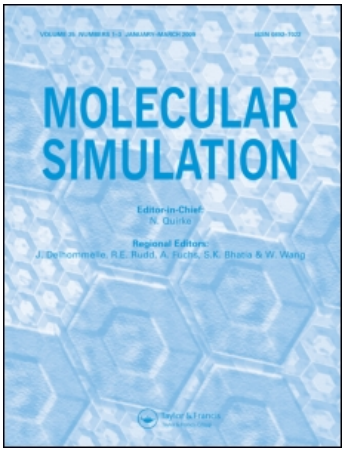

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Quantum mechanical study of the inclusion process of adamantanol isomers by l-tryptophan-modified-β-cyclodextrin

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Quantum mechanical study of the inclusion process of adamantanol isomers by L-tryptophan-modified-β-cyclodextrin

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The complexation processes of 1 and 2-adamantanol with L-tryptophan-β-cyclodextrin have been studied using *ab initio* Hartree–Fock and density functional theory levels. For the host: guest inclusion processes, the *up* mode with the OH group of the alcohol oriented towards the secondary rim, is found to be in qualitative agreement with the experimental finding. A molecular recognition mechanism is proposed based on the host: guest relative dipole orientation. For the complex with the 2-Ada isomer the host and guest the dipoles are parallels favoring the interaction energy and. This mechanism can explain the small energy difference for the processes involving the adamantanol isomers and modified cyclodextrins.

Keywords: Adamantanol isomers; Inclusion process; β-Cyclodextrin; Molecular recognition

1. Introduction

The supramolecular chemistry is certainly one of the most challenging and interesting area of the modern science [1,2]. The systems and processes in this field account mainly for intermolecular interactions, responsible for the formation and stabilization of the supramolecular structures. In this context, the molecular recognition must play an important role in the interaction mechanism of chemical species. The natural cyclodextrins (CDs) are important representatives of supramolecular blocks [3], used in the construction of pseudorotaxanes and poly-pseudorotaxanes with interesting properties and applications [3,4]. The common α, β and γ-CDs are cyclic oligosaccharides with six, seven and eight α-1,4-linked D-glucopyranose units, respectively. The CDs geometries are often described as a torus, but are somewhat more realistically pictured as a shallow truncated cone with a cavity of suitable size to accommodate most of the chemical species [5]. The wider and narrower rims are lined with the secondary and primary hydroxyls groups respectively, making the CD exterior fairly hydrophilic compared to the interior of the cavity [6].

Complexation of chemical molecules by CDs is governed by several intermolecular forces between host and receptor (guest), such as dipole–dipole, dispersion (Van der Waals) and hydrogen-bonding [7,8]. In addition the molecular recognition processes are usually accompanied by conformational changes or strain relief of the CD molecule due to the release to the bulk solution of water molecules initially included in the cavity. Hydrophobic forces for the exclusion of nonpolar solute from the bulk water are also important for the overall host–guest binding [7]. Much effort has been paid to elucidate, on molecular basis, the significance of the distinct contribution to the inclusion compound stability. Among the various techniques used in this sense, NMR is the most widely applied for determination of molecular structure in solution [9] with an increasing importance of fluorescence spectroscopy for the measurement of thermodynamic quantities [10–14]. Fluorescence is sensitive to changes in the polarity of the microenvironment and this can cause

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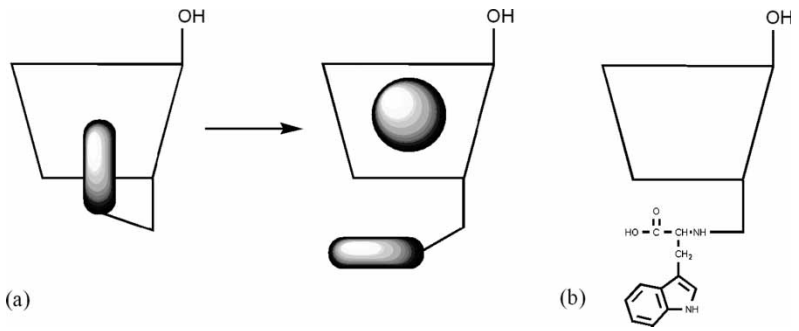

Figure 1. (a) scheme of self- and guest-inclusion processes; (b) structure of the L-Trp-β-CD.

fluorescence of active species to be shifted to longer or shorter wavelengths (more or less polar environment) or to changes in the quantum yield.

Substitution of one hydroxyl group of the macrocycle induces substantial changes and additional or more specific interactions will therefore occur with guests. This was used as a resource to modify the CDs spectroscopic transparency: by covalently attaching a spectroscopically active moiety, complexation events can result in changes in UV absorption and fluorescence emission spectra of the modified CD [10–14]. If the appending moiety tends to self-inclusion in the cycle, changes in the self-inclusion behaviour of this type of molecule–induced by inclusion of an external guest–enable the optical detection of spectroscopically inactive guests, and the modified CD is thus acting as a chemosensor [13–14].

