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ORIGINAL PAPER

Structural elucidation of supramolecular alpha-cyclodextrin dimer/aliphatic monofunctional molecules complexes

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Abstract The structural elucidation of 2α-cyclodextrin/1-octanethiol, 2α-cyclodextrin/1-octylamine and 2α-cyclodextrin/1-nonanoic acid inclusion complexes by nuclear magnetic resonance (NMR) spectroscopy and molecular modeling has been achieved. The detailed spatial configurations are proposed for the three inclusion complexes based on 2D NMR method. ROESY experiments confirm the inclusion of guest molecules inside the α-cyclodextrin (α-CD) cavity. On the other hand, the host-guest ratio observed was 2:1 for three complexes. The detailed spatial configuration proposed based on 2D NMR methods were further interpreted using molecular modeling studies. The theoretical calculations are in good agreement with the experimental data.

Keywords Host-guest interaction · Structural elucidation · Supramolecular complexes

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Introduction

Cyclodextrin inclusion complexes, particularly those leading to supramolecular self-assemblies, continue to be a fascinating topic in modern organic chemistry as they serve as models for understanding molecular recognition, precursors in the design of novel nanomaterials [1] and for their electronics and biological applications [2]. CD molecules are of interest to synthetic chemists due to their chemical stability and their ability to be modified in a regioselective manner. Also, the paramount importance in supramolecular chemistry relies in their ability to form a series of water-soluble host molecules that can be used as models for studying intermolecular interactions (e.g., hydrogen bonding and van der Waals forces). CDs are widely used in pharmaceutical science, catalysis, drug delivery and more recently in the field of chemical nanostructures [2–5]. Thus, structural characterization of CDs is of particular significance, in order to address the basis of most CDs applications.

It has been reported that α-CD host forms three types of structural packing: the so-called "cage", "layer" and "channel types" [6]. In the latter packing, three possible arrangements of the α-CD hosts have been observed, namely head-to-tail (HT) and head-to-head (HH) and tail-to-tail (TT) orientations [7], where HH and TT were found to represent 80 % (HH being the most stable) of the possible spatial arrangement. In fact, complexes with a 2:1 stoichiometry between the α-CD host and guest molecules consisting of an extended hydrocarbon chain have been reported by means of NMR spectroscopy and powder XRD [8]. Valeric acid, 1-octanol [9], dialkylamine [10] and lauric acids [11] are some examples of aliphatic molecules able to form

α-CD inclusion complexes with hexagonal symmetry. In most cases, guest molecules bearing an aromatic moiety have been synthesized and studied, because of their potential use in biomedical applications.

Several possible mechanisms exist when CDs interact to form supramolecular assemblies [12]. The study of the corresponding driving forces involved in the complexation processes, as well the responsible factors involved in their stability, become a problem of great interest [5, 13–15]. The energetic of CDs inclusion complexes depends not only on the shape and size of the guests, but also in the equilibrium constants and in the solvent used in the complexation process [16], which can be measured by a range of physicochemical methods. One of the most popular techniques used to study these systems which have provided an understanding of the structure and energetics of the inclusion process is nuclear magnetic resonance (NMR) spectroscopy [16, 17]. In this regard, as Fielding mentioned in his review, [18] NMR has become a routine tool for the study of host-guest complexes yielding hundreds of reports where this spectroscopy has been used to measure their intermolecular association. However, these studies fail to consider CDs dimerization (two or more CD molecules), or other aggregation phenomena.

To the best of our knowledge, new efforts have been put toward the structural elucidation and understanding of the complexation processes of α-CDs with aliphatic monofunctional molecules to form inclusion complexes which have yield in the understanding of the physicochemical and pharmaceutical properties of the guest molecules, namely increased solubility, improved chemical stability and bio-availability [19].

