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Article

Theoretical Study of α-CD Based [3]Pseudorotaxanes: the Role Played by Threadlike Polymer on the Stability of Cyclodextrin Dimers

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As interações entre ciclodextrinas e seus agregados com cadeias poliméricas, têm atraído a atenção de pesquisadores em diferentes subáreas da química supramolecular. Esses compostos, conhecidos como "necklaces", podem ser empregados na formulação de fios e nanotubos moleculares. No presente artigo a formação de dímeros de α-CD foi estudada teoricamente considerando as três possíveis orientações relativas, denominadas "head-to-head" (HH), "tail-to-tail" (TT) e "head-to-tail" (HT). A influência da cadeia polimérica na estabilidade relativa das diferentes associações foi avaliada através do estudo dos compostos de inclusão de $(\alpha\text{-CD})_2$ com oligo(etilenoglicol) (OEG). Os resultados mostram que a orientação relativa das CDs é definida, primeiramente, pelas interações intermoleculares entre as unidades de α-CD, tendo a cadeia polimérica um papel secundário no processo de agregação.

Cyclodextrins (CDs) and polymeric chains have attracted considerable attention, being addressed in the literature as novel molecular assembly. The so-called "Molecular Necklace" synthesized by the inclusion of a polymeric chain inside CDs cavity has been employed in the formulation of molecular wires and nanotubes. In this paper we applied our previous reported mixed basis set approach in order to investigate theoretically the α-CD inclusion complexes formed by two CD units and an oligo(ethylene glycol) (OEG). In attempt to analyze the role played by the OEG in the formation of pseudo-rotaxane in gas-phase, DFT calculations were performed for six possible dimer associations of CDs, named head-to-head (HH), tail-to-tail (TT) and head-to-tail (HT) with or without an OEG threadlike molecule included in the cavity formed by the α-CD dimer. The comparison between relative energies of empty (HH, TT and HT) and filled associations (HH-OEG, TT-OEG and HT-OEG) shows that the OEG chain does not interfere significantly in the relative stabilization energies of the supramolecular systems, therefore the relative arrangements of CDs in the necklace structures should be primarily driven by interactions between cyclodextrin units.

Keywords: DFT, alpha cyclodextrin, dimer, OEG, inclusion complex

Introduction

Cyclodextrin (CD) is a cyclic oligomer of α-D-glucose obtained by the action of certain enzymes on starch. Generally described as shallow truncated cones, this class of carbohydrate presents a hydrophobic cavity of different sizes, depending on the number of elementary glucose units. In addition, the structure of the CD molecule possess two different rims, a wider (head) containing all secondary hydroxyl groups and a narrower (tail) containing all primary hydroxyl groups. There are three natural cyclodextrins readily available having six, seven or eight glucose units named α-CD, β-CD and γ-CD, respectively.

The applications of CDs in supramolecular chemistry have been widely addressed in the literature and the applicability of this class of carbohydrate is closely related to its ability to form inclusion compounds with a very wide range of guest molecules in aqueous solutions.[1,2] In the context of the supramolecular chemistry, due to its singular architecture, CDs can be used in a large number of molecular devices such as molecular reactors,[3,4] molecular nanotubes,[5-8] molecular wires[9-11] and also in molecular recognition

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processes.[12-16] Over several decades, the encapsulating phenomena of low molecular weight compounds by CDs have been subject of numerous investigations[17,18] attracting the attention of the scientific community interested in this research area. In the beginning of the 1990s, there were a limited number of works concerning the threading of polymers with CDs. The number of publications related to these host-guest compounds displayed an increasing after the independent and pioneer studies of Harada and Kamachi[19] and Wenz and Keller.[20]

It is well known that cyclodextrins can form inclusion compounds in high yields with various polymers. This threading process is chain-length selective for the different types of CDs[21] (α-, β- and γ-CD), besides the yields obtained from the synthesis of [CD…polymer] complex usually depend on the polymerization degree of the included polymer used. Another important factor that affects directly the complex formation is the correlation between the relative sizes of the cavities of CDs (hosts) and the cross-sectional areas of the polymers (guests).[22] In addition, the inclusion complexation comprises secondary interactions, which are often of solvophobic nature. In general, each weak interaction such as van der Waals, hydrophobic or hydrogen-bonding, is not individually sufficient to lead inclusion complex formation. Therefore, the driving force responsible for the inclusion phenomena can be given by the sum of such interactions.[17,23]

