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An efficient methodology to study cyclodextrin clusters: application to α-CD hydrated monomer, dimer, trimer and tetramer

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Abstract The hydrated α-cyclodextrin (α-CD) clusters resulting from the following process: $n\alpha$-CD + $n(H_2O)_6$ → α-CD$_n$ · $6nH_2O$, with $n = 1$, 2, 3, 4, have been investigated using semiempirical (PM3), ab initio Hartree-Fock and Density Functional Theory (BLYP functional) levels of theory. The largest structure containing 576 atoms and 5,760 contracted basis functions (6-31G(d,p) basis set) poses as a considerable hard task for quantum chemical calculations. As the number of basis function increases rapidly with the cluster size, an alternative procedure to make the calculations feasible is certainly welcome, in order to perform BLYP calculations with an adequate basis set. Through the aid of a computer program that we developed, it became of practical use the selection of atom by atom basis sets, using the common chemical sense, enabling quantum mechanical calculations to be performed for very large molecular interacting systems (inclusion complexes), at an affordable computational cost. In this article we show how an appropriate selection of basis functions, leaving the CH$_n$ groups with a minimal basis set and the oxygen atoms (and OH groups) with a better quality basis set, lower considerably the computational cost with no significant loss in the calculated interaction energies. A regular pattern is observed for α-CD hydrated monomer, dimer, trimer and tetramer, therefore adding support to the use of this procedure when studying larger hydrogen bonded clusters where electron correlation effects are important. We show that the procedure reported here enables DFT calculations for hydrated cyclodextrin using basis set up to the 6-311++G(3df,3pd) triple zeta quality .

Keywords Cyclodextrin · DFT · Inclusion complex · Interaction energy · Molecular structure · Supramolecular chemistry

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Introduction

Over the past years marked scientific effort leading to significant advances in the study of large molecular systems has been brought about by many research groups. In this context, the supramolecular chemistry has been considered as one of the most important and promising areas 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. Supramolecular self-assembled species may be achieved by means of the association of two or more molecular entities through weak interaction such as electrostatic forces, hydrogen bonding and hydrophobic effect or van der Waals interactions.

Cyclodextrins (CD's) are cyclic oligosaccharides formed by α-D-glucose units connected through glycosidic α-1,4 bonds. The most common among the native CD's are the α-, β- and γ-CD, which consist of six, seven and eight gluco-pyranose units, respectively [3]. This class of

molecules, which are important representatives of supra-molecular systems, can be usually characterized as a doughnut or wreath-shaped truncated cones, having a hydrophobic cavity of appropriate dimensions and hence, can form inclusion complexes with variety non-polar organic molecules of suitable size [4].

Because of the diverse applications of CD's, during the last decades considerable efforts have been devoted to the investigation of the chemistry of this class of compounds. In order to get a deeper knowledge about CD's, a number of experimental [5, 6] and theoretical studies [7, 8] have been performed over the past years. Thus, a proper combination of both studies have proven to be extremely powerful in solving the structural, energetic, and dynamic problems associated with CD's and their complexes.

Most of theoretical works on CD's are carried out using molecular mechanics (MM) and molecular dynamics (MD) simulations based on various empirical force fields [9–13]. The large size of the CD's precludes the use of computational methods based on ab initio molecular orbital theory with the inclusion of electronic correlation effects. In addition, these compounds can form supramolecular self-assembled species by association of two or more CD's through weak interactions such as electrostatic forces, hydrogen bonding and hydrophobic effect or van der Waals interactions. In this way, the formation of cyclodextrin dimer, trimer, tetramer can be considered and hence, high level ab initio calculations becomes unfeasible due to the increase of CD's cluster size. Nevertheless, quantum mechanical (QM) study of CD's has gained much attention [8]. Generally, these works emphasize the use of QM methods to find global minimum structures, binding energies, driving forces for cyclodextrin complexes, as well as the chemical reactions occurring inside the CD cavity. In addition, some studies have pointed out the problems associated with the application of approximated quantum chemical methods in cyclodextrin chemistry [8]. In this sense, Casadesús et al. [14] have performed recently a computational study using a wide variety of approaches (Molecular Mechanics, semiempirical and hybrid methods, namely ONIOM calculations) to obtain the energy and geometry of a supramolecular system formed by the molecular inclusion. The aim of the study reported in Ref. [14] was to examine the performance of these computational methods when describing the short range H···H intermolecular interactions between guest and host molecules. The results provided from that study showed that most of the current semiempirical methods have not been able to describe the intermolecular interactions leading to unphysical results when used to treat the entire supramolecular system. On the other hand, pure ab initio methods and hybrid ONIOM calculations behave well, but they can become too expensive in practice for most of the sizeable systems currently of interest in supramolecular chemistry.

In this context, our previous works [15, 16] attempted to find an appropriated theoretical approach to study the hydration process of α-CD. In both articles, we have made use of a combined methodology for the calculation of interaction energies and thermodynamic properties of hydrated α-CD monomeric [15] and dimeric structures [16] where structural parameters and vibrational frequencies were calculated using the semiempirical PM3 method and interaction energies at the BLYP/6-31G(d,p) level in single point calculations using PM3 fully optimized geometries, with the Pople's standard split valence 6-31G(d,p) basis set containing polarization functions on all atoms (BLYP/6-31G(d,p)//PM3). Our goal in these studies was to analyze the interactions between water molecules and α-CD, based on thermodynamic quantities, and then to predict the preferred hydrated structures for the α-CD monomer and α-CD dimer. Our results were satisfactory when compared with experimental data [17] and the theoretical approach we used concerning the combined methodology (BLYP/6-31G(d,p)//PM3) was promptly validated.

The previous results [15, 16] gave us strong motivation for investigating large CD's aggregates based on α-CD with 3 and 4 monomeric units having water clusters surrounding their supramolecular structure. However, it is clear that as the cluster size of CD's increases the ab initio quantum chemical calculations become a considerable hard task. Thus, in order to solve this computational task, we proposed an alternative and efficient procedure to make the calculations with large α-CD system feasible. This is based on a prior choice of atom by atom basis sets, using common chemical sense, with the aid of a computer program developed to ease the basis set selection for very large molecular interacting systems relevant to the area of supramolecular chemistry. This procedure is shown to be an alternative way to make possible total quantum mechanical calculations for very large systems, involving for example molecules of biological interest, which are commonly treated using molecular mechanics or hybrid approaches.

Theoretical methodology

It is known that cyclodextrins are able to form both intramolecular and intermolecular hydrogen bonds. The first one are established between the C-2–OH group of one glucopyranoside unit with the C-3–OH group of the adjacent glucopyranose. These intramolecular H-bonds lead to the formation of a hydrogen-bond belt which confers rigidity to the structure [18]. Concerning the second one, CD's are also able to form intermolecular H-bonds due to the presence of secondary and primary hydroxyls groups

located outside the cavity. The presence of these hydroxyl groups confers to the CD's a hydrophilic character and make them water-soluble [5].

