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Molecular Modelling Study of the 2:1 γ -Cyclodextrin: C_{60} Complex. Dummy Atoms Simulating Bond Electron Distribution

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The 2:1 γ -cyclodextrin: C_{60} inclusion complex was studied by molecular dynamics simulations with the AMBER package. Dummy atoms were used to incorporate the various electron densities on the fullerene bonds into the molecular mechanics scheme. According to our MD simulations, the two γ -cyclodextrins adopt a V-shape in the complex, which strengthens some intermolecular hydrogen bonds. Fullerene interacts better with O2 than with O3 oxygens (from the secondary hydroxyl groups on C2 and C3, respectively); no interactions with glycosidic O4 were detected.

Keywords: Cyclodextrins; Inclusion complexes; Molecular modelling; Molecular dynamics; Fullerene

INTRODUCTION

Buckminsterfullerene [1], more commonly called fullerene (or C_{60}), with a diameter [2] of 6.83 Å is a highly symmetric (I_h point group) non-polar molecule. Due to its size, it forms complexes with γ -cyclodextrin (γ -CD) and with calix[8]arenes, whose cone-shaped cavity have suitable internal diameters and depths. The γ -CD/ C_{60} complex has been experimentally studied by mass spectroscopy [3], circular dichroism [4], kinetic studies [5,6], and chromatography [7,8]. The rest of the most common CDs are too small to include fullerene: the diameters of β - and α -CD vary from 6.0 to 6.5 Å and from 4.7 to 5.3 Å [9], respectively. However, some CD derivatives, such as prepolymers of α -, β - and γ -CD, have recently been used to improve the complexation of fullerene [10].

Since the discovery of C_{60} in 1985 by Kroto [11], many publications have documented its properties and reactivity. It has been used for the inhibition of the HIV-1 protease [12], and as a component of the hydrophobic active sites of enzymes [13,14] which throws light on resulting biologic functions. It is also used in a wide variety of reactions: it forms endohedral structures [15] and substitution compounds [16], and has been used in rotaxanes [17,18], in self-assembling [19,20], and as a superconductor material [21,22] (compound of intercalation and nanotubes). Nevertheless, due to its high price, experimental activity is still limited. The theoretical studies on C_{60} are numerous and it has been studied by any possible existing computational method (*ab initio* and DFT [23], semi-empirical methods [24], empirical force field calculations [25–27], and graph-drawing algorithms [28]). The theoretical studies have also been performed on its complexes with calix[8]arenes [29], and with γ -CD [30,31]. These last studies are mostly centred to obtaining the most probable geometry for the complex formation by Monte-Carlo simulations [30] or to study the complexation kinetics [31]. Clusters of $(C_{60})_n$ molecules have also been studied by molecular mechanics [32] and molecular dynamics computations [33].

Being a highly symmetric and non-polar molecule, fullerene is not soluble in polar solvents [34]. In a polar environment (such as water) and in the presence of γ -CD, complexes having a 2:1 stoichiometry (dimer of γ -CD: C_{60}) are formed. Various experimental studies have sought to increase the yield of complexation during its chemical synthesis

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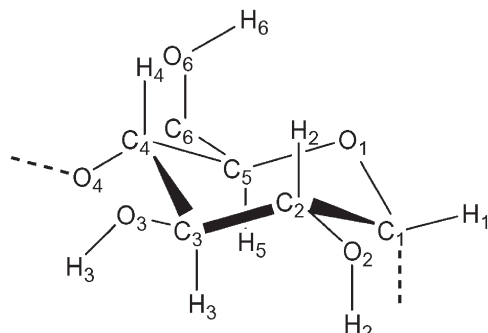


FIGURE 1 Chemical structure and atomic numbering used for each glucose unit making up the γ -CD.

[35]. Depending on the proportion of γ -CD: C_{60} used, a 2:1 complex or an aggregate of fullerene surrounded with γ -CDs is formed [36]. Some papers [37,38] put forward the hypothesis that the stability of the complex is due to an n -donor effect from O3 and from the interglycosidic O4 (see Fig. 1). Fullerene is mainly an electron-acceptor [39] (electronic affinity 2.7 eV [40]), and oxygen atoms from ether functions and primary hydroxyl groups are known to be n -donors in the formation of charge transfer complexes. Finally, the isolated γ -CD structure obtained by X-ray diffraction shows that O4 and O3 adopt a position that could allow a charge transfer effect with C_{60} and facilitate the formation of hydrogen bonds between two adjacent glucose units of type C3–O3–H3...O2(H2)–C2 [41,42]. The formation of a core-shell charge transfer complex has also been described in the C_{60} complexes with various water-soluble calixarenes [43,44].

This paper reports a computational study designed to establish the geometry of the 2:1 γ -CD: C_{60} complex in a water-solvated environment, and to find the intermolecular interactions that hold the supramolecular structure.