Based on the supramolecular particularities, the inclusion compounds formed by CD and polymeric chain are named, depending on the number of CDs units threaded, as rotaxanes or polyrotaxanes. In addition, the so-called pseudo-polyrotaxanes are formed when threadlike molecules are located inside the cavities of cyclic molecules. Linear chain CD-based pseudo-polyrotaxanes can be synthetically obtained either by the polymerization of a monomer complexed inside a CD or by threading of CD rings onto polymer chain.[17] Ending capping pseudo-polyrotaxanes give rise to polyrotaxanes, also named "molecular necklace",[18,24] which has been employed in the formulation of novel materials. The condensation of α-CD threaded on a polymer chain with epichlorohydrin results in the formation of molecular tubes (MT).[25]

In sequential supramolecular structures as "necklaces", CDs can be assembled in different forms, being the dimeric conformation the smallest representative structure of them. In this sense, three possible isomers can be obtained, the so-called head-to-head (HH), tail-to-tail (TT) or head-to-tail (HT). These alignments are defined depending how each CD rim are faced toward another as depicted in Figure 1. CDs units orientation are supposed to play an important role in the synthesis of pseudo-polyrotaxane derivatives. Very recently, our group demonstrated, through statistical assumptions, that a particular CD orientation, the head-to-tail (HT) (see Figure 1), is responsible for the molecular weight distribution of molecular tubes, synthesized by the Harada's procedure.[26] Our results strongly indicated that the CD pair interaction plays a major role in the probability distribution of the entities formed in the self-assembly system containing α-CD and OEG. Similar arguments were previously used by Harada's group, in attempt to explain the existence of 20% of HT conformation among CD associations in "necklaces" formed by the same host-guest system.[27] Despite the dependence of combined interactions requested in the complex formation, a question could be raised: Can the polymeric chain interfere in CD dimer formation, along the pseudo-polyrotaxane self-assembly process?

Due to the intrinsic nature of intermolecular interactions that can be established in host-guest compounds, quantum mechanical calculations are recommendable to treat this process in a molecular level. Nonetheless, the large size of the CD precludes the use of computational methods based on high level *ab initio* molecular orbital theory. In spite of that, our group gained considerable experience combining distinct theoretical methodologies, such as semi-empirical and Density Functional Theory (DFT) in order to obtain structures and reliable interaction energies of hydrated CD systems.[28,29]

According to Moreno and co-workers,[30] optimized structures at semi-empirical level of theory, such as

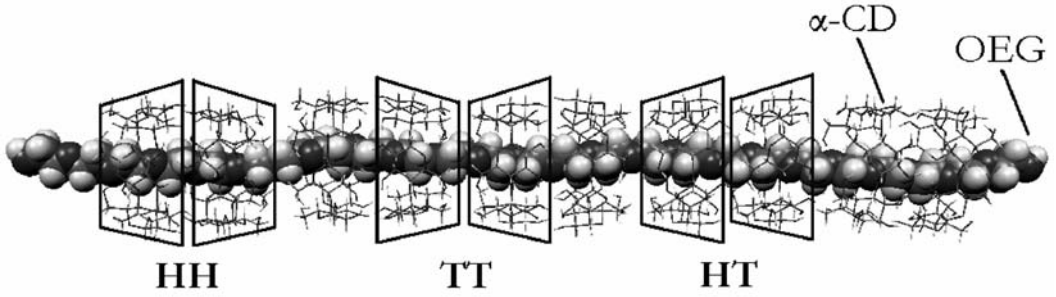

Figure 1. Pseudo-polyrotaxane supramolecular model contructed by α-CD units and an OEG chain. The three possible dimeric associations named head-to-head (HH), tail-to-tail (TT) or head-to-tail (HT) are shown.

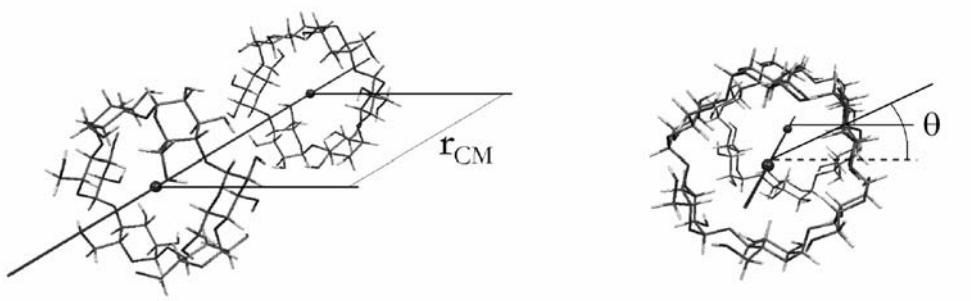

Figure 2. Illustration of the intermolecular parameters used to constructed the PES for CD dimer formation.