Many of the reported studies on the cyclodextrin chemistry point to the importance of hydrogen bonds on the stabilization of this class of compounds [19, 20]. Thus, in the present work, our proposal was to select an appropriate basis set for different parts of the molecule taking into account the role played by the moiety on the intra- and inter-molecular hydrogen bonds. To do this, we have considered the key atoms as being treated with a better quality basis set, hence, oxygen atoms and hydrogen attached to them were treated with a basis set containing polarization functions, leaving the carbon atoms, and also the hydrogen attached to them, with a minimal STO-3G basis set [21]. In this work all input files containing mixed basis sets were obtained from a Fortran 77 computer program [22], designed to ease the construction of the Gaussian package input file which makes use of the keyword Gen. It is a tedious and hard task to construct an input for a 500 atoms system by hand. Our goal with this approach was an attempt to decrease the computational cost with no significant loss in the quality of the interaction energies, through a careful choice, based on chemical sense, of atom-by-atom basis set. Our computer code [22] uses as input only the atomic numbers and XYZ coordinates, and makes an appropriated choice of the atom by atom basis set automatically (obviously using a common chemical sense built in as a computer routine), generating
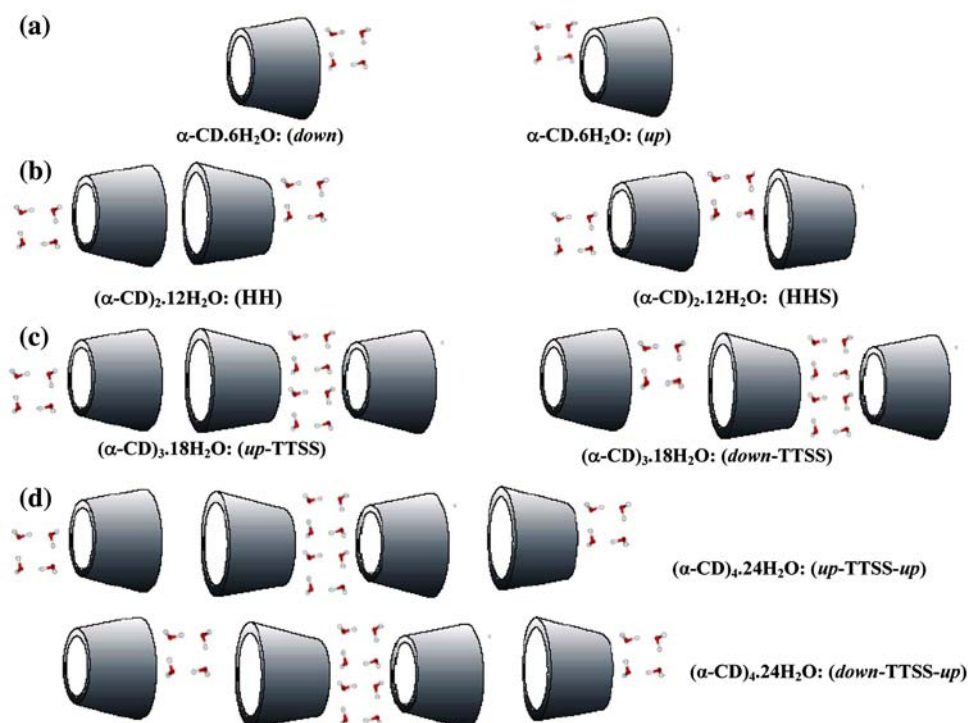
an usual input for Gaussian jobs, which makes the procedure straightforward and of practical use (the type of basis set is decided a priori by the user and is part of the input of the Fortran program). The computer program that we made initially to treat hydrated cyclodextrin clusters can be easily adapted to any other application, where the use of atom by atom mixed basis sets may be of relevance.

The geometries of eight hydrated forms considering the α-CD monomer, dimer, trimer and tetramer (Fig. 1) were fully optimized without any geometrical or symmetry constraints using the semiempirical PM3 method [23]. The electronic plus nuclear repulsion contribution ($\Delta E_{ele-nuc}$) was evaluated at the Density Functional Theory (DFT) level [24] using the gradient generalized BLYP functional [25], in single point calculations at the fully optimized PM3 geometries, with the Pople's standard split valence 6-31G(d,p) basis set [26] containing polarization functions on all atoms (BLYP/6-31G(d,p)//PM3), and also mixed basis sets named here BLYP/Gen. All calculations were carried out at the Laboratório de Química Computacional e Modelagem Molecular (LQC-MM), Departamento de Química, ICEx, UFMG, using the Gaussian Program [27] quantum mechanical package.

Results and discussion

The α-CD hydrated monomer, dimer, trimer and tetramer are shown in Fig. 1, as schematic cone representations. The

Fig. 1 (a) monomeric, (b) dimeric, (c) trimeric and (d) tetrameric schematic representations of α-CD hydrated structures. There is a water dimer structure inside each α-CD cone, not shown in this picture for reason for simplicity

α-CD·6H₂O: (down)

α-CD·6H₂O: (up)

(α-CD)₂·12H₂O: (HH)

(α-CD)₂·12H₂O: (HHS)

(α-CD)₃·18H₂O: (up-TTSS)

(α-CD)₃·18H₂O: (down-TTSS)

(α-CD)₄·24H₂O: (up-TTSS-up)

(α-CD)₄·24H₂O: (down-TTSS-up)

nomenclature used follows from Ref. [16], where HH, TT and S stand for head-to-head, tail-to-tail and sandwich mode, respectively. On choosing the basis set, care was taken to describe adequately the O···H type hydrogen bond interactions, with the use of the 6-31G(d,p) basis set [26] on all oxygen atoms and hydrogen atoms participating in H-bonds (OH groups). For the atoms belonging to the CH_n groups a minimal STO-3G basis set [21] was assigned. This mixed basis set was denominated *Gen-1*. The reason behind this approach is a simple one. The α-CD hydration process is determined basically by electrostatic interactions of the O···H type, so, it seems natural to consider the CH and CH_2 groups as "spectators" or "supporting" groups due to the fact that they play a minor role. The spatial

