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# Molecular Modeling of β-Cyclodextrin Inclusion Complexes with some N-2-chloroethyl, N-Nitroso, N´-sulfamoyl Molecules

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The use of molecular modeling techniques to study inclusion complexes attract a great importance. Because the combination of the experimental results and those obtained by calculation became a very powerful means to understand the inclusion complexation phenomena. In present study the computer simulations was carried out by using the Hyperchem 6.0 software to study the inclusion of N-nitroso, N-(2-chloroethyl), N´-sulfamoylpiperidine, product with antitumor activity, in the β-cyclodextrin. The inclusion of CENS to cyclodextrin cavity was carried out according to two orientations and three orientations. We found that using MM+ force field, the difference of studied orientation is, kcal/mol. This difference exceeds 25 kcal/mol when these systems were put in box water. The energy complexation was determined kcal/mol. The heat of formation and binding energy were calculated with AM1 and PM3 semi empirical methods.

**Key Words: β-Cyclodextrin, 2-Chloroethylnitrososulfamoyl, Docking, Complex inclusion, Molecular modeling.**

## INTRODUCTION

Many mineral and organic molecules present a cavity for making the inclusion complex, which is the host molecule admits in cavity interior one or two invited molecules without any covalent bond being established. The complex stability rests only on the adaptation quality between partners. Among the hosts molecules which became very popular to form inclusions complexes, the cyclodextrins (CyDs). There are cyclic oligosaccharides obtained starting from the enzymatic degradation of the starch. Natural cyclodextrins comprise 6, 7 or 8 units of glycopyranose symbolized respectively, by α, β and γ cyclodextrin.

The 3D cylodextrins structure represents molecule like a truncated cone, with a hydrophobic cavity. The narrow rim (*ca.* 6.4 Å) bears the primary hydroxyl group whereas the wide rim (*ca.* 15.4 Å) bears the secondary OH groups. This cavity draw the attention by its capacity to include molecules

hydrophobic subject. The molecule exterior is hydrophilic. Several parameters can influence the formation of the inclusion complex *e.g.*, size of the invited molecule and the cavity diameter of cyclodextrin[1-4].