PM3, for inclusion complexes, are unacceptable due to the establishment of non-physical interactions between hydrogen atoms (H…H) belonging to the cyclodextrin hydrophobic cavity and to the guest molecules. Therefore, our previous reported methodology[28,29] could not be applied to study pseudo-polyrotaxanes, or another inclusion complex. In this case it is necessary to use a higher level of theoretical methodology to avoid the appearing of such kind of non-physical interactions. In attempt to solve this computational task to large CD systems, very recently,[31] we employed a mixed basis set (MBS) methodology for quantum mechanical calculations involving distinct hydrated α-CD clusters. Within this approach, a significant decrease on computational cost was pointed out, enabling interaction energy evaluations for systems containing an expressive number of atoms (*e.g.* 576 atoms). In addition, depending on the size of the system to be modeled, the evaluation of energy for supramolecular structures sampled in the PES (Potencial Energy Surface) can be performed at the ab initio level of theory. Therefore, according with our previous results, DFT based method can be employed rather than semi-empirical in order to investigate CD inclusion complexes.

In this paper we focus our study on pseudo-rotaxanes models formed by α-CD and OEG. The main goal of this theoretical investigation was an attempt to obtain reliable information about the influence of the polymeric chain in the relative stability of the CD units associations along the pseudo-polyrotaxane supramolecular structures. The elucidation of the role played by the intermolecular interactions in a molecular level can be important to understand the formation process of CD-based supramolecular inclusion compounds.

Methodology

Cyclodextrins can form different types of intramolecular hydrogen bonds from the interaction of primary and secondary hydroxyl groups with either OH groups or glycosidic oxygens of adjacent glucoses. Due the flexibility of cyclodextrin, several conformations may exist in equilibrium, leading to many possible isomers for HH, TT and HT arrangements. Thus, the full PES for CD dimer formation must contain a huge number of stable species, which can not be sampled completely at *ab initio* level of theory. Nonetheless, initial guesses for dimers can be constructed by variation of appropriated intermolecular parameters, taken stables forms for the monomer. In the present work the starting geometries for the distinct dimers were found as minimum point on the rigid-PES defined by the pair of parameters r_{CM} and θ (Figure 2), which are the CDs center of mass distance and relative rotation between the monomers, respectively.

The structure for the monomer with alcohol-ether (AE) hydrogen bonding belt in the narrower rim of α-CD, and a complete belt in the wider rim, named α-CD^{AE}, was employed in order to construct the supramolecular structures investigated. The choice of this conformer among many others can be justified based on the gas phase stability and structural important features. The α-CD^{AE} form employed here comprises the most stable gas phase open cavity conformer. Rather than an alcohol-ether (AE) hydrogen bonding belt, the gas phase global minimum, named α-CD^{AA}, contain an alcohol-alcohol (AA) hydrogen bonding arrangement in the narrower rim, possessing a similar secondary belt when compared to AE structures, as depicted in Figure 3. However, due the existence of the alcohol-alcohol hydrogen bonding arrangement in the narrower rim, this extremity of the cavity is almost closed, incompatible with inclusion compounds experimentally observed. Then, the form α-CD^{AA} was not further considered in the present study.

All α-CD^{AE} associations submitted to quantum mechanical investigation were automatically generated by a simple FORTRAN computational program. All single point calculations were performed at BLYP[32-34] level with the mixed basis-set MBS2, constructed by the attribution of the 6-31++G(d,p)[35] basis set to **O** and **O**-**H** and the minimal basis set STO-3G[36,37] to **C**-**H** groups. In all calculations, the previously BLYP/MBS1 fully optimized monomers were