The molecular recognition behaviour of β-CD derivatives that possess a spectroscopic probe was reported and their complexation behaviours were investigated (see [13–16] and references therein). A modified β-CD (figure 1(b)) bearing a L-tryptophan moiety (L-Trp-β-CD) as a probe has been demonstrated to recognize minimal structural differences in a set of guest alcohols examined on the basis of their size/shape rigidity and hydrophobicity [13]. The self–and guest–inclusion behaviour of L-Trp-β-CD were monitored by fluorescence and circular dichroism spectroscopy and fluorescence lifetime measurement. In the formation of 1:1 host–guest complexes experiments revealed that part of the tryptophan probe is originally self-included in the CD cavity but is driven out of the cavity upon guest inclusion. It was also established that L-Trp-β-CD recognizes not only size and hydrophobicity of guests but also their enantiomeric and geometrical isomers. Among the alcohols analyzed in [13], the highest stability constants values (Ks) were obtained for 1-adamantanol (1-Ada, Ks = 4730) and 2-adamantanol (2-Ada, Ks = 13,900) as in these cases size/shape-matching leads to optimum distances between the adamantanol molecular surface and the interior of the CD cavity, affording strong hydrophobic interactions. The isomer selectivity for 2-Ada vs. 1-Ada amounts to ~3, indicating that L-Trp-β-CD can recognize such a minor difference in substitution position. It was suggested that the formation of hydrogen bonds with the secondary hydroxyls of CD is more favourable for the OH on the 2 than on the 1-position of adamantanol [13].

From the large set of alcohols forming complexes with L-Trp-β-CD that was experimentally analyzed in [13], the understanding of the way the molecular recognition and selectivity of L-Trp-β-CD would take place and would be reflected by energy and structures is a quite challenging task. Therefore in the present article quantum mechanical *ab initio* and density functional theory (DFT) calculations were carried out for the complexation processes of 1 and 2-Ada with L-Trp-β-CD modified CDs and the outcomes analyzed with regard to the molecular recognition mechanism.

2. Methodology

The geometries for the 1-Ada, 2-Ada (figure 2(a)) and L-tryptophan-modified β-CD (L-Trp-β-CD, figure 1(b)) were fully optimized in gas phase at the *ab initio* HF/3-21G level of theory. Two inclusion processes were

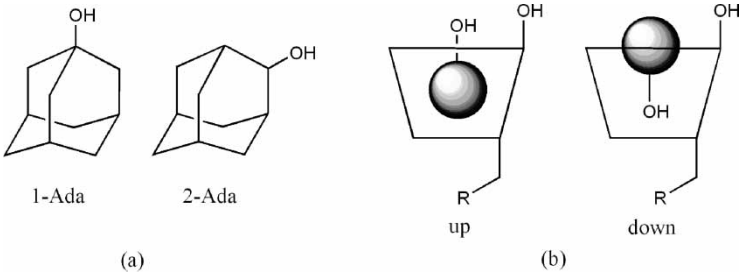

Figure 2. Structures of the adamantanol isomers (a) and representation of the two inclusion arrangements analyzed (b).

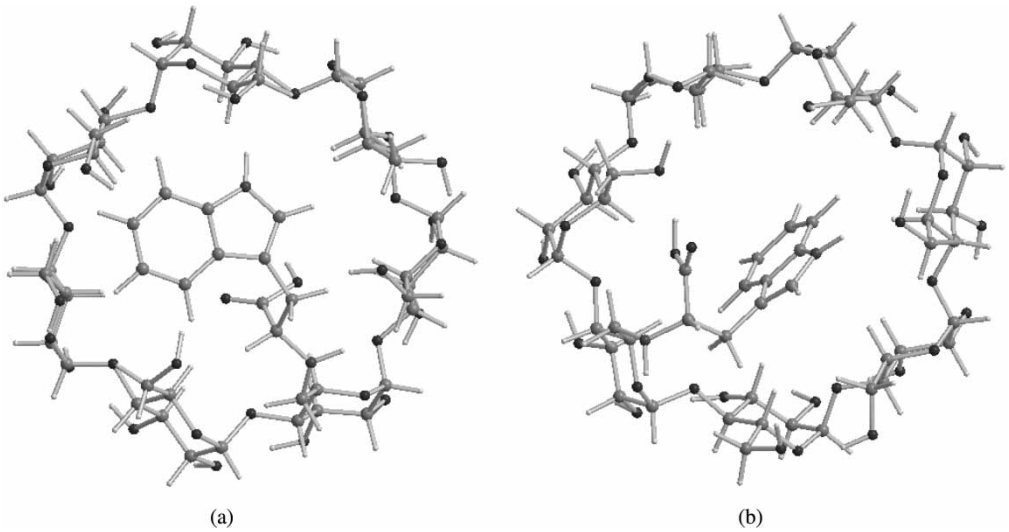

Figure 3. HF/3-21G optimized geometries for the free L-Trp-β-CD (a) and its self-included compound (b).

investigated, considering the guest–host inclusion (at the *up* and *down* arrangements, figure 2(b)) and the CD self-inclusion. The initial guess for the structures of the inclusion compounds were taken from reference [17] with the substitution of one primary hydroxyl of β-CD by a tryptophan moiety (figure 1(a)) and then optimized at the HF/3-21G level without any constraint. The optimizations were performed in Cartesian coordinate using the modified GDIIS algorithm [18] which is recommended for use with large molecules. Single point energy calculations were also carried out at the BLYP/3-21G//HF/3-21G level of theory in order to account for the electronic correlation contribution to the binding energy [19–20].

All the calculations were carried out using the Gaussian 03 Revision B.05 suit program [21].