COMPUTATIONAL METHODOLOGY

All computations for the γ -CD dimer, the C_{60} and the 2:1 γ -CD: C_{60} complex were made with the AMBER v.5 package [45]. Each system was studied under two well-defined conditions: (i) *in vacuo*, (ii) in a cubic box of TIP3P [46] water molecules (size of the box changes with the solute but for the 2:1 complex a box of 35 Å was used). More specific details are: 8 Å for the primary cutoff and 13 Å for the secondary cutoff were applied to non-bonded interactions; bond lengths involving hydrogen atoms were held fixed using the SHAKE [47] algorithm; and periodic boundary conditions were used only for computations involving solvent.

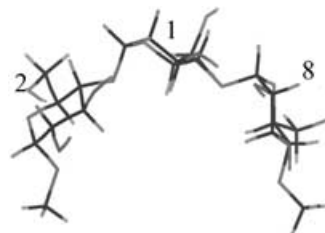


FIGURE 2 Fragment of γ -CD used for obtaining the atomic charges from *ab initio* computations. Only charges of the central glucose unit (marked as 1) were used in the RESP program.

Determination of the Atomic Charges of γ -CD

γ -CD contains too many atoms to be treated as a whole by *ab initio* programs. The macrocycle was fragmented into 8 pieces consisting of three glucose units (Fig. 2) and cut bonds were filled with methyl groups. The fragments were fully optimised using the GAUSSIAN-94 program [48] at the Hartree-Fock level with the STO-3G basis set. Each optimised fragment then underwent RHF/6-31G* single-point calculation. The 8 resulting electrostatic potentials were used for two-stage multiple-conformation RESP [49,50] charge fitting, giving rise to a single set of charges for glucose atoms.

Parameters complementary to those already described in the parm94 force field [51] were added for the glycosidic linkage.[†]

Determination of the Atomic Charges of Fullerene

Fullerene belongs to the I_h point group. All its carbon atoms have the same null atomic charge because the molecule is neutral. Nevertheless, the fullerene structure contains 12 pentagons and 20 hexagons. The X-ray structure of fullerene [52,53] shows two different bond lengths (1.432 and 1.389 Å) for bonds between a hexagon and a pentagon, and for those between two hexagons, hereinafter referred as [6,5]

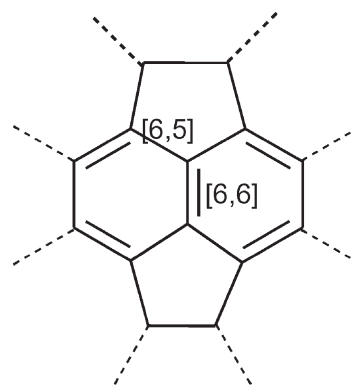


FIGURE 3 The two binding types of the C_{60} .

[†]The parameter used is: ANGLE OS–CT–OS: $K\theta = 80.0$, $\theta_{ef} = 126.0^\circ$.

TABLE I Experimental (IR) and calculated (without and with dummy atoms) bond lengths and diameter for fullerene (in Å)

	Experimental*	Without dummies	With dummies
[6,6] length	1.39	1.40	1.42
[6,5] length	1.46	1.41	1.50
Diameter	7.09	7.03	7.17

* Refs. [43,44].

and [6,6], respectively (Fig. 3). Both numbers lie between standard sp^3 - sp^3 (1.54 Å) and sp^2 - sp^2 (1.33 Å) bond lengths. These different bond lengths reflect different bond electron densities (and consequently we can assume a different charge distribution). All molecular mechanics schemes assume that charges are held by atoms. We were, thus, faced with a new problem: different electron densities on bonds. Dummy atoms were located on the mid point of each bond to mimic these electron density differences. The new structure, now generated by the 90 dummy atoms, no longer had I_h symmetry. The *ab initio* computed electrostatic potential for C₆₀ was thus distributed between the 90 dummy atoms, and not between the 60 carbon atoms.

Computed (RESP) atomic charges are 0.026217 and -0.052434 for the 60 dummy atoms in the middle of the [6,5] and for the 30 over the [6,6] bonds, and they will be termed DP and DN, respectively. The electrostatic energy involved in the host-guest interaction can thus be evaluated with these charged dummy atoms.

The introduction of these 90 charged dummy atoms into the C₆₀ structure caused severe vdW repulsions between carbon atoms.[‡] New parameters[¶] were introduced to maintain the fullerene geometry.[§] Table I contains the most representative bond lengths obtained in these computations. It is worth noting here that computed bond lengths do not significantly depend on the use of dummy atoms, and always reasonably reproduce experimental differences.

MOLECULAR DYNAMICS SIMULATIONS

The 2:1 γ -CD:C₆₀ complex (Fig. 4) was studied with and without dummy atoms to compare their effect on the intermolecular electrostatic interactions, as well as *in vacuo* and solvated with water. Fullerene is too large as to be able to form a stable 2:1 complex with γ -CD in other relative arrangement than the Head-to-Head (calling Head to the wider rim). Consequently, only this arrangement has been studied. Two different relative orientations for the two γ -CD units were used as starting points: one with "eclipsed" and the other with "staggered"

glucose units from different CD units. The energy and geometry of the system along the simulations were almost identical.

