NMR Detection of the Conformational Distortion Induced in Cyclodextrins by Introduction of Alkyl or Aromatic Substituents

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Keywords: Cyclodextrins / NMR spectroscopy / NOE

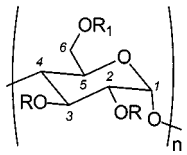
The conformational features of alkylated, benzoylated, and benzylated cyclodextrins in solution were analysed by NOE and proton-selective relaxation methods and were compared to those of native compounds.

Introduction

Cyclodextrins (CDs) have received considerable attention because of their ability to form inclusion complexes and to discriminate between enantiomeric species by virtue of the chirality of the single units.[1] These cyclic oligosaccharides have in fact found widespread applications in many fields of molecular and chiral recognition, such as catalysis,[1][2] asymmetric synthesis,[1][3] analytical or preparative chromatography[1][4] and, also, as chiral auxiliaries for NMR spectroscopy.[5]

All the chemico-physical and complexing properties of commonly available native CDs can be attributed to their high degree of structural preorganization determined by the ordered network of intramolecular hydrogen bonds between adjacent glucose units. Functionalization at the hydroxy sites may remove the internal hydrogen bonding stabilization, to modify the overall shape of the cyclodextrins; the bulkiness of the substituents may also affect the conformation of the monomeric units, to influence their properties significantly.[1] In fact, a great deal of interest has been devoted to the modification of cyclodextrins, in the attempt to produce changes in their solubility or to affect the pathways involved in the molecular recognition. The conformations of the derivatized cyclodextrins have been found to differ significantly from the expected symmetries, as evidenced for both the solid state, by X-ray analyses,[1c,6] and for the solution state, by NMR;[7] theoretical calculations were also used to make predictions.[8]

We recently successfully employed alkylated cyclodextrins [hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (**1**) and heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (**2**)] as chiral solvating agents (CSAs) for the determination by NMR of the enantiomeric composition of nonpolar substrates.[9] Subsequently, cyclodextrins bearing aromatic substituents attracted our attention when we attempted to produce new cyclodextrinic CSAs with enhanced solubility in non-aqueous solvents. The outcome of this research was the synthesis[10][11] of hexakis(2,3-di-*O*-benzoyl)-α-cyclodextrin (**3**), hexakis(2,3,6-tri-*O*-benzoyl)-α-cyclodextrin (**4**), hexakis(6-*O*-benzoyl)-α-cyclodextrin (**5**), hexakis(2,3-di-*O*-benzyl)-α-cyclodextrin (**6**), hexakis(6-*O*-benzoyl-2,3-di-*O*-benzyl)-α-cyclodextrin (**7**), which were proposed as CSAs, soluble in $CDCl_3$ for a wide range of chiral organic compounds containing a 3,5-dinitrophenyl moiety.[11][12]



n	R	R_1	cyclodextrin
6	Me	Me	**1**
7	Me	Me	**2**
6	Bz	H	**3**
6	Bz	Bz	**4**
6	H	Bz	**5**
6	Bn	H	**6**
6	Bn	Bz	**7**

Bz = COPh; Bn = CH_2Ph (1)

An accurate NMR investigation[11] of the stereochemistry and dynamics of cyclodextrin **4** revealed that it retains the C_6 symmetry but it is characterized by a closed structure where the benzoyl groups occlude both the wider and narrower torus rims. In the case of **3**, benzoylation reduced the global symmetry to C_3, at least in $CDCl_3$ as solvent, and the presence of two different kinds of glucopyranoside residues was revealed, undistorted and distorted.[11]

We report now the results of an NMR investigation on the conformational features of the cyclodextrins chemically modified by means of the introduction of alkyl groups (*O*-methylation), **1**–**2**, and aromatic moieties (*O*-benzoylation and/or *O*-benzylation), **3**–**7**. Of the latter, cyclodextrins selectively substituted at the primary hydroxy groups (**5**) or at the secondary ones (**3**, **6**) and persubstituted cyclodextrins (**4**, **7**) were studied. This investigation focuses on the nature of the distortion introduced in the cyclodextrins by the substituents, to provide a basis for the rationalization of the behaviour of substituted cyclodextrins as complexing agents.