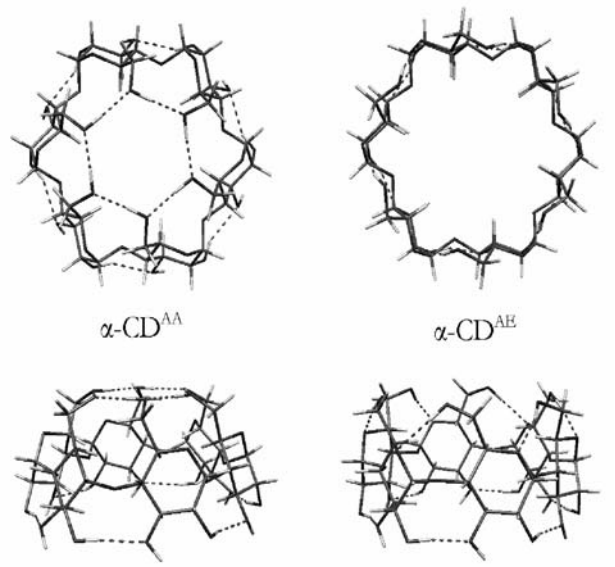

Figure 3. Fully optimized geometries (BLYP/MBS1) of free α-CD named α-CD^{AA} or α-CD^{AE} depending on the hydrogen bond arrangement formed on the narrower rim. The superscripts AA and AE stand for alcohol-alcohol and alcohol-ether, respectively.

employed (MBS1 stands for 6-31G(d,p)[38-43] for **O** and **O-H** and STO-3G for **C-H** groups). After the determination of the best parameters concerning the starting geometries (θ and r_{CM} defining the minimum point on the rigid-PES) an OEG was included in the three distinct $(\alpha\text{-}CD^{AE})_2$ cavities, giving rise to the three distinct dimers containing OEG, named HH-OEG, TT-OEG and HT-OEG. The six structures obtained were submitted to optimization at the BLYP/MMBS level, where MMBS (minimal mixed basis set) stand for an mixed basis set with the 4-31G[39,41-43] basis set attributed to **O**, **O-H** and the hydrogen atoms directed towards the CD cavity, usually identified as **H3** and **H5,** and the minimal basis set STO-3G to **C-H** groups. After geometry optimization, we carried out BLYP single point calculations employing the full triple zeta quality basis set 6-311++G(d,p)[44,45] for all structures obtained, in order to investigate the influence of the OEG in the relative stabilization of the obtained dimers. All calculations were performed using the Gaussian 03 Program quantum mechanical package revision D.01.[46]

Results and Discussion

As mentioned, in the determination of more suitable starting geometries, the PES for $(\alpha\text{-}CD^{AE})_2$ formation was constructed taking the relative rotation (θ) and the center of mass distance (r_{CM}) as variation parameters. The θ values ranged from 0 to 60 degrees, with an increment of 5 degrees. In addition, the r_{CM} parameter was modified in distinct ranges for the three possible dimers associations. In order to sample a reasonable number of distinct structures, the r_{CM} parameter was varied from 7.4 to 9.4 Å, 8.0 to 9.4 Å, and 7.8 to 9.4 Å for HH, TT and HT, respectively, with an increment of 0.2 Å, for all associations. For TT association additional points were calculated in the range of 8.2 to 9.0 Å with stepsize equal to 0.1 Å. The supramolecular structures sampled based on fixed θ and r_{CM} parameters, according to the defined ranges, corresponds to a number of 416 single point calculations. It is noticeable that the rigid approximation comprising the above defined ranges, and bearing in mind the number of atoms present in each molecule investigated (252 atoms), is feasible only through the use of our previously proposed MBS approach.[31] Three energy profiles evaluated along the rigid approximation for optimized θ values are depicted in Figure 4, where energy differences are relative to $(\alpha\text{-}CD^{AE})_2$ at r_{CM} = 9.4 Å. The best parameters have been determined from the analysis of 39 curves (13 for each possible α-CD association) each one concerning a specific relative rotation (θ). The geometric parameters established for HH, TT and HT minimum points in Figure 4 are 7.8, 8.7 and 8.4 Å for r_{CM} and 20, 30 and 40 degrees, for θ, respectively.

