Oriental Journal of Chemistry Vol. **24**(1), 43-48 (2008)

Determination of interaction in the inclusion complex of zwitterionic phenylalanine and β-cyclodextrin: (molecular mechanics study)

MADI FATIHA, KHATMI DJAMELEDDINE and LARGATE LEILA

Guelma University, Sciences and Engineering Faculty - 240 00 (Guelma)

(Received: February 08, 2008; Accepted: April 24, 2008)

ABSTRACT

The formation of inclusion complexes between zwitterionic phenylalanine and β cyclodextrin was theoretical studied by molecular mechanics using MM+ force field implemented in Hyperchem 7.5 software. In the present work we considered two modes to introduce the phenylalanine in the cyclodextrin cavity, A and B orientations. We were interested by the bimodal complexation and the chiral recognition of this inclusion. In the bimodal complexation study we found that B orientation in which the cycle is outside the cavity is more favorable with 0.443 kcal.mol^{-1} in vacuum for L.phenylanaline and 1.226 kcal.mol $^{-1}$ for D. The best chirale recognition is given in B orientation it is of 0.674 kcal.mol^{-1} in vacuum and 1.397 kcal.mol^{-1} in water.

Key words: MM+, β-cyclodextrin, zwitterionic phenylanaline, chirale recognition, docking.

INTRODUCTION

The chiral discrimination is a subject of great importance in fine chemistry because the biological activity of the enantiomers is often different and therefore 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 [3,4].

The formation of inclusion complex between β cyclodextrin (CD) and amino acids (AA) constitutes an ideal system to evaluate different interaction in gas phase and in solution[5-10]. The amino acids are molecules having a carbon skeleton 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 zwetterionic form in aqueous solution in broad large of pH. They can be localized on principal chain: an ammonium ion in N terminal and a carboxyl group in a C terminal.

The two charged spice can stabilized with solvent. The absence of solvent molecules in gas phase does not make to stabilize charge of zwetterionic form compared to these isomers without separation of charge.Recently, there have been several theoretical studies of binding guests with cyclodextrins[11-27], where molecular mechanics gave results close to those to the experiments[28-29].

In this paper we will study the bimodality inclusion of the phenylanaline in their zwetterionic

form in the β -cyclodextrin cavity by molecular modelling methods in solution and gas phase.

The aim of the study in the gas phase was to give access to the intrinsic interaction of zwetterionic phenylanaline in complex and it could be essential to understand the interaction in solution.

Computational methods

The molecular mechanics calculations were performed in three steps, in all computations the polack-Ribiere algorithm was used at RMS of 0.01 Kcal/mol.

The initial structure of both enantiomer L or D of phenylalanine was taken from database of Hyperchem 7.5, then these structures was optimized by AM1 methods and MM+.

The structure of β-CD was taken from CDB and minimized by means MM+ force field. To control the inclusion process of L or D phenylalanine in β-CD cavity, we have studied the two possible regioselectivity (A or B). When A represent the encapsulation of the ring in the cavity and the B process is given by the introduction of ammonium and carboxylic group fig. 1. According to the two orientations, the L and D phenylalanine were placed at a distance of 14Å defined between an atom of the guest and the centre of the mass of β-CD, when the β-CD was aligned to xy plan and the guest aligned to z axis. The rapprochement was done by 1Å, in each step the system was optimized and the complexation energy was recorded.

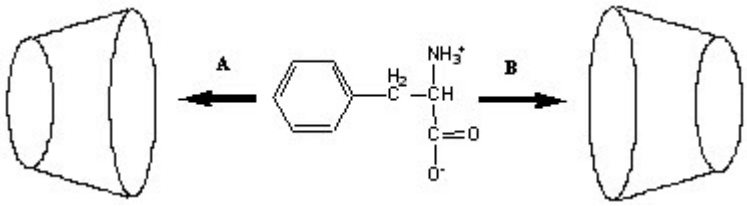


Fig. 1: Docking strategy of zwiterionic phenyl alanine in CD

Salvation

The lowest conformation found in vacuum for each complex was placed in a cubic box of 20×20×20Å which contain 265 water molecules, and then the system was optimized by maintaining the distance between solute and solvent at 2.3Å.

