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Experimental (NMR) and Theoretical (MD Simulations) Studies on the Conformational Preference of Three Cycloalkanols when Included in β-Cyclodextrin

MARILUZ ZUBIAUR, MIGUEL DE FEDERICO, KEPA K. BURUSCO, IVAN BEÁ, ALBERT VIRGILI, FRANCISCO SÁNCHEZ-FERRANDO and CARLOS JAIME*
Departament de Química, Facultat de Ciéncies, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain

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Abstract

The inclusion complexes between three cycloalkanols (cyclopentanol, cyclohexanol and cycloheptanol) and β-cyclodextrin (β-CD) have been studied by NMR experiments, and by molecular dynamics (MD) simulations. Complexes present medium to small association constants. All experimental data show the equatorial conformer as the most stable after complexation because no changes were detected in the coupling constants of the H1 protons. Intermolecular ROE experiments suggest that while cyclopentanol is deeply included into the β-CD cavity, cyclohexanol and cycloheptanol occupy mainly the wider entrance. The MD simulations agree with the experimental data (equatorial conformers are always the most stable), and average geometries coincide with those deduced from the ROE experiments.

Abbreviations: β-CD – beta-cyclodextrin; MD – molecular dynamics; MM – molecular mechanics; NMR – nuclear magnetic ressonance; NOE – nuclear overhauser effect

Introduction

The conformational behavior of small cycloalkanes has been the object of many experimental and theoretical studies [1]. Cyclopentane experiments a free pseudorotation [2] with an almost null barrier of interconversion [3] between the practically isoenergetic envelope and half-chair conformers. This pseudorotation has been studied by theoretical methods (molecular orbital [4], molecular mechanics [5] and molecular dynamics (MD) [6, 7] calculations) and the barrier to planarity was experimentally determined to be 5.2 kcal/mol [3, 8]. The introduction of a hydroxyl group as ring substituent almost not modifies this pattern. While ring conformers become different, the vibrational spectrum of cyclopentanol suggests a relatively small barrier to pseudorotation [9].

The six- and seven-membered rings behave differently from the five-membered ring, but similarly between them [1]. They largely prefer chair conformations, and have medium interconversion barriers (cyclohexane: 12.1 kcal/mol in gas phase [10], 10.3–11.5 kcal/mol in solution [11, 12], 10.5–11.1 kcal/mol when forming inclusion compounds [13], and 10.9 kcal/mol in plastic crystal [14]; cycloheptane: has been computed to be in the range 8.1–9.6 kcal/mol [15–17]). Their cycloalkanols exclusively adopt the equatorial-chair conformer [18, 19], and both chairs are separated also by a medium barrier (cyclohexanol: 9.9 kcal/mol [20]).

While the behavior of these small cyclic molecules is very well known in gas phase or in solution, not much is known on their conformational behavior when they are interacting with another molecule. It is nowadays accepted that the reactive conformation of a substrate or of an enzyme may be different from that adopted when they are 'isolated'. Not much attention has been paid to this fact in the host–guest chemistry, an intermediate step between the molecular and biological chemistry. Hosts are molecules having convergent binding sites, while guests must have divergent binding sites [21, 22]. Cyclodextrins (CDs) and calixarenes are among the most widely used hosts in this area of supramolecular chemistry [23].

CDs are cyclic oligomers of α-D-glucopyranose that are easily prepared by enzyme degradation of starch [23]. Three are the native CDs, the α-, the β-, and the γ-CD (with 6, 7, and 8 glucoses, respectively). The β-CD is probably the most largely used, in spite of its very low solubility in water [24]. It forms stable inclusion complexes with a large variety of compounds, but groups like phenyl, *tert*-butyl or adamantyl are very much preferred by this host [25].