In this sense, the aim of this work is to describe the spatial configurations acquired upon complexation through the structural elucidation of three inclusion complexes, such as 2α-cyclodextrin/1-octanethiol (2α-CD/$C_8H_{17}SH$), 2α-cyclodextrin/1-octylamine (2α-CD/$C_8H_{17}NH_2$) and 2α-cyclodextrin/1-nonanoic acid (2α-CD/$C_8H_{17}COOH$), by means of 2D ROESY NMR spectroscopy and molecular modeling techniques. The theoretical calculations were carried out in order to provide a more detailed description of the intermolecular interactions, so as to rationalize the experimental data.

Experimental

Chemicals and starting materials

All reagents and solvents used in this work were commercially available from Sigma-Aldrich Chemical Company and were used without further purification.

Synthesis of α-cyclodextrin inclusion complexes

The synthesis of the inclusion complexes was based on a previously reported method for α-CD/$C_8H_{17}SH$ [20]. The 2α-CD/$C_8H_{17}SH$ complex used in the NMR tritation experiments was obtained by the reaction of 1-octanethiol (from 0.1 mmol to 0.7 mmol) and 2 mL of α-CD (0.1 mmol). The resulting white suspension was allowed to react for 24 h. The obtained microcrystals were filtered and washed with small amounts of water and acetone.

^{1}H nuclear magnetic resonance (^{1}H-NMR) analysis

The spectra were obtained at room temperature in a Bruker Advance 400 MHz superconducting NMR spectrometer in Dimethyl sulfoxide-d_6 (DMSO-d_6). All spectra were recorded at 400 MHz. The resonance at 2.5 ppm was used as internal reference due to residual solvent DMSO-d_6. The complexation was investigated by means of 2D ROESY NMR method, using the wg-ROESY (watergate-ROESY) pulse sequence. ROESY measurements were carried out using the following experimental conditions: 62 scans, acquisition time 0.150 s, pulse delay 8 s and 1024 data points.

NMR titration

Chemical shifts were given on the δ scale (ppm) and referenced to the internal reference. The experiment consisted of holding one component (usually the host) at constant concentration and varying the concentration of the second component. A series of samples were studied, as described in "Synthesis of α-cyclodextrin inclusion complexes".

Molecular modeling of α-cyclodextrin/aliphatic monofunctional molecules

The crystal structure of α-CD dimer was obtained from [21]. The guests, 1-octanethiol, 1-octylamine and 1-nonanoic acid were built using Gaussview program and then optimized at the B3LYP/6-31G(d,p) level as implemented in Gaussian98 package of programs [22].

AutoDock 4.0 [23] with Lamarkian genetic algorithm (LGA) was used to generate the starting complexes. The parameters used for the global search were an initial population of 50 individuals, with a maximal number of energy evaluations of 1,500,000 and a maximal number of generations of 50,000 as an end criterion. An elitism value of 1 was used, and a probability of mutation and crossing-over of 0.02 and 0.08 was used, respectively. From the best solutions obtained according to these parameters, some of them defined by the user as the best probabilities (in our case

0.06) were further refined by a local search method such as pseudo Solis and Wets 'PSW'.

Autodock defines the conformational space implementing grids all over the space of the possible solutions. With the aim of testing the ability of Autodock to converge into solutions that are inside of the α-CD, a grid of 50×50×50 points by side and 0.375 Å spacing between each point was set up in such a way that it covered both the external surface and the internal cavity of the α-CD.

The following procedure was employed on the α-CD docking simulations: 250 independent runs were done for each α-CD dimer. At the end of each run, the solutions were clustered according to their lowest RMSD and the best score value based on a free empiric energy function. Cluster solutions whose average score was not over 1 kcal·mol^{-1} with respect to the best energy obtained in the respective run were then selected. Thus, the solution that represents most of the complexes obtained in the run was compared with the 2D NOESY experimental data, providing that the obtained solution is able to represent it accurately.