representations of these structures are depicted in Fig. 2. For the α-CD hydrated monomer there are 144 atoms, being 36 carbons, 36 oxygen and 72 hydrogen atoms. The CH_n groups comprehend 36 carbon and 42 hydrogen atoms corresponding to 100% of carbon and 58% of hydrogen atomic basis set. Therefore, attributing a minimal basis set to these atoms should lower considerably the computational cost of a given Hartree-Fock (HF) [28], DFT [24, 25] or Post-HF (MP2 for example) [29] calculation for large interacting systems. In addition, it was assessed the use of a better description of the atoms participating in the relevant intermolecular interactions adding diffuse functions [26, 30] (6-31++G(d,p) basis set) and also the use of the 6-311++G(2d,2p) [30], 6-311++G(2df,2pd) [30] and
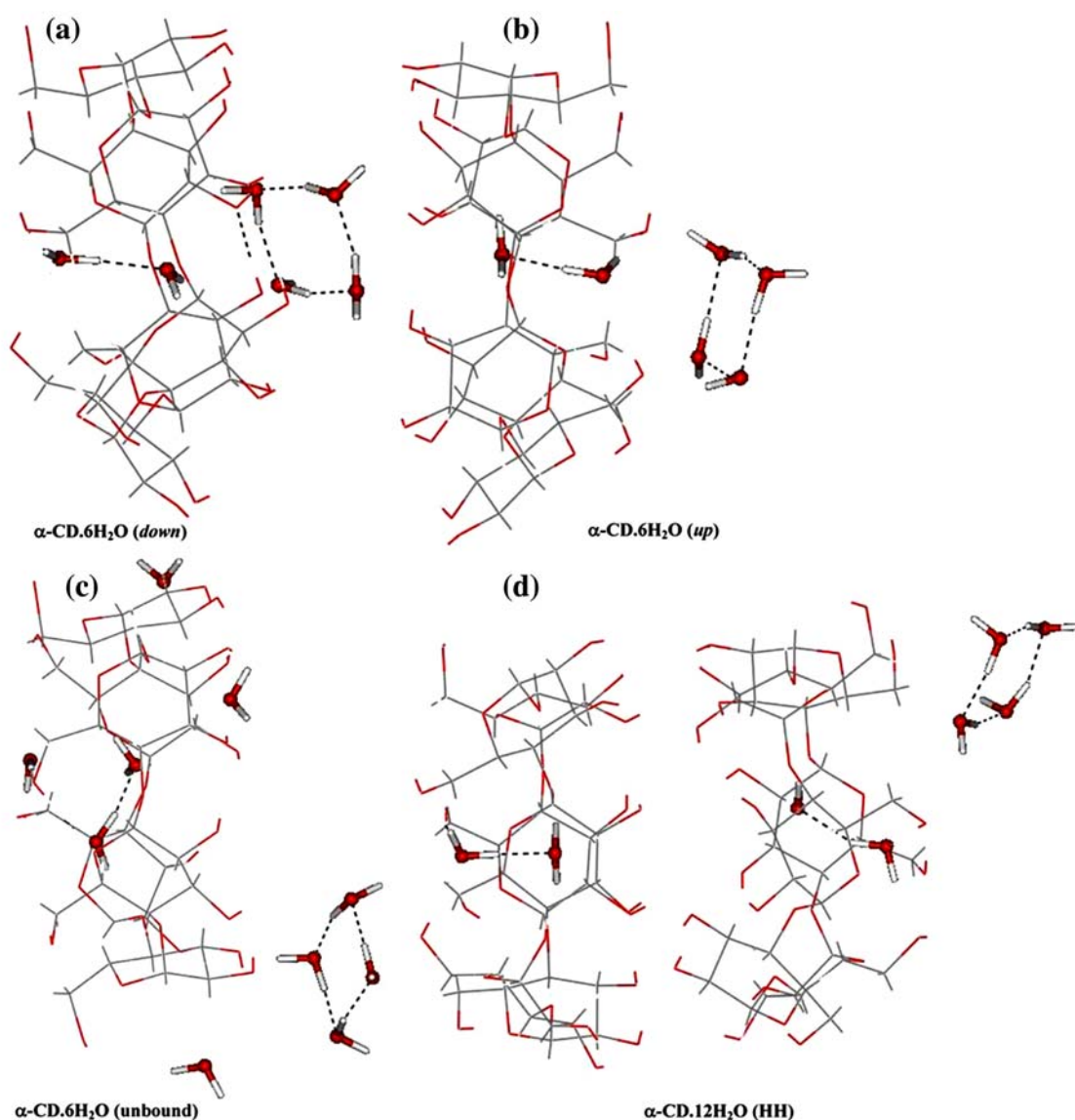

Fig. 2 PM3 fully optimized structures of α-CD hexahydrated species: Monomers (**a**, **b**, **c**); Dimer (**d**, **e**); Trimer (**f**); Tetramer (**g**). The water molecules interacting with the α-CD, forming the hydrated species, are highlighted

(e) α-CD.12H₂O (HHS)

(f) (α-CD)₃.18H₂O (*down*-TTSS)
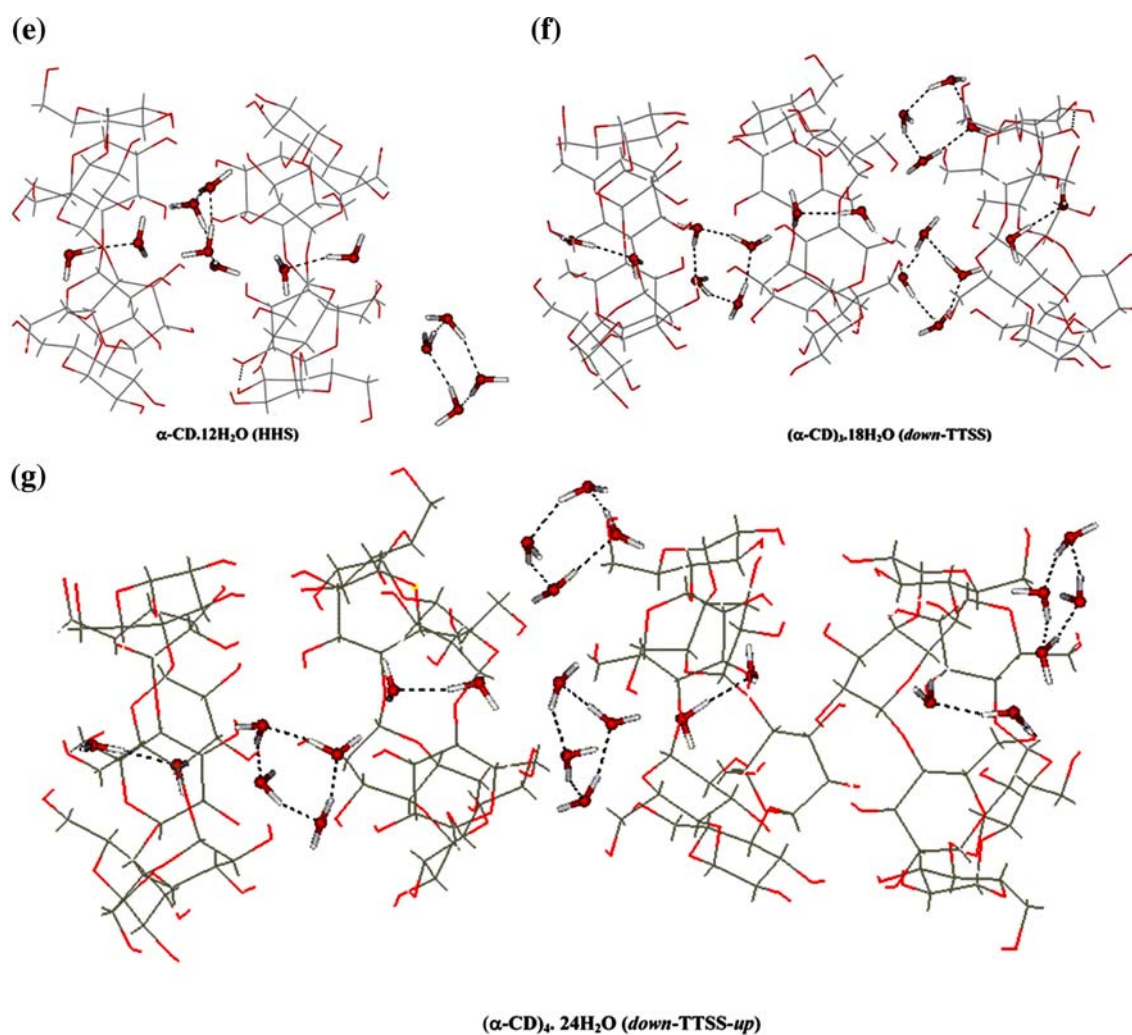
(g) (α-CD)₄. 24H₂O (*down*-TTSS-*up*)