*Author for correspondence: E-mail: carlos.jaime@uab.es

The conformational changes associated with the formation of inclusion complexes have been experimentally studied when thiourea acts as the host [26–28]. Chloro-, bromo-, and iodocyclohexane adopt the axial conformation when included in the thiourea channels [29–32]. A theoretical study, based on mathematical models [33], suggests that this preference is due to a much better packing in the thiourea channels by the axial isomer than by the equatorial. Our own molecular mechanics (MM) and MD simulations agree with this assumption [34]. The width of the thiourea channel (about 9 Å) is about 50% larger than that of β-CD (about 6–7 Å), but their lengths are totally different. While the former accommodates many guests in its channel, the latter has only room for one guest. Will this single guest change its conformation?

Years ago, the conformational changes produced by the inclusion of *n*-alkanes, cyclohexane and methylcyclohexane in the three native CDs was studied by MM calculations [35]. The results indicated that no detectable conformational changes can be expected upon complexation with CDs. However, more recently, a study on the complexation of cyclohexane with α-CD using semiempirical (PM3) molecular orbital calculations has been published [36], and it claims that after the inclusion the cyclohexane prefers the boat conformation over the chair one by 1.1 kcal/mol. Experimental results based on volatilization rates suggest a lack of a 1:1 inclusion complex between cyclohexane and α-CD [37]. The experimentally determined ΔH^0 between chair and twist-boat cyclohexane conformations is 5.5 kcal/mol [38]. The chair cyclohexane, with dimensions (5.033 Å × 4.352 Å × 2.703 Å) very similar to those of the twist-boat (4.389 Å × 4.325 Å × 2.948 Å), must suffer from a strong destabilization when complexed (about 6.6 kcal/mol). This is hardly understandable, especially because no interactions between host and guest other than dispersion forces could be envisaged, and also because the complexation of methylcyclohexane with α-CD did not significantly modify the position of the axial-equatorial conformational equilibrium from this system, which requires only 1.74 kcal/mol [35].

In this article, NMR experiments and MD simulations will be used to study the complexation of three cycloalkanols (cyclopentanol. cyclohexanol, and cycloheptanol, **C5OH**, **C6OH**, and **C7OH**, respectively) with β-CD, and to explore the capability of CDs for reversing or changing the direction of their conformational equilibria. It will be shown that there is neither experimental evidence nor theoretical predictions supporting conformational changes on these systems in spite of presenting much smaller conformational energies than the corresponding methyl derivatives.

Experimental section

Samples for the NMR spectra were prepared following an already described procedure [39]. The concentration of the samples were always $1.542 \cdot 10^{-2}$ M. NMR experiments were performed in a Bruker ARX 400 MHz spectrometer at 300 K and with D_2O as solvent. ROESY-2D experiments were performed to study the host/guest interactions. The crossed relaxation was obtained using an *Off Resonance* low power continuous wave irradiation. Mixing times were set between 600 and 800 ms to obtain a maximum NOE value; they were determined by dpfgenoe sequences with a relaxation time of 2 s.

Guest structures were generated by standard procedures while host initial coordinates were taken from the available neutron diffraction data [40]. Both, host and guest, were fully minimized before building the complexes. Initial coordinates for the complexes were built by simple juxtaposition of individual coordinates but were afterwards fully minimized before using them as starting structures for the MD simulations. The two most probable orientations were considered (the OH group pointing towards the wide or narrow host rim).

The MD simulations in gas phase and in water modeled as a continuum were carried out with MacroModel and BatchMin V.5 software packages [41] using MM3* force field [42]. Movement restraints had to be imposed to prevent guest to escape from host. The distances between the C1 of the guest and three selected glycosidic oxygens (on alternate glucoses) were fixed to be equal to 6 Å using a square well with half width of 3 Å and a 100 kJ/Å^2 force. The SHAKE option was applied over all bonds. The simulations were performed with the following scheme: the system was heated up to 300 K in 5 steps of 25 ps (increasing 50 K at each step), a 25 ps short run was performed to allow the equilibration of the system at 300 K, and from there on productive runs of 3 ns were performed. All time steps were of 1 fs, and a total of 200 structures were sampled in the productive runs.