Results and discussion

^{1}H-nuclear magnetic resonance

NMR spectroscopy is one of the most efficient experimental techniques used to investigate molecular interactions [24]. Thus, the interpretation of the observed chemical shifts of host and guest species allows determining the formation and stoichiometry of an inclusion complex. Many techniques have been used for inclusion complex characterization, but only NMR provides conclusive data about the complexation at the molecular level [16]. Schneider and co-workers mentioned that NMR spectroscopy provides a detailed picture of the inclusion complexes, at least through three different and independent sets of information [16]. First, NMR can be used to measure complexation shifts, i.e., the difference between free and bound resonance frequency (in ppm) for the same nucleus. Second, "through space" proximity of nuclei of the host and the guest, can be quantitatively monitored by means of intermolecular Overhauser effects, measured through ROESY. Finally the information regarding stoichiometry and complexes association constants can be extracted through treatment of the data from NMR titrations.

Chemical shifts data for the inclusion complexes are shown in Table 1. According to these values and from the structure of free α-CD, it is clear that the α-CD protons, namely H-3, H-5 and H-6 are located inside or at the edge of the cavity, experiencing significant upfield changes in the NMR chemical shift signals. In contrast, the H-1, H-2 and H-4, which are expected to be outside the cavity, experience only minor changes upon complexation. Thus, the observed chemical shifts of H-3 and H-5 of α-CD host unequivocally indicate that the complexes were obtained.

The complexes stoichiometry were determined considering as reference the methyl integration of -CH_3 group of the guests, that appear at 0.8 ppm (see Table S2). Table 1 shows the characteristic signals of guests to high fields (0.8–2.5 ppm), generating new chemical shifts and splitting with respect to pure compounds upon complexation. Also, the interpretation of α-CD chemical shifts (3–5.5 ppm) allows for determining the host number per guest. It is worth mentioning that the observed host-guest ratio were 2:1 for the three inclusion complexes. In some ^{1}H NMR spectra of α-CD/$C_8H_{17}SH$, the ratio was 1:1. This difference can be attributed to the higher polarizability and size of -SH group (sulfur van der Waals radius is 180 pm) compared to -NH_2 (nitrogen van der Waals radius is 150 pm) and -COOH (oxygen van der Waals radius is 140 pm) moieties, "forcing" the guest molecule to move outside of α-CD cavity generating some 1:1 complexes by steric effects. As a consequence, there is a higher interaction between -NH_2 or -COOH moieties and the α-CD host, leaving the aliphatic chain inside the cavity and forming 2:1 complexes. In order to clarify the host-guest ratio to α-CD/$C_8H_{17}SH$, NMR tritation studies were carried out.

Table 1 ^{1}H NMR chemical shifts, δ (ppm), of protons in pure α-CD, inclusion complexes and their complexation shifts (Δδ)

Compound	H-1	H-2	H-3	H-4	H-5	H-6	OH-2	OH-3	OH-6
α-CD	4.796	3.441	3.768	3.276	3.580	3.638	5.496	5.422	4.459
2α-CD/$C_8H_{17}SH$	4.794	3.439	3.760	3.273	3.577	3.631	5.508	5.422	4.467
Δδ[a]	0.002	0.002	0.008	0.003	0.003	0.007	0.011	0.000	0.008
2α-CD/$C_8H_{17}NH_2$	4.793	3.425	3.749	3.273	3.583	3.632	5.449	5.449	4.462
Δδ[a]	0.003	0.016	0.019	0.003	0.003	0.006	0.047	−0.027	−0.003
2α-CD/$C_8H_{17}COOH$	4.799	3.437	3.762	3.277	3.577	3.632	5.503	5.424	4.464
Δδ	−0.003	0.004	0.005	−0.001	0.003	0.006	−0.007	−0.002	−0.005

[a] $\Delta\delta = \delta_{\text{pure } \alpha\text{–CD}} - \delta_{\text{complex}}$

NMR shift tritations

Measurements of chemical shift changes as a function of species concentration are called NMR tritations. One advantage of this method is that the observed chemical shift changes provide insights into the conformation of the formed inclusion complexes [16]. NMR shift tritations have thus become one of the most widely used methods to determine association constants of CDs complexes. The association constant (K_a) is defined as the following:

$$K_a = [\text{host} \cdot \text{guest}]/[\text{host}][\text{guest}]. \quad (1)$$

Equation 1 describes the equilibrium constant (or association constant to supramolecular chemistry) between host-guest complex and reactant species. When there is a high degree of complexation between host and guest, the K_a is expected to be large ($>10^5 M^{-1}$) and therefore, the inclusion complex is formed in high yields. In this study, α-CD/$C_8H_{17}SH$ complex is a solid (yield≈97 %), allowing us to conclude that the complexation process is almost complete leading the [host guest] near to unity. This assumption, allows us to estimate that K_a is larger than $10^5 M^{-1}$.

