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Theoretical Study of the Inclusion Processes of the Phenylurea Herbicide Metobromuron in β-cyclodextrin

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Abstract: We investigated the inclusion process of phenylurea herbicide metobromuron (MB) in beta cyclodextrin (β-CD) with 1:1 stoichiometry using: (1) MM+ force field of molecular mechanics in order to research the lowest energy structure of the inclusion complex. (2) Superior levels of calculations were made such PM3, B3LYP/6-31G*, HF/6-31G* and ONIOM2 methods in order to approach the ideal geometry and provide further insight into the different complexation properties of the guest molecule. The data suggest that: The B orientation is significantly more favourable than the A orientation by an energy difference of 1.02 kcal mol^{-1} according to PM3 calculations. The geometry of the most stable complex shows that the aromatic ring is deeply self-included inside the hydrophobic cavity of β-CD also an intermolecular hydrogen bond is established between host and guest molecules. The formation of the inclusion complex is predicted to be an enthalpy-driven process in gas phase which is in accord with the experimental results. The statistical thermodynamic calculations by PM3 demonstrate that 1:1 MB/ β-CD complex is favored by a negative enthalpy change.

Key words: Molecular modeling, inclusion complex , complexation energy, optimized geometries, hydrogen bond, deformation energy

INTRODUCTION

CDs are cyclic oligosacharides with a small number of glucose units. The most common CDs are α, β and γ-CDs that differ in the number of D-glucopyranose ($C_6H_{10}O_5$) units (Uitdehaag *et al*., 1999): 6, 7 and 8, respectively (Hisham Abou-Auda *et al*., 2006; Letsididi *et al*., 2011). Cyclodextrins are doughnut-shaped molecules hydrophilic outer surface and hydrophobic cavity (Yap *et al*., 2010).

The resultant inclusion complexes can induce modification of the physicochemical properties of the 'guest' molecules, particularly in terms of water solubility and solution stability (Selvam and Geetha, 2008; Lyng *et al*., 2005). Therefore, it is important to clarify the structures of the inclusion complexes from a view point of enzyme-substrates within the hydrophobic cavities of CDs (Brewster and Loftsson, 2007). Formulation and practical application of pesticides are often rendered difficult due to their adverse physicochemical properties such as poor solubility, chemical and thermal instability, mammalian toxicity, malodor, volatility, high soil mobility, persistence and poor wettability. Complexation between pesticides and cyclodextrins can result in products with superior performance (e.g., enhanced pesticide solubility and stability, reduction of volatility) (Dodziuk, 2006). Metobromuron [3-(p-bromophenyl)-1-methoxy-1-methylurea] (Fig. 1) is a phenylurea herbicide that is used for the control of broadleaf weeds in cereal and vegetable crops, acting through the inhibition of photosynthesis (Zhang *et al*., 2008; Bonnemoy *et al*., 2006). The compound has a relatively low aqueous solubility ($3.3.10^{-4}$ g mL^{-1} at 25°C). Cyclodextrins can increase the solubility of phenylurea herbicide metobromuron.

Recently, Smith *et al*. (2009) have studied experimentally the encapsulation of MB in β-CD to test its affinity for CD. To our knowledge, the complexation of CD with MB has not yet been studied theoretically. So, the aim of this investigation is to study the inclusion complex between MB and β-CD with stoichiometry 1:1 specifically to determine its optimum geometrical structure, to describe the nature of intermolecular binding, the conformational changes of MB inside the β-CD cavity, the stability of the complex as well as the inclusion energetic of the formation process between the guest molecule and the host CD including thermodynamic parameters.