The MD simulations in aqueous solution were performed with AMBER v.7 package [43] using the parm99 [44] force field and TIP3P [45] water molecules as solvent using periodic boundary conditions. The MD simulation scheme was: 20 ps for the heating of the system up to 300 K under NVT conditions, 120 ps for the equilibration (20 ps under the NVT conditions, and 100 ps under the NPT conditions), and productive runs of 1000 ps under the NPT conditions, with time steps of 1 fs and with samplings taken every 1 ps.

Results and discussion

NMR study of the complexation process

Fourteen samples were prepared with different host/guest ratios for each of the studied cycloalkanols, as indicated in the experimental section. The NMR spectrum was recorded for each sample. The observed $\Delta\Delta\delta$ for the internal host (H3′, and H5′) and all possible guest protons were relatively small (usually

Table 1. Association constants for the complexation of **C5OH**, **C6OH** and **C7OH** with β-CD

Guest	Proton	$\Delta\Delta\delta$(ppm)	K
C5OH	H2ax	−0.0734	1614 ± 130
C6OH	H3eq	0.1053	382 ± 34
C7OH	H3eq	0.1343	1148 ± 96

Values obtained by the EQNMR program from NMR data.

< 0.08 ppm). Job's diagrams [46] indicate a 1:1 stoichiometry for all the complexes formed.

Association constants (K) were determined by NMR titration with the help of EQNMR program [47] (Table 1). Most of the protons suffered from changes in their δ after the complexation. However, the absolute movements were very small and, to diminish the errors, only protons presenting the largest movements were considered. K values are medium to small, and are also indicative of a fast exchange between complexed and uncomplexed forms. They follow the order **C5OH** > **C7OH** > **C6OH**, which is in agreement with their solubility in water (slightly, soluble, and slightly, respectively) [48] but in disagreement with the recently published values (168, 707, and 2344, respectively) obtained from isothermal microcalorimetric titration [49].

The changes in the axial-equatorial ratio produced by the complexation, if any, should be detected on the guest H1 atoms. Any increase of the population for the axial conformer will be translated into a smaller coupling constant (J) for H1. Experimentally, the J values of H1 after complexation with β-CD did not significantly differ from those obtained for the corresponding isolated guest in water solution (differences were always smaller than 1 Hz). This proves that, when included, these guests are in practically the same conformational equilibrium as when isolated.

ROE experiments were performed by irradiation the two inner host protons and observing the effect on the intensities of guest protons to know the geometry of the inclusion complexes. Absolute values are gathered in Table 2.

Table 2. Direct integral obtained from the ROESY off resonance experiments on the guest protons after saturation of H3′ and H5′ host protons

		Saturated CD proton	
Substrate	Proton observed	H3′	H5′
C5OH	H1	436	331
	H2eq	456	409
	H2ax	440	342
	H3eq,ax	368	289
C6OH	H2eq	88	37
	H2ax,H3ax	78	37
	H3eq	86	41
	H4eq	117	64
	H4ax	136	59
C7OH	H2eq	31	14
	H3eq	20	12
	H4ax	22	10
	H2ax,H3ax,H4eq	57	31

Similar NOE values over the guest protons were obtained on saturation of both host protons for **C5OH** (Table 2). This guest is very likely totally included into the host cavity, spinning, and entering and exiting almost freely. In contrast, values for **C6OH** and **C7OH** were significantly different depending on the saturated host proton. In both cases, NOE effects on saturation of H3′ protons were larger. These results suggest that these guests were mainly occupying the wider part of the host cavity, although some occupancy of the narrower can not be excluded due to the presence of reasonable NOE values over the guest protons on saturation of H5′ host protons. These experimental NOE values also suggested that the guests did not adopt a single orientation but very likely they formed complexes in any possible orientation (bimodal complexes; i.e., with the OH group pointing towards the narrower and towards the wider rims while the cycloalkane remains included).

MD simulations

The three studied cycloalkanols were subject of several MD simulations (see Experimental section for more details). The starting geometries for the isolated guests were considered to be either in equatorial or in axial conformations. When complexed with β-CD, in addition to the axial and equatorial conformations, the two most probable orientations were also considered. They were called Head and Tail depending on the position of the OH group (Figure 1): Head for pointing towards the wider rim and Tail for pointing the narrower rim.