Fielding [18] mentioned that the problem of obtaining large K_a values is that there is no curvature in the Δδ versus $[Host]_0/[Guest]_0$ plot at realistic reagent concentrations. In these conditions, the guest is effectively and completely complexed with any available host. Therefore, as an alternative to this method, we can use a plot to represent the inclusion process, in the form $\Delta\delta_{host}$ (ppm) as function of the [α-CD]/[$C_8H_{17}SH$] to determine when the guest is completely complexed inside the α-CD cavity. The titration curve will allow us to estimate the stoichiometry of the inclusion complexes by considering one guest in the cavity.

Figure 1 shows the NMR tritation of α-CD/$C_8H_{17}SH$ complex formation when different concentration of guest are added. The chemical shift corresponding to the host protons changes, especially hydroxyl groups, H-5 and H-3, when an increasing amount of the guest is added. However, all chemical shifts remain constant from 0.36 mmol of 1-octanethiol (mole excess), evidencing that the complexation process is complete.

The plot $\Delta\delta_{host}$ (ppm) as function of the [α-CD]/[$C_8H_{17}SH$] corresponds to Fig. 2 which shows the tritation curve of H-3 and H-5 protons, which are inside of α-CD. As both protons are very sensitive to the chemical environment, it is possible to infer when the complexation process is complete, due to at this point the chemical shifts remain steady, independent of guest amount added. This behavior is observed from a 0.4 mole concentration ratio, where the Δδ values remain constant, meaning that the guest is completely

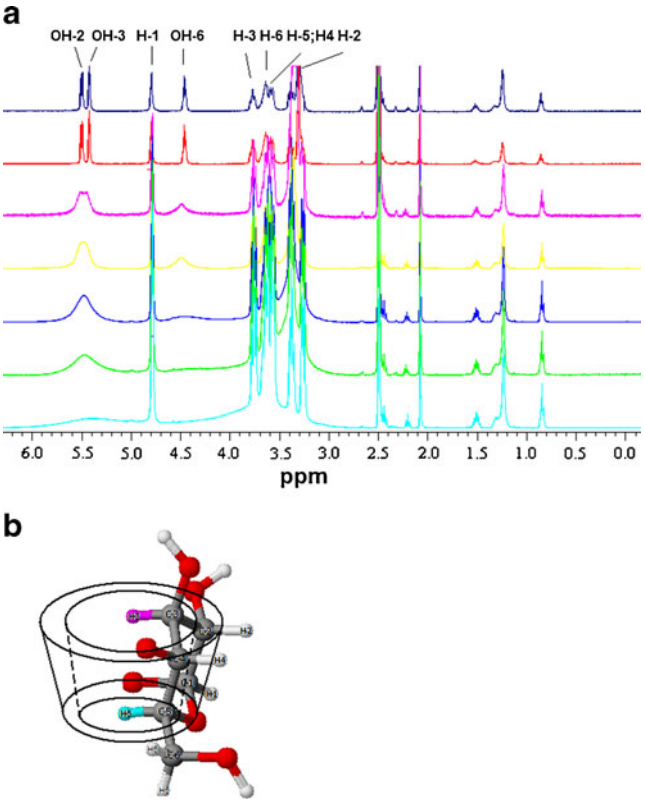

Fig. 1 **a** NMR tritation of 2α-CD/$C_8H_{17}SH$ in DMSO-d_6 at ambient temperature. **b** Schematic representation of a glucopyranose unit, showing proton spatial distribution

inside the α-CD cavity of any available host leading to a maximum yield. It is worth mentioning that other important mechanistic aspects can be extracted from the data plot during the complexation process. According to these, this process starts from the tight cone side of α-CD (near H-5) and finishes in the broad cone side (near H-3). At first, the H-5 environment is clearly changing, while H-3 remains unalterable. However, at the end of the curve the chemical environment H-3 changes, due to the guest molecules are effectively included inside the host cavity.