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Results and Discussion

For a mainly undistorted cyclodextrin, the glycosidic oxygen atoms lie in a plane, bringing the H^1 and H^4 protons of adjacent units in close spatial proximity (Figure 1a). In such a conformational arrangement, interresidue OH2···OH3 hydrogen bonds can form; as a consequence, the H^1 proton, pointing to the outside, is far away from any H^3 or H^5 protons, located into the cavity, and on average, the interresidue distance H^1-H^4 should be minor relative to the intraresidue H^1-H^2 one. The latter distance can be considered to be more or less fixed for an undistorted glucopyranose ring.

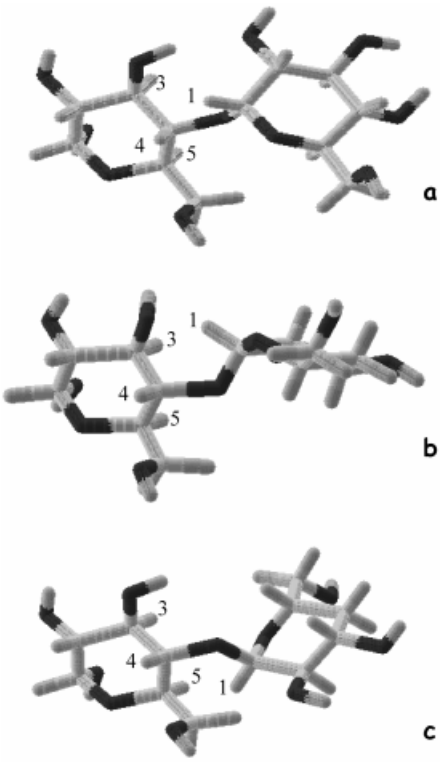

Figure 1. Schematic representation of two adjacent glucose units of cyclodextrin: (a) undistorted, (b) clockwise rotation, and (c) anticlockwise rotation around the glycosidic linkage

As far as derivatized cyclodextrins are concerned, the chemical modification of the primary or secondary hydroxy groups or both could lead to distortions of the glucopyranose ring[7h,11] or/and rotation of one or more glucose units around the glycosidic linkages. The first ones are well reflected in the variation of the NMR *J* coupling patterns of the glucose protons, the latter are more suitably detected by NOE[13] or proton-selective relaxation rate measurements.[14] In particular, the anomeric proton H^1 can generate different patterns of intra- and interresidue dipole−dipole interactions, depending on the degree of the average tilting of glucose units around glycosidic linkages. For a mainly unperturbed situation, the proton H^1 could produce a relevant NOE on the proton H^4 of the adjacent unit, greater than the inter-NOE H^1-H^2. However, rotations about the glycosidic linkages remove proton H^1 from proton H^4 of the adjacent unit and can bring it in the proximity of the internal protons H^3 and H^5. As a consequence, the inter-NOE H^1-H^4 would diminish relatively to the H^1-H^2 one, and dipolar interactions H^1-H^3 and H^1-H^5 would originate. Therefore, taking into account that the measured NOEs reflect the average contributions from all the glucose residues, the relative intensities of the above NOEs reflect the extent of the average distortion.

These may also be detected by the determination of the cross-relaxation parameters σ_{ij} for the proton pairs H^1-H^4 and H^1-H^2. In the initial rate approximation,[15] these relaxation parameters describe the magnetization transfer between the spins *i* and *j* and depend on the internuclear distances r_{ij} and on the rotational correlation times τ_c of the vector *ij*, as described in Equation 2.

$$\sigma_{ij} = \frac{1}{10}\gamma^4\hbar^2\langle r_{ij}\rangle^{-6}\left[\frac{6\tau_c}{1+4\omega_0^2\tau_c^2} - \tau_c\right] \quad (2)$$

where γ is the proton magnetogyric ratio, ω_0 is the proton Larmor frequency and is the reduced Planck constant. In the fast motion regime ($w_0^2\tau_c^2$), the cross-relaxation rates are:

$$\sigma_{ij} = \frac{1}{2}\gamma^4\hbar^2\langle r_{ij}\rangle^{-6}\tau_c \quad (3)$$

In the slow motion regime ($w_0^2\tau_c^2$), the cross-relaxation rates are:

$$\sigma_{ij} = -\frac{1}{10}\gamma^4\hbar^2\langle r_{ij}\rangle^{-6}\tau_c \quad (4)$$