RESULTS AND DISCUSSION

In the following the inclusion compounds in molar proportion 1:1formed between one molecules of β-CD and ones of L.Phenylalanine and D.phenylalanine are abbreviated L.Phe/ β-CD and D.Phe/ β-CD respectively.

In docking process, the complexation energy for each enantiomer in the two orientations was calculated by MM+ force field in vacuum, which was calculated by subtracting the sum of the energy of individual free host and guest molecules to the energy of the inclusion complex.

The pathway of docking simulation fig. 2 showed a general tendency of lowering complexation energy when the enantiomers bring closer to the cavity.

In B orientation the minimum was located at -4 Å forL enantiomer and -3 Å for D, and the complexation energy was in the range of -17 kcal/mol.

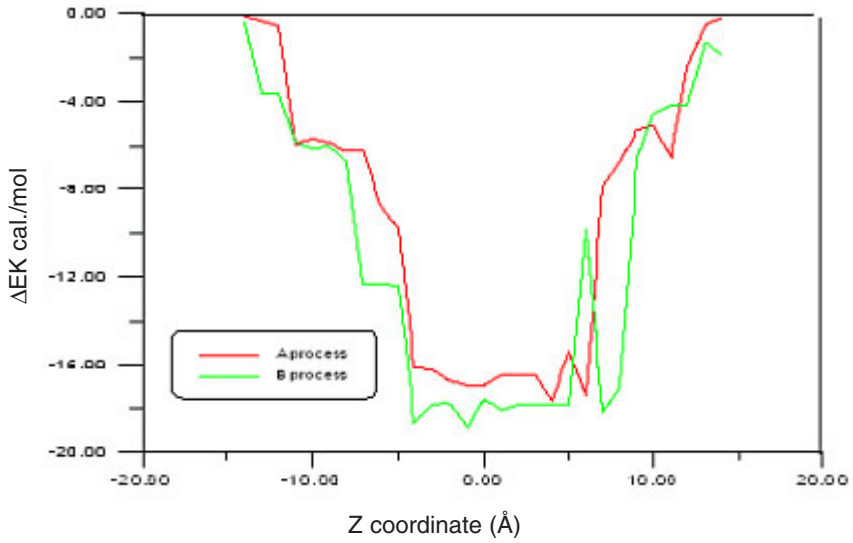
The structure of the inclusion complex shown in fig. 3 shows that the ammonium and carboxylic groups were totally embedded in β-CD cavity, which favorite the establishment of hydrogen bond, these were in agreement with experiment results that show that the phenylalanine is stabilized in β-CD by the hydrogen bond[5].

In A orientation, the lowest conformation was found at +4 Å and +3 Å for L and D respectively. The complexation energy accompanying the

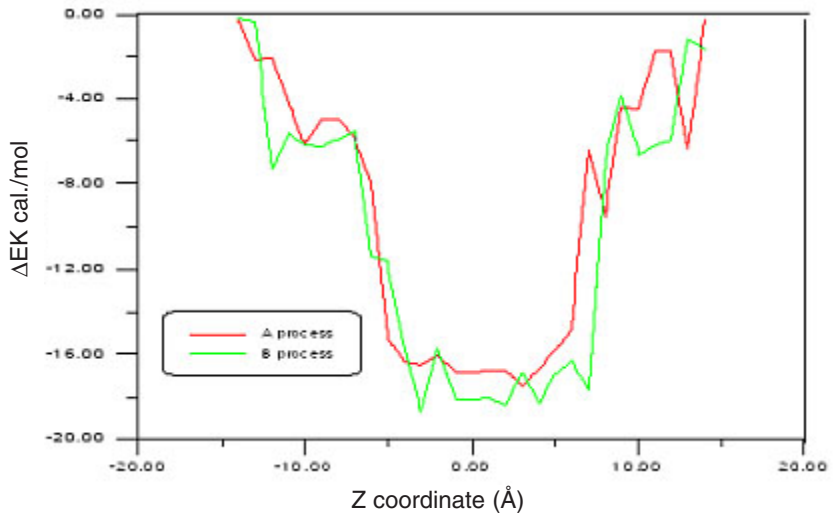
formation of inclusion complex between each enantiomers of phenylalanine can be calculated as