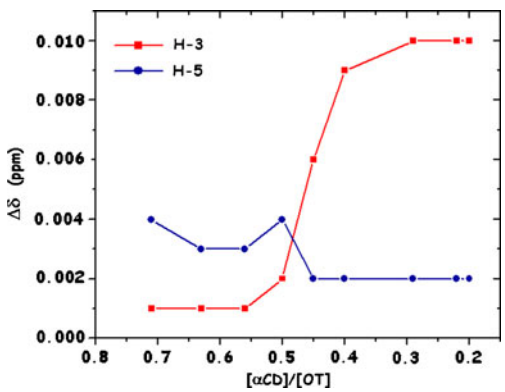

Fig. 2 Plot of chemical shift differences versus titration values with 1-octanethiol. The *blue* and *red lines* correspond to H_3 and H_5, respectively

2D ROESY NMR

2D ROESY NMR intermolecular cross peak signals are obtained when the distance among hydrogen nuclei from the functionalized hydrocarbons and α-CD are above 0.5 nm [25]. Figure 3 shows a contour plot of a section of the ROESY spectrum of the α-CD/$C_8H_{17}SH$, α-CD/$C_8H_{17}COOH$ and α-CD/$C_8H_{17}NH_2$ inclusion compounds.

Intermolecular correlations among internal H-3, H-5 and H-6 protons of α-CD, the bulk $(-CH_2-)_n$ and methyl groups of the functionalized hydrocarbons were observed. These correlations prove total complexation between aliphatic monofunctional molecules and α-CD. Other weak cross peak of external protons H-4 and H-2 of α-CD with bulk and methyl are also observed. Strong intermolecular correlations among the thiol functional group and H_5 and H_6, and