Fig. 2 continued

6-311++G(3df,3pd) [30] improved triple-zeta quality basis sets, which contain polarization and diffuse functions on all atoms, keeping the CH$_n$ "spectator" groups with a STO-3G basis set. These basis sets are denominated *Gen-2*, *Gen-3*, *Gen-4* and *Gen-5*, respectively.

The BLYP/6-31G(d,p) and BLYP/*Gen-1* stabilization energies for the α-CD · 6H$_2$O, (α-CD)$_2$ · 12H$_2$O, (α-CD)$_3$ · 18H$_2$O and (α-CD)$_4$ · 24H$_2$O, monomer, dimer, trimer and tetramer species respectively, are given in Table 1, along with the number of basis functions in the 6-31G(d,p) and *Gen-1* basis sets. It can be promptly seen that the effect of treating the CH$_2$ groups as spectators, having a minimal basis set, is to cause a small variation in the stabilization energies within 2–10%, also maintaining the relative energies of the two complexes within 1–5 kcal mol^{-1}, systematically for monomer, dimer, trimer and tetramer species. So, the stabilization energies can be considered very satisfactorily reproduced by the *Gen-1* basis set compared to the full 6-31G(d,p). In addition, the

number of basis functions are reduced in 37% on going from the 6-31G(d,p) to the *Gen-1* basis set and also the computer time decreased, for example, by a factor of 5 for the HH dimeric species, having a tendency to reach higher values for larger associations. Therefore, an enormous gain in computational cost (saves in rigid disk space and CPU time) is observed, without significant loss in the quality of the evaluation of stabilization energies, which promptly provide strong support to the use of the *Gen-1* basis set in quantum chemical calculations involving larger molecular associations where hydrogen bonds play an important role. We also report in Table 1 BLYP/6-31G(d,p) enthalpy values for α-CD · 6H$_2$O and (α-CD)$_2$ · 12H$_2$O species along with an experimental value available. As it has been shown before [15] there is a good agreement with the experimental hydration enthalpy. In addition, it can be seen that the main contribution to the theoretical calculated enthalpy comes from the electronic plus nuclear repulsion energy ($\Delta E_{ele-nuc}$) term (ca. 97% for the monomer and

Table 1 BLYP single point energy calculations[a] using the fully optimized PM3 geometry (BLYP//PM3) for the process: $n\alpha$-CD (free) + $n(H_2O)_6$ → α-$CD_n \cdot 6nH_2O$

	Number of atoms	6-31G(d,p): all atoms		Gen-1: 6-31G(d,p): O; O–H STO-3G: C–H	Gen-1: 6-31G(d,p): O; O–H STO-3G: C–H	Energy difference[c] (Gen-1)
		$\Delta E_{ele-nuc}^a$	Number of basis functions[b]	$\Delta E_{ele-nuc}^a$	Number of basis functions[b]	
α-CD · 6H₂O "down"	144	−24.6 {−23.9}[e] {−22.7}[g]	(1440/2520)	−23.3	912/1884	1.3 (5%)
α-CD · 6H₂O "up"	144	−17.9 {6.7}[d] {−18.8}[e]	(1440/2520)	−15.8 {7.5}[d]	(912/1884)	2.1 (12%)
(α-CD)₂ ·12H₂O "HH"	288	−82.6 {−80.2}[f]	(2880/5040)	−78.2	(1824/3768)	4.4 (5%)
(α-CD)₂ · 12H₂O "HHS"	288	−72.2 {10.4}[d] {−70.5}[f]	(2880/5040)	−68.5 {9.6}[d]	(1824/3768)	3.6 (5%)
(α-CD)₃ · 18H₂O "down-TTSS"	432	−100.3	(4320/7560)	−98.2	(2736/5652)	2.1 (2%)
(α-CD)₃ · 18H₂O "up-TTSS"	432	−86.1 {14.2}[d]	(4320/7560)	−79.1 {19.1}[d]	(2736/5652)	7.0 (8%)
(α-CD)₄ · 24H₂O "down-TTSS-up"	576	−143.7	(5760/10080)	−141.1	(3648/7536)	2.6 (7%)
(α-CD)₄ · 24H₂O "up-TTSS-up"	576	−124.9 {18.8}[d]	(5760/10080)	−116.5 {24.6}[d]	(3648/7536)	8.4 (2%)

a $\Delta E_{ele-nuc} = E_{ele-nuc}(\alpha$-$CD_n \cdot 6nH_2O) - \{nE_{ele-nuc}(\alpha$-CD (free)$) + nE_{ele-nuc}((H_2O)_6)\}$

b Number of contracted/primitive basis functions

c Energy difference in relation to the full 6-31G(d,p) basis set $(\Delta E_{ele-nuc}^{BLYP/Gen1} - \Delta E_{ele-nuc}^{BLYP/6-31G(d,p)})$

d Energy difference relative to the lowest minimum energy structure

e ΔH value taken from Ref. [15]

f ΔH value taken from Ref. [16]

g Experimental ΔH value taken from Ref. [17]

dimer species) with the thermal contribution playing a minor role. This result provide support for the need of a trustable computational method to be used for evaluating gas phase interaction energies, in order to obtain reliable enthalpy data amenable to comparison with experimental determination of heats of reactions.