The study was performed over the isolated fullerene, over the γ -CD dimer and over the 2:1 γ -CD/C₆₀ complex. The structure of each system was initially minimized, and then heated to 300 K at three intervals (1, 10 and 10 ps). A time step of 2 fs was used with constant temperature and pressure. Once systems were equilibrated (about 10 ps were needed), collection runs of 500 ps for the isolated C₆₀, 5000 ps for the γ -CD dimer, and of 2000 ps for the complex (formed using the final γ -CD dimer structure) were performed. Trajectories were saved every 5 ps (100 snapshots for the fullerene, 1000 for the γ -CD dimer, and 400 for the complex).

Results for the Calculations without Using Dummy Atoms in Fullerene

Table II shows the energy contributions found in the MD simulations in the absence and in the presence of solvent (water) for fullerene, for the γ -CD dimer, and for the 2:1 γ -CD:C₆₀ complex. In the absence of solvent, the electrostatic energy of fullerene was null because atomic charges of C₆₀ carbons are all zero. The isolated γ -CD dimer keeps its Head-to-Head arrangement during the simulation time. However, the presence of one C₆₀ molecule between the two γ -CD units separates both moieties and debilitates the stabilizing intermolecular hydrogen bonds. This fact together with the absence of solvent, which prevents the formation of solute-solvent hydrogen bonds, force the two γ -CDs to change their relative orientation from Head-to-Head (Fig. 4) to almost Tail-to-Tail (Fig.5) to maximize their intermolecular hydrogen bonds. The C₆₀ is therefore complexed with only one γ -CD unit. Due to all these geometrical rearrangements, the complexation process is energetically unfavourable ($\Delta E = E(\text{complex}) - E(\text{C}_{60}) - 2E(\gamma\text{-CD})$) by as much as 326 kcal/mol (see Table II). This energy mainly comes from the bond and angle energy contribution in the complex, which highly destabilizes the system.

[‡]For example, the C1-C2-C3 unit is now converted into the C1-D1-C2-D2-C3 unit. Consequently, C1 and C3 have strong repulsive vdW interactions.

[¶]BOND DP-CA: Kr = 5000.0, r_{eq.} = 0.7265 Å, BOND DN-CA: Kr = 5000.0, r_{eq.} = 0.695 Å, ANGLE CA-DP-CA: K θ = 0.00, $\theta_{\text{eq.}}$ = 180.0°.

[§]This methodology was checked against its behavior with the benzene molecule.

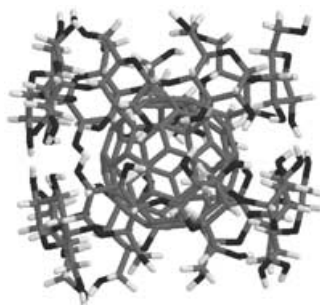


FIGURE 4 Initial structure for the 2:1 γ -CD: C_{60} complex used in the MD simulations.

In contrast, in the presence of solvent, the three studied systems are stable during the entire simulation. Interestingly, in the case of the 2:1 γ -CD/ C_{60} complex, the two γ -CD units adopt an oval shape (Fig. 6), and thus they wrap better the C_{60} (like a tennis ball).

Results for the Calculations Using Dummy Atoms in the Fullerene

Table III contains the energy data for the MD simulations of this system. Energy values for the C_{60} with and without dummy atoms (Tables II and III, respectively) cannot be compared due to the not identical number of "atoms" in the system. Interestingly, the presence of charges over the dummy atoms generated an electrostatic energy of 11 kcal/mol, a rather small value in comparison with the total energy (2657 kcal/mol) which was too big due to the artificial vdW interactions (*vide supra*). As before, the complex was unstable ($\Delta E = 463$ kcal/mol) according to the MD simulation *in vacuo* due to the formation of a 1:1 complex as in the case of not using dummy atoms.

In the presence of solvent, the 2:1 complex was again stable during all the simulation time. Figure 7 shows the total energy variation for the last 1000 ps

of the MD simulations. Figure 8 shows the variation of the potential energy (E_{gas}) of the complex after the contribution of the solvent energy was removed (with the ANAL program) from the total energy to better estimate the energy variation. A stable complexation of the C_{60} by the γ -CD dimer during the simulation run can be inferred because the energy was stable.

The final structure for the solvated 2:1 γ -CD: C_{60} complex (Fig. 9) shows the γ -CD dimer adopting a V form, and allowing the interaction of solvent molecules (water) with one face of the C_{60} . Interestingly, there are no water molecules inside the complex in the region where the two γ -CDs are separated. As far as we know, this geometrical arrangement has never been described before.