Simulations in water modeled as a continuum

The results obtained from the MD simulations in water (modeled as a continuum with MM3* force field [42] within MacroModel program [41]) indicated, as expected, that **C5OH** was in a fast equilibrium between both conformations (Table 3). The computed equatorial/axial ratio was 60/40. The equatorial/axial interconversion barrier for **C6OH** was much higher and the substrate did not change its initial conformation during the simulation time (Table 3). In contrast, **C7OH** had a somewhat lower barrier and the molecule achieved the 97/3 equatorial/axial ratio independently from the initial conformation (Table 3).

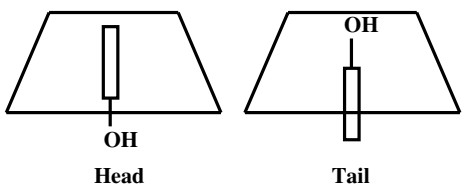

Figure 1. Schematic representation of the Head and Tail orientation for the β-CD/cycloalkanol complexes studied.

Table 3. Population (%) of equatorial and axial conformers for the **C5OH**, **C6OH** and **C7OH** compounds obtained by MD simulations in water as continuum solvent when isolated or included into β-CD

		Isolated		Included Head		Included Tail	
Compound	Starting	Equatorial	Axial	Equatorial	Axial	Equatorial	Axial
C5OH	Equat.	62	38	68.5	31.5	71	29
	Axial	57.5	42.5	64	36	68	32
C6OH	Equat.	100	0	100	0	100	0
	Axial	0	100	0	100	0	100
C7OH	Equat.	98	2	85	15	90.5	9.5
	Axial	96.5	3.5	96.5	3.5	94	6

The results obtained with the inclusion complexes were more interesting. The β-CD/**C5OH** also achieved an equilibrium favoring equatorial conformation. The equatorial/axial ratio was now in average of 68/32, a small increase of the equatorial conformation was observed, although should not be experimentally detectable. **C6OH** did not change its ratio, and the substrate was always kept in the initial conformation. The **C7OH** always preferred the equatorial conformation, and the equatorial/axial ratio was now in average of 92/8, a small increase in the proportion of the axial conformer was detected (about 5%) although it should not be experimentally detected either.

MD simulations in explicit water

The three substrates were also subject of MD simulations with explicit water as a solvent. The AMBER program [43] (version 7) with the parm99 force field [44] and TIP3P water [45] were used in these simulations (see the Experimental section for more details). The obtained results reasonably agreed with those obtained in water as a continuum solvent (see Table 4).

The **C5OH** adopted a 52/48 equatorial/axial ratio when isolated and freely moved in the cavity of the β-CD when included (see Figure 2). The MD simulations indicate that the **C5OH** freely exchanges between equatorial and axial conformations (Figure 3). In average, the equatorial conformation was preferred when included into the β-CD by a 59/41 ratio, although in two cases the axial conformer remained slightly preferred with equatorial/axial ratios of about 48/52 (Table 4). Very likely in these cases, the simulations had been not long enough as to get convergence.

Neither the **C6OH** in equatorial nor in axial conformation changed from the starting conformation (Table 4, and Figure 4). However, they also freely moved inside the host cavity and even they changed from Head to Tail orientation (or *vice versa*) (Figure 5). No conclusions on the conformational preference after the inclusion of **C6OH** could be extracted from the conformational average energies because differences were within the rms for the simulations.

The **C7OH** presents a behavior similar to that of **C5OH**. The conformation of the ring changes along the simulation, independently from the starting point (Table 4, and Figure 6). When the **C7OH** is isolated, the equatorial conformation is preferred over the axial by a 64/36 ratio. However, when simulations are performed after the inclusion into the β-CD cavity, the average over all the possibilities studied (four in total) indicate that the equatorial is even more preferred than the axial by a 77/23 ratio, in agreement with the experimental observations. The MD simulations also show that the guest freely moves inside the host cavity (Figure 7).