Currently, there is great interest in the theoretical study of supramolecular systems. For this purpose, Molecular Mechanics (MM) (Haiyun *et al*., 2003) or semi empirical methods (Santos *et al*., 2000; Avakyan *et al*., 2001) are the most widely used as ab initio and Density Functional Theory (DFT) methods are prohibitively

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expensive in treating such large systems. Unfortunately, in general, MM methods do not accurately describe the geometries or energetic of intermolecular interactions. With no representation of electron density, many chemically important quantum based effects are missed. Additionally, intermolecular interactions for a number of MM force fields are known to be poorly reproduced (Avakyan *et al*., 2001). Semi empirical methods employ approximations to accelerate solution of the Roothan-Hall equations; thus, they are quantum mechanical in nature and are an improvement over MM methods in accounting for quantum phenomena. However, empirical solutions are substituted for the large number of multi electron integrals and these are parameterised to reproduce experimental observable for a large number of molecules. These approximations sharply limit the precision of semi empirical methods, particularly in treating systems that were not present in the initial parameterisation procedure (Madi *et al*., 2009). However, such investigation of larger molecular system is limited by the computational effort required and the accuracy of the method used, theoretical chemistry has turned its interest to the so-called hybrid methods that use multiple approaches of varying accuracy and cost to simultaneously treat different parts of a system. The use of hybrid methods is very important for the study of large molecules or supramolecular systems. Among these hybrid approaches, the hybrid ONIOM method developed by Kuno *et al*. (2003) is especially appealing as it can combine any quantum mechanics/quantum mechanics (QM/QM) or QM/MM method within one other. In CD chemistry, under many circumstances the CD only provides an environment effect and we are more interested in the chemistry of the guest molecules in the CD environment. Therefore, it appears a promising field to use the ONIOM method to study CD chemistry.

To this purpose, we have performed an ONIOM study of the complex reactions of β-CD with the herbicide metobromuron. The complexes were divided into two layers. The inner layer (the herbicide metobromuron molecule) was treated by the Density Functional Method (DFT) B3LYP and ab initio Hartree-Fork (HF) employing the 6-31G* basis set, respectively, while the outer layer (β -CD) by the semi empirical PM3 method. Liu and Guo (2004) suggested PM3 should be advantageous in direct structure optimization of β-CD. The inclusion of the outer layer was important for obtaining reasonable results for the proposed complexes configuration. The results offer significant insights into the inclusion interactions between β-CD and the herbicide metobromuron.

Computational method: All calculations were carried out using Hyperchem 7.51 (Hyperchem, 2002) and Gaussian 03W version 6.0 (Frisch *et al*., 2003) packages, respectively for molecular and quantum mechanics methods.

Starting geometries of β-CD and phenylurea herbicide metobromuron (MB) were built with the help of Chem-office 3D ultra (Version 6.0, Cambridge software). MB was optimized with B3LYP method at 6-31G* level and the β-CD was optimized by PM3 method (Barbiric *et al*., 2000).

For the construction of MB/β-CD complex, the glycosidic oxygen atoms of β -CD were placed onto the XY plane; their centre was defined as the origin of the coordinate system. The second hydroxyl groups were oriented pointing towards the positive Z axis. The guest molecule placed on the Z axis was allowed to approach the β-CD cavity from the large side at a distance of 8 Å which separates the β-CD equatorial plane and the reference atom (N-8) in MB (Fig. 1a).

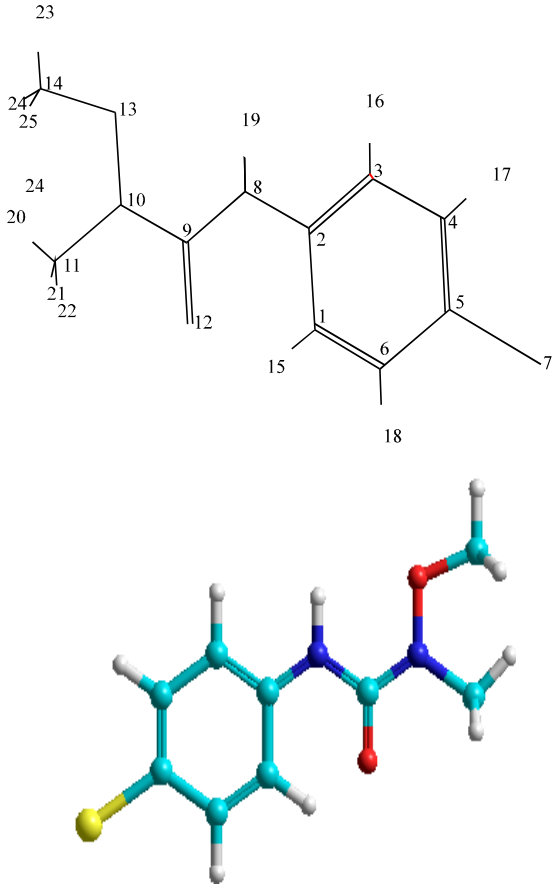

Fig. 1: Molecular structures of (a) the phenylurea herbicide metobromuron and (b) RB3LYP/6-31G* optimized the phenylurea herbicide metobromuron