If one assumes that the molecules tumble isotropically, then the same reorientation time can be attributed to all the molecules, and the ratio of the different σ_{ij} values can be simply correlated to the ratios of the internuclear distances:

$$\frac{\sigma_{ij}}{\sigma_{ik}} = \frac{r_{ik}^6}{r_{ij}^6} \quad (5)$$

The cross-relaxation parameters can be determined in a very simple way, by measuring the proton mono- (R_i^s) and biselective (R_{ij}^{bs}) relaxation rates.[14] These values, which are, respectively, determined by selectively inverting the proton *i* (the other protons are left unperturbed) or by inverting the protons *i* and *j* together, and following the recovery of *i* in the time, are given by:

$$R_i^s = \sum_j \rho_j + \rho_i^* \quad (6)$$

$$R_{ij}^{bs} = \sum_j \rho_j + \sigma_{ij} + \rho_i^* \quad (7)$$

where ρ_i^* takes into account the contributions of external sources (no dipolar interactions) to the relaxation.

Therefore, by subtracting R_i^s from R_{ij}^{bs}, the cross-relaxation rate σ_{ij} can be calculated according to Equation 8.

$$\sigma_{ij} = R_{ij}^{bs} - R_i^s \quad (8)$$

We determined, for selected cyclodextrins, the monoselective relaxation rate of the proton H^1 and its biselective relaxation rates under simultaneous inversion of the proton

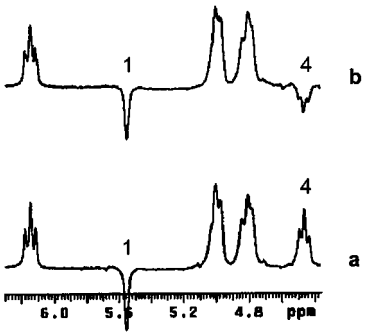

Figure 2. Experiments of proton (300 MHz, [D_6]DMSO, 25 °C) selective inversions: (a) monoselective inversion of H^1, (b) biselective inversion of protons H^1 and H^4 of **4**

H^2 or H^4 (Figure 2). In this way, we calculated the cross-relaxation rates σ_{1-2} and σ_{1-4} and, hence, from Equation 5, the ratio between the distances r_{14} and r_{12} (in the cases in which no glucopyranose ring distortions are suggested by the *J* couplings).

On this basis, the conformational behaviour of *O*-substituted cyclodextrins were analyzed in comparison to the reference case of the native cyclodextrins (α-cyclodextrin, α-CD, and β-cyclodextrin, β-CD). All the investigations were carried out in [D_6]DMSO, in which all cyclodextrins showed the best solubility; for systems bearing aromatic and alkyl groups, $CDCl_3$ and CD_3OD were also, respectively, considered, as these solvents were involved in their use as CSAs.[9][12]

Native Cyclodextrins

According to what was stated above, the proton H^1 of the underivatized cyclodextrins generates the expected dipolar interactions, corresponding to an on average undistorted stereochemistry: the remarkably higher interresidue NOE H^1-H^4 relative to the intraresidue H^1-H^2 one (Figure 3) is strongly indicative of the close proximity between the H^1 and H^4 protons of the two adjacent units and hence of the coplanarity of their $C-H^1$ and $C-H^4$ bonds (Figure 1a). No dipolar interactions were detected with internal protons. Proton-selective relaxation rate measurements gave the cross-relaxation rates for the proton pairs 1−2 and 1−4 of α-CD (in the case of β-CD, the partial superimposition of H^2 and H^4 did not allow us to perform accurate determinations). On the basis of Equation 5, an average value of 0.94 (Table 1) was calculated for the ratio between its distances r_{14} and r_{12}. Therefore, according to NOE data, the former distance is shorter that the latter one.

Cyclodextrins Bearing Alkyl Substituents (1, 2)

Analogous data were acquired for permethylated α-cyclodextrin **1** in three different solvents: [D_6]DMSO, $CDCl_3$ and CD_3OD (Figure 4). In dimethyl sulfoxide, the inter-NOE H^1-H^4 was larger than the H^1-H^2 one, and the proton H^1 also gave a remarkable dipolar interaction with the protons

Table 1. The r_{14}/r_{12} ratios as calculated by cross-relaxation rate measurements for selected cyclodextrins (300 MHz, [D_6]DMSO, 25 °C)

	α-CD	**1**	**2**	**3**	**4**	**5**	**6**	**7**
r_{14}/r_{12}	0.94	0.94[a]	0.92[a]	1.04	1.04	0.95	0.98	0.98

[a] Calculated in $CDCl_3$.