Analysis of the Interaction Energy

The interaction energy ($\Delta E_{\text{binding}}$) was calculated using the MM/PBSA [54] methodology, which evaluates the contribution of each species to total energy by removing the undesirable molecules.

C_{60} and γ -CD structures were taken from the same trajectory file as the complex. Solvent contribution was eliminated from the energy computation because MM/PBSA methodology only takes into account solutes. Results for the simulations with and without dummy atoms are shown in Table IV. The $\Delta E_{\text{binding}}$ (defined as $E(\text{complex}) - E(C_{60}) - E(2\gamma - \text{CD})$) is about the same for the two cases studied (with and without dummy atoms). The smallness of the difference found (8 kcal/mol) reinforces the validity of the simulations with dummy atoms. It is worth mentioning that, unlike the findings for the simulations *in vacuo*, the complexation process was now favoured by about -78 kcal/mol.

Interestingly, the use of charged dummy atoms in the simulations does not significantly modify the contribution of the non-bonded electrostatic energy

TABLE II MD simulations of the complexation process between C_{60} (without using dummy atoms) and two γ -CDs. Energy contributions (kcal/mol) for the isolated C_{60} , for the γ -CD Head-to-Head dimer, and for the 2:1 γ -CD: C_{60} complex, as well as the complexation energy ($\Delta E = E(\text{Complex}) - E(C_{60}) - E(\gamma\text{-CD dimer})$)

	No solvent				Solvent (water)		
	C_{60}	γ -CDs*	2:1 γ -CD: C_{60} †	ΔE	C_{60} ‡	γ -CDs*†§	2:1 γ -CD: C_{60} §
NB vdW energy	-32.67	-121.45	-186.99	-32.87	541.28	1566.97	1523.92
NB electrostatic energy	0.00	-1229.17	-1207.78	21.31	-4730.71	-14972.43	-15296.94
Bond energy	9.56	22.27	107.87	76.04	33.22	76.28	108.03
Angle energy	171.34	97.58	416.85	147.93	189.84	226.48	411.63
Dihedral energy	530.62	192.72	746.78	23.44	537.07	182.22	742.74
1.4 vdW energy	90.22	105.12	215.24	19.90	92.89	114.68	208.36
1.4 Elec. energy	0.00	1553.97	1570.91	16.94	0.00	1543.24	1550.57
Total potential energy	769.05	621.03	1662.90	272.82	-3336.40	-11262.57	-10751.70
Total kinetic energy	0.00	251.12	304.36	53.24	838.29	2512.31	2617.57
Total energy	769.05	872.15	1967.26	326.06	-2498.11	-8750.26	-8134.12
Rms (Total energy)	0.00	2.46	5.12	5.68	20.20	36.69	37.45

*Head-to-Head dimer. †In fact, this is a 1:1 complex. ‡430 water molecules. §1266 water molecules. §1233 water molecules.



FIGURE 5 Snapshot of the final structure of the MD simulations of the 2:1 γ -CD:C₆₀ complex in the absence of solvent.

term to the $\Delta E_{\text{binding}}$ (see Table IV); however, it mainly modifies the contribution of van der Waals energy for about 8 kcal/mol (Table IV). Nevertheless, careful analysis of the energy data in Table IV shows that the non-bonded electrostatic interaction for the γ -CD dimer when dummy atoms are used is 14 kcal/mol smaller than when no dummy atoms are used. This difference indicates very subtle conformational changes in the γ -CD dimer, which lower its contribution without altering the contribution of any other energy.

The use of a single trajectory file for computing the interaction energy may hide the real binding energy when one of the molecules differs in conformation between the isolated and the complexed forms. Independent MD simulations with only two γ -CD units were performed to calculate the most stable arrangement and the binding energy for the γ -CD dimer [55]. The consideration of the most stable arrangement of the solvated γ -CD dimer allows evaluation of the contribution of the γ -CD conformational changes to the binding energy. The absence

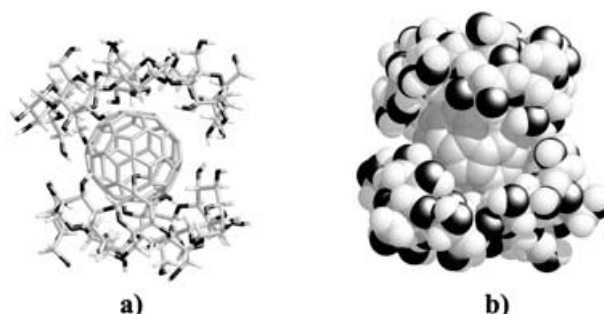


FIGURE 6 Average structure obtained in the MD simulations with solvent (water) for the 2:1 γ -CD:C₆₀ complex (water molecules were removed for clarity): (a) sticks model; (b) CPK model.

of the C₆₀ lets the two γ -CD units adopt always a parallel arrangement, but the most stable γ -CD dimer has the Tail-to-Tail orientation. The $\Delta E_{\text{binding}}$ computed considering this Tail-to-Tail orientation are gathered in the final columns of Table IV (contributions for the complex and for the C₆₀ are taken from the previous trajectory). These newly obtained $\Delta E_{\text{binding}}$ are now about -31 kcal/mol smaller than when the orientation of the γ -CDs in the complex is considered. However, the difference between the binding energy when dummy atoms are or are not in the simulations is much smaller (only 4 kcal/mol).