Once obtained the starting geometries for the α-CD dimers, a single OEG chain composed by five ethylene glycol units was accommodated inside the cavities of the three possible associations. Bearing in mind that the pseudo-rotaxanes are employed in the synthesis of polyrotaxanes, in which the α-CD molecules are almost closed packed from end-to-end of a poly(ethylene glycol)

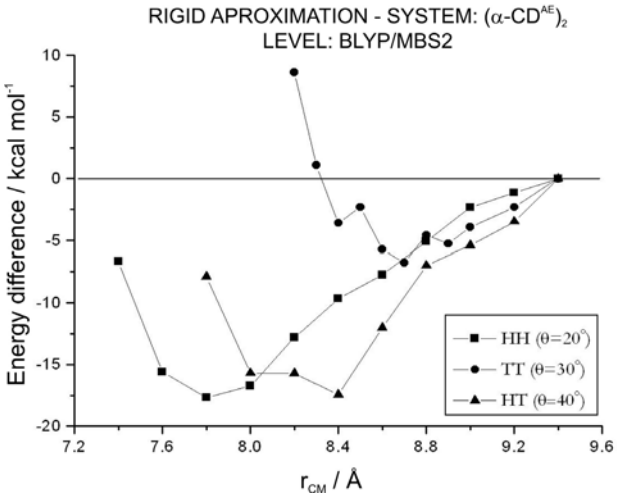

Figure 4. Energy profile calculated for the rigid-PES at BLYP/MBS2// BLYP/MBS1 level. Only the variation along r_{CM} is shown with θ corresponding to the optimized value. The energy differences corresponds to the process: $(\alpha\text{-}CD^{AE})_2[r_{CM}=9.4\ Å] \rightarrow (\alpha\text{-}CD^{AE})_2[r_{CM}=X]$, for X value defined in the corresponding specific range. For clarity, the data concerning the TT at r_{CM}=8.0 Å was omitted. From the analysis of 416 BLYP/MBS single point calculations, the geometric parameters of the starting structures have been established. The determined values correspond to 7.8, 8.7 and 8.4 Å for r_{CM} and 20, 30 and 40 degrees, for θ, concerning the associations HH, TT and HT, respectively.

(PEG) chain,[47] the r_{CM} parameter, obtained from the rigid approximation, determines the molar ratio of ethylene glycol units to α-CD. The molar ratios of ethylene glycol units to α-CD determined theoretically are in perfect agreement with the experimentally findings,[21] concerning all the possible associations. In addition, it has been pointed out that α-CD forms inclusion complexes with monodisperse OEG in a crystalline state in yields that increases sharply with an increasing in the degree of polymerization (DP) from 5 to 12.[48] This experimental fact can be partially understood by the data obtained by the rigid approximation, in what concerns the distance of center of mass determined. The r_{CM} parameter determines the minimal OEG chain length, directly related to the DP, compatible with the most stable dimer associations. This strongly indicates that at least one stable α-CD dimer is requested in order to increase considerable the yields of the complexes obtained experimentally.

The systems constructed, containing or not an included OEG, were optimized without any symmetry constraint at the BLYP/MMBS level. In what concerns the mixed basis set attributed to the OEG structure in this work, only the carbon atoms were treated with STO-3G, being the 4-31G basis set attributed to the other atoms (including hydrogens), according to the restrictions related to the MBS approach discussed in our previous work.[31]

The six fully optimized structures are depicted in the Figures 5-7. Except for the TT and TT-OEG, it can be seen, from the optimized structures, the formation of a considerable number of intermolecular hydrogen bonds, assigned using the following criteria: rOH…O≤2.3Å and 90°≤∠O-H…O≤180°. The use of monomers containing a complete alcohol-ether

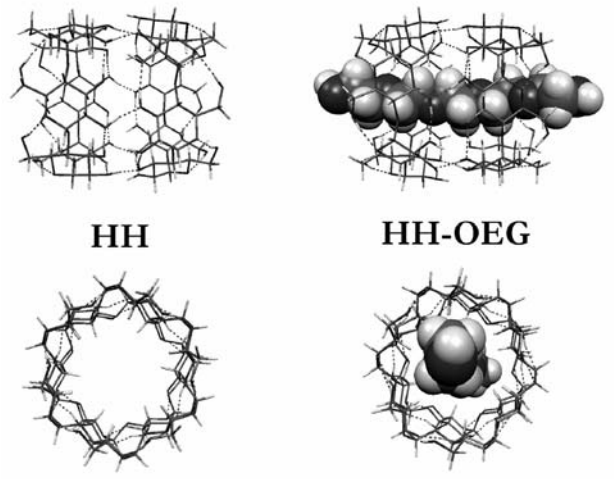

Figure 5. BLYP/MMBS fully optimized geometries for $(\alpha\text{-CD}^{AE})_2$ and $(\alpha\text{-CD}^{AE})_2$-OEG, named HH and HH-OEG, respectively. It can be seen a considerable number of hydrogen bonds between CD units. For the HH-OEG structure, all H…H distances between the host and the guest hydrogen atoms, were greater than 2.2 Å.