$$\Delta E = E_{complex} - E_{guest} - E_{\beta\text{-}CD}$$

The calculating complexation energy is all negative which indicate the formation of the inclusion complex, and the mutual host-guest interactions contribute greatly to the complexation energy ,the differences between the regioselectivity A or B are from 0.443 Kcal/mol and 1.226Kcal/mol for L and D phenylalanine respectively, which indicate the coexistence of the two orientations. The preference of B orientation is do to the VDW forces and the formation of the inclusion complex is do to the exchange energy between Host and Guest.

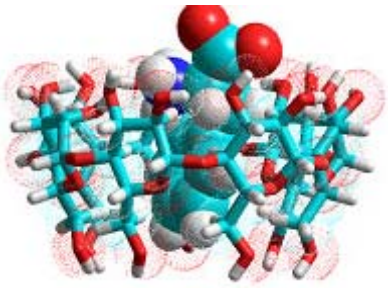


(a) Docking process of L.Phe in β-CD for the two orientations A and B

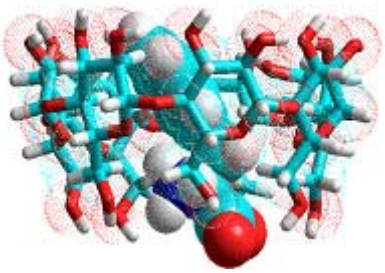


(b) Docking process of D.Phe in β-CD for the two orientations A and B

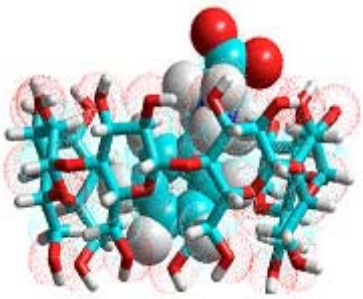
Fig. 2: Energy pathway of docking process



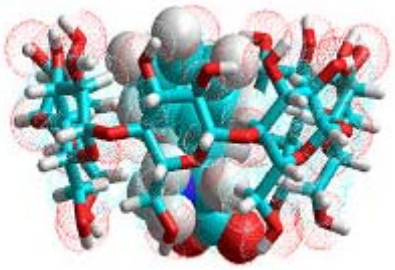
L.Phe/ β-CD (A)



L.Phe/ β-CD (B)



L.Phe/ β-CD (C)



L.Phe/ β-CD (D)

Fig. 3: Structures of lowest inclusion compound found by MM+ optimization

Table 1: Energy of formation values and the energy changes (changes in L or D Phe β-CD and their mutual interactions) accompanying the formation of the inclusion complexes, obtained by MM+ calculations in vacuum

	Energy values (Kcal/mol)							Energy exchanges (Kcal/mol)	
	Energy of complex	Free guest	Freeβ-CD	Energy format-ation of complex	Guest in complex	β-cd in complex	ΔE guest	ΔEβ-CD	ΔE guest-β CD
L.Phe/ β-CD (A)	67.690	-1.530	86.807	-17.587	-1.389	87.459	0.141	0.652	-18.380
L.Phe/ β-CD (B)	67.246	-1.530	86.807	-18.030	-1.339	87.517	0.191	0.710	-18.931
D.Phe/ β-CD (A)	67.739	-1.590	86.807	-17.478	-1.557	87.313	0.033	0.506	-18.017
D.Phe/ β-CD (B)	67.503	-1.590	86.807	-18.704	-1.512	87.055	0.078	0.248	-18.792

Table 2: Recognition energy (kcal/mol) of cyclodextrin

	Total	bend	angle	dihedral	Vdw	Strech -bend	Electrostatic
ΔrE (l-D) A orientation	-0.049	-0.024	-0.05	-0.096	0.126	-0.021	0.02
ΔrE (L-D) B orientation	0.743	-0.002	0.303	0.002	0.41	0.006	0.032

The calculating complexation energy and its components showed that the major contributions of the complex formation were VDW interactions.