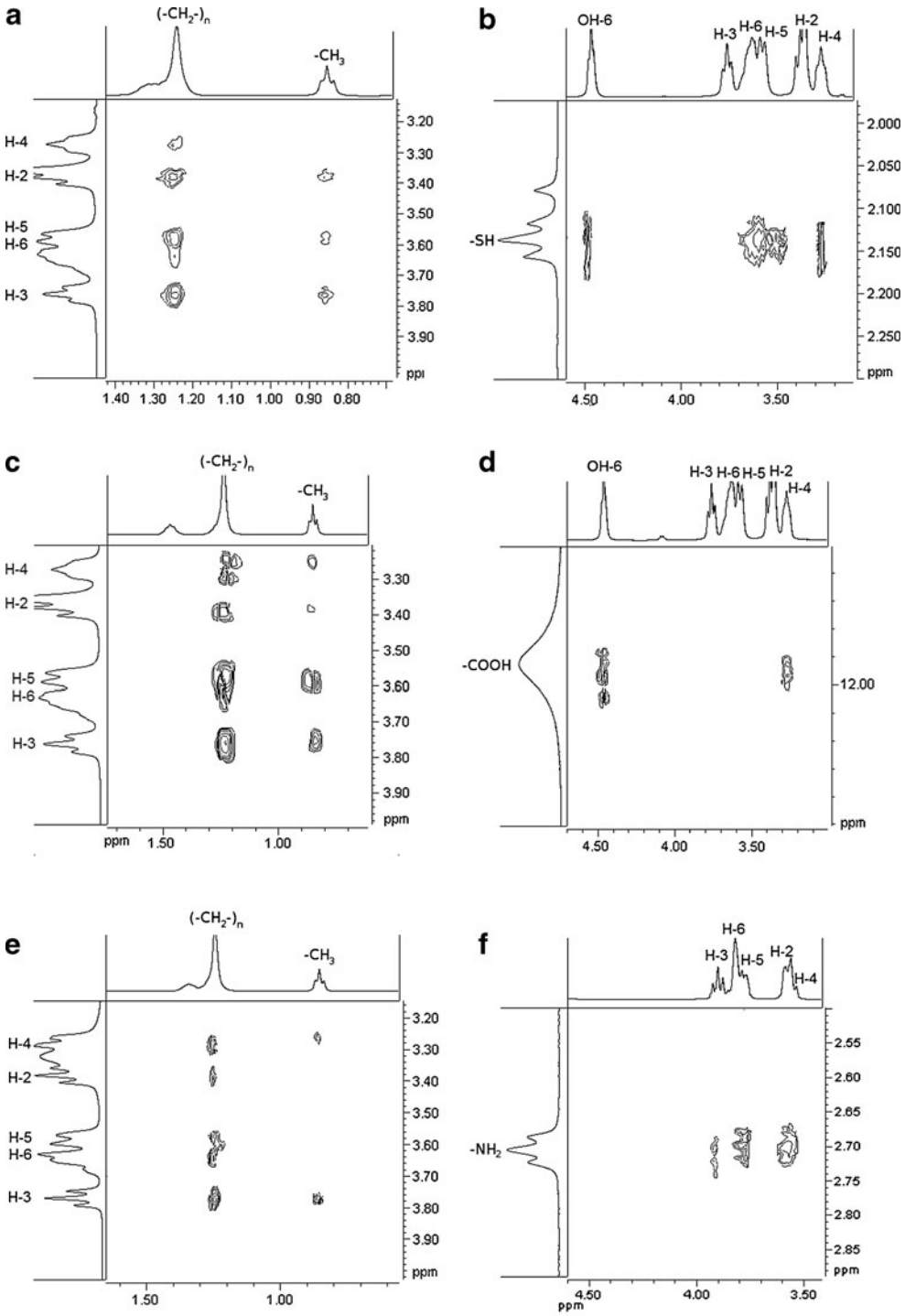

Fig. 3 ROESY spectra: **a**, **b** correspond to the α-CD/$C_8H_{17}SH$; **c**, **d** to the α-CD/$C_8H_{17}COOH$ and **e**, **f** to the α-CD/$C_8H_{17}NH_2$

weak interaction with primary hydroxyl (OH-6) and H-4 protons of the α-CD.

The carboxylic moiety of $C_8H_{17}COOH$, displayed a strong correlation with OH-6 and weak with H-4 proton of α-CD. Finally, -NH_2 functional group showed a strong correlation with H-5 and H-4 and weak correlation with H-3 protons of host. In all cases the 2D ROESY NMR experiments show that complexes between the functionalized hydrocarbons and α-CD were clearly formed, indicating that the non-polar portion of the guest structure was encapsulated.

Molecular modeling of α-cyclodextrin complexes

In order to rationalize the 2D ROESY NMR experimental results described vide supra, molecular modeling studies of the complexes were achieved. The modeling revealed a preferred orientation for the ligands studied despite the randomly imposed initial configurations. Minimum energy complexes obtained for the head-to-head cyclodextrin dimer under study are shown in Figs. 4, 5 and 6. It is worth noting that during docking studies no fixed distances are imposed to the complexes. Nevertheless, the results are in good agreement with distances obtained by 2D ROESY NMR spectra. Observable differences between the complexes can be noticed, where the ligand orientation upon binding inside the host molecule being one of the most relevant aspect. A detailed description of the main topological features of the ligand- α-CD complexes is given below.