3. Results and discussion

3.1 Structural analysis

Considering firstly the free guests, we found that the isomer 2-Ada was less stable than 1-Ada in gas phase by 1.53 (HF/3-21G) and 1.90 kcal/mol (BLYP/3-21G//HF/3-21G). The calculated dipole moments were 1.872 (1-Ada) and 1.672 D (2-Ada) (HF/3-21G) and 1.459 (1-Ada) and 1.376 D (2-Ada) (BLYP/3-21G//HF/3-21G) showing that in solution of polarizable solvent the isomer 1-Ada should also be more stabilized. The HF/3-21G optimized geometries for the free CD (L-Trp-β-CD) and its self-inclusion compound (L-Trp-β-CD-*si*) are depicted in figure 3. Some structural parameters are reported in table 1. The average hydrogen bond distances involving the secondary hydroxyl r(H...O) were equal to 1.82 ± 0.07 Å (free CD) and 1.81 ± 0.05 Å (self-inclusion compound). The angle defined by the consecutive glycoside oxygens α(O—O—O) was found to be 128 ± 1 and 128 ± 4° for the free molecule and its self-included compound, respectively, which are close to the expected value for a perfect heptagon: $\alpha = 128°$. The average value calculated for the dihedral angles τ(O—O—O—O) were −0.0 ± 11 and 0.2 ± 15°, respectively. The values of α and τ are close to those expected for a completely symmetric structure, however the large standard deviations, mainly for τ, implies the structures can not be regarded as strictly symmetrical [22]. The improvement of basis-set to 6-31G does not cause any significant change in the geometries that could justify the extra computational effort then this will not be discussed in detail here. The only point which deserves attention is the hydrogen bond on the secondary hydroxyl rim that was slightly longer at HF/6-31G level. For the β-CD parent compound the following values were found (HF/3-21G): r(H...O) = 1.79 ± 0.02 Å, $\alpha = 128.4 \pm 0.9°$ and $\tau = 3 \pm 7°$ [17]. The L-tryptophan substituent interacts with the CD moiety

Table 1. Structural parameters calculated for the modified CD in the free form and its inclusion compounds. Average values over the seven glucose units are reported.

	$\alpha(O-O-O)$/°	$\tau(O-O-O-O)$/°	$R(H...O)$/Å	$r(O...O)$/Å
L-Trp-β-CD	128 ± 1	−0.0 ± 11	1.82 ± 0.07	2.79 ± 0.06
L-Trp-β-CD-*si*	128 ± 4	0.2 ± 15	1.81 ± 0.05	2.78 ± 0.04
1-Ada-*up*	128 ± 3	−0.2 ± 15	1.8 ± 0.1	2.8 ± 0.1
2-Ada-*up*	128 ± 2	−0.0 ± 13	1.9 ± 0.1	2.8 ± 0.1
1-Ada-*down*	128 ± 4	0.0 ± 11	1.9 ± 0.1	2.8 ± 0.1
2-Ada-*down*	128 ± 2	0.0 ± 11	1.9 ± 0.1	2.8 ± 0.1

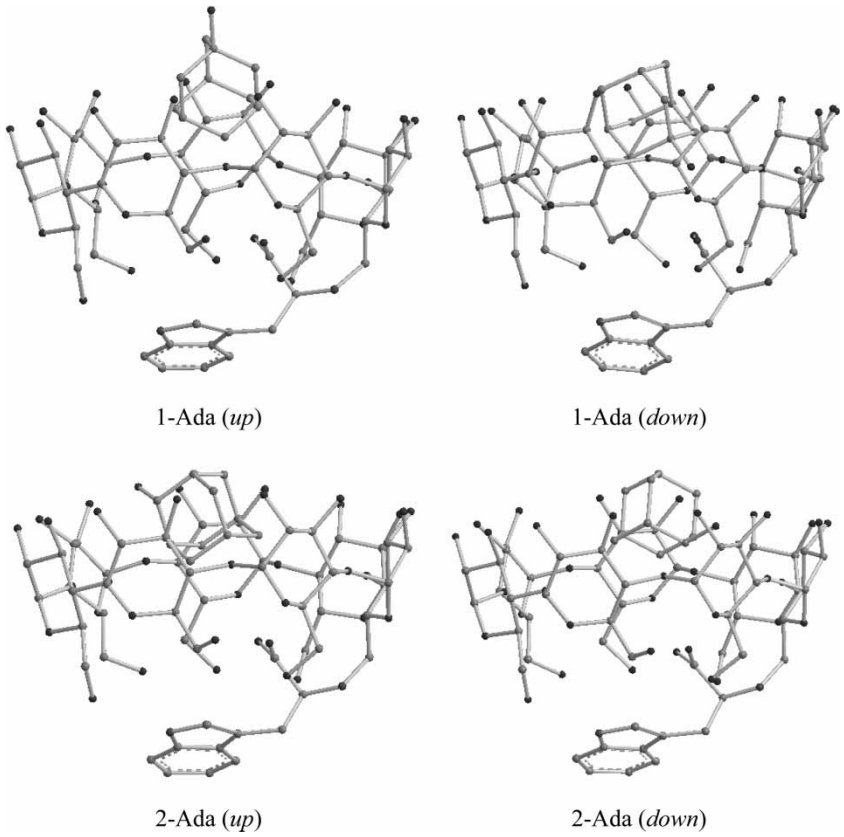

Figure 4. HF/3-21G optimized geometries for the inclusion compounds of L-Trp-β-CD with 1 and 2-Ada in the *up* and *down* arrangements. The hydrogen atoms were omitted in the figure.

somehow. For the free L-Trp-β-CD a short hydrogen bond was found between the tryptophan group (N—H) and the primary hydroxyl. The distance N—H...O was only 1.894 Å with the ∠N—H...O equal to 162.76°. The carboxyl group of L-Trp was located inside the cavity being stabilized by a hydrogen bond with the primary hydroxyl of CD (the distance O—H(CD)...OH(L-Trp) was 1.821 Å). For the self-inclusion compound the N—H...O distance was 1.939 Å and a very short hydrogen bond was observed with the O—H(L-Trp)...OH(CD) distance found to be 1.593 Å. The later was 1.66 Å at HF/6-31G level and the others hydrogen bonds noted before were longer (~2 Å) at this level of theory. For the native CDs the average O...O distance for the secondary hydroxyls were found to be 3.062 (α-CD), 2.772 (β-CD) and 2.751 Å (γ-CD) (HF/3-21G) in good accordance with the experimental data, 3.230, 2.850 and 2.823 Å for α-, β- and γ-CD, respectively [17].