In Table 2, we report stabilization energies for three structures of the α-CD . $6H_2O$ monomer, being two very stable (I and II) and one strongly unbound (III) in relation to the free α-CD and water hexamer (See Figs. 2a–c), at the HF and DFT levels, using two distinct functional BLYP [25] and PW91 [32], in order to asses the behavior of the *Gen-1* basis set with respect to the level of theory employed. A quite similar behavior, as seen in Table 1, is observed for the three levels of calculation with respect to the effect of using the *Gen-1* basis set, independent of the attractive (I and II) or repulsive (III) character of the interaction energy. The well-known and expected behavior of the HF/6-31G(d,p), BLYP/6-31(d,p) and PW91/6-31G(d,p) stabilization energy calculation for hydrogen bonded species [33] is promptly observed for the *Gen-1* basis set, i.e., an overall underestimation and overestimation of the interaction energies by the HF and PW91 approaches respectively. Therefore, no changes in the performance of the HF and DFT methods are observed when the *Gen-1* basis set is used, and we would anticipate this same behavior for other DFT functional or MPn methods.

It is well known that the semiempirical PM3 method is suitable to estimate geometrical parameters for biochemical systems [34]. In this sense, we have shown in a previous paper that PM3 gave very reasonable geometrical parameters for cyclodextrins [35]. However, this can not be taken as a general trend concerning the CD structure. Recently Casadesús and coworkers [8] showed that PM3 methods led to unphysical stabilization for short-range H⋯H interactions in inclusion complexes of organic molecules with CDs. They discussed this effect on the structures and energies of the complexes, concluding that at least low level ab initio calculations (for instance HF level) must be used to correctly describe these geometries. Furthermore, for isolated CDs and their hydrates this kind of H⋯H short contacts are not observed, and therefore the PM3 geometry may be considered satisfactory [34]. Nevertheless, even for these structures the PM3 relative energies are not reliable for hydrogen bond interactions, as can be seen from the data in Table 2. At the PM3 level all three structures are predicted as "unbound", which is quite wrong since structure III is indeed unbound but I and II are good minima according to HF and DFT single point calculations. This result stresses the importance of using ab initio or DFT methods for the calculation of interaction energies involving cyclodextrins. The regular behavior of the energies calculated with the *Gen-1* basis set for different H-bonded complexes and methods is particular interesting. The HF/*Gen-1*, BLYP/*Gen-1* and PW91/*Gen-1* values agree with the result for the corresponding full 6-31G(d,p) basis set within ±3 kcal mol^{-1}, which may be considered as the degree of confidence of the *Gen-1* basis set for the evaluation of interaction energies, compared to the full 6-31G(d,p) basis set. Therefore, it can be seen that the plausibility of the use of the *Gen-1* basis set does not depend on a specific spatial arrangement, having more or less hydrogen bonds, and also on the level of calculation employed (in this case we tested HF, BLYP and PW91, but we are confident that this is a more general trend).

Rising our computational ambitions we report in Table 3 stabilization energies calculations for the three α-CD · $6H_2O$ monomer structures addressed in Table 2 improving the 6-31G(d,p) basis set in *Gen-1* by adding diffuse functions on all atoms (6-31++G(d,p)) and also using a triple-zeta quality basis set containing polarization and diffuse functions, i.e., 6-311++G(2d,2p), 6-311++G(2df,2pd) and 6-311++G(3df,3pd) (named here

Table 2 HF, BLYP and PW91 single point energy calculations[a] using the fully optimized PM3 geometry (HF//PM3, BLYP//PM3, PW91//PM3) for the process: α-CD (free) + $(H_2O)_6$ → α-CD · $6H_2O$

	$\Delta E_{ele-nuc}$	$\Delta E_{ele-nuc}$	$\Delta E_{ele-nuc}$	$\Delta E_{ele-nuc}$	$\Delta E_{ele-nuc}$	$\Delta E_{ele-nuc}$	$\Delta E_{ele-nuc}$
	PM3	HF/6-31G(d,p)	HF/*Gen-1*	BLYP/6-31G(d,p)	BLYP/*Gen-1*	PW91/6-31G(d,p)	PW91/*Gen-1*
α-CD · $6H_2O$ "*down*": Struc. I [c]	7.8	–14.3	–16.2 {–1.9}[b]	–24.6	–23.3 {1.3}[b]	–32.85	–31.3 {1.5}[b]
α-CD · $6H_2O$ "*up*": Struc. II [c]	15.1	–11.1	–11.5 {–0.4}[b]	–17.9	–15.8 {2.1}[b]	–25.17	–22.8 {2.3}[b]
α-CD · $6H_2O$ "*Unbound*" [d] Struc. III	11.6	25.7	22.8 {–2.8}[b]	16.2	12.7 {–3.5}[b]	7.48	5.1 {–2.4}[b]

[a] $\Delta E_{ele-nuc}$ calculated as shown in Table 1

[b] Energy difference relative to the full 6-31G(d,p) basis set

[c] Structures reported in Ref. [15]

[d] Unbound structure previously reported in Ref.[31]

Table 3 BLYP single point interaction energy (in kcal mol⁻¹) calculations using the fully optimized PM3 geometry (BLYP//PM3), employing distinct *Gen*-type basis sets, for the process: α-CD (free) + (H₂O)₆ → α-CD · 6H₂O

