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Determination of the intermolecular interactions in β-cyclodextrin / histidine inclusion complex: molecular mechanics study

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ABSTRACT

The formation of inclusion complexes between histidine amino acid and β cyclodextrin was theoretical studied by molecular mechanics using MM+ force field implemented in Hyperchem 7.5 software. Thus, we considered two modes to introduce the amino acid in the cyclodextrin cavity, named A and B orientations. We will be interested by the bimodal complexation and the chiral recognition. In the bimodal complexation study we found that B orientation in which the cycle part is outside the cavity is more favorable of 1.97 kcal.mol^{-1} in vacuum and of 12.03 kcal.mol $^{-1}$ in water than A orientation. Furthermore, for the chiral recognition the A orientation in which the cycle is totally embedded in the cyclodextrin cavity is more favorable of 7.75 kcal.mol^{-1} in vacuum and 30.92 kcal.mol^{-1} in water than B orientation.

KEYWORDS

β Cyclodextrin;
Histidine;
Inclusion complex;
Molecular mechanics.

INTRODUCTION

The chiral discrimination is a subject of great importance in fine chemistry because the biological activity of the enantiomers is often different. Consequently, the quantitative enantiomeric composition of these drugs should be determined[1]. The use of cyclodextrin for this aim starts to become a very successful tool for the chiral recognition[2].

Cyclodextrin (CDs) are cyclique α-1, 4 linked oligomers of D glucopyranose. Natural cyclodextrin comprise 6, 7 or 8 units of glucopyranose symbolized by α, β and γ cyclodextrin. In particular, β CD has an internal cavity shaped like a truncated cone about 8 Å deep and 6.0-6.4 Å in diameter and the cavity possesses hydrophobic character and relatively low polarity and can include a variety of organic compounds in a reversible way[3-5].

The formation of the inclusion complex between β cyclodextrin (β CD) and amino acids (AA) constitutes an ideal system to evaluate different interaction in gas phase and in solution. The amino acids are molecules having a carbon squeleton and two functional groups, an amine (NH_2) and carboxylic acid (COOH). The amino acids exist in several forms, neutral, ionic and a zwetterionic form according to the medium. The amino acids are in a zwetterionic form in aqueous solution in large range of pH. They can be localized on principal chain: an ammonium ion in N terminal and a carboxyl group in a C terminal.

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The two charged spice can stabilized with the solvent. The absence of solvent molecules in gas phase does not make to stabilize the charge of zwetterionic form compared to the form without separation of charge.

In the present work we have study the bimodality in the inclusion process of the amino acids in their zwetterionic form inside the cyclodextrin cavity using molecular modelling methods in solution and the gas phase. We note that the study in the gas phase allows knowing the intrinsic interaction of AA zwetterionic in complex that could be essential to understand the interaction in solution[6-21].

METHODS

The determination of the interaction between β CD and histidine molecules was made by the MM+ force field implemented in Hyperchem. The energy optimization was carried out with Polack Ribiere algorithm until energy gradient of 0.01 kcal.mole $^{-1}$.

A Histidine structure in dimmer form was extract in data base implemented in Hyperchem. Then some atoms of dimmer structure were removed to leave only one structure of Histidine with zwetterionic form. The β CD structure was taken from the Cambridge structural data base.

The β CD/histidine inclusion complex was obtained by placing firstly the β CD structure so as to coincide the centre of the cavity with the origin of the reference. Then the L or D histidine structure is placed in the origin according A and B orientation (Figure 1).

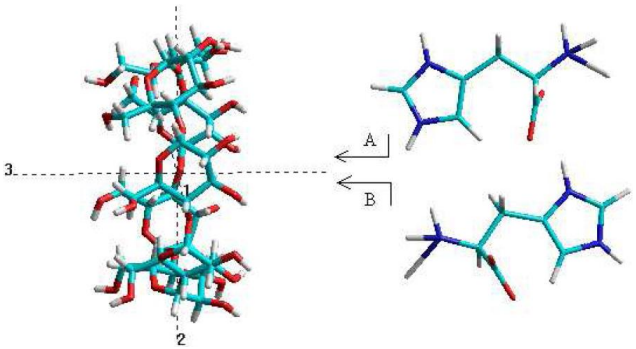


Figure 1 : Docking strategy

The structures of inclusions complexes for D and L enantiomers in A and B orientations are optimized. Theses complexes undergoes several simulated annealing in order to find the lowest energy structure of each complex. The conditions of the simulated annealing are shown in TABLE 1.

