ISSN : 0974 - 7524 Volume 6 Issue 1

Physical CHEMISTRY
An Indian Journal

Trade Science Inc.

Full Paper

PCAIJ, 6(1), 2011 [49-53]

Investigate the semi empirical PM6 and PM6-DH2 methods accuracy for the prediction of the β-cyclodextrin / piroxicam inclusion complex's stability

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Received: 4th October, 2010 ; Accepted: 14th October, 2010

ABSTRACT

The inclusion complex piroxicam/ β-cyclodextrin was modeled theoretically using semi empirical quantum method. In this study, we have applied the PM6, PM6-DH2 and PM3 methods in order to investigate the contribution of the H-bonding driving force in the inclusion complex's stability. In fact, we have demonstrated that the PM6 and PM6-DH2 are more efficiency than PM3 concerning the complexation energy results: 25.3 kcal/mol, -74.81 kcal/mol and -8.55 kcal/mol for PM6, PM6-DH2 and PM3, respectively. Thus, the PM6-DH2 method could estimate easily the H-bond force between host and guest which improved the stability of the complex.

KEYWORDS

β Cyclodextrin;
Piroxicam;
Inclusion complex;
H-bond correction;
PM6;
PM6-DH2.

INTRODUCTION

Piroxicam (PX) [4-hydroxy-2- methyl-N-2-pyridyl-2H-1, 2-benzothiazine-3-carboxamide-1, 1-dioxide] **is** one of the oxicam family which has optical, analgesic and antipyretic properties[1,2]. It was proven experimentally, that its dissolution as its absorption is increased when it is included in the β- cyclodextrin (β-CD) cavity[3,4].

The formation of non-covalently bound inclusion complexes between drug and cyclodextrin become a significant field of theoretical investigations, especially in the determination of intermolecular H-bond interaction and driving forces[5-10]. The research of the lowest energy minimum of the inclusion complexes, which was the object of several studies, constitutes the most significant stage because it is carried out in several steps, needs especially geometrical handling and requires many precautions. Generally, two procedures are used[11]. The first one consists to optimize various geometries of the inclusion complexes obtained usually with dynamic molecular simulation. The second one, considered as a systematic research, is made in several steps by scanning the energy surface potential. It was proven according to various results obtained by different authors, that the second method is more effective than the first[11]. It is important to claim herein that the use of ab initio and DFT methods is for the moment not recommended in this long systematic research of the lowest energy minimum considering the importance of the (CPU demanding) computational cost. Actually, only the molecular mechanics or semi empirical methods were used,

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in particular the PM3 semi empirical method which was found more efficiency particularly in the descriptions of the non covalent interactions[12-17].

In the present article we have used PM6 and PM6-DH2 methods which were implemented recently in MOPAC. In fact, they were parameterized for more than 70 elements; these methods include empirical corrections for H-bond interactions[18,19].

We were interested to localize the lowest energy minimum of the β-CD/PX inclusion complex. Based on our experience, these methods didn't test for this type of problem yet. The PM6 and PM6-DH2 results were compared with those obtained by PM3 and HF (3-21G*) methods. Finally, using the H-bond contribution calculated with PM6-DH2, we have determined the H-bond effect in the formation of the β-CD/PX complex.

METHODS

All calculations were carried out using the Gaussian 03 quantum mechanical package[20] and MOPAC2009[21]. The initial structures of β-CD and piroxicam molecules were built with the help of Chemoffice 3D ultra (version 6. Cambridge software). To locate the lowest energy minimum, we have used the method which was described in several articles[12,17,22,23]. We have given herein a short outline of this method. First, the glycosidic oxygen atoms of β-CD were placed onto the **(**xoy**)** plane, the centre of β-CD being defined as the centre of the coordinate system. For the complexation process, the host β-CD was kept in this position while the guest approaches, by 1Å, along the X-axis toward the wide rim of the β-CD torus. In each step the guest molecule was rotated around the bond N-C by 20°, from 0° to 360° (Figure 1).

The generated structures at each step were optimized using PM3, PM6 and PM6-DH2 methods which allows us to calculate the energy of complexation and the H-bond contribution (PM6-DH2), defined as follows (Eq. 1 and 2).

$$E_{complexation} = E_{complex} - (E_{\beta\text{-}CD} + E_{PX}) \quad (1)$$

$$E_{H\text{-}bond} = E_{H\text{-}bond\ (complex)} - (E_{H\text{-}bond\ (\beta\text{-}CD)} + E_{H\text{-}bond\ (PX)}) \quad (2)$$

Finally, the lowest energy structure obtained by PM6-DH2 was optimized at the HF/3-21 G (d) level.