Conclusions

The NMR study of the complexes between **C5OH**, **C6OH**, and **C7OH** and β-CD indicate that not detectable conformational changes were observed, as deduced from the unobserved changes (if any, smaller than 1 Hz) in the coupling constants for the H1 guest protons. The association constants, determined by NMR titration, were of 1610, 380, and 1150, respectively. All the **C5OH** protons present similar NOE values on irradiation of internal CD protons, indicating that it was totally

Table 4. Population (%) of equatorial and axial conformers for the **C5OH**, **C6OH** and **C7OH** obtained by MD simulations (AMBER) in water solution

		Isolated		Included head		Included tail	
Compound	Starting	Equatorial	Axial	Equatorial	Axial	Equatorial	Axial
C5OH	Equat.	51.8	48.2	48.5	51.5	68.5	31.5
	Axial	52.5	47.5	72.5	27.5	47.5	52.5
C6OH	Equat.	100	0	100	0	100	0
	Axial	0	100	0	100	0	100
C7OH	Equat.	77	23	66.3	33.7	77.5	22.5
	Axial	63.7	36.3	86.7	13.3	79	21

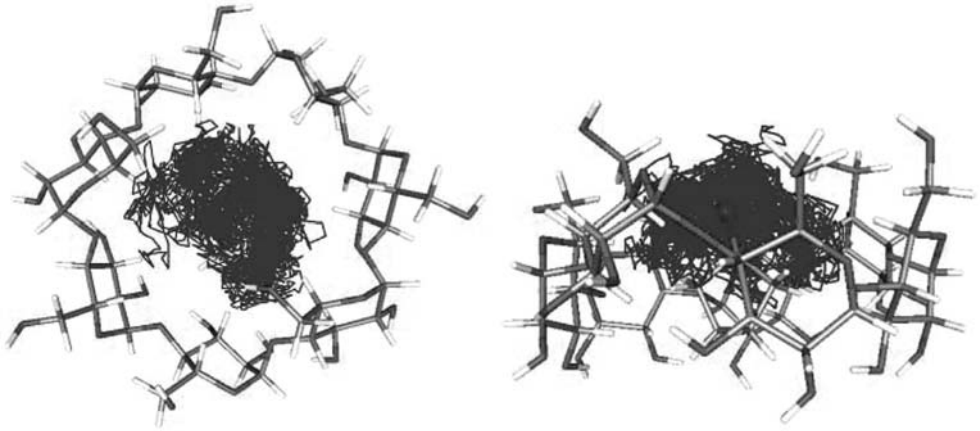

Figure 2. Trace followed by the oxygen atom of **C5OH** when included into the β-CD cavity.

