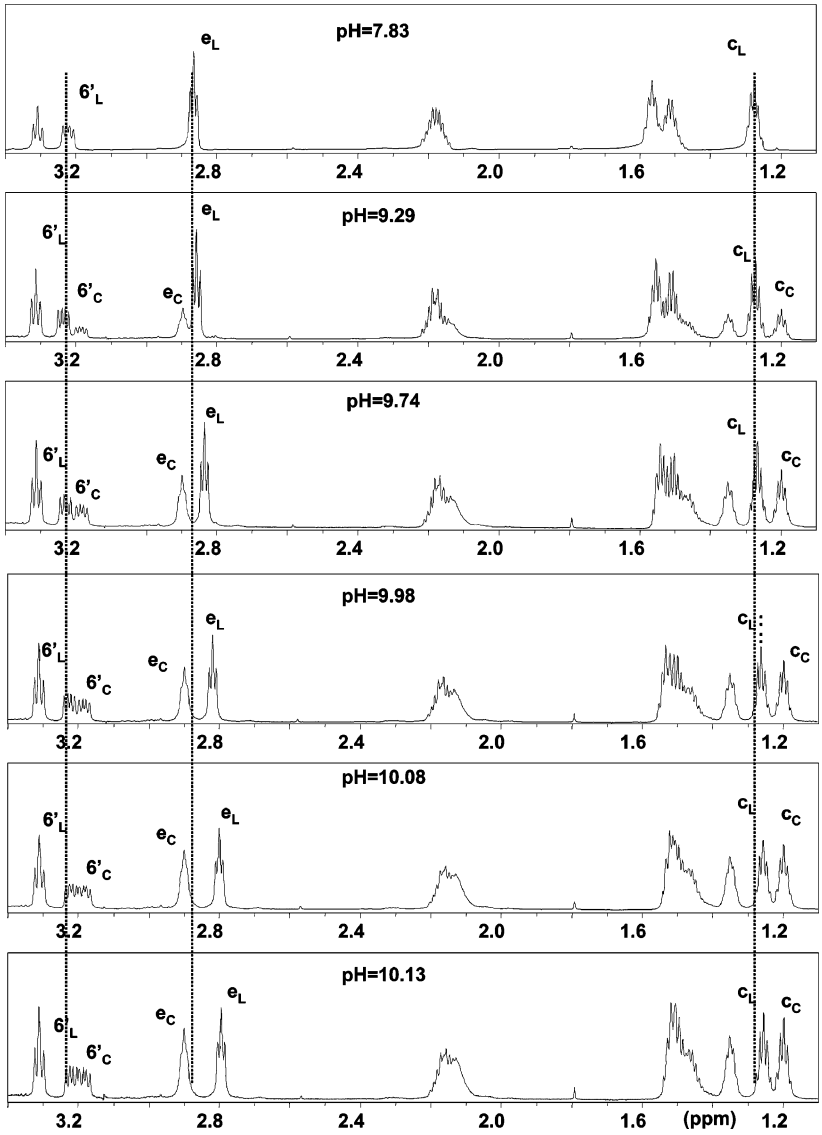

Figure 5. ^{1}H NMR spectra of 6-βCD in D_2O at different pH values; [6-βCD] = 10 mM.

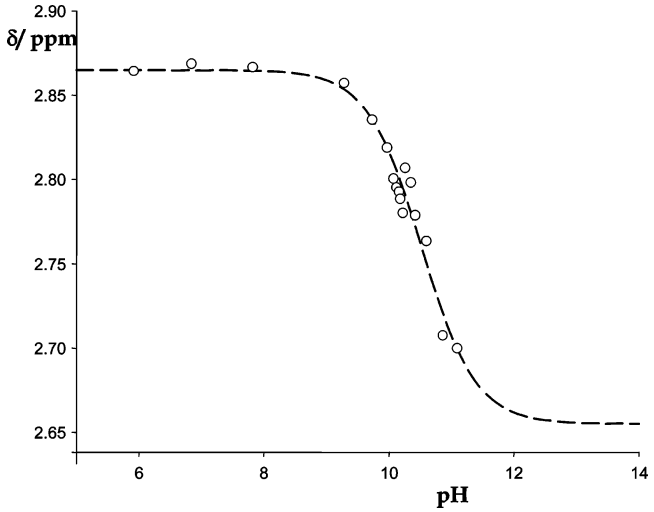

Figure 6. ^{1}H chemical shift dependence of e_L with pH. The dashed line was generated with the values $pK_a = 10.53 \pm 0.09$, $\delta_{RNH_3^+} = 2.865 \pm 0.005$ ppm, and $\delta_{RNH_2} = 2.65 \pm 0.02$ ppm. $T = 298$ K.