The HF/3-21G optimized geometries for the inclusion compounds with 1-Ada and 2-Ada at the *up* and *down* arrangements are depicted in figure 4. From the structural parameters given in table 1 it can be seen that the geometry of CD is kept almost unchanged upon inclusion that can be understood considering the small size of the guest molecules. For the *up* mode only long range Van der Waals interactions were found between the guest and host molecules and for the *down* structures the intermolecular hydrogen bonds play an important role on the complex stabilization. For the *down* inclusion compound with 1-Ada isomer the hydroxyl group of the alcohol is involved in two hydrogen bonds, one very strong with the carboxyl group of L-tryptophan (r(H...O) = 1.522 Å) and the other of medium intensity with the bridging oxygen atoms of CD (r(H...O) = 1.954 Å). For the 2-Ada isomer only one intermolecular hydrogen bond was assigned between the hydroxyl group and the glycosyl oxygen with the r(H...O) distance equal to 1.878 Å. The center of mass (cm) distance (r(cm...cm)) was strongly dependent on the host–guest arrangement. For the *up* mode of inclusion the r(cm...cm) were 3.98 and 2.89 Å for 1-Ada and 2-Ada isomers respectively. The deeper inclusion of 2-Ada alcohol will be discussed further based on the energetic analysis. For the *down* structures the opposite was found with the 1-Ada located in deeper position on the CD cavity due mainly to the intermolecular hydrogen bonds. The r(cm...cm) for the *down* arrangement were 2.61 (1-Ada) and 3.11 Å (2-Ada). From figure 4 it can be seem that the optimized *down* structures might in fact be called *middle* orientation, with the OH group pointing laterally inside the cavity.

3.2 Energetic analysis

The chemical equation used to calculate the reaction energy is expressed in equation (1). For the self inclusion process the reaction energies (ΔE) were 4.491 kcal/mol at

Table 2. Stabilization energies (ΔE) for the inclusion compounds with adamantanol isomers.

	ΔE/kcal mol^{-1}				ΔG/kcal mol^{-1}	
	HF/3-21G		*BLYP/3-21G//HF/3-21G*		*Expt.*[†]	
	1-Ada	*2-Ada*	*1-Ada*	*2-Ada*	*1-Ada*	*2-Ada*
up	−5.739	−7.674	−8.862	−11.64	–	–
down	−28.49	−11.22	−36.84	−18.92		
–					−5.019	−5.664

[†] From Ref. [12].

HF/3-21G and 6.380 kcal/mol at BLYP/3-21G//HF/3-21G level showing that this process is unfavorable in gas phase from an energetic point of view. At the HF/6-31G level ΔE was 4.66 kcal/mol supporting the previous lower level result. The role of basis-set on the energy change of this intramolecular process was also analyzed by single point calculations at BLYP/6-31G//HF/3-21G and BLYP/6-31G(d,p)//HF/3-21G levels. The ΔE values were raised from 4.49 (HF/3-21G) to 14.2 kcal/mol (BLYP/6-31G(d,p)//HF/3-21G) with the equilibrium position shifted toward the non-included compound as the basis-set is improved. A similar level of theory has been applied recently to account for hydration energy of α-CD [19,20] with the results found in perfect accordance with the experimental data, and then the energies reported here as relative quantities can be taken as reliable enough considering the size of the systems studied.

$$n\text{-Ada} + \text{L-Trp-}\beta\text{-CD} \rightarrow [n\text{-Ada}\ldots\text{L-Trp-}\beta\text{-CD}]. \quad (1)$$

Experimentally, there is evidence based on the analysis of the fluorescence spectra that the L-Trp residue is within the CD cavity [13] and more recently [14] a similar intramolecular process was reported for azobenzene modified CDs from the analysis of induced circular dichroism spectrum. Then it is supposed that the driving force for this kind of process might be attributed to the hydrophobic effect. In aqueous medium the intramolecular inclusion might be favored due to the increasing of reaction entropy upon inclusion (*dewetting* process) and this should play a minor role for inclusion process in non-polar solvent. In reference [14] the authors observed a gradual exclusion of azobenzene side group from CD cavity with the increasing of the ratio of DMSO in aqueous solution. This was analyzed as a competitive process involving the guest and the solvent molecules; furthermore, it can also be viewed as a consequence of the hydrophobic effect.