TABLE 1 : Condition of the simulated annealing

Time (ps)		Temperature (K)	
Heat time	0.01	Starting temperature	0
Run time	0.1	Simulation temperature	200
Cool time	3.0	Final temperature	0
Step time	0.001	Temperature step	20

In the aim to study the explicitly effect of water molecules we introduced the structures of the inclusion complexes into boxes water of 17.17.17 Å dimension which contains 98 water molecules with a 2.3 Å distance between water and β CD/histidine complex. The systems are optimized with Newton Raphson algorithm until a 0.01 kcal.mol^{-1} energy gradient. A single point calculation was determined on the complexes after having to remove all the water molecules from the box before applying the relation 1.

RESULTS AND DISCUSSION

The following nomenclature will be used in order to interpret the computational results obtained in the present work. Two orientations modes were used. The first one in which the cycle is inside of the cyclodextrin cavity is named A orientation, furthermore when the cycle is localized outside of the cyclodextrin cavity this orientation is named B.

We determined binding energies of L and D histidine/ β CD inclusion complexes according A and B orientations. Binding energy was defined as the difference between the energy of inclusion complex and the sum of individual host and guest molecule.

$$\Delta E_{binding} = E_{Histidine\text{-}\beta cd} - (E_{\beta cd} + E_{hstidine}) \quad (1)$$

The values of binding energy (kcal.mol^{-1}) in the vacuum and in water are summarized in TABLE 2.

TABLE 2 : Binding energy (kcal.mol^{-1}) in vacuum and in water

	$D_{his\text{-}\beta cd\_A}$	$D_{his\text{-}\beta cd\_B}$	$L_{his\text{-}\beta cd\_A}$	$L_{his\text{-}\beta cd\_B}$
$E_{binding}$ in vacuum	-135.35	-137.32	-143.19	-137.97
$E_{binding}$ in water	-213.29	-198.61	-240.56	-231.68

We note that the values of binding energies are all negative what shows that all the complexes are stable in vacuum and in water.

TABLE 3 : Energy detail in binding energy between the two orientations.

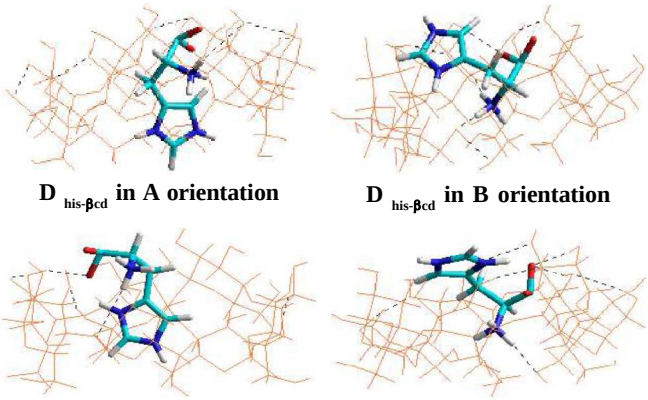
	$D_{his\text{-}\beta cd}$		$L_{his\text{-}\beta cd}$	
	Δ (A-B)		Δ (A-B)	
	vacuum	water	vacuum	water
$\Delta_{bonding}$	1.76	-23.97	-5.71	0.28
Δ_{vdw}	6.75	21.25	-2.40	-6.19
Δ_{elec}	-6.54	12.75	2.89	-9.16
$\Delta_{binding}$	1.97	12.03	-5.22	-15.07

For each structure we represented different contributions of bonding energy, vand der waals interaction and electrostatic energy, in the difference of binding energies between the two orientations of D and L histidine/ β CD complex.

The results of TABLE 3 show that the $D_{his\text{-}\beta cd}$ complex in B orientation is more favorable in vacuum of 1.97 kcal.mol^{-1} and in water of 12.03 kcal.mol^{-1}.

An detailed inspection of the obtained geometries (Figure 2) show that in the favorable orientation the ammonium group takes position in the centre of the cavity and it establishes hydrogen bonds with glycosidic oxygen's while the carboxyl group and the cycle are keeped on the wider part of the cyclodextrin cavity. We noted that hydrogen bonds are observed between the oxygen of the carboxyl group and the secondary hydrogen of cyclodextrin.