The inclusion process emulation was then achieved along the Z axis to -8 Å with a step of 1 Å. The structure generated at each step is then optimized allowing changes from the initial conformations but keeping the movement of the reference atom (N-8) and β-CD totally restricted. Once the preliminary energy minimum was determined for each orientation, we re-optimized the system removing all restrictions. In order to explore more conformational space and to find an even more stable structure of the complex, MB was rotated in the cavity around the Z axis at 30° intervals from 0° to 360° and the system was re-optimized at each position without imposing any restrictions . Two possible orientations were considered (Fig. 2).

- Aromatic ring orientated to the centre of mass of β-CD, namely orientation-A
- Aliphatic ring orientated to the centre of mass of β-CD, namely orientation-B

The lowest energy complexes obtained by MM+ calculations were in turn fully optimized using a semi-empirical PM3 method. To quantify the interaction between host and guest in the optimized geometries, we have evaluated binding (E binding) and complexation energy (E compl) using the following formulae (Matei *et al*., 2007; Fatiha *et al*., 2009; Ohashi *et al*., 1990):

$$E_{binding} = E_{MB/\beta\text{-}D} - (E_{isolated\ MB} + E_{isolated\ \beta\text{-}CD}) \quad (1)$$

$$E\ complexation = E\ complex - (E_{opt\ \beta\text{-}CD} + E_{opt\ MB}) \quad (2)$$

$$DEF\ (component) = E\ (component)_{sp}^{opt} - E(component)\ opt \quad (3)$$

According the relation (2), the complexation energy is defined as the energy difference between the optimized complex and the energies of isolated host and guest, on their optimized conformations from complex. The deformation energy for each component, host and guest throughout the formation of the complex was defined as the difference in the energy of the totally optimized component compared to its energy in the complex (Eq. 3) (Leila *et al*., 2011).

ONIOM calculations: For a deeper understanding of the molecular recognition, the equilibrium geometries of both MB/β-CD complexes were also completely optimized using the ONIOM method. The ONIOM method is a hybrid computational method that allows different levels of theory to be applied to different parts of a molecular system. In the two-layered ONIOM method, the molecular system under study is divided into an inner and an outer layer. The inner layer consists of the most critical

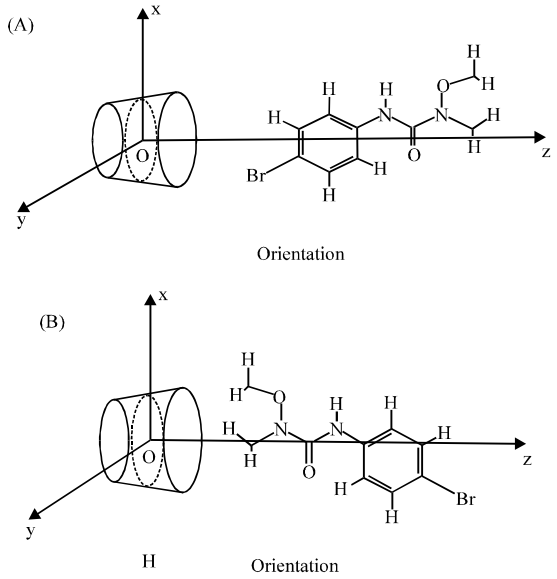

Fig. 2: Coordinate systems used to define the process of complexation for: A and B orientations

elements of the system and the rest of the system comprises the outer layer. In the terminology of Kuno *et al*. (2003), the full system is called ''real'' and is treated with a low level of theory. The inner layer is termed ''model'' and is treated with both the low level of theory and a high level of theory. The total ONIOM energy EONIOM is given by:

$$EONIOM = E\ (high;\ model) + E\ (low;\ real) - E\ (low;\ model) \quad (4)$$

where, E (high, model) is the energy of the inner layer at the high level of theory (the MB molecule), E (low, real) is the energy of the entire system at the low level of theory (the complexes) and E (low, model) is the energy of the model system at the low level of theory (β-CD). In this study the MB/β-CD complexes generated from PM3 optimization were divided into the high level of calculation (RHF/6-31G* and RB3LYP/6-31G* are carried out on the MB and the low level on the β-CD is treated with a low level method (PM3).