The *ab initio* stabilization energies (ΔE) calculated for the inclusion processes of the isomers 1-Ada and 2-Ada at *up* and *down* arrangements according to equation (1) are given in table 2. For both alcohols the *down* mode of inclusion was found to be more favorable in gas phase, with the extra stability assigned to the intermolecular hydrogen bonds. The *down* inclusion compound with the 1-Ada molecule is strongly stabilized ($\Delta E = -36.84$ kcal/mol at the BLYP//HF level) due to the two hydrogen bonds with the CD ring. For the complex with 2-Ada only one medium intensity intermolecular hydrogen bond was obtained and consequently the stabilization energy was lower: −18.92 kcal/mol (BLYP//HF). Thus for the *down* arrangement the process for 1-Ada isomer is ∼17 kcal/mol more favorable at both levels of theory used if compared with the same reaction for the 2-Ada derivative. From the experiment described in reference [13] it was recognized that the alcohol's hydroxyl is located outside the CD cavity near the secondary rim as our *up* arrangement even though no structures were reported. The experimental data also showed that the inclusion process with the 2-Ada presented lower reaction Gibbs free energy (ΔG were −5.019 and −5.664 kcal/mol for 1-Ada and 2-Ada, respectively). From the energy values in table 2 it can be seem that the stabilization energy calculated for the *up* mode of inclusion, having the alcohol OH group of the guest oriented towards the secondary rim of the CD, were −5.739 and −7.674 kcal/mol (HF/3-21G) and −8.862 and −11.64 kcal/mol (BLYP/3-21G//HF/3-21G) respectively for 1-Ada and 2-Ada, with the formation of the inclusion compound with 2-Ada isomer being more favorable at both levels of theory. These results are in agreement with the experimental trend of ΔG for the inclusion processes [13]. It is worth mentioning that the reduced basis-set used here might affect the absolute values for stabilization energies reported in table 2. Following the trend found for the self-inclusion process discussed previously, it is expected higher values for ΔE with the enhancement of the basis set, but nevertheless the relative stability order should be maintained. Thus the energetic analysis carried out in the present work and also the proposal discussed in the next paragraphs, must be viewed on a qualitative sense, making clear the need to improve the level of theory to account for quantitative description of the whole inclusion process.

Experimentally the greater stabilization of 2-Ada inclusion compound was attributed to the possibility of formation of intermolecular hydrogen bond between 2-Ada and the CDs hydroxyls [13]. These same substrates were used as guest in the inclusion processes reported recently in reference [14] where the 2-Ada was also found to yield more stable complex with a different modified CD. An interesting point from the analysis reported in references [13,14] is that the experimental proposal for the structures of the inclusion compounds of 1-Ada and 2-Ada

with two distinct modified CDs are completely different even though the stabilization free energies are similar. For the processes with the L-Trp-β-CD [14] the ΔG were -5.019 (1-Ada) and -5.664 kcal/mol (2-Ada) and the alcohol hydroxyl group is supposed to be located outside of the CD cavity near the secondary hydroxyl side (*up* arrangement). In the inclusion compounds with azobenzene modified β-CD [14] the ΔG were -5.545 (1-Ada) and -7.003 kcal/mol (2-Ada) and in this case the OH group of the 2-Ada isomer is proposed to be inside the cavity toward the primary hydroxyl side of CD (*down* structure). Moreover for the 1-Ada a kind of *middle* arrangement is proposed, similar our *down* geometry for 1-Ada isomer (figure 4), with the azobenzene substituent changing the configuration toward the *Z* form. In both cases the greater stabilization of the inclusion compound with the 2-Ada was attributed to the intermolecular hydrogen bond between the primary or secondary hydroxyl groups of CD and the alcohol. From the structures investigated in the present work intermolecular hydrogen bonds were found only for the *down* mode of inclusion and do not involve the hydroxyl groups of CD. In this case the host–guest intermolecular interactions favor the 1-Ada isomer that is not supported by the experimental thermodynamic data [13,14]. Then it can be said that only the *up* structures must be presented in aqueous medium with the process for 2-Ada being more favorable. The observed preference for the *up* complex in aqueous solution might be attributed to the possibility of formation of hydrogen bonds with the water molecules from the solvent. This hypothesis has already been considered in our previous paper [23] for the CH_3–Hg–Cl: α-CD inclusion complex. In that case the guest–solvent interaction played a primary role to the stability of the inclusion compound.

It is well known that several weak forces are responsible for the host–guest stability [7,8] and their differences can define the molecular recognition factor [24]. Furthermore, the quantitative description of these weak interactions at a molecular level is a quite difficult task; however a qualitative analysis can be done in order to get insight on their importance for the inclusion processes. This is the basis of the size/shape-fit concept. For the process studied in the present work the actual molecular recognition