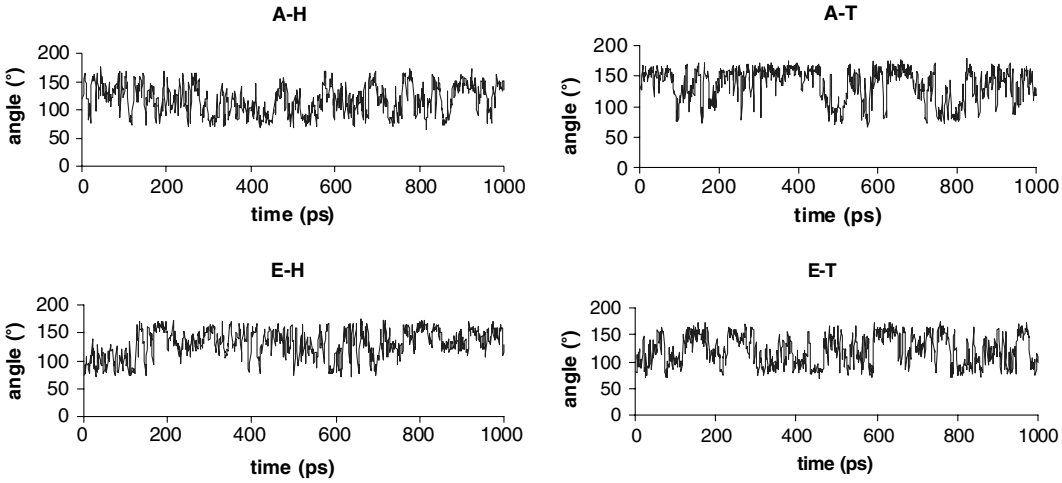

Figure 3. Variation of the C–C–C–O dihedral angle of **C5OH** with simulation time in the four different computed possibilities (A-H: axial-head; A-T: axial-tail; E-H: equatorial-head; E-T: equatorial-tail).

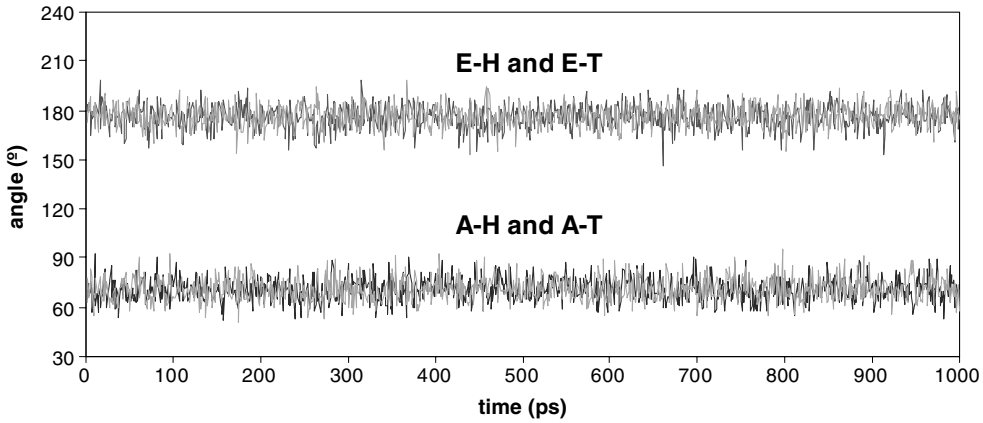

Figure 4. Variation of the C–C–C–O dihedral angle of **C6OH** with simulation time in the four different computed possibilities (A-H: axial-head; A-T: axial-tail; E-H: equatorial-head; E-T: equatorial-tail).

included in the host cavity, and very likely moving freely without any preferred geometry. The **C6OH** and **C7OH** presented larger NOE values on saturation of the H3′ than on saturation of the H5′ CD protons, clearly indicating a preference for these two molecules to occupy the wider rim of the β-CD.