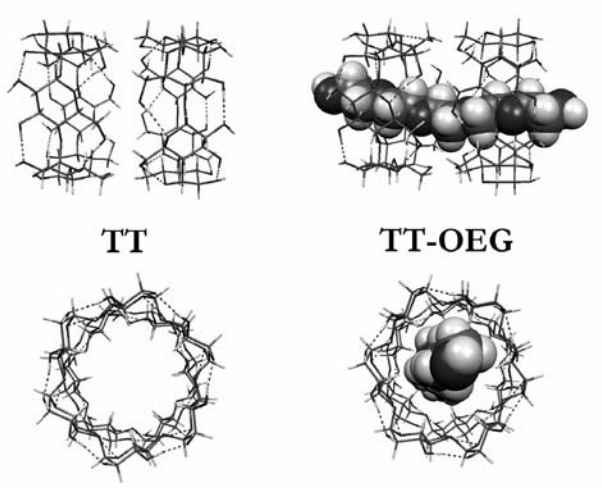

Figure 6. BLYP/MMBS fully optimized geometries for $(\alpha\text{-CD}^{AE})_2$ and $(\alpha\text{-CD}^{AE})_2$-OEG, named TT and TT-OEG, respectively. No intermolecular hydrogen bonds between CD units can be observed. This probably occurs due to the use of monomers containing a complete alcohol-alcohol belt in the narrower rim. For the TT-OEG structure, all H…H distances between the host and the guest hydrogen atoms were greater than 2.0 Å.

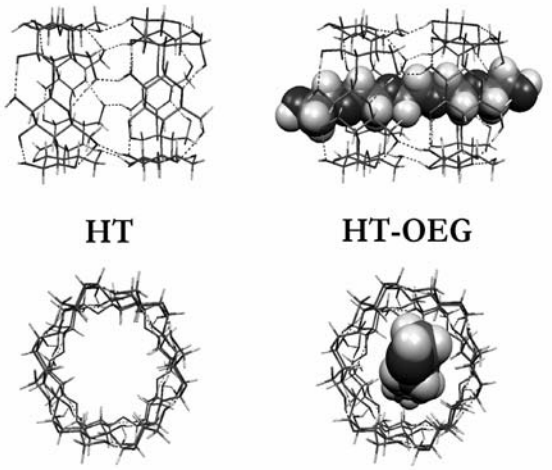

Figure 7. BLYP/MMBS fully optimized geometries for $(\alpha\text{-CD}^{AE})_2$ and $(\alpha\text{-CD}^{AE})_2$-OEG, named HT and HT-OEG, respectively. It can be seen a considerable number of hydrogen bonds between CD units. For the HT-OEG structure, all H…H distances between the host and the guest hydrogen atoms were greater than 2.0 Å.

belt in the narrower rim of α-CD must be the responsible for the absence of intermolecular hydrogen bonds of the TT and TT-OEG systems. For all the systems containing an included OEG, the methodology based on DFT mixed basis set do not provide unphysical H…H short contacts between the host and the guest hydrogen atoms. According to Moreno and co-workers,[30] the use of pure *ab initio* methods in the treatment of supramolecular systems would precludes short contact interactions between host and guest molecules. Despite of that, Moreno and co-workers also pointed out that such level of theory may be too expensive in practice.

Our results showed that by using mixed basis set, pure *ab initio* calculation can be done at a computational reasonable cost. Moreover, our procedure can contribute to the field of molecular modeling of supramolecular systems, including other CD host-guest complexes.