RESULTS AND DISCUSSION

Force field calculations: In this study we have considered only the inclusion compounds in molar proportion 1:1 formed between one molecule of β-CD and one molecule of phenylurea Herbicide metobromuron (MB).

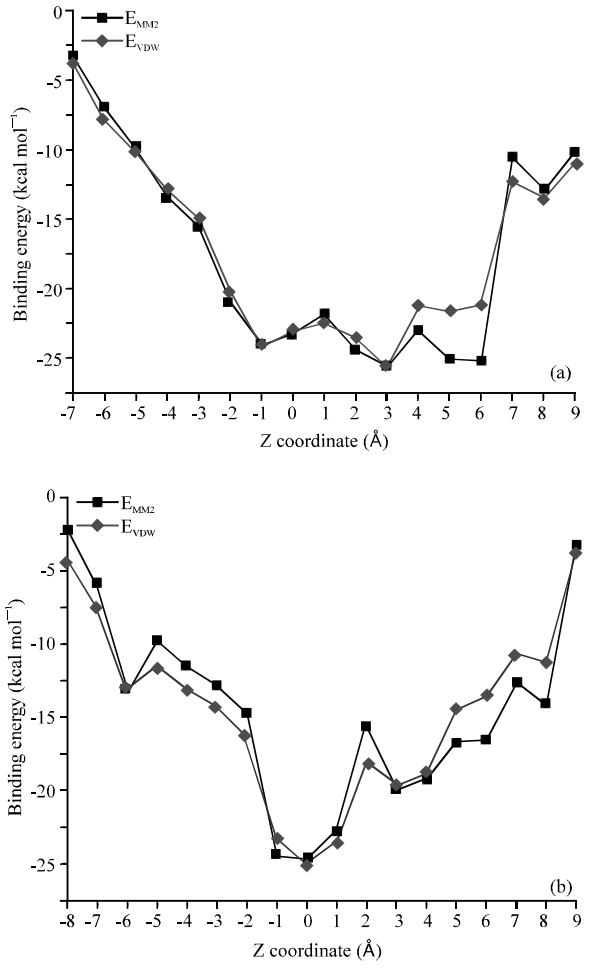

Fig. 3: (a,b) Binding energy of the inclusion complexation of MB into β-CD at different positions (Z) for both orientations

We have adapted MM+ method with a Root Mean Square gradient of 0.01 kcal mol^{-1}; to search for the lowest energy structures. Different minima were localized for the whole system. The graphical representation of the binding energy involved in the inclusion process for the two orientations is displayed on Fig. 4.

The energy minimum for the A orientation is located at 6 Å but for the B orientation is located at 0 Å.

The results summarized in Table 1 for the most stable structures obtained by MM+ study confirm that both complexation, binding and Van der Waals energies are in favor of B orientation and the energy difference of the complexes in the two orientations correspond, respectively to- 0.9 , -0.15 and -0.41 kcal mol^{-1}.

It is important to note that the binding energy and VDW energy have similar results, which signify that the inclusion process is governed by Van Der Waals interaction.

Semi empirical and quantum mechanical calculations: The intermolecular interactions and hydrogen bond cannot be accurately estimated by the MM+ approach because this method does not treat explicitly the electrons (Avakyan *et al*., 2001). Though, we have undertaken quantum calculations (PM3) in order to help us to have a deeper comprehension.