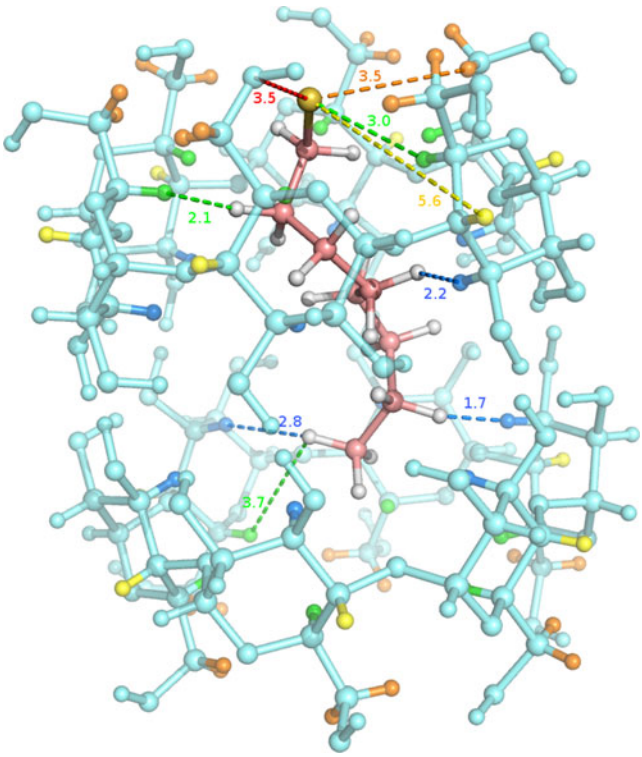

Fig. 4 Inclusion complex between 1-octanethiol and the head-to-head α-cyclodextrin dimer. Hydrogens H-3, H-4, H-5 and H-6 are depicted in *marine blue*, *yellow*, *green* and *orange balls*, respectively. The guest carbons are shown in *pink balls and sticks*, sulphur atom is shown in *dark yellow*, while the cyclodextrins dimer skeleton is shown in *cyan ball and stick*. *Dash lines* correspond to distances between selected atoms

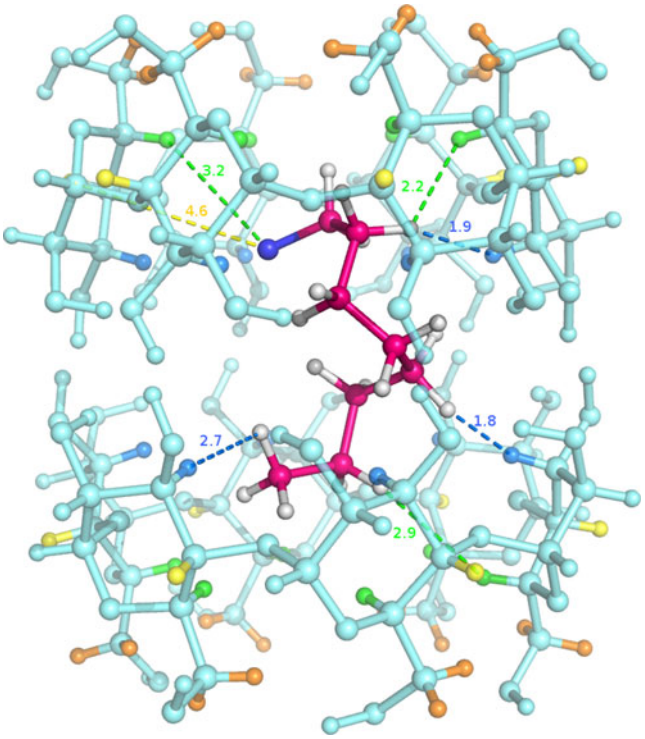

Fig. 5 Inclusion complex between 1-octylamine and the head-to-head α-cyclodextrin dimer. Hydrogens H-3, H-4, H-5 and H-6 are depicted in *marine blue*, *yellow*, *green* and *orange balls*, respectively. The guest carbons are shown in *magenta balls and sticks*, nitrogen atom is shown in blue, while the cyclodextrins dimer skeleton is shown in *cyan ball and stick*. *Dash lines* correspond to distances between selected atoms

Figure 4 shows the α-CD/$C_8H_{17}SH$ complex. The conformation obtained by molecular modeling was in agreement with the ROESY results. The thiol moiety is oriented toward the primary rim displaying interactions with H-5 and H-6 protons, and with the primary OH-6 (3.5 Å) and H-4 proton (5.6 Å). Bulk methylene groups interact with H-2, H-3 (2.2 Å) and H-5 (2.1 Å) protons and also with H-4. The methyl group at the end of the guest molecule is oriented toward the secondary rim, interacting with H-3 (2.8 Å) and H-5 (3.7 Å). The ligand remains mainly inserted in one of the cyclodextrin of the dimer.