The main results obtained in the present work are compiled in Table 1, which contains the energy changes for dimer formation (1), inclusion of OEG on the dimer cavity (2) and the whole threading process (3) (=(1)+(2)). The values from BLYP/MMBS and BLYP/6-311++G(d,p)// BLYP/MMBS levels of theory are given in order to assess the effect of basis-set in the calculated interaction energies.

$$2\alpha\text{-CD}^{AE} \rightarrow (\alpha\text{-CD}^{AE})_2 \quad (1)$$

$$(\alpha\text{-CD}^{AE})_2 + \text{OEG} \rightarrow (\alpha\text{-CD}^{AE})_2\text{-OEG} \quad (2)$$

$$2\alpha\text{-CD}^{AE} + \text{OEG} \rightarrow (\alpha\text{-CD}^{AE})_2\text{-OEG} \quad (3)$$

It can be seen from values in Table 1 that the results are quite sensitive to the basis-set used to calculate energies. Using the smaller mixed basis-set (MMBS) the HH dimer is predicted as global minimum, whereas the HT arrangement is preferred relative to HH by 4.6 kcal mol^{-1} when a unique (all atoms) basis-set (6-311++G(d,p)) is used. It is opportune to refer to our previous paper,[31] where the hydration energies of cyclodextrins were calculated using distinct mixed basis-set. In that study we found overestimated interaction energies when small basis-sets were used for O and O-H moieties. For example, the hydration energy calculated for α-CD.6H_2O formation was -23.3 (BLYP/6-31G(d):O,OH; STO-3G:CH) and -15.8 kcal mol^{-1} (BLYP/6-311++G(2d,2p):O,OH; STO-3G:CH). Therefore, care is needed in analyzing the results obtained at BLYP/MMBS level of theory.

Interesting is to note that the stability order does not change upon inclusion of OEG, with $\delta\Delta E_3$ close to $\delta\Delta E_1$, regardless the basis-set used. It is also worth pointing out that the relative stability order determined in this work, at our higher level of theory (BLYP/6-311++G(d,p)//BLYP/MMBS), is not the same reported by Jaime and co-workers obtained through Molecular Dynamic (MD) simulations in the absence of solvent.[49] However, it is noticeable that in MD simulations the average number of hydrogen bonds of the three possible associations is different, what cannot be observed in the structures optimized in this work at the BLYP/MMBS level of theory, in which both HH and HT associations posses a number of intermolecular hydrogen bond equal to six. In addition, the relative stability is also distinct of the recently determined by Rudyak and co-workers using DFT calculations concerning the same three possible associations.[50] In the two mentioned works, the HH association is the most stable one, which is in accordance with our BLYP/MMBS results. Despite of the apparent discrepancy observed, even considering the distinct level of theory employed, the monomers used in the construction of the starting associations employed in the cited theoretical investigation are different. In the DFT study developed by Rudyak and co-workers it is clear that the monomers employed does not contain a complete H-bond belt in the narrower rim of α-CD unit. Thus the possible dimers investigated by Rudyak are not the same treated in the present work. As discussed, the arrangements HH, TT and HT must be represented as an equilibrium mixture of a set of supramolecular entities, moreover in order to represent definitively the stability trends, at least the most stable forms must be taken into account. This is not the fundamental subject of investigation focused in this work, therefore will not be discussed in details here.

The interaction energies showed in Table 1 obtained with our highest level of theory indicates that when an OEG chain is trapped inside the cavities formed by two CD units, the respective supramolecular structures are destabilized in gas phase, with ΔE_2 raging from 5.2 to 11.1 kcal mol^{-1} . The opposite is observed at lower level of theory, with inclusion process (2) found to be exothermic for all dimers. It is worth noting that, despite the values calculated for ΔE_2, the OEG inclusion processes for HH and HT dimer are equally probable, with the former being slightly more favorable. Therefore, the trend found for the whole threading process (3) is mainly due the dimer formation represented by process (1).

Due to the small difference in relative energies observed when empty and filled dimers are compared (see $\delta\Delta E_1$ and $\delta\Delta E_3$ values), it can be said that the OEG chain should not be responsible for the relative orientation of the CDs units. Thus, as discussed experimentally,[27,48,51] the complex formation is thought to be promoted by hydrogen bonds between CDs units. If the solvent effect is taken into account, a stabilization of hydrophobic nature should favor the filled interaction in comparison to the empty complex. Nonetheless, based on geometrical arguments, it can be predicted that the solvophobic contribution to the interaction energies due to the inclusion of an OEG chain along the supramolecular structures will be approximately the same for the three possible associations. Moreover, the probability of occurrence of a determined association that gives rise to a particular pseudo-polyrotaxane depends for the most part of the interaction between the CDs units. Therefore, the pair interactions play a fundamental role in the formation of such kind of inclusion complex, as so far pointed out based on statistical analysis.[26] Despite of that, the polymer chain and the solvent play an important role in the complex formation. The empty associations, as determined in