	Basis Set: *Gen-1* 6-31G(d,p): O; O–H STO-3G: C–H	Basis Set: *Gen-2* 6-31++G(d,p): O; O–H STO-3G: C–H	Basis Set: *Gen-3* 6-311++G(2d,2p): O; O–H STO-3G: C–H	Basis Set: *Gen-4* 6-311++G(2df,2pd): O; O–H STO-3G: C–H	Basis Set: *Gen-5* 6-311++G(3df,3pd): O; O–H STO-3G: C–H
(H₂O)₆	(150/252)[a]	(186/288)[a]	(282/396)[a]	(384/528)[a]	(450/600)[a]
$\Delta E_{\text{ele-nuc}}$	−62.53 {−66.26}[b]		−39.91 {−42.55}[c] {−46.12}[d]	−38.41	−38.23
α-CD-Free	(762/1632)[a]	(900/1770)[a]	(1212/2142)[a]	(1512/2550)[a]	(1716/2784)[a]
α-CD · 6H₂O "down" - "*Struc-I*"	(912/1884)[a]	(1086/2058)[a]	(1494/2538)[a]	(1896/3078)[a]	(2166/3384)[a]
$\Delta E_{\text{ele-nuc}}$	−23.3 $\Delta^{6311++G(3df,3pd)}$ = −5.5[e]	−16.4 $\Delta^{6311++G(3df,3pd)}$ = 1.4[e]	−15.8 $\Delta^{6311++G(3df,3pd)}$ = 2.0[e]	−15.9 $\Delta^{6311++G(3df,3pd)}$ = 2.0[e]	−17.8
α-CD · 6H₂O "up" - "*Struc-II*"					
$\Delta E_{\text{ele-nuc}}$	−15.8 $\Delta^{6311++G(3df,3pd)}$ = −0.5[e]	−15.1 $\Delta^{6311++G(3df,3pd)}$ = 0.1[e]	−14.8 $\Delta^{6311++G(3df,3pd)}$ = 0.5[e]	−14.9 $\Delta^{6311++G(3df,3pd)}$ = 0.3[e]	−15.3
α-CD · 6H₂O "*Struc-III*"					
$\Delta E_{\text{ele-nuc}}$	12.7 $\Delta^{6311++G(3df,3pd)}$ = 0.1[e]	17.4 $\Delta^{6311++G(3df,3pd)}$ = 4.8[e]	15.1 $\Delta^{6311++G(3df,3pd)}$ = 2.5[e]	15.0 $\Delta^{6311++G(3df,3pd)}$ = 2.4[e]	12.6

[a] Total energies in hartree/particle and interaction energies in kcal mol⁻¹

[a] Number of contracted/primitive basis set

[b] BLYP/6-31G(d,p) fully optimized value. The corresponding $\Delta E^{\text{BLYP-BSSE}}$ value is 12.6 kcal mol⁻¹

[c] BLYP/6-311++G(2d,2p) fully optimized value from Ref. [36]. The corresponding $\Delta E^{\text{BLYP-BSSE}}$ value is 0.42 kcal mol⁻¹

[d] CCSD(T)/aug-cc-pVDZ//MP2/aug-cc-pVDZ fully optimized value from Ref. [36]. The corresponding $\Delta E^{\text{CCSD(T)-BSSE}}$ value is 6.04 kcal mol⁻¹

[e] $\Delta^{6311++G(3df,3pd)}$; energy difference relative to the value calculated with the *Gen-5* basis set (6-311++G(3df,3pd))

Gen-2, Gen-3, Gen-4 and Gen-5), keeping the CH_2 as "spectator" groups described by the minimal basis set (STO-3G). Results for the formation of water hexamer (planar hexagonal structure) from six isolated free water monomers are also reported for reason of comparison only. As expected the 6-31G(d,p) basis set significantly overestimate the stabilization energy for the water hexamer [33], with the 6-311++G(2d,2p) basis set providing a very good description compared with the computational much more expensive 6-311++G(3df,3pd) basis set. It can also be seen that the 6-31++G(d,p) split valence basis set perform very satisfactorily keeping a lower computational cost, and therefore, may be recommended for calculations on very large systems. A comparison with results for the fully optimized BLYP structures and CCSD(T)//MP2 energy calculations reveal a very good agreement for the stabilization energies evaluated with the BLYP functional and PM3 fully optimized water hexamer geometry. Looking at the interaction energy values for the structures I, II and III of the α-CD.6H₂O monomer, it can be seen that the 6-311++G(2d,2p) basis set (Gen-3) is also sufficient for the prediction of the hydrogen bond energies. As in the water hexamer case, the 6-31G(d,p) basis set does indeed overestimate the interaction energies, however the degree of the energy exaggeration depends on the spatial orientation of the potential hydrogen bond groups in the molecule, having a sizeable variation within the three structures (–7.5, –1.0 and –2.4 kcal mol^{-1}, respectively for structures I, II and III). An important feature of Table 3 is that it reports for the first time in the literature interaction energy values for cyclodextrins using DFT methodology (BLYP functional) and a very good quality basis set (6-311++G(3df,3pd)) at an affordable computational cost. These results indeed rises our hope to treat very large interacting, systems relevant to the supramolecular chemistry, using a reliable quantum mechanical method, with the inclusion of electron correlation effects. The (α-CD)$_4$. 24H₂O tetramer species depicted in Fig. 2 g, containing 576 atoms and 3648 contracted Gen-1 basis functions, is our starting point in direction to the supramolecular chemistry. Our group is already engaged in the study of necklaces of cyclodextrin and higher molecular aggregates employing quantum chemical approaches.

In order to better assess the effect of the full and Gen basis sets on the stabilization energies, four distinct dimers, which contain the relevant type of H-bond interactions present in the hydrated α-CD, i.e., water–water, water–alcohol and alcohol–alcohol types, were investigated using ab initio MP2 and DFT (BLYP functional) methods. These results are summarized in Table 4. The STO-3G basis set was assigned to the CH_3 group with the 6-31G(d,p), 6-311++G(2d,2p) and 6-311++G(3df,3pd) basis set used for the OH groups. As it is well-known the 6-31G(d,p) basis

set causes an overestimation of the stabilization energy for both MP2 method and BLYP functional, producing also a large basis set superposition error (BSSE) evaluated with the counterpoise approach [37]. For a more detailed discussion on the BSSE corrections see Ref. [38] and references therein (for a discussion on the effect of this correction for TS structures see Ref. [39]). If we take the size of the BSSE correction as a measure of degree of the completeness of a given basis set, in what interaction energies are concerned, it can be seen from Table 4 that the 6-311++G(2d,2p) and 6-311++G(3df,3pd) basis sets produced a BSSE value below 1 kcal mol^{-1} at the MP2 level of theory, also taken as a chemical precision index, therefore, being recommended for high level ab initio calculations. It can also be noted that the HF contribution to the MP2 energy presents a much smaller BSSE correction for a given basis set, approaching indeed negative values in some cases. This is a general trend for BSSE correction. The behavior for the BLYP functional is rather different. For the smaller 6-31G(d,p) basis set the BSSE correction matches the corresponding MP2 values, being larger in some cases. However, as the basis set is improved the BSSE decreases very rapidly, being considerably smaller than the MP2 values and also, as in the case of the HF method, may approach to negative values. When the Gen basis set is used the behavior observed depends strongly on the geometry of the dimer, however, the size of the BSSE correction found at the BLYP level is always considerably smaller than the MP2 value. As can be seen from Table 4, for the water–methanol dimer I, where the water molecule acts as a proton acceptor, the difference between the stabilization energies calculated with the full basis and the Gen basis set is insignificant, with an almost similar behavior found for the BSSE correction, with all three basis sets employed. However, for the other two dimers, only for the Gen-1 basis set a good agreement is obtained. As the basis set is enlarged, the difference between the full basis and the Gen basis set becomes noticeable, which may be an indication that this specific Gen basis set is not well-balanced for these two dimers. In order to better understand this geometrical dependence, MP2/6-311++G(2d,2p) fully optimized structures of the water–methanol and methanol-methanol dimers are shown in Fig. 3, along with the main distances between the CH_3 and OH groups. By looking at Fig. 3a and b it can be promptly seen that for dimer-I the CH_3 group, which carries the minimal STO-3G basis set, is more than 3.5 Å away from the water oxygen atom, while for the dimer-II case the distance between the proton donor hydrogen from water molecule to the CH_3 group is 2.7 Å, i.e., much closer to the water molecule. A similar behavior is found for the methanol dimer. This explains, in a clear way, why the Gen basis set works nicely for the methanol-water dimer-I. An important factor that must be taken into