The contribution of dihedral energy is no longer null, consistent with the change observed in the geometrical arrangement of the γ -CD dimer (from parallel orientation of isolated units to a V shape in the complex). This change in shape produces a destabilization of about 40–50 kcal/mol (about 30 kcal/mol in the non-bonding van der Waals, and 26 kcal/mol in the dihedral contribution energies). These two destabilizing effects are partly compensated for by the stabilization of 13–27 kcal/mol observed in non-bonding electrostatic energy. This difference of 4 kcal/mol, favoring the system

TABLE III MD simulations of the complexation process between C₆₀ (using dummy atoms) and two γ -CDs. Energy contributions (kcal/mol) for the isolated C₆₀ and for the 2:1 γ -CD:C₆₀ complex, as well as the complexation energy ($\Delta E = E(\text{Complex}) - E(\text{C}_{60}) - E(\gamma\text{-CD dimer})$)

	No solvent			Solvent (water)	
	C ₆₀	2:1 γ -CD:C ₆₀	ΔE^*	C ₆₀ [†]	2:1 γ -CD:C ₆₀ [‡]
NB vdW energy	2200.11	2101.27	22.61	2829.89	3827.18
NB electrostatic energy	11.32	-1194.98	22.87	-4713.44	-15359.52
Bond energy	445.53	594.95	127.15	521.40	594.03
Angle energy	0.00	218.09	120.51	0.00	224.20
Dihedral energy	0.00	206.42	13.70	0.00	205.71
1,4 vdW energy	0.00	117.36	12.24	0.00	114.75
1,4 electrostatic energy	0.00	1564.15	10.18	0.00	1550.87
Total Potential energy	2656.95	3607.25	329.27	-1362.15	-8842.79
Total kinetic energy	0.00	384.37	133.25	918.27	2710.27
Total energy	2656.95	3991.62	462.52	-443.88	-6132.52
Rms (Total E.)	0.01	3.64	4.39	20.30	34.27

* Computed using the data for the γ -CD dimer from Table II. [†] 430 water molecules. [‡] 1273 water molecules.

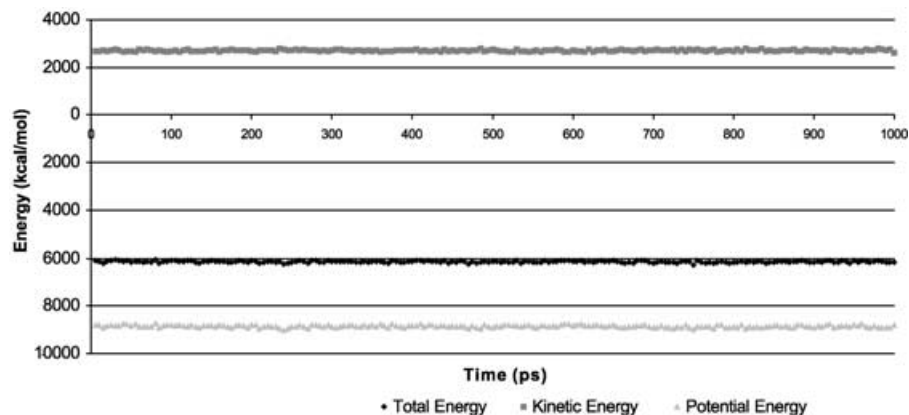


FIGURE 7 Variation of the different energies of the solvated complex with dummy atoms.

when dummy atoms are used, can be assigned to the stabilization due to the charges in the C_{60} .

The similarity of the results when C_{60} has or has not dummy atoms in its structure allows affirming that the 2:1 γ -CD/ C_{60} complex is about 32 kcal/mol more stable than the isolated fragments.

Hydrogen Bonds Analysis

An in-house program (ANAHB) was used for a quantitative analysis of the hydrogen bonds of each conformation during all the simulation runs. This program counts how many hydrogen bonds there are between the two γ -CDs in each snapshot, and gives the final result as an average. The CARNAL [56] module of the AMBER program was used to study the bonding percentages.

Analysis of the Complex without Using Dummy Atoms in Fullerene

No significant differences were found between the percentages of intraglycosidic O3–H3···O2 and O2–H2···O3 hydrogen bonds in the complex. Percentages were relatively low (about 45%), which indicates other hydrogen bond interactions stabilizing the complex.

The analysis of the interglycosidic hydrogen bonds indicates that the deformation of some glucose residues was due to the formation of O2–H2···O2 and O3–H3···O3 hydrogen bonds between both γ -CD units. Moreover, some glucose units lose their parallel arrangement and turn due to the formation of O6–H6···O6 interglycosidic hydrogen bonds.