lecular entities can arise when a ditopic guest is complexed by a cyclodextrin dimer,[58] and further details on the use of these techniques can be found in ref 58. From SLS experiments, a value of 1.1×10^3 g mol^{-1} was obtained for the molecular weight, which is very close to the molecular value for the unimer. Analogously, the hydrodynamic radius was determined from DLS experiments, the value being 1.05 nm (polydispersity 0.29) at 30 mM, which is compatible with the molecular size of this species (the height of one cyclodextrin cone is around 0.8 Å).[59] Thus, the intermolecular process can be ruled out. Furthermore, as "C" signals are not affected by the pH, the amino group is unprotonated inside the cyclodextrin cavity. Only the unprotonated species gives rise to the intramolecular complex. Such an interpretation is in agreement with observations by Rekharsky et al.[60] when studying the complexation of several ammonium ions. They concluded that these polar groups lie outside the cyclodextrin cavity and make no significant contribution to the stabilization of the cyclodextrin/ligand complex. Figure 7 shows the two fast and slow processes. In previous Figures, signals "L" and "C" corresponded to the species with the chain (either protonated or unprotonated) in the bulk solvent and inside the cyclodextrin cavity, respectively.

The peak area of a signal in ^{1}H NMR spectra is proportional to the concentration of the species and can be used for measuring concentrations, allowing the determination of equilibrium

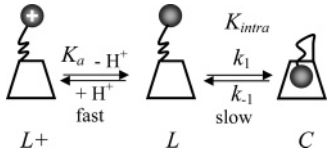

Figure 7. Protonation equilibrium of the amino group in the bulky solvent which is a fast exchange rate-NMR time-scale process and can be in the protonated or unprotonated forms. The intramolecular inclusion is slow on the same time scale, and the alkyl chain carrying the unprotonated amino group is inside the cavity.

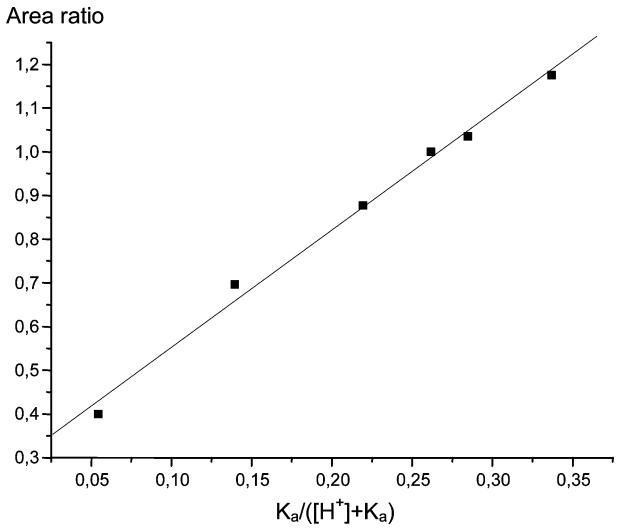

Figure 8. Determination of the intramolecular equilibrium constant for 6-βCD from the areas ratio of protons according to eq 4. The value pK_a = 10.53 was used in the calculations.

constants.[10,22,40] By taking into account the equations for the equilibria of Figure 7

$$K_a = [L][H^+]/[L^+]K_{intra} = [C]/[L] \quad (2)$$

and the mass balance

$$[6\text{-}\beta CD]_o == [L^+] + [L] + [C] \quad (3)$$

it is straightforward to show that the ratio between the areas for the complex and uncomplexed forms is given by eq 4,

$$\frac{area_C}{area_L} = K_{intra}\frac{K_a}{K_a + [H^+]} \quad (4)$$

where $area_C$ and $area_L$ are the signals for the complexed and uncomplexed chains and K_a was determined from eq 1. Equation 4 allows the determination of K_{intra}, the value being 2.7 ± 0.1 (Figure 8). For that purpose, only signals corresponding to *e* protons have been taken into account.