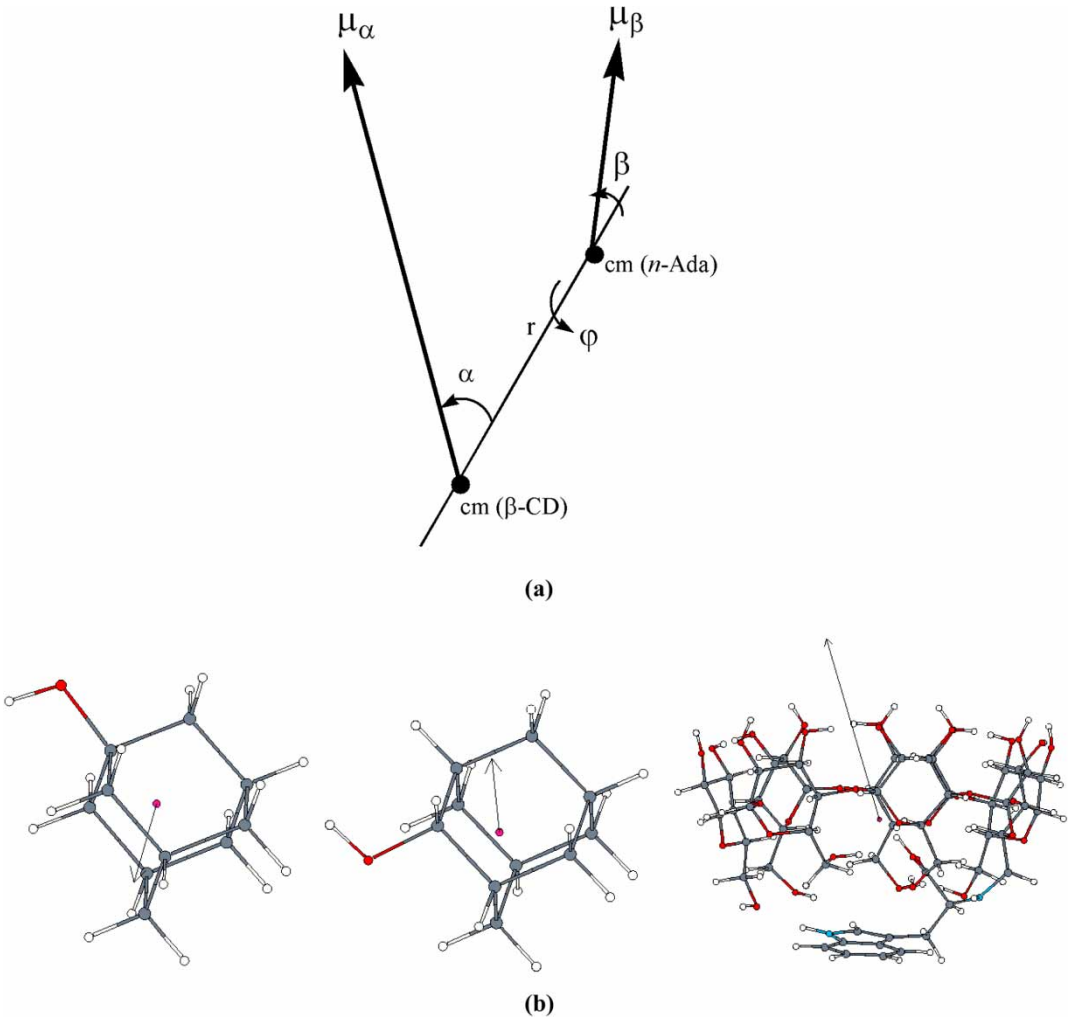

Figure 5. (a) definition of the parameters for the relative dipole moment orientation; (b) electric dipole moment vector calculated for the molecules studied in the present work (BLYP/3-21G//HF/3-21G).

Table 3. Parameters of the relative orientation of the dipole moment vectors calculated at BLYP/3-21G//HF/3-21G.

	up		*down*	
	1-Ada	*2-Ada*	*1-Ada*	*2-Ada*
μ_{Ada}/D	1.446	1.368	1.419	1.503
μ_{CD}/D	5.538	5.444	5.466	6.036
r(cm. . .cm)/Å	3.980	2.893	2.613	3.106
α/°	19.04	9.026	18.50	40.85
β/°	147.8	45.35	30.23	158.5
φ/°	85.08	73.47	215.9	163.1
χ	−1.61	1.36	1.77	−1.18

mechanism is still unclear, although the host–guest orientation could be deduced [13]. Then an attempt to propose a molecular recognition mode was done here based on the dipole–dipole interaction. The importance of this kind of interaction to the general host–guest complex stabilization was first raised by Sakurai and collaborators [25]. The classical dipole–dipole potential energy is described by equation (2) [26–28], where μ is the dipole moment calculated at the quantum mechanical level of theory and the parameters r, α, β and φ define the relative orientation of the dipole vectors (figure 5(a)).

$$U_{\mu_\alpha\mu_\beta} = -\frac{\mu_\alpha\mu_\beta}{4\pi\varepsilon_0 r^3}\chi \therefore$$
$$\chi = (2\cos\alpha\cos\beta - \sin\alpha\sin\beta\cos\varphi). \quad (2)$$

The calculated values for the dipole moments and orientation parameters for the inclusion compounds are reported in table 3. Figure 5(b) shows the dipole vector on the isolated molecules and in figure 6 the relative orientations of the electric dipoles on the inclusion complexes are shown. The dipole moment values and orientations were calculated for the host and guest molecules in the geometries they present on the inclusion