No intermolecular hydrogen bonds (populations < 40%) were present between three of the glucoses of

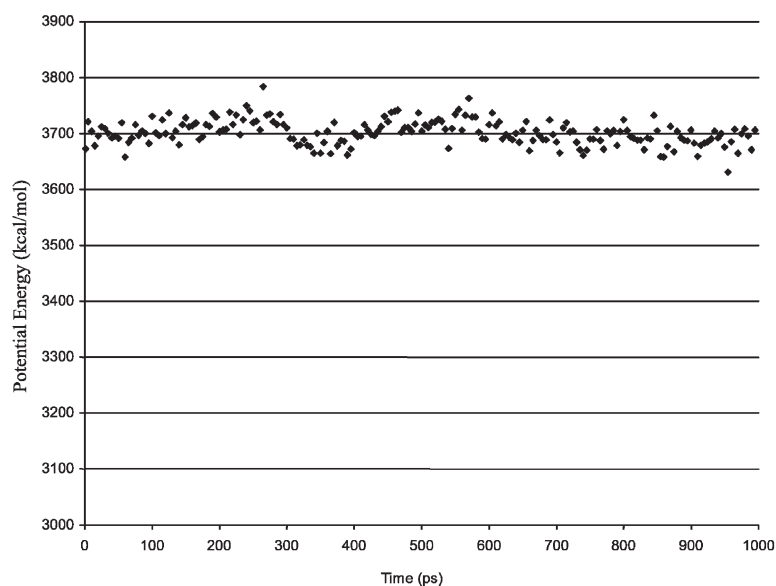


FIGURE 8 Potential energy (E_{gas}) from the complex with dummy atoms (energy coming from water molecules was subtracted, using the ANAL program, for better analysis).

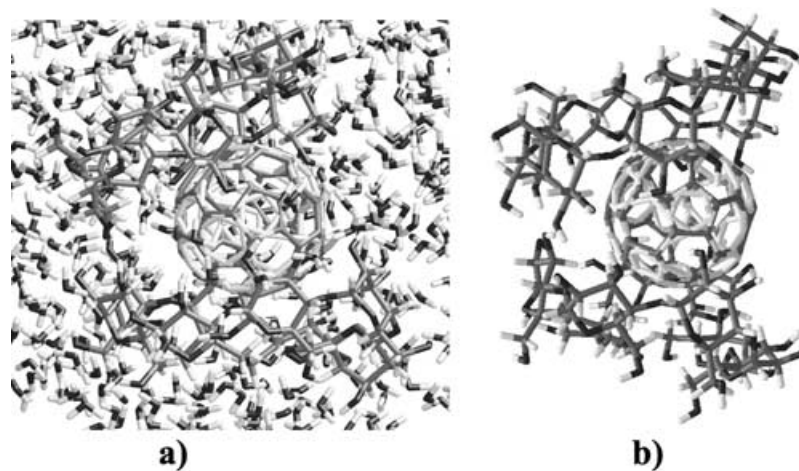


FIGURE 9 Snapshot of the final structure of the solvated 2:1 γ -CD:C₆₀ complex: (a) view with water molecules; (b) water molecules removed for clarity.

one γ -CD and three other glucoses from the other γ -CD unit, corresponding to the open part of the V shape. However, three other different glucose units of one γ -CD always interacted (populations >70%) with the same three other glucoses of the other γ -CD. This indicates that the two γ -CD units are held fixed during the simulation.

Analysis of the Complex Using Dummy Atoms in Fullerene

No significant differences between the percentages of intramolecular O3–H3···O2 and O2–H2···O3 hydrogen bonds (55.5 and 45.5%, respectively) were observed; almost the same values were obtained as for the simulations without dummy atoms. One of the γ -CD units was strongly deformed along the simulation due to the presence of intramolecular O3–H3···O6 interactions (51.5%) in one of its

glucoses. Moreover, the presence of interglycosidic interactions of the type O6–H6···O6 (46.5%) between two non-consecutive glucose units caused several glucoses to turn over during the simulation run, as was found for the interglycosidic hydrogen bonds for the complex without dummy atoms. Figure 10 depicts the inter- and intra-glycosidic hydrogen bonds for both γ -CD units (an arrow marks the presence of the turned glucose for each CD).

Several figures for the intermolecular hydrogen bonds are really high (from 85.5 to 100%), indicating that some glucoses from one γ -CD unit stay in front of another glucose from the other γ -CD during the entire simulation, and so prevent the spinning of one unit over the other. The absence of strong intermolecular hydrogen bonds (<40%) between three pairs of glucoses confirms the V form of the two γ -CD during the entire simulation.