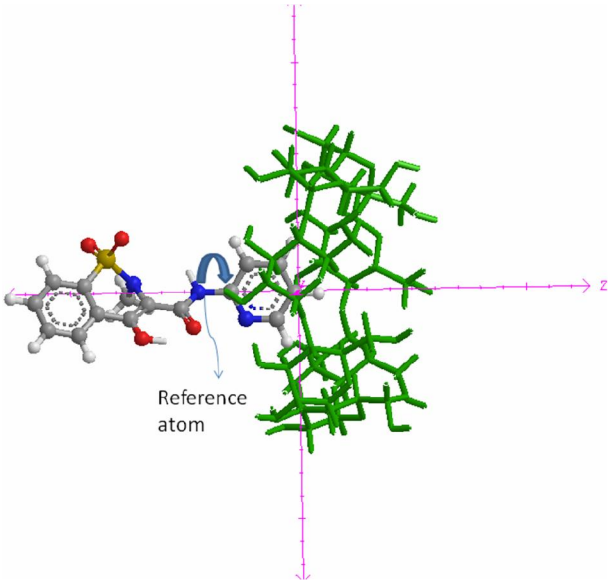

Figure 1 : The relative position between piroxicam and β-cd.

RESULTS AND DISCUSSION

As given by the PM3, PM6 and PM6-DH2 semi empirical methods, the inclusion process produced three different curves of complexation energy (Figure 2a). The energy minimum was determined without ambiguity with PM6 and PM6-DH2 contrary to PM3, where the minimum is observed in two positions (Figure 2a). Thus, the lowest energy minimum has been observed at -3 Å with complexation energies of -25.3 (PM6) and -74.81 (PM6-DH2) kcal/mol. However, two energies minimum were obtained with PM3. One was rejected because its structure**,** in which the enolic part is located outside the cavity**,** is not in agreement with experimental observations[24]. Then, we have considered only the minimum at -2 Å with complexation energy of -8.55 kcal/mol (PM3). In all cases the complexation energies obtained were negative, which means that the inclusion complex is thermodynamically stable.

In order to investigate the hydrogen bonding role more accurately, we studied the variation of the of H-bond contribution during the formation of β-cd/PX which is calculated using eq. 2 and is depicted in (Figure 2b). As it can be observed that the complexation energy curve is similar as the H-bond contribution curve. Which means that H-bond is an interesting element in the formation of the inclusion complex. Figure 3 shows the lowest energy minimum geometries obtained with PM6, PM6-DH2 and HF 3-21g*.

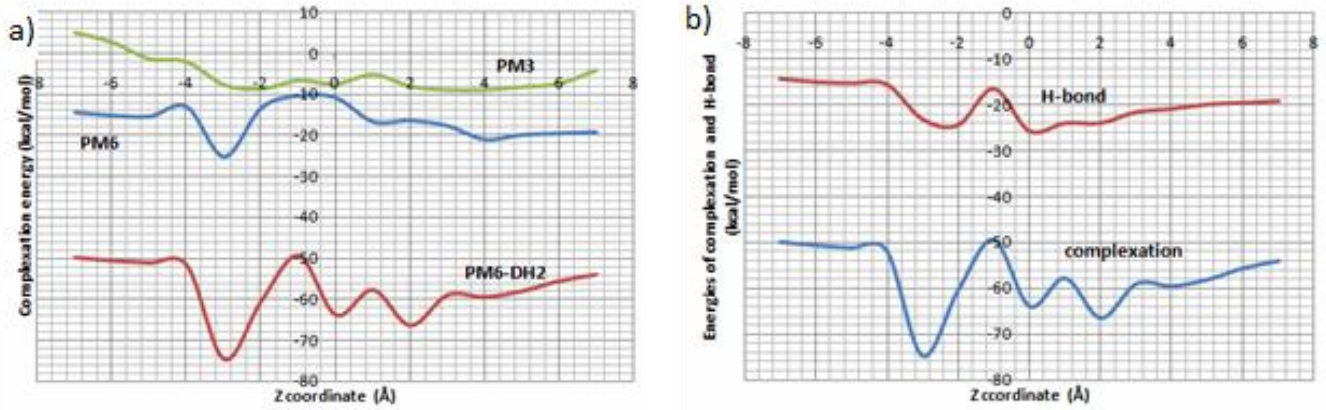

Figure 2 : a) Complexation energy of the inclusion complex (β-cd-piroxicam). b) Contribution of H-bond (PM6-DH2).