By accepting that the minimum proportion of any of the two conformers detectable by ^{1}H NMR is 5% of the other one, the range of available equilibrium constant values which can be measured by this technique is $K_{intra} = 0.05-20$. So, it is not surprising that all the reported values[22,38,40] for K_{intra} determined from NMR experiments are just in the middle of that interval. The value obtained for K_{intra}, is also similar to the values obtained in aqueous solutions by Ikeda et al.[29] and Matsumura et al.[47] for dansyl derivatives of βCD, from fluorescence measurements.

Simple molecular models evidence that the side chain can easily acquire the kinked conformation to enter fully inside the cyclodextrin cavity, keeping the amide group as the only one in touch with the polar solvent. This is supported by the interactions H5(5′)-b_L and H3(3′)-e_C observed at the ROESY spectrum in a basic medium (Figure 9). The inclusion process requires that the water molecules surrounding the alkyl hydrophobic chain (while it is in the bulky solvent) will recover their normal and less ordered structure, leading to a positive entropy value (i.e., favorable for the inclusion process). The thermodynamic parameters for the inclusion of the series propanol−hexanol in βCD[61] support this interpretation since the inclusion of the alcohol is entropy driven ($\Delta H° > 0$, $\Delta S° > 0$, and $|\Delta H°| < |T\Delta S°|$, for the whole series). This comment is also valid for the complexation of the series 1-hexylammonium to 1-octylammonium (although for this last compound $\Delta H° \approx -2$ kJ mol^{-1}) by βCD.[60]

The in−out isomerism demonstrated above only requires the movement of the side chain which enters inside the cyclodextrin cavity when its final amino group is unprotonated. Thus, this mechanism is different for those involving the turning (a given angle) of the glucose bearing the guest residue,[22,38,62] the most clear example being the "somersault mechanism" claimed by Yamada et al.[22,38,62] which requires a turning of 360°. This glucose turning would justify the high free energy of activation (= 81 kJ mol^{-1}) observed by Ellwood et al.,[62] resulting in the observed slow exchange rate in the NMR time scale. For the present case, the values for both kinetics constants k_1 and k_{-1} were determined by EXSY experiments, the values being 0.174 and 0.161 s^{-1}, respectively ($K_{intra} = k_1/k_{-1} = 1.1$, in reasonable agreement with the value given above). The high energy barrier, which originates the low values for the kinetic constants, can be due to the necessary loss of water molecules hydrating the amino group before entering inside the cavity. This dehydration

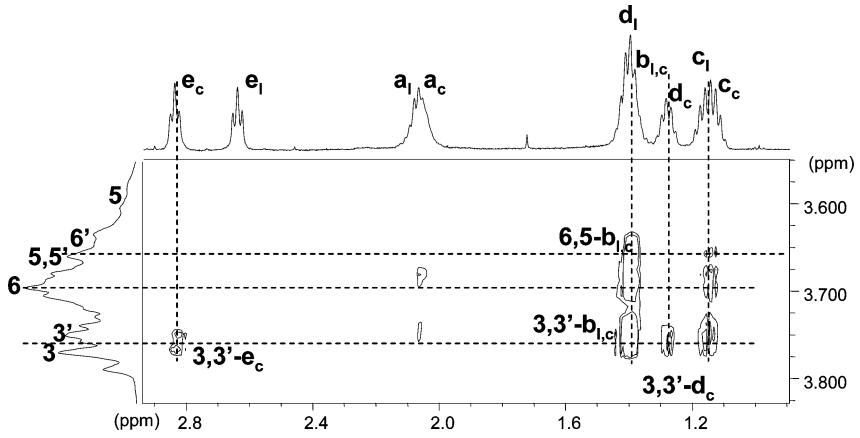

Figure 9. Details of the ROESY spectrum of 6-βCD in D_2O at pH 11.0.

process has been claimed to explain similar slow processes for other systems involving cyclodextrins.[63]

Conclusion

The deprotonation/protonation of the amino group stimulates an in/out movement of the pendant side chain toward/from the cyclodextrin cavity. In fact, the protonation of the amino group prevents the entrance of the chain inside the cyclodextrin cavity. This is another example of a mechanical movement relating two states, which is the basis of the design of molecular machines.[64−67] This is a simple system in which a reversible chemical stimulus modifies the status of a pendant group attached to a cyclodextrin macrocycle. The protonation of the amino group is a fast exchange rate-NMR time-scale process, but the chain movement is a slow one. ^{1}H NMR spectroscopy allows the determination of the equilibrium constants of both processes.

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