Table 4 MP2 stabilization energies for hydrogen bonded dimers related to the hydrogen bond interaction present in the hexahydrated-α-CD. In the *Gen* basis set all carbon and hydrogen atoms from CH$_n$ groups are assigned a minimal STO-3G basis set, with the 6-31G(d,p), 6-311++G(2d,2p) and), 6-311++G(3df,3pd) basis sets being assigned to the remain atoms. The geometry optimizations were carried out with the full basis sets (6-31G(d,p) and 6-311++G(2d,2p))

MP2	HF^{Contribution} / 6-31G(d,p)^b	MP2/ 6-31G(d,p)	MP2/Gen-1	HF^{Contribution}/ 6-311++G(2d,2p)^b	MP2/ 6-311++G(2d,2p)^b	MP2/Gen-2	HF^{Contribution}/ 6-311++G(3df,3pd)^b	MP2/6-311++G (3df,3pd)//MP2/ 6-311++G(2d,2p)	MP2/Gen-3/MP2/ 6-311++G(2d,2p)
(H$_2$O)$_2$^{c}									
$\Delta E_{ele-nuc}$	−5.33 {−4.23}^{a}	−7.05 {−4.68}^{a}	–	−3.88{−3.69}^{a}	−5.36 {−4.49}^{a}	–	−3.82 {−3.64}^{a}	−5.30 {−4.62}^{a}	
$\Delta E_{ele-nuc}^{BSSE\ d}$	1.10 (21%)	2.37 (34%)	–	0.19 (5%)	0.87 (16%)	–	0.18 (5%)	0.68 (13%)	
CH$_3$OH–H$_2$O: I									
$\Delta E_{ele-nuc}$	−5.29 {−4.24}^{a}	−7.22 {−4.89}^{a}	−6.51 {−4.28}^{a}	−3.67{−3.40}^{a}	−5.42 {−4.45}^{a}	−5.12 {−3.61}^{a}	−3.61 {−3.38}^{a}	−5.37	−5.40
$\Delta E_{ele-nuc}^{BSSE\ d}$	1.05 (20%)	2.33 (32%)	2.23 (34%)	0.27 (7%)	0.97 (18%)	1.51 (29%)	0.23 (6%)	0.75 (14%)	1.59 (30%)
CH$_3$OH–H$_2$O: II									
$\Delta E_{ele-nuc}$	−4.90 {−3.48}^{a}	−7.50 {−4.25}^{a}	−7.68 {−4.83}^{a}	−3.83{−3.82}^{a}	−6.10 {−5.15}^{a}	−9.11 {−5.91}^{a}	−3.76	−6.12 {−5.38}^{a}	−10.0l
$\Delta E_{ele-nuc}^{BSSE\ d}$	1.42 (29%)	3.25 (43%)	2.85 (37%)	0.015(0.4%)	0.95 (16%)	3.2 (36%)	−0.02	0.74 (12%)	4.02 (40%)
(CH$_3$OH)$_2$									
$\Delta E_{ele-nuc}$	−4.69 {−3.25}^{a}	−7.87 {−4.46}^{a}	−7.12 {−4.19}^{a}	−3.62{−3.51}^{a}	−6.25 {−5.19}^{a}	−8.41 {−4.83}^{a}	−3.53 (−3.51)	−6.27 {−5.45}^{a}	−9.47
$\Delta E_{ele-nuc}^{BSSE\ d}$	1.44 (31%)	3.41 (43%)	2.93 (41%)	0.11 (3%)	1.06 (17%)	3.58 (43%)	0.017 (0.5%)	0.82 (13%)	4.43 (47%)
BLYP		BLYP/6-31G(d,p)	BLYP/Gen-1		BLYP/6-311++G(2d,2p)	BLYP/Gen-3		BLYP/6-311++G (3df,3pd))//BLYP/ 6-311++G(2d,2p)	BLYP/Gen-5/BLYP/ 6-311++G(2d,2p)
(H$_2$O)$_2$^{c}									
$\Delta E_{ele-nuc}$		−7.69 {−4.51}^{a}			−4.60 {−4.25}^{a}			−4.45 {−4.18}^{a}	
$\Delta E_{ele-nuc}^{BSSE\ d}$		3.18 (41%)			0.35 (8%)			0.27 (6%)	
CH$_3$OH–H$_2$O: I									
$\Delta E_{ele-nuc}$		−7.77 {−4.65}^{a}	−7.18 {−4.14}^{a}		−4.35 {−3.96}^{a}	−4.09 {−3.40}^{a}		−4.23 {−3.95}^{a}	−4.04 (−3.39)^a
$\Delta E_{ele-nuc}^{BSSE\ d}$		3.12 (40%)	3.04 (42%)		0.39 (9%)	0.69 (17%)		0.28 (7%)	0.65 (16%)
CH$_3$OH–H$_2$O: II									
$\Delta E_{ele-nuc}$		−7.84 {−3.39}^{a}	−7.91 {−3.30}^{a}		−4.92 {−4.61}^{a}	−6.76 {−5.41}^{a}		−4.79 {−4.59}^{a}	−7.05 {−5.27}^{a}
$\Delta E_{ele-nuc}^{BSSE\ d}$		4.45 (57%)	4.61 (58%)		0.31 (6%)	1.35 (20%)		0.20 (4%)	1.78 (25%)
(CH$_3$OH)$_2$									
$\Delta E_{ele-nuc}$		−7.36 {−4.11}^{a}	−7.05 {−4.11}^{a}		−4.68 {−4.35}^{a}	−5.95 {−4.46}^{a}		−4.56	−6.28 {−4.36}^{a}
$\Delta E_{ele-nuc}^{BSSE\ d}$		3.25 (44%)	2.94 (42%)		0.33 (7%)	1.49 (25%)		−1.30	1.92 (31%)

^{a} BSSE corrected stabilization energy values (ΔE^{BSSEc})