Table 1. Interaction (ΔE) and relative (δΔE) energies (in kcal.mol-1) calculated for the systems: $(\alpha\text{-CD}^{AE})_2$ and $(\alpha\text{-CD}^{AE})_2$-OEG employing BLYP/MMBS and BLYP/6-311++(d,p)//BLYP/MMBS levels of theory

	BLYP/MMBSa			BLYP/6-311++G(d,p)//BLYP/MMBS		
	$\Delta E_1(\delta\Delta E_1)$	ΔE_2	$\Delta E_3(\delta\Delta E_3)$	$\Delta E_1(\delta\Delta E_1)$	ΔE_2	$\Delta E_3(\delta\Delta E_3)$
HH	-79.1(-16.9)	-17.7	-96.8(-18.4)	-7.6(4.6)	5.2	-2.4(4.4)
TT	-11.8(50.4)	-14.8	-26.6(51.8)	8.9(21.1)	11.1	20.0(26.8)
HT	-62.2(0.0)	-16.2	-78.4(0.0)	-12.2(0.0)	5.4	-6.8(0.0)

[a]MMBS=4-31G: O, O-H, H3 and H5, STO-3G: C-H.

the BLYP/MMBS PES should not exist in condensed phase. The empty species should be solvated and, the water molecules surrounding the CDs units will precludes the hydrated species with appropriated geometries, as determined in gas phase. When solvated, the α-CD dimer will not maintain the gas phase parallel arrangement, similarly as has been observed for explicit hydrated species investigated by MD simulations.[52] Therefore, it is reasonable to argue that the OEG chain can influence the orientation of CDs units in order to form an arrangement similar to obtained in gas phase, contributing to the formation of the CD-based host-guest supramolecular systems.

Conclusions

In this paper the α-CD dimer formation was revisited considering the role played by threadlike OEG oligomer on the stability order of the distinct arrangements named HH, TT and HT. Mixed basis-sets were employed in the calculations in order to make feasible full geometry optimization at DFT (BLYP) level of theory. The effect of mixed basis-set was evaluated by calculating relative energies for distinct species at full triple-zeta quality basis-set. The PES for interaction between α-CD monomers was partially sampled using the center of mass distance and the angular orientation between the interacting molecules.

The interaction energies calculated showed distinct trends for MMBS and 6-311++G(d,p) basis-sets. At the former level, the HH arrangement is preferred, whereas the HT dimer is the global minimum with a more complete basis-set. The OEG inclusion process is also energetically favored at BLYP/MMBS level giving positive interaction energy at BLYP/6-311++G(d,p) level of theory. Nonetheless, the comparison between relative energies of empty (HH, TT and HT) and filled associations (HH-OEG, TT-OEG and HT-OEG) indicates that the OEG chain does not interfere in the relative stabilization energies of the supramolecular systems focused. At our higher level of theory, the HT arrangement was found to be more stable in gas phase, followed by the HH orientation (4.6 kcal mol-1 higher in energy). This same trend was found when the OEG is included in CD cavity, with a HT-OEG favored by 4.4 kcal mol^{-1}. These results suggest that the OEG does not play a primary role on the relative arrangements of CD units in a necklace, which is evidence that the whole process of formation of these supramolecular structures should be driven mainly by CD interaction, in accordance with experimental hypothesis. Finally, the main conclusion drawn from the present study corroborates with our previous study, where it was addressed that the CD pair interaction plays a major role in the probability distribution of the entities formed in the self-assembly system containing α-CD and OEG, what seems to be a fundamental feature of the chemistry of the CD host-guest inclusion compounds.

Abbreviation List

The full list of abbreviations used throughout the text was HH (head-to-head), TT (tail-to-tail), HT (head-to-tail), OEG (oligo(ethylene glycol)), CD (cyclodextrin), PES (Potential Energy Surface), MBS (mixed basis set), MMBS (minimum mixed basis set: O, O-H: 4-31G; C-H: STO-3G), MBS1 (mixed basis set 1: O, O-H: 6-31G(d,p); C-H: STO-3G), MBS2 (mixed basis set 2: O, O-H: 6-31G++(d,p); C-H: STO-3G), MT (molecular tube), AE (alcohol-ether), AA (alcohol-alcohol), DP (degree of polymerization), r_{CM} (distance of center of mass).

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