Chiral recognition

The enantiomer recognition of cyclodextrin (ÄrE), exhibited in Table2, was computed from the energy difference of their inclusion complexes with L- and D-phenylalanine.

where E_L and E_D are complexation energies of corresponding L.Phe/ β-CD and D.Phe/ β-CD respectively for each orientation A or B. The D.Phe/ β-CD showed the best enantiomer recognition with ΔrE of-0.674 kcal/mol. The negative value expressed that the complex of L was more stable than that of D- configuration. The important contribution to the enantiomer discrimination was the energy rising from dihedral angle torsion, ΔrE dihedral, which was contributed from structural deformation.

These results are in agreement with the experimental results that indicate that the inclusion of D phenylalanine is more favourable than L enantiomer[5].

Solvation

From the results of the salvation studies, it is evident that the B orientation is the most favored, the selectivity of L and D phenylalanine toward this particular conformation could presumably facilitate specific interactions taking place between the host and the guest.

For the inclusion complex in water it was shown that the guest is partially encapsulated in the cavity because it does to the competition between water molecules and guest.

Table 3: calculated salvation energy of complexes

	E Complex in water	$\Delta E = E_L - E_D$ E complex	E hydratation
L.Phe/ β-CD (A)	-514.766	-510.425	72.139	-76.48
L.Phe/ β-CD (B)	-509.000	-494.410	71.060	-85.96
D.Phe/ β-CD (A)	-514.674	-508.062	74.456	-81.068
D.Phe/ β-CD (B)	-522.180	-508.226	73.403	-87.357

Table 4: AM1 calculation of Binding energy and heat of formation of complexes (kcal.mol^{-1})

	L.Phe/ β-CD (A)	L.Phe/ β-CD (B)	D.Phe/ β-CD (A)	D.Phe/β-CD (B)
E binding	-16797.55	-16862.58	-16857.58	-16861.96
Heat of formation	-1545.22	-1610.24	-1605.25	-1609.64

To verify our method, an AM1 study was used to obtain binding energy and heat of formation. It should be known that the structure of the complexes minimized using MM+ are taken as initial structure for calculation with AM1. The Polak-Ribiere algorithm was used to a maximum energy gradient of 0.01 kcal.mol^{-1} .

Table 4 summarize the results of AM1 calculation, the negative value of the binding energy of the four complexes suggested their stabilities. B orientation is more favoured for the two enantiomers and it supports the MM+ results.

CONCLUSION

The geometry and the stability of L.Phe/ β-CD and D.Phe/ β-CD complexes were investigated by using molecular mechanics. The results are summarized below:

1. The MM+ docking simulation recommends the B process as the more favored.
2. The arrangement in witch the carboxylic and ammonium groups were embedded in β-CD cavity is the most favorable.
3. The complexation energy suggests that the two enantiomers can form a stable inclusion complex with a week energy difference coming from VDW interactions.
4. On the other hand the AM1 semi empirical calculation confirm these results and gives the B orientation the more preferred.

ACKNOWLEDGEMENTS

This study was supported by Algerian minister of scientific research (research project 1.1.2005)