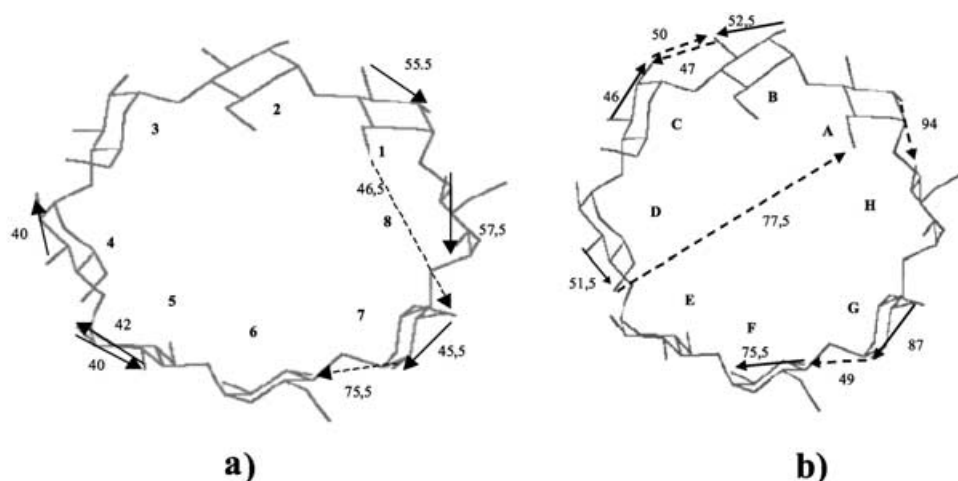


FIGURE 10 Diagram of the intra- (filled line) and inter-glycosidic (dotted line) hydrogen bonds (with percentage >40%) existing in both γ -CD units (the direction of the arrow shows the donor effect O···H–O); (a) one of the γ -CD units, (b) the other γ -CD unit.

TABLE IV Interaction energies ($\Delta E_{\text{binding}} = E(\text{complex}) - E(C_{60}) - E(\gamma\text{-CDs})$) and energy contributions (kcal/mol) obtained using the MM/PBSA methodology on the complexation process between C_{60} and two γ -CDs in the presence of solvent. Binding energies were obtained considering two different γ -CD energies: that from the complex and that from its most stable orientation (Tail-to-Tail)

	Without dummy atoms			With dummy atoms			Tail-to-Tail γ -CD dimer				
	2:1 γ -CD: C_{60}	2 γ -CDs	C_{60}	$\Delta E_{\text{binding}}$	2:1 γ -CD: C_{60}	2 γ -CDs	C_{60}	$\Delta E_{\text{binding}}$	2 γ -CDs	$\Delta E_{\text{bin.}}^*$	$\Delta E_{\text{bind.}}^\dagger$
NB vdW energy	-197.36	-82.53	-32.87	-81.96	2095.91	-82.53	2252.27	-73.84	-115.05	-49.44	-41.31
NB Electrostatic energy	-1089.27	-1089.27	0.00	0.00	-1092.17	-1103.40	11.33	-0.10	-1076.28	-12.99	-27.17
Bond energy	108.08	77.28	30.80	0.00	596.31	77.16	519.15	0.00	75.19	2.09	1.97
Angle energy	412.34	223.11	189.22	0.00	222.97	205.74	0.00	0.00	220.44	2.68	-2.53
Dihedral energy	742.46	205.70	536.76	0.00	205.74	114.85	0.00	0.00	179.76	25.94	25.98
1.4 vdW energy	207.82	114.30	93.52	0.00	114.85	1551.84	0.00	0.00	116.30	-2.00	-1.45
1.4 electrostatic energy	1550.26	1550.26	0.00	0.00	3695.47	986.64	2782.76	-73.94	1546.25	4.01	5.59
Total potential energy	1734.33	998.86	817.43	-81.96	19.92	17.34	7.52	27.45	946.62	-29.72	-33.91
Rms (Pot. E.)	18.65	18.80	5.32	27.14					18.15	26.56	27.97

* Without dummy atoms. † With dummy atoms.

Host-guest Structural Analysis

The number of close contacts between the glucose oxygens and the dummy atoms of the C_{60} were computed during all the simulation runs by the ANAHB program. The contacts between hydrogen and dummy atoms were ignored since C_{60} is not an electron donor [37–39].

Table V shows the number of positively charged dummy atoms (DP) close to the O2, O3 and O4 γ -CD oxygens (at distances less than 2, 2.5 and 3 Å). The frequency of contacts (defined as the number of contacts divided by the number of dummy atoms giving rise to them) is also included in Table V. There were always more close O2···DP contacts than O3···DP ones. This finding contradicts a publication [37] that assumed there was charge transfer from O3 to the C_{60} molecule. In that study, the geometrical data deduced from the X-ray structure for an isolated γ -CD were analysed, and showed interglycosidic hydrogen bonds of the type C3–O3–H···O2(H2)–C2; the O2 atoms were using their lone pairs, and thus their capacity for being electron-donors was much less. Thus, O3 atoms were thought to behave as electron-donors and to interact with the C_{60} molecule, but no real proof of this interaction was given.