Semi-empirical (PM3) calculations were performed starting from the structures of minimal binding energy obtained in the previous MM+ study. Table 2 shows the calculated Binding Energy (BE) of MB complexed with β -CD. The negative Binding Energy (BE) changes upon complexation clearly demonstrate that β-CD can form stable complexes with MB, which is observed in the experiments (Smith *et al*., 2009). The B orientation is significantly more favourable than the A orientation by an energy difference of 1.02 kcal mol^{-1} according to PM3 calculations. The same result is also obtained with the B3LYP/6-31G* and HF/6-31G* single point calculation in vacuum in which the energy difference becomes -4.00 and -5.48 kcal mol^{-1}, respectively. The BE difference with BSSE correction is -7.59 and -4.72 kcal mol^{-1} for the DFT and HF methods. While these energy differences may be contribute to intermolecular hydrogen bond formation for the B orientation.

To investigate the thermodynamics of the binding process, the statistical thermodynamic calculation were carried in vacuum by PM3 method, their B3LYP/6-31G* and HF/6-31G* single point energies (Holdgate and Ward, 2005). The thermodynamic quantities, the enthalpy change, the thermal Gibbs free energy (ΔG) and entropy contribution (ΔS) are given in Table 2. From Table 2, we can be seen that the complexation reactions of MB with β-CD are exothermic judged from the negative enthalpy changes. And the negative enthalpy changes suggest that both the inclusion processes are enthalpically favourable. On the other hand, the enthalpy changes for B orientation is more negative than the A orientation, which is surely attributed to the more tightly van der Waals interactions. The two complexation reactions have negative ΔG values and are therefore spontaneous processes, implying that binding interactions are favored. The enthalpy changes and the thermal Gibbs free energy are of similar magnitude to the experimental data ΔH and ΔG (Smith *et al*., 2009).

On the other hand, the results of the investigation of deformation energy reported in Table 2 demonstrate that the MB molecule in B orientation requires a slightly more energy for conformation adaptation inside the β-CD

Table 1: Binding, Van der Waals and complexation energies (kcal mol^{-1}) at the minimum energy for both orientations

Energetic terms	Phenylurea herbicide	β-CD	A Orientation	B Orientation	ΔE[a] metobromuron
MM+					
E_{comp} (kcal mol^{-1})	-1.27	113.01	85.98	85.08	
ΔE_{comp} (kcal mol^{-1})			-25.76	-26.66	-0.90
E (kcal mol^{-1})	2.61	108.13	84.18	84.03	
BE (kcal mol^{-1})			-26.56	-26.71	-0.15
EVDW (kcal mol^{-1})	0.83	-53.35	-77.18	-77.59	
ΔEVDW (kcal mol^{-1})			-24.66	-25.07	-0.41

ΔE[a]: The relative energy difference of the optimized complexes in B and A orientations, ΔE = E complexation (B)-E complexation (A)

Table 2: Energies, thermodynamic characteristics and the deformation energy of substrate calculations using PM3 method and single point energy evaluated at B3LYP and HF level for MB/β-CD inclusion complexes

	MB	β-CD	Orientation A	Orientation B	ΔE[c]
PM3					
E[a] (kcal mol^{-1})	-0.54	-145.70	-1474.38	-1475.0	
BE[a] (kcal mol^{-1})			-16.74	-17.76	-1.02
E_{comp} (kcal mol^{-1})	-6.68	-1454.67	-1474.38	-1475.40	
ΔE_{comp} (kcal mol^{-1})			-12.54	-14.05	-1.51
DEF (guest)			0.02	6.35	6.33
DEF (host)			1.50	2.43	0.93
H° (kcal mol^{-1})	124.92	-667.31	-555.04	-555.98	
ΔH° (kcal mol^{-1})			-12.65	-13.59	-0.86
G° (kcal mol^{-1})	90.09	-784.46	-696.59	-697.60	
ΔG° (kcal mol^{-1})			-2.22	-3.23	-1.01
S° (cal mol^{-1}-Kelvin)	116.82	406.38	474.75	474.55	
ΔS[c] (cal mol^{-1}-Kelvin)			-48.45	-48.65	-0.2
RHF/6-31G*					
E[a] (kcal mol^{-1})	-1992532.88	2666495.63	-4659088.51	-4659093.99	
BE[a] (kcal mol^{-1})			(-4659078.26)[b]	(-4659083.86)[b]	
			-60.00	-65.48	-5.48
			(-50.63)[b]	(-55.35)[b]	(-4.72)[b]
RB3LYP/6-31G*					
E[a] (kcal mol^{-1})	-1995976.53	-2681832.20	-4677880.93	-4677884.93	
BE[a] (kcal mol^{-1})			(-4677870.91)[b]	(-4677878.50)[b]	
			-72.20	-76.20	-4.00
			(-62.18)[b]	(-69.77)[b]	(-7.59)[b]