H^6 at the narrower torus rim, whereas its inter-NOE H^1-OMe^6 was negligible. This indicates that this derivatized α-cyclodextrin exists in a mainly undistorted conformation, and its substituents at the primary sites are bent mainly at the narrower opening of the cavity.

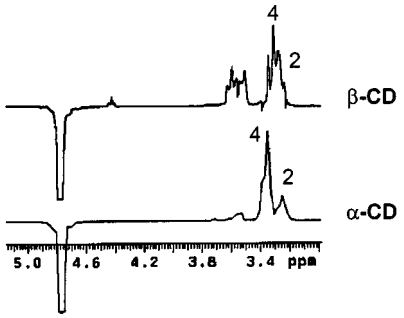

Figure 3. Traces of the 2D ROESY maps (300 MHz, [D_6]DMSO, 25 °C, τ_m = 0.15 s) of α- and β-CD, corresponding to H^1

The same trend was found in $CDCl_3$ (Figure 4), i.e., the H^1-H^4 inter-NOE is larger than the H^1-H^2 one. It is notable that in this solvent the dipolar interaction of the proton H^1 with the methoxy groups OMe^6 is more intense than it is in [D_6]DMSO, whereas a very weak NOE with the H^6 protons is measured.

The same situation holds in methyl alcohol as solvent (Figure 4), i.e., the H^1-H^4 NOE is more intense than the H^1-H^2 one, and the NOE on the OMe^6 groups is more intense than the one to the methylene protons at the same sites.

Therefore, the global conformation of the cyclodextrin **1** in the three solvents is very similar to that found for underivatized cyclodextrin, being mainly undistorted (Figure 1a). However some differences are evidenced by the orientation of the primary methoxy groups: they are pointing at the narrow rim in [D_6]DMSO, whereas they are far away from it in the other two solvents. The same conformational features were found for the permethylated β-cyclodextrin **2**.

Proton-selective relaxation data (Table 1) are in accord with the NOE measurements; in fact, the ratio between the distances r_{14} and r_{12} (obtained from the ratio of the cross-relaxation terms σ_{14} and σ_{12}, see general discussion) follows the same trend found by the NOEs, as discussed above, being always less than 1.00.

Cyclodextrins Bearing Aromatic Substituents (3−7)

Benzoylation or benzylation produces more significant deviations from the undistorted stereochemistry than meth-

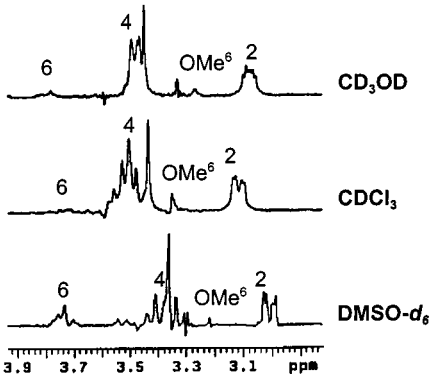

Figure 4. $^1H-^1H$ dipolar interactions produced by the proton H^1 of **1**, detected by difference spectroscopy (CD_3OD, $CDCl_3$) and 2D ROESY ([D_6]DMSO)

ylation does; the degree of distortion strongly depends on the location of the substituents. Cyclodextrins selectively derivatized at the secondary sites, such as **3** and **6**, show a significant deviation of the relative intensities of the inter-NOEs H^1-H^4 and H^1-H^2 from that of unmodified α-CD (Figure 5); in fact, for **6**, these two NOEs are comparable, and for **3**, the first becomes minor compared to the latter. Concomitantly, significant inter-NOEs H^1-H^3 and H^1-H^5 are detected, to indicate the relative tilting of the units, bringing each H^1 external proton in spatial proximity to the internal protons H^3 and H^5 of the adjacent glucose residues (Figure 1b,c).

The completely substituted cyclodextrins, e.g., **4** and **7**, also show a similar degree of distortion, well reflected in the relative intensities of the inter-NOEs produced by the proton H^1. It is notable that, also in the case of **4**, for which there is superimposition of resonances of protons H^2 and H^6, a clear inter-NOE H^1-H^3 is distinguishable.

Cyclodextrins bearing substituents only on the primary groups undergo only minor distortion. In fact, for **5** the inter-NOE H^1-H^4 is greater than the H^1-H^2 one, even if very weak dipolar interactions with internal protons are detected, which could originate from the tilting of isolated units.