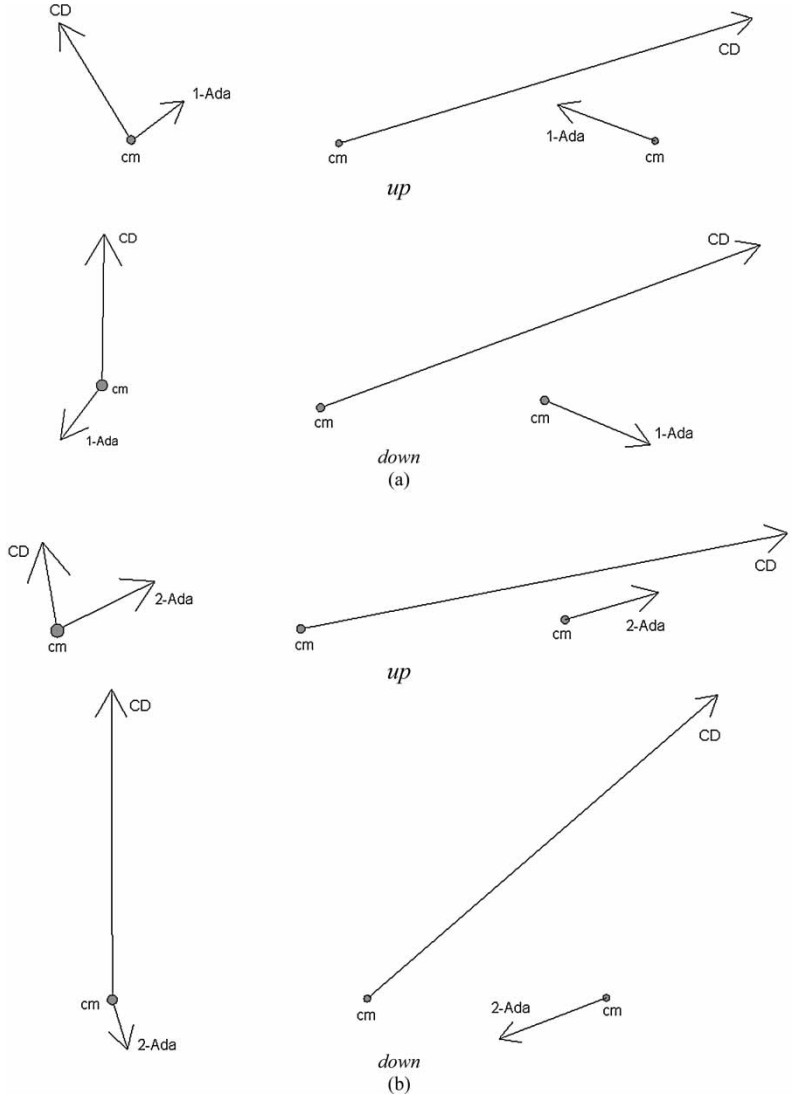

Figure 6. Relative orientations of the molecular dipole moments for the host and guest molecules on the inclusion complexes at *up* and *down* modes (BLYP//HF data). The centers of masses (cm) are along the *Z* axis and two different views are shown: *YX* plane (left) and *YZ* plane (right); (a) 1-Ada and (b) 2-Ada.

compound structure. The figure 6 and values in table 3 show that dipoles orientation are distinct for both molecules and the main difference is found for the β angle which defines the dipole orientation of the alcohol (figure 5(a)). In the last lines of table 3 we report the calculated values for χ (equation (2)) where it can be seen that the dipole orientation in the complexes with 1-Ada (*up*) and 2-Ada (*down*) (the least stable forms) lead to repulsive dipole–dipole potential and for the inclusion compound with the isomer 2-Ada (*up*) and 1-Ada (*down*) (the most stable forms) it is attractive. For the *down* structures the dipole–dipole contribution should be less important once the driving force for this inclusion mode is the intermolecular hydrogen bond. However for the *up* mode where only Van der Waals forces are present the dipole–dipole interaction might play a major role for such polar molecules. In this case the orientation for the isomer 2-Ada is favorable (figure 6 and data on table 3), justifying the experimental finding [13]. This result might be useful to understand the molecular recognition mechanism involving the adamantanol isomers and the modified β-CD. In addition, it gives a molecular picture of the qualitative size/shape relationship which has been proved to play a primary role in the complexation behavior of inclusion compounds with modified CDs [13,14].

4. Conclusion

In the present study *ab initio* HF and DFT calculations for the modified L-tryptophan-β-CD host, the 1 and 2-Ada guests and their host: guest inclusion complexes were performed with the aim of understanding the recognition mechanism at molecular level. In gas phase at the *ab initio* level of theory with the improved basis-set up to 6-31G (d, p), the self-inclusion of the L-tryptophan moiety was not energetically favourable relative to the capped one, which suggests that the driving forces for such process might be due to the hydrophobic effect that can not be accounted for in gas phase. Two distinct host: guest inclusion modes were analyzed with the OH group of the guest oriented towards the secondary rim (*up*) and towards primary rim (*down*). The *down* mode is favourable for both isomers in gas phase due to the intermolecular hydrogen bonds, however the *up* arrangement is expected to be preferred in aqueous solution due to the guest–solvent hydrogen bond interactions. In the *up* mode the 2-Ada inclusion is favoured, adding to the experimental evidence, however the absence of intermolecular hydrogen bond in our simulated complexes would not support the suggestion that the higher stability of 2-Ada complex may be attributed to the formation of efficient host–guest hydrogen bonding interaction. A new proposal was described here based in the host: guest dipole orientation and successfully used to explain the molecular recognition factor found for adamantanol isomers. In the *up* mode, where no hydrogen bond was observed this dipole–dipole interaction may play a primary role. For the 2-Ada isomer the dipoles are parallels making the potential attractive and for the 1-Ada they are antiparallels and the dipole–dipole potential is repulsive. This may explain the small difference between the interaction energy for the isomers in the direction of the 2-Ada one.