E[a]: Total optimized energy (heats of formation), DEF: Deformation energy of the substrate, BE: Binding energy upon complex, BE = E[C]opt-E[S]opt-E [CD] opt.[b] The HF and DFT BEs in vacuum using the counterpoise method for correcting the basis set superposition error (BSSE). ΔE [c] = $\Delta E_{comp\ B}$-$\Delta E_{comp\ A}$

cavity than that of A orientation. The corresponding values are respectively 0.02 and 6.35 kcal mol^{-1}.

The main features of the favourable structure obtained by PM3 method are, the aromatic ring entered full into the cavity of β-CD and one intermolecular H-bond of B orientation is formed between O (12) atom of CO group of MB and one primary OH of β-CD is shown in Fig. 4. This explains why the complexation energy of the B orientation is more favored than that of A orientation.

By B3LYP and HF methods it was observed two intermolecular H-bonds. The first H-bond is defined between the N (18) atom, the second with O (12) of MB and an H of primary hydroxyl of β-CD, the H-bond length ranges from 3.16Å and 1.80 Å, respectively. In A orientation no hydrogen bonding is reported.

Conformational analysis of β-CD/MB complexation based on PM3 and ONIOM2 theoretical methods: In order to further understand molecular recognition between the guest and the host we adopted ONIOM2 methods (HF/6-31G*:PM3 and B3LYP/6- 31G*:PM3).

The geometries of both complexes obtained by PM3 calculations were optimized at two different levels of theory, (RHF/6-31G*: RPM3) and (RB3LYP/6-31G*: RPM3 are given in Fig. 5.

In Table 3, we reported and compared the energetic values computed with ONIOM 2 method to those obtained from PM3 calculations.

We found that the ONIOM calculations confirm PM3 results. In fact both ONIOM (RHF/6-31G*: RPM3) and ONIOM (RB3LYP/6- 31G*: RPM3) predicted B orientation to be more favorable than A orientation by respectively -6.27 and -6.28 kcal mol^{-1}.

The relative energy difference of the optimized complexes has the same order of magnitude than that obtained by PM3 method.

The aromatic ring of the MB molecule is totally inserted in the hydrophobic cavity of the most favorable