^{b} HF contribution to the MP2 stabilization energy. The correlation energy may be evaluated as: $\Delta E^{Corr} = \Delta E^{MP2} - \Delta E^{HF\text{-}Cont}$

^{c} Values taken from Ref. [33]

^{d} Basis set superposition error (BSSE) evaluated with the counter poise approach (see Ref. [37])
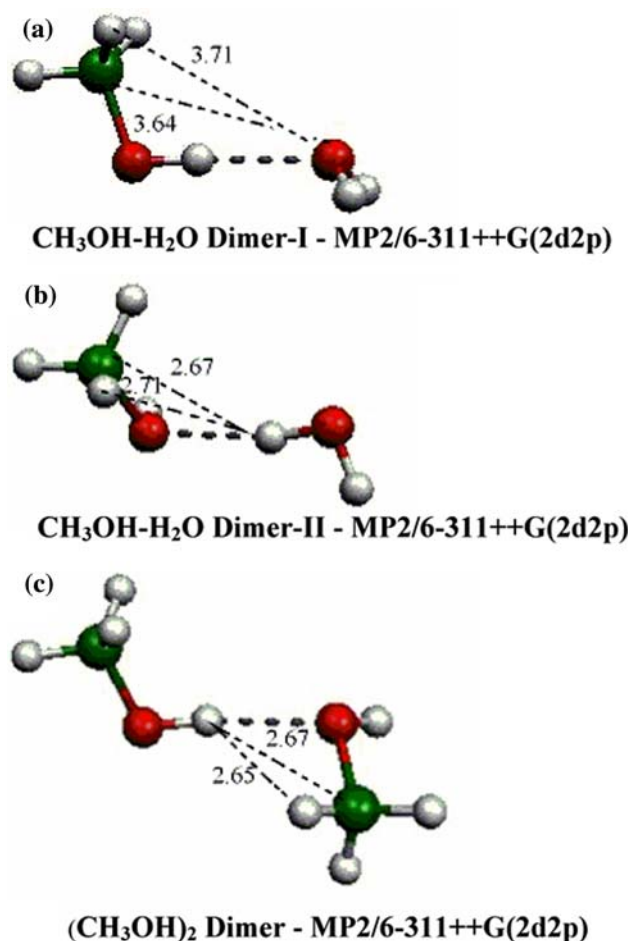
Fig. 3 Model dimers containing the hydrogen bond interactions present in the α-CD hexahydrated species with the relevant distances (in angstrom) involving the CH$_n$ group given. (**a**) CH$_3$OH–H$_2$O Dimer-I—MP2/6-311++G(2d2p), (**b**) CH$_3$OH–H$_2$O Dimer-II—MP2/6-311++G(2d2p), (**c**) (CH$_3$OH)$_2$ Dimer—MP2/6-311++G(2d2p)

account is the proximity of the CH$_3$ group with the H-bond centre. In the case of the hydrated α-CD species the large macrocycle keeps the CH$_n$ groups at a safe distance from the hydration sites, and so, the use of *Gen* basis sets can be justified.

From the last discussion and the results presented here for the α-CD$_n$ · 6nH$_2$O hydrated species we can affirm that, in what the use of the BLYP functional in conjunction with *Gen* type basis set is concerned, the 6-311++G(2d,2p) is recommended for the O-H groups, and also other oxygen atoms present, without performing BSSE correction. From the BLYP/6-311++G(2d,2p) BSSE results reported in Tables 4 and 3 for water dimer and hexamer, i.e. 0.35 and 0.42 kcal mol^{-1} respectively, we would not expect a sizeable increase in the BSSE value for the α-CD hydrated species. There is a great gain in the quality of the BLYP interaction energies calculated with the *Gen*-STO-3G/6-311++G(2d,2p) basis set, relative to

the smaller 6-31G(d,p) basis set, at a reasonable computational cost which confer credibility and plausibility to this approach. Nevertheless, care is needed in order to choose chemical sense criterions for selecting the sites in a supramolecuar system that can be assigned to a minimal STO-3G basis set. Through the use of a computer program developed in our group [22] we made this tedious and hard procedure of allocating the basis set atom by atom for a 500 atoms system operational, and so, we have ease and safe control of the basis set attribution to a large molecular system. The approach proposed here has also some advantages over standard hybrid methods such as ONIOM. By using mixed basis-set it is possible to set distinct levels of calculation to specific moieties in the molecule, which is not possible in ONIOM (as implemented in Gaussian) where up to three layers can be defined. In the ONIOM method the structure, energy and properties are quite sensitive to extrapolation scheme, increasing error with the number of layers. Finally, we hope that the procedure presented here can be of aid to people working on quantum chemical calculations of large interacting systems, enabling them to tackle real big problems within the computational facilities available.

Conclusions

In this work we proposed an efficient procedure for the calculation of interaction energies for hydrated α-CD$_n$ · 6 nH$_2$O species (n = 1, 2, 3, 4) using HF and DFT methods, where an atom by atom basis set is specified through the aid of a computer code that we developed which creates automatically an usual input for the Gaussian program (which makes use of the *Gen* option), therefore making the process of practical use for systems containing more than 500 atoms, lowering substantially the computational cost (allocation of hard disk space and CPU time) of a quantum chemical calculation. In the calculation of dimer, trimer and tetramer α-CD structures, the split valence 6-31G(d,p) basis set was used for the O–H groups which are capable of participating in H-bond interactions, and also all oxygen atoms present in the molecular structure, with a minimal STO-3G basis set being assigned to the "spectator" CH$_n$ groups. We also report for the first time in the literature DFT quantum chemical calculations for hydrated cyclodextrin using a large triple quality basis set (6-311++G(3df,3pd) containing 2166 contracted basis functions), showing the plausibility of performing such type of calculations for very large interacting systems. The procedure proved to be adequate for treating α-CD monomer, dimer, trimer and tetramer hydrated species, and can also be extended to other H-bonded interacting systems of any size and inclusion complexes. Among the five basis set

utilized in this work (6-31G(d,p), 6-31++G(d,p), 6-311++G(2d,2p), 6-311++G(2df,2pd) and 6-311++ G(3df,3pd)) the *Gen-2* basis set (6-31++G(d,p)/STO-3G) in conjunction with the BLYP functional, was found to produce very satisfactory interaction energy values, at a computational reasonable cost, and therefore, may be recommended in further studies on larger molecular associations. However, care is needed on choosing which CH_n groups within a given supramolecular structure can be assigned to a minimal STO-3G basis set. Through the use of the procedure proposed here, we hope to be able to tackle the task of calculating the interaction energy of large structures that presents a challenge in supramolecular chemistry (and also the area of inclusion compounds), where hydrogen bond interactions play a major role, and, therefore, electron correlation effects must be adequately taken into account.

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