The ratios between the distances r_{14} and r_{12}, from cross-relaxation measurements, increase (relatively to α-CD or **1** and **2**) to approximately 1.00 for the remarkably distorted cyclodextrin bearing substituents at the secondary sites (**3**), as well as for exhaustively derivatized cyclodextrin **4**. The value corresponding to a mainly undistorted situation (0.95) is obtained for cyclodextrins derivatized at the primary sites (**5**). No significant differences were found between the values obtained in $CDCl_3$ and those in [D_6]DMSO.

Conclusions

Alkylation does not lead to significant departures from the truncated torus shape in solution, but the orientations of the OMe groups of **1** and **2** in [D_6]DMSO differ from those in $CDCl_3$ and CD_3OD. This fact could affect their

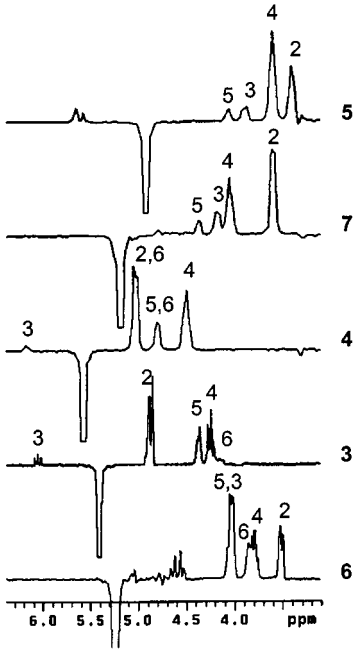

Figure 5. Traces of the 2D ROESY maps (300 MHz, [D_6]DMSO, 25 °C, τ_m = 0.1−0.3 s) of cyclodextrins **3**−**7**, corresponding to H^1

hydrophobic−hydrophilic distribution and hence their complexing properties. In fact, only superficial interactions were detected between **2** and apolar substrates, in particular trisubstituted allenes in CD_3OD as solvent.[9a−9d]

Aromatic substituents affect the symmetry of the cyclodextrins more significantly. Derivatization at the secondary sites lead to a significant rotation of the glucose units around the glycosidic linkages, thus leading to a "flattening" of the global structure. This kind of tilting can lead to a lowering of the global symmetry of the cyclodextrin if a hydrogen bond acceptor group is present at the secondary site (cyclodextrin **3**), allowing hydrogen bond interactions with the primary hydroxy group of the adjacent unit.[11] This is also the only case in which a glucopyranose ring distortion is detected, as reflected by the change in the vicinal coupling constants.[11] For **6**, which contains a benzyl group instead of a benzoyl one, this interaction is not allowed.

Exhaustive derivatization produces similar relevant tilting of the glucose units. Their presence on the primary sites produces only minor tilting of the glucose units, thus confirming the role of the OH2···OH3 hydrogen bond interactions between the secondary hydroxy groups in determining the truncated torus shape

Experimental Section

General: NMR measurements were performed with a Varian VXR-300 spectrometer; the temperature was controlled by the Varian control unit (±0.1 °C). The $^1H\{^1H\}$ NOE experiments were performed in the difference mode. The decoupler power used was the minimum required to saturate the spin of interest. A waiting time of 5−10 s was used to allow the system to reach the equilibrium.

Each NOE experiment was repeated at least four times. All the solutions were accurately degassed by freeze−pump−thaw cycles for 1D and 2D NOE experiments. The 2D NMR spectra were obtained by using standard sequences. The phase-sensitive ROESY (Rotating-frame Overhauser Enhancement SpectroscopY)[13] spectra were acquired with a spectral width of 1000−3000 Hz in 2 K data points with 8 scans for each of the 512 t_1 increments. The spin-lock time was set to 100−300 ms depending on the nature of the cyclodextrin derivative. The data were zero-filled to 2 K × 1 K and a Gaussian function was applied for processing in both dimensions. The selective relaxation rates were measured in the initial-rate approximation[15] by employing a selective π pulse with the proton decoupler at the selected frequency for 25 ms. After the delay τ, a non-selective π/2 pulse was employed to detect the longitudinal magnetization. For the biselective measurements, the two protons were inverted consecutively. − The α- and β-cyclodextrin used were obtained from Fluka. Compounds **1** and **2** were purchased from Cyclolab and Sigma, respectively. Synthetic procedures and characterization data for cyclodextrins **3−7** are reported in refs.[10][11]

Acknowledgments

This work was supported by the Ministero della Ricerca Scientifica e Tecnologica (MURST) and CNR, Italy.

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Received February 8, 1999
[O99069]