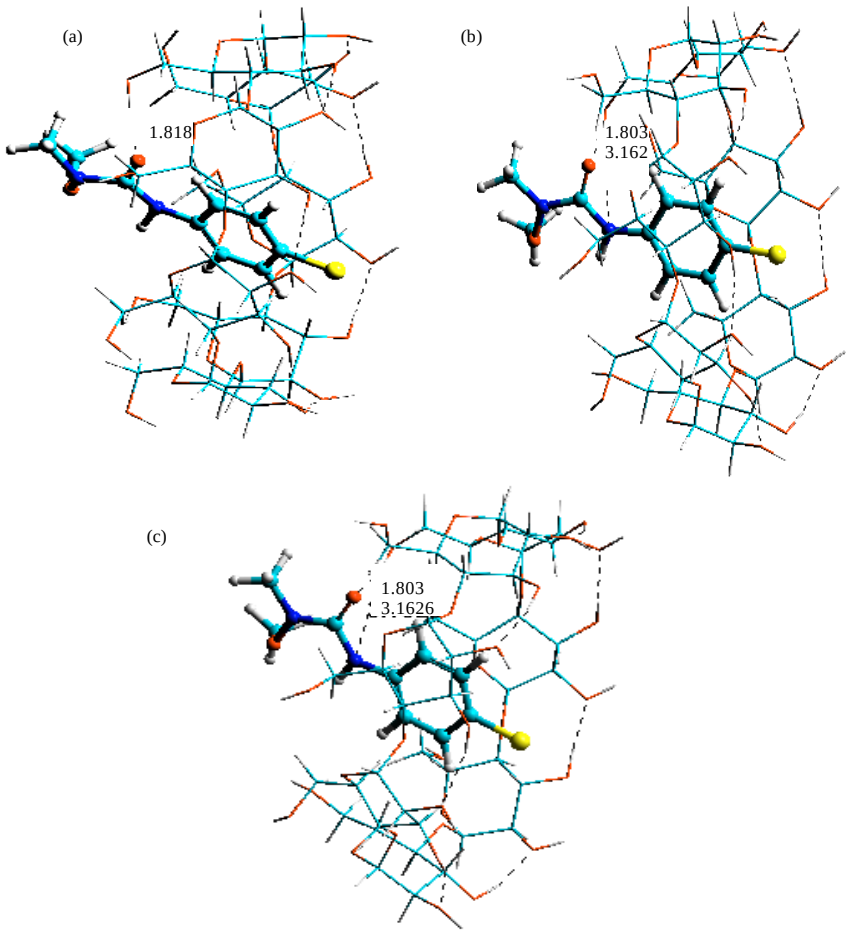

Fig. 4: Structures of the energy minimum of B orientation obtained by the (a) PM3, (b) B3LYP/6-31G* and (c) RHF/6-31G*

Table 3: E ONIOM, E binding and relative energy difference ΔE (kcal mol^{-1}) and intermolecular hydrogen bonds distance (A°)

Computational methods	A orientation	B orientation	ΔE
E (PM3)	-1474.38	-1475.40	-1.02
d (O12…H128)		1.821	
EONIOM (RB3LYP/6-31G*:RPM3)	-1997571.86	-1997578.14	-6.28
d (O12…H128)		1.81	
EONIOM (RHF/6-31G*:RPM3)	-1994057.75	-1994064.02	-6.27
d(O12…H128)		1.81	

E: Total optimized energy for the PM3 method. EONIOM: Total ONIOM optimized energy based on the PM3-optimized complexes, EONIOM = E (high, model)+E (low, real) -E (low, model), ΔE is relative energy difference, ΔE = E (B Orientation)-E (A Orientation)

structure (B orientation) positioned at the secondary rim and aliphatic ring closer to the primary one; and one intermolecular H-bond of B orientation is formed between O (12) atom of CO group of MB and one primary OH of β-CD is shown in Fig. 5.

These remarks are the same for the energy minimized PM3 structure illustrated in Fig.4a.

The calculated ONIOM2 optimized O-H distance is 1.810 A° smaller than that of the PM3.

In Table 4, we report the bond distances, bond angles and the most interesting dihedral angles MB molecule before and after complexation as calculated by PM3, HF6-1G*, B3LYP6-31G* and ONIOM2 methods for the most stable structures in B orientation.

It is evident that in β-CD, the geometry of MB is completely altered. The alteration is significant in dihedral angles, which, indicates that MB must adapt a specific conformation to form a more stable inclusion complex.

Table 4: Geometrical parameters of MB before and after inclusion in β-CD, bond distances (Å), angle (°) and dihedral angles (°) calculated by PM3 and ONIOM2 methods