REFERENCES

1. Armstrong, D., Ward, T.J, Beesley, T.E, science, **232**: 1132 (1986).
2. Redondo, J, Blazquez, M.A, Torrens, A, *Chirality*, **11**: 694 (1999).
3. J.Szejtli, Cyclodextrin and their Inclusion Complexes.Académiai Kiado, Budabest (1982).
4. J.Szeytli,Cyclodextrin Technology, Kluwer Academic Publishers, Dordrecht,1988 hyperchem, Hypercube, Inc,USA (2002).
5. Sompornpisut, P., N. Deechalao, J. Vongsvivut, *Sci Asi.,* **28**: 263-270 (2002).
6. Ahn S., J.Ramirez,G.Gregorean and C.B.Lebrilla: *J of Am.Soc for Mass Spectro* **3**:278-287 (2001).
7. T. Kitae, T. Nakayama and K. Kano, *J. Chem. Soc,* perkin Trans **2**: 207-212 (1998).
8. K.B. Lipkwitz, S. Raghothama, J. Yang, *J. am. Chem. Soc.,* **114**: 1554-1562 (1992).
9. S.Ahn,X.Cong,C.B.Lebrilla:*J.Am.Soc for Mass Spect*., **16**: 166-175 (2005).
10. W.Sun, M.Cui, S.Liu, F. Song, Y.N. Elkin: *Rapid Cammum Mass spect*,**12**: 2016-2022 (1998).
11. G.Marconi, B.Mayer, *Pure and applied Chem* **69**:779-783 (1997).
12. D.Bogdan,C.Morari: *Rom. J. Phy*, **50**: 1003-1008 (2005).
13. B. Pascal, G. Maud, D. George, A.A Delin, B.Valery, P. Bruno, C. Didier, P. Géraldine, D. Lue, E. Bridgitte, *J. Phar. Pharmaceut Sci.,* **8**: 164-175 (2005).
14. M.J.Huang,J.D.Watts,N.Bodor:Int. *J of quan Chem.,* **65**:1195-1152 (1997).
15. F.M. Menger, M.J. Sherrod, *J. Am. Chem. Soc,***110**: 8606-8611 (1988).
16. M.Ero, S.Kubota, H.Nakagawa, Y. Yoshitake, K.Harano, *Chem. Pharm. Bull*.**,** **48**:1652-1659 (2000).
17. Y.Choi, D.W. Kim,H. Park, S. Hwang, K. Jeong, S. Jung, *Bull.Korean Chem Soc.,* **26**: 769-774 (2005).
18. S.A.D.Costa, E. Monflier, D.Landy, S. Fourmentin, G.Surpateaunu: *Surface Scien.* **470**: 275-283 (2001).
19. L.Liu, X.S. Li, T.W. Mu, Q.X. Guo,Y.C.Liu, *J of Inc. Phe and Macro. Chem.,* **38**:199-206 (2000).
20. C. Morari, D. Bogdan, M. Bogdan, *Rom.J.Phy* **50**:995-1002 (2005).
21. A.O. Desouza, J. B. Aldesete, A.F. Alario, G.L. Silvia,N.Duran,*J.Chi.Chem.Soc* **50**:591-596 (2005).
22. I.Perdomo-lopez,A.I.Rodriguez-Pere, J.M.yzquierdo-Peiro, A. White, E.G. Estrada, T.G.Villa,J.J.Torres-Labandeira, *J.Phar-Sci.,* **9**: 2408-2415 (2002).
23. B.P.Vilarnovo,I.Perdomo-Lopez, M.E. Lopez, P.S. Pardo, E.Estrada, J.J.T. Labandeira, *Euro.J of Phar Sci* **13**: 325-331 (2001).
24. E.Estrada,I.Perdom-Lopez, J.J.T. Labandeira, *J. Org. Chem* **05**: 8510-8517 (2000).
25. E. Jung, K. Jeong, S.Lee, J.I.Kim, S.Jung, *Bull.Korean Chem.Soc.,* **24**: 1627-1631 (2003).
26. G.Decock, S.Fourmentin, D.Landy. G. Surpateaunu, P.Decock and G. Surpateaunu: *Int.Elec.J. of Mol.Des* **5**: 376-386 (2006).
27. S.Chen,Q.Ten,S.Wu:Cent,*Eur J of Chem* **4**: 223-233 (2006).
28. A.Baneree, B.Sengupta,S.Chaudhuri,K.Basu and P.K.Sengupta : *J.Mol.Stru* **794** : 181-189 (2006).
29. K.Alsou'od :*J.inc.Phen and Mac Chem.,* **54**: 123-127 (2006).