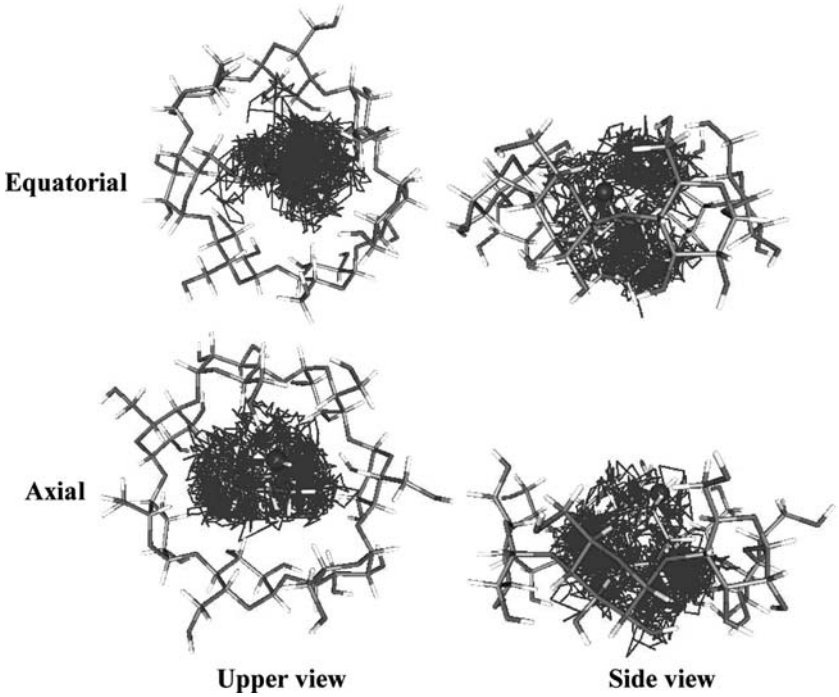

Figure 5. Trace followed by the oxygen atom of **C6OH** when included into the β-CD cavity.

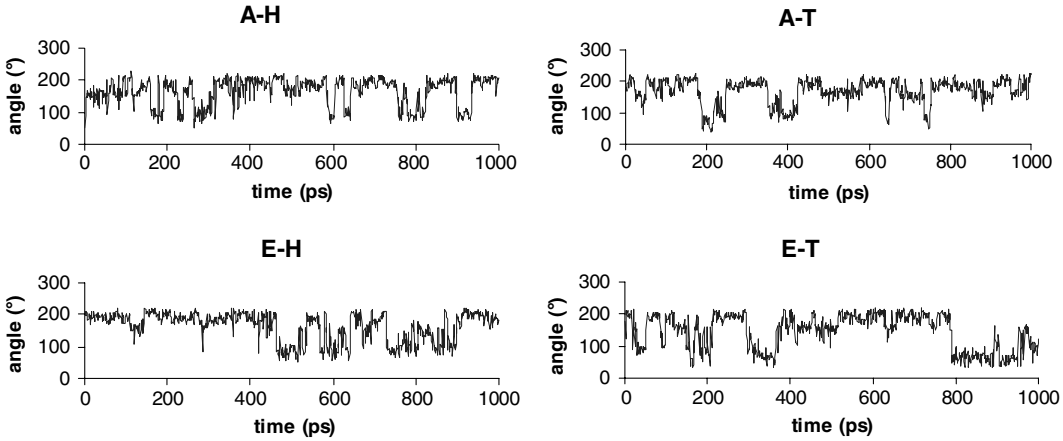

Figure 6. Variation of the C–C–C–O dihedral angle of **C7OH** with simulation time in the four different computed possibilities (A-H: axial-head; A-T: axial-tail; E-H: equatorial-head; E-T: equatorial-tail).

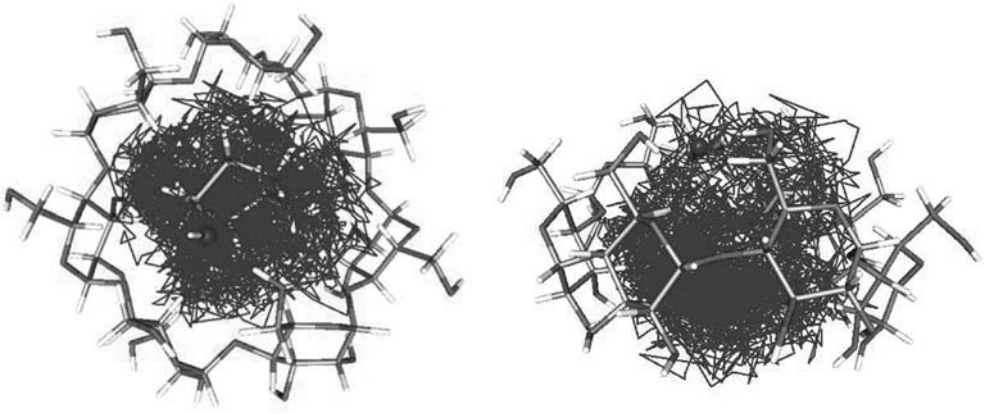

Figure 7. Trace followed by the oxygen atom of **C7OH** when included into the β-CD cavity.

The MD simulations (either with MM3* and a continuum solvent model for water or AMBER and explicit water molecules) totally agreed with these experimental results.

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