	PM3/RHF6-31G* /B3LYP6-31G* Free MB	B orientation PM3/RHF6-1G* /B3LYP6- 31G*	B orientation (RHF/ 6-31G*: RPM3)/ (RB3LYP/6-31G*: RPM3)
Bond lengths (Å)			
O13C14	1.3906 /1.42996 /1.4300	1.40197/1.41063/1.41061	1.4720/1.4432
O13-N10	1.51665 /1.3600 / 1.3600	1.49095/1.33272/1.33267	1.4400 / 1.4700
N10-C11	1.46732 /1.47004/ 1.4700	1.47377/1.46139/1.46145	1.4500/1.4600
N10-C9	1.4194 / 1.31995 /1.3200	1.44401/1.38060/1.38060	1.3723/1.3910
C9-N8	1.41818 /1.32004 /1.3200	1.41782/1.38002/1.38003	1.3521/1.3710
N8-C2	1.43049 1.2200 /1.3200	1.43952/1.42734/1.42734	1.4121/1.4160
C9-O12	1.23302 /1.31995 /1.3200	1.23519/1.22923/1.22929	1.2332/1.2265
O5-Br7	1.86786 /1.90994 /1.2200	1.86837/1.88741/1.88742	1.8530/1.8400
Bond angles (°)			
C14-O13-N10	115.361/109.469/109.47	114.763/112.82/112.832	112.718/110.31
O13-N10-C11	122.848/119.999/120.00	114.722/119.48/ 119.478	115.180/113.981
O13-N10-C9	114.81/120.001 /120.00	114.756/121.916/121.921	121.781/114.651
C11-N10-C9	122.342/120.000/120.00	119.028/118.578/118.577	115.600/121.502
N10-C9-N8	120.102/120.000/120.00	118.963/118.371/118.371	124.431/114.852
O12-C9-N8	122.492/119.999/120.00	121.593/121.196/121.195	128.044/128.090
C9-N8-C2	124.033120.000/120.00	122.769/129.547/129.546	122.230/124.012
Dihedral angle (°)			
C14-O13-N10-C11	0/0/0	54.6071/78.0844/78.088	90.2421/81.70
C14-O13-N10-C9	180/180/180	-88.5737/-100.059/-100.057	-121.4510/-122.02
C11-N10-C9-N8	180/ 180/180	-167.44/173.217/173.22	153.8312/153.4912
O13-N10-C9-N8	0 /0/0	-25.9446/-8.62352/-8.61872	8.1021/10.0230
O12-C9-N8-C2	0 /0/0	19.3417/8.11855/8.12536	-4.6941/-2.5702

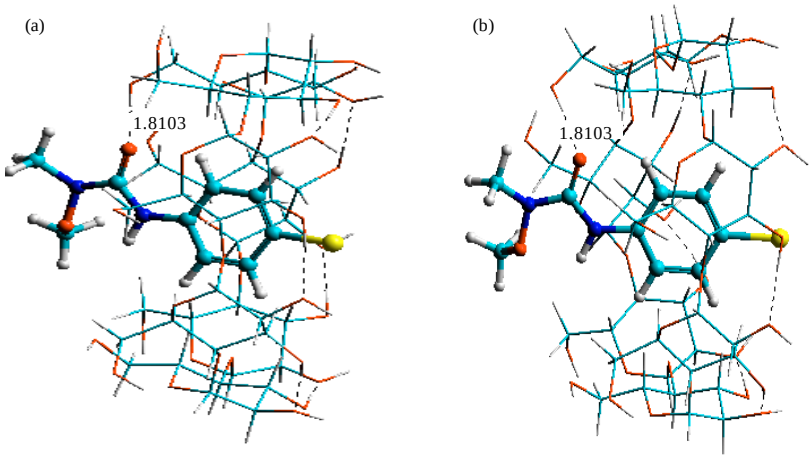

Fig. 5: Geometrical structures of MB/b β-CD complex of B orientation optimized at ONIOM2 by (RB3LYP/6-31G*: RPM3) (a) and (RHF/ 6-31G*: RPM3) (b)

The intermolecular hydrogen bonds also play pivotal role for the conformational exchange. The calculation dihedral angle (12-9-8-2) was changed to 19.3417°,-2.57702° and -4.6941° for the B orientation based on PM3, ONIOM (RHF/6-31G*: RPM3 and ONIOM (RB3LYP/6-31G*: RPM3)) methods, respectively.

CONCLUSION

In this study we confirmed by molecular modeling the inclusion process of the phenylurea herbicide metobromuron in β-cyclodextrin.

The stable structures and the inclusion process for MB/β-CD inclusion complexes were studied by use of force field MM+; quantum mechanics PM3 and ONIOM2 methods.

From force field MM+ study, MB/β-CD inclusion complex in B orientation was predicted to be the most stable structure. This result is completely similar to that obtained from semi-empirical PM3, single point HF, DFT calculations and hybrid ONIOM 2 approach. One intermolecular hydrogen bond is formed, a driving force responsible for its stability.

The aromatic ring entered full in β-CD hydrophobic cavity and located near the secondary hydroxyls and aliphatic ring near the primary hydroxyls of β-CD is preferred according to the calculated energies. The statistical thermodynamic calculations suggest that both of the complex processes are enthalpically favorable and the driving forces of cyclodextrin inclusion complexation are mainly van der Waals and hydrophobic interactions.

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