The γ -CD conformation in the solvated complex can be completely different from the conformation of an isolated and solvated γ -CD dimer (*vide supra* and Table II). It is, thus, reasonable to think that the interglycosidic hydrogen bond chain would also be different in the solvated complex. According to Table V, the pairs O2···DP have the largest number of close contacts. As these calculations give short-distance frequencies, we cannot ensure that these distances represent real interactions. Nevertheless, these results suggest that C_{60} interacts better with the O2 than with the O3 atoms.

The very small frequencies for DP···O4 indicate that O4 are far enough from the C_{60} atoms to interact. Table V also shows that the frequencies of close contacts for the non-solvated complex are always smaller than those for the solvated complex. Thus, studies and deductions from X-ray structures of the isolated host and guest do not provide sound conclusions for the solvated complex.

The average distance between the centre of mass of the two γ -CDs in the solvated 2:1 complex was computed as 9.618 Å, while the figure was 5.086 Å for the simulation of a solvated γ -CD dimer. Therefore, the two γ -CDs are much farther from each other in the 2:1 complex with C_{60} , due to the presence of fullerene (diameter = 7.1 Å). This geometrical arrangement also produces hydrogen bond interactions between the two CD units, which are energetically weaker for the complex than for the isolated γ -CD dimer.

TABLE V Number and frequencies of close contacts between the positive dummy atoms (DP) of the C₆₀, and the O2, O3, and O4 glucose oxygens for the solvated and unsolvated 2:1 γ -CD:C₆₀ complex, classified depending on distances

Contact	Solvated complex						Unsolvated complex		
	<2 Å	Frequency*	<2.5 Å	Frequency*	<3 Å	Frequency*	<2.5 Å	<3 Å	Frequency*
DP...O2	24	0.8	72	1.2	138	2.3	0	98	1.63
DP...O3	0	0	4	0.06	28	0.46	0	3	0.05
DP...O4	0	0	0	0	11	0.18	0	9	0.15

*Frequencies were computed dividing the total number of close contacts between the total number of positive (60) dummy atoms.

Complex-solvent Interactions

The radial distribution function representing the distance between the complex (solute) and the solvent oxygen atoms (Fig. 11) demonstrates the presence of two well-defined solvation layers around the complex. The first goes from 1.5 up to 2.3 Å, and the second from 2.3 to 4.00 Å. Water molecules closest to the solute are situated at 1.46 Å. The closest water molecules to the C₆₀ were located at 2.8 Å (further than the first solvation layer, 2.2 Å). No water molecules interact with fullerene even in the region where it is not covered by the γ -CD dimer, in agreement with the C₆₀ hydrophobicity.

The radial distribution function for the distance between the water and the hydroxyl groups of the γ -CDs shows a clear arrangement of the water molecules around the γ -CDs (Fig. 11). The water hydrogens interact with the CD oxygens (O-HW) and the water oxygens interact with the CD hydroxyl hydrogens (H-OW), giving rise to two well-defined solvation layers.

CONCLUSIONS

The results of the computational study (MD simulations and analysis) of the solvated 2:1 γ -CD:C₆₀ complex challenge the hypotheses expressed in other publications. The two γ -CDs adopt a V shape, exposing a part of the C₆₀ to the solvent. Nevertheless, the water molecules are far

away from fullerene due to its hydrophobicity. The γ -CD conformation is modified when it complexes C₆₀. The number of inter- and intramolecular hydrogen bonds changes, depending on the presence of the C₆₀. The two γ -CDs adopt a "V" form in the presence of one C₆₀ but are in a parallel disposition in its absence. The γ -CD units did not spin during the simulation time, suggesting that interactions between close glucoses are much stronger than the interactions between two slightly separated parallel γ -CD units.

The presence of solvent is necessary to stabilize the complex. The MD simulations performed *in vacuo* gave rise to a 1:1 complex between host and guest. The solvent forms two well-defined solvation zones around the complex.

According to our calculations, fullerene interacts more with O2 than with O3, and no interaction was detected with the interglycosidic oxygen atoms (O4).

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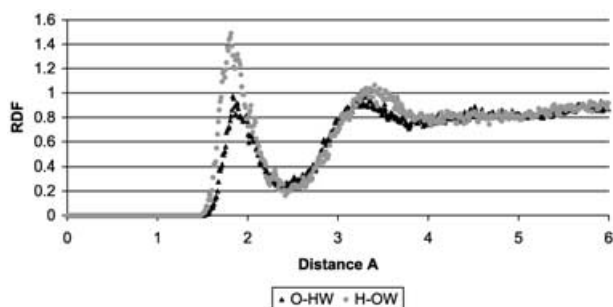


FIGURE 11 Radial distribution function for the distance between water oxygens and hydrogens (OW and HW) and the hydroxyl groups (H or O, respectively) of the γ -CD/C₆₀ complex.

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