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References

[1] J.-M. Lehn. Supramolecular chemistry: from molecular information towards self-organization and complex matter. *Rep. Prog. Phys.*, **67**, 249 (2004).
[2] H.E. Toma. Supramolecular chemistry and technology. *An. Acad. Bras. Cienc.*, **72**, 5 (2000).
[3] S.A. Nepogodiev, J.F. Stoddart. Cyclodextrin-based catenanes and rotaxanes. *Chem. Rev.*, **98**, 1959 (1998).
[4] G. Wenz, B.-H. Han, A. Muller. Cyclodextrin rotaxanes and polyrotaxanes. *Chem. Rev.*, **106**, 782 (2006).
[5] J. Szejtli. *Encyclopedia of Nanoscience and Nanotechnology*, **2**, 283 (2004).
[6] K.A. Connors. The stability of cyclodextrin complexes in solution. *Chem. Rev.*, **97**, 1325 (1997).
[7] K.B. Lipkowitz. Applications of computational chemistry to the study of cyclodextrins. *Chem. Rev.*, **98**, 1829 (1998).
[8] L. Liu, Q.-X. Guo. Use of quantum chemical methods to study cyclodextrin chemistry. *J. Incl. Phenom. Macrocycl. Chem.*, **50**, 95 (2004).
[9] H.-J. Schneider, F. Hacket, V. Rüdiger. NMR studies of cyclodextrins and cyclodextrin complexes. *Chem. Rev.*, **98**, 1755 (1998).
[10] Y. Xu, M.E. McCarroll. Fluorescence anisotropy as a method to examine the thermodynamics of enantioselectivity. *J. Phys. Chem. B*, **109**, 8144 (2005).
[11] F. D'Anna, S. Riela, M. Gruttadauria, P. Lo Meo, R. Noto. A spectrofluorimetric study of binary fluorophore-cyclodextrin complexes used as chiral selectors. *Tetrahedron*, **61**, 4577 (2005).
[12] Y. Liu, Y. Song, Y. Chen, Z.-X. Yang, F. Ding. Spectrophotometric study on the controlling factor of molecular selective binding of dyes by bridged bis(β-cyclodextrin)s with diselenobis(benzoyl) linkers. *J. Phys. Chem. B*, **109**, 10717 (2005).
[13] Y. Liu, B.-H. Han, S.-X. Sun, T. Wada, Y. Inoue. Molecular recognition study on supramolecular systems. 20. Molecular recognition and enantioselectivity of aliphatic alcohols by L-tryptophan-modified β-cyclodextrin. *J. Org. Chem.*, **64**, 1487 (1999).
[14] Y. Liu, Y.-L. Zhao, H.-Y. Zhang, Z. Fan, G.-D. Wen, F. Ding. Spectrophotometric study of inclusion complexation of aliphatic alcohols by β-cyclodextrins with azobenzene tether. *J. Phys. Chem. B*, **108**, 8836 (2004).
[15] A. Matsushita, T. Kuwabara, A. Nakamura, H. Ikeda, A. Ueno. Guest-induced colour changes and molecule-sensing abilities of p-nitrophenol-modified cyclodextrins. *J. Chem. Soc. Perkin Trans. 2*, 1705 (1997).
[16] R. Corradini, A. Dossena, G. Galaverna, R. Marchelli, A. Panagia, G. Sartor. Fluorescent chemosensor for organic guests and copper(II) ion based on dansyldiethylenetriamine-modified β-cyclodextrin. *J. Org. Chem.*, **62**, 6283 (1997).
[17] M.A.F.O. Britto, C.S. Nascimento, Jr., H.F. Dos Santos. Structural analysis of cyclodextrins: a comparative study of classical and quantum mechanical methods. *Quim. Nova*, **27**, 882 (2004).
[18] Ö. Farkas, H.B. Schlegel. Methods for optimizing large molecules. II. Quadratic search. *J. Chem. Phys.*, **111**, 10806 (1999).

[19] C.S. Nascimento, Jr., H.F. Dos Santos, W.B. De Almeida. Theoretical study of the formation of the α-cyclodextrin hexahydrate. *Chem. Phys. Lett.*, **397**, 422 (2004).
[20] C.S. Nascimento, Jr., C.P.A. Anconi, H.F. Dos Santos, W.B. De Almeida. Theoretical sudy of the α-cyclodextrin dimer. *J. Phys. Chem. A*, **109**, 3209 (2005).
[21] M.J. Frisch, *et al.* Gaussian 03 (Revision B.05), Gaussian, Inc., Wallingford CT (2003).
[22] V.G. Avakyan, V.B. Nazarov, M.V. Alfimov, A.A. Bagatur'yants, N.I. Voronezheva. The role of intra- and intermolecular hydrogen bonds in the formation of β-cyclodextrin head-to-head and head-to-tail dimers. The results of *ab initio* and semiempirical quantum-chemical calculations *Russ. Chem Bull. Int. Ed.*, **50**, 206 (2001).
[23] H.F. Dos Santos, H.A. Duarte, R.D. Sinisterra, S.V. De Melo-Mattos, L.F.C. De Oliveira, W.B. De Almeida. Quantum-mechanical study of the interaction of α-cyclodextrin with methyl mercury chloride. *Chem. Phys. Lett.*, **319**, 569 (2000).
[24] K.B. Lipkowitz, S. Raghothama, Jia-na Yang. Enantioselective binding of tryptophan by alpha-cyclodextrins. *J. Am. Chem. Soc.*, **114**, 1554 (1992).
[25] M. Sakurai, M. Kitagawa, H. Hoshi, Y. Inoue, R. Chujo. A molecular-orbital study of cyclodextrin (cyclomaltooligosaccharide) inclusion complexes. 3. Dipole-moments of cyclodextrins in various types of inclusion complex. *Carbohydr. Res.*, **198**, 181 (1990).
[26] A. Hinchliffe. *Molecular Modelling for Beginners*, Wiley, UK (2003).
[27] A.R. Leach. *Molecular Modelling: Principles and Applications*, 2nd ed., Pearson—Prentice Hall, UK (2001).
[28] W.B. De Almeida. An investigation of the dispersion forces in weakly bound complexes using quantum chemical and multipole expansion methods. *J. Braz. Chem. Soc.*, **16**, 345 (2005).