For the 2α-CD/$C_8H_{17}NH_2$ complex, the amine moiety interacts with H-4 (4.6 Å) and H-5 (3.2 Å). Bulk methylene groups interact with H-3 (1.9 Å) in one cyclodextrin and (1.8 Å) in the second cyclodextrin, also they interact with H-5 (2.2 Å) and H-6 (2.9 Å). The methyl group interacts with H-3 of the second cyclodextrin (2.7 Å) (see Fig. 5). In this

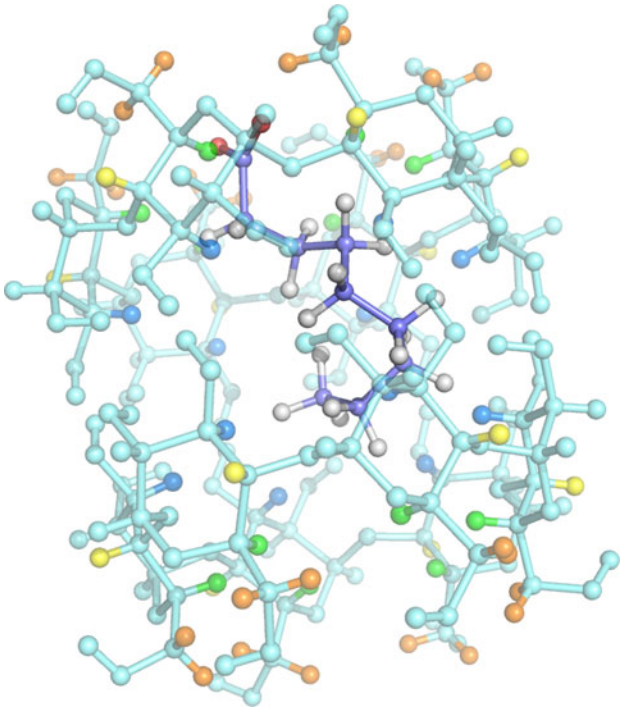

Fig. 6 Inclusion complex between 1-nonanoic acid and the head-to-head α-cyclodextrin dimer. Hydrogens H-3, H-4, H-5 and H-6 are depicted in *marine blue*, *yellow*, *green* and *orange balls*, respectively. The guest carbons are shown in violet ball and sticks, carboxylic oxigens are shown in *red balls and sticks*, while the cyclodextrins dimer skeleton is shown in *cyan ball and stick*. *Dash lines* correspond to distances between selected atoms

complex, the 1-octylamine remains less elongated than its thiol counterpart.

For the complex formed between1-nonanoic acid and α-CD, the -COOH moiety interacts mainly with H-6 (3.7 Å), the primary OH-6 group (3.2 Å) and with H-4 atom (5.1 Å). The bulk methylene groups interact with H-3 and H-5 at (2.2 Å) and (1.9 Å), respectively. The methyl group of the ligand interacts with H-3 (2.2 Å) and H-5 (3.9 Å). However, as docking calculations do not take into account solvent effects it is possible to find less elongated structures for the ligand.

Conclusions

The structural elucidation of 2α-CD/$C_8H_{17}SH$, 2α-CD/$C_8H_{17}NH_2$ and 2α-CD/$C_8H_{17}COOH$ by NMR spectroscopy and molecular modeling has been achieved. NMR nuclear Overhauser effect (NOE) signals confirmed total inclusion of guests to form complexes with α-CD. By means of ^1H NMR using 2D ROESY method it was possible to elucidate close interactions between the aliphatic monofunctional molecules and two α-CD molecules interacting as a dimer, forming supramolecular host-guest complexes. The docking methods unambiguously allowed us to determine the geometrical inclusion parameters of guests on the different α-CD dimer and they are in complete agreement with the determined signal assignment by ROESY experiments.

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