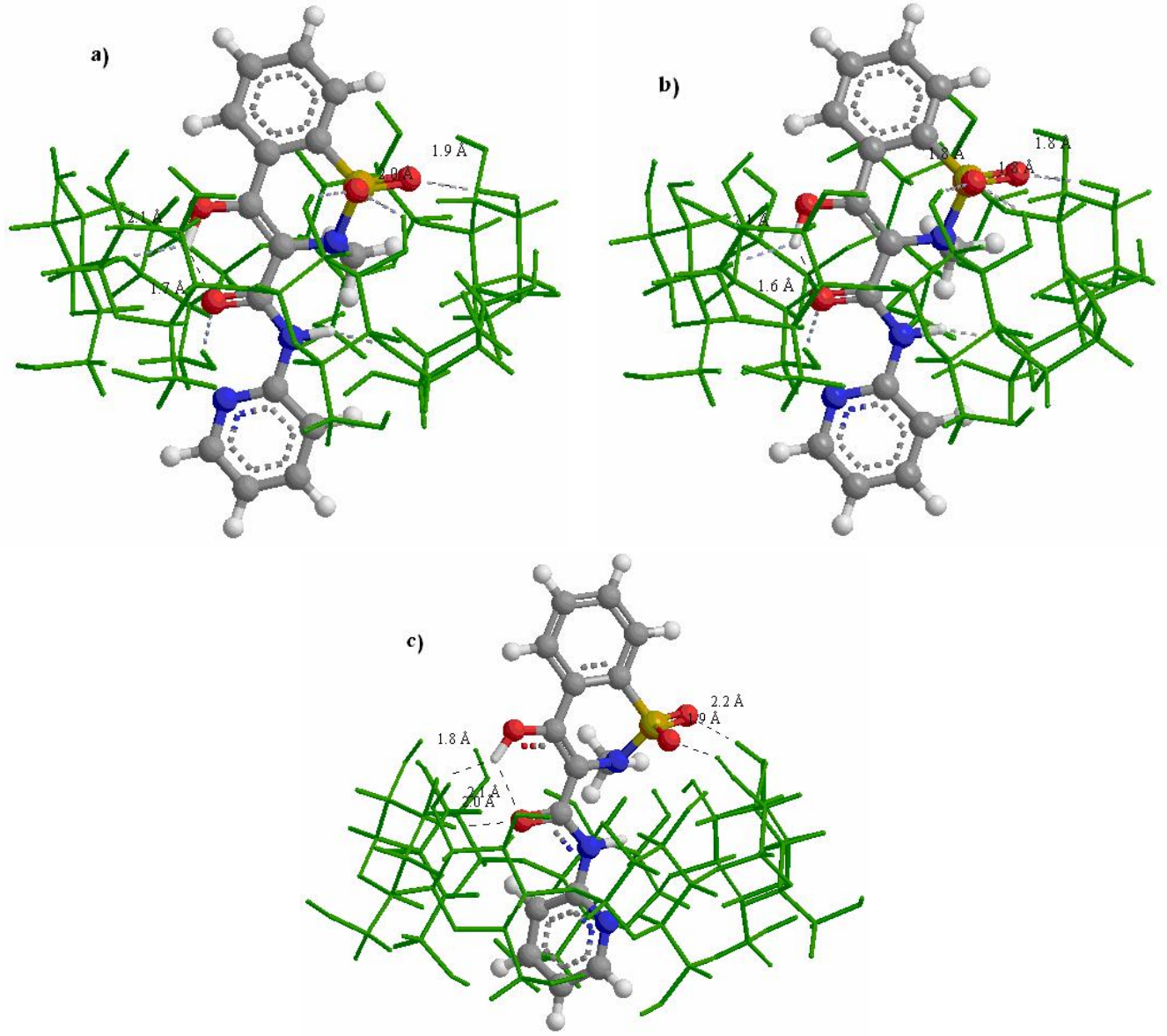

Figure 3 : The lowest energy minimum structure obtained with: a) PM6. b) PM6-DH2. c) HF-3-21 G*.

It appears clearly that the semi empirical geometries have almost the same shape and they approach to the

HF geometry, especially by the same number of hydrogen bond. An inspection of the HF geometry shows that the pyridine ring is totally embedded in the CD cavity while the SO_2 group remains on the rim of the β-CD and could form H-bond with two OH of β-CD. Therefore, the methyl group remains outside the cavity to avoid making steric interactions with hydrogen atoms of β-CD. In the semi empirical geometries (PM6 and PM6-DH2), the pyridine ring is located outside the cavity behind the primary OH of β-CD and the SO_2 group is on the secondary periphery and established H-bond with β-CD. However, the methyl group is located inside the cavity and unfortunately establishes steric interactions with hydrogen atoms of β-CD. Furthermore, we have remarked that the geometry of β-CD (PM6-DH2) is more compacted certainly because the distance between atoms undergo in the intramolecular H-bond in the β-cyclodextrin is reduced; it passes from 1.8 Å (PM6) to 1.6 Å (PM6-DH2).

At last, it was proven according to experimental results on the β-CD/PX inclusion complex that the nitrogen amid atom and the enolic part are located inside the cavity of the cyclodextrin. From Figure 3 it can be seen that nitrogen amid atom and enolic part are inside the cavity in the three geometries, hence, they are in good agreement with experimental observations and can be a model for the inclusion complex β-CD-PX[24].

CONCLUSION

In this study, it has been demonstrated that PM6-DH2 can be successfully used to locate the lowest energy minimum of the piroxicam- β CD complex. The obtained geometry has the enolic part inside the cavity which is in accordance with experimental observations. The determination of the H-bond contribution with PM6-DH2 allows concluding that the establishments of the H-bond intermolecular interactions stabilize the complex in spit of the steric effect of the methyl group inside the cavity.

ACKNOWLEDGEMENTS

The investigation was supported by the Algerian Ministry of Higher Education and Scientific Research through Project CNEPRU N° 01520080026.

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