However, in A orientation, we observed a total inclusion of the cycle while the ammonium group is includes partially in the cyclodextrin cavity with the establishment of one hydrogen bond with a secondary oxygen of the β CD. The carboxyl group is located on the wider part of cyclodextrin cavity.



$D_{his\text{-}\beta cd}$ in A orientation $D_{his\text{-}\beta cd}$ in B orientation

$L_{his\text{-}\beta cd}$ in A orientation $L_{his\text{-}\beta cd}$ in B orientation

Figure 2 : Geometrical structure of more stable inclusion complexes.

This preference between the two orientations of $D_{his\text{-}\beta cd}$ complex can be explained by the establishment of more significant number of hydrogen bonds in B than A orientation.

In the $L_{his\text{-}\beta cd}$ complex, A orientation is more favorable in the vacuum of 5.22 kcal.mol^{-1} and in water of 15.97 kcal.mol^{-1}. As we can see in the favorable orientation the cycle is totally embedded in the cyclodextrin cavity while the ammonium group is partially included and one of its hydrogen establishes hydrogen bond with glycosidic oxygen. The carboxyl group remains outside the cavity and one oxygen atom establishes hydrogen bond with secondary hydrogen. However in the unfavourable orientation we distinguish the ammonium group inside the cavity and one hydrogen atom establishes hydrogen bond with primary oxygen of β cyclodextrin. The cycle and the carboxyl group remain on the wider part of the cyclodextrin cavity. In this orientation several hydrogen bonds are established between oxygen of the carboxyl group and secondary hydrogen.

According to these observations we can estimate that the hydrogen bond between hydrogen atom of the ammonium group and oxygen's glycosidic, presents only in the favorable orientation, played apparently a determining role in the stability of the complex and ensures a better adaptation of the invited molecule in the cyclodextrin cavity.

The enantiomeric recognition (ΔE_{CR}) are exhibited in TABLE 2, there are computed from the energy difference of their inclusion complexes, $D_{his\text{-}\beta cd}$ and $L_{his\text{-}\beta cd}$.

$$\Delta E_{CR} = E_{D\ his\text{-}\beta cd} - E_{L\ his\text{-}\beta cd} \quad (2)$$

Where $E_{D\ his\text{-}\beta cd}$ and $E_{L\ his\text{-}\beta cd}$ are the energies of corresponding D and L histidine cyclodextrin complex.

TABLE 4 : Chiral recognition (E_{CR}) and energetic detail in kcal.mol^{-1}.

	A orientation		B orientation	
	Δ ($D_{his\text{-}\beta cd}$ - $L_{his\text{-}\beta cd}$)		Δ ($D_{his\text{-}\beta cd}$ – $L_{his\text{-}\beta cd}$)	
	Vacuum	Water	Vacuum	water
$\Delta_{bonding}$	4.44	15.98	2.70	11.74
Δ_{vdw}	0.94	0.24	-8.62	-21.74
Δ_{elec}	2.36	14.71	5.92	-2.74
ΔE_{CR}	7.84	30.92	0.65	-12.74

Concerning the chiral recognition, A orientation has a better recognition in the vacuum and the energy

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difference between the two isomers is 7.84 kcal.mol $^{-1}$. In water, the energy differences increase between the two structures, it becomes 30.92 kcal.mol^{-1}. Furthermore in the B orientation, in vacuum we obtained a weak energetic difference which does not exceed 0.65 kcal.mol^{-1} what means a bad chiral recognition. While in the water the obtained recognition was found better and the difference energy between the two enantiomers is 12.74 kcal.mol^{-1}.

We can say in conclusion that the more stable structure is that which contain hydrogen bond between hydrogen of ammonium group and glycosidic oxygen.

Finally, we distinguished during simulated annealing that β cyclodextrin structure was slightly distorted especially in the B orientation when the cycle is outside the cavity.

CONCLUSION

In the bimodality case we found that B orientation in which the cycle is outside the cavity is more favorable and this preference is increased in the presence of water molecules. However for the chiral recognition A orientation gives the best preference and this is increased in the presence of water molecules. The analysis of the obtained structures shows that the hydrogen bond established between hydrogen of ammonium group and glocosidic oxygen play a significant role in the stability of b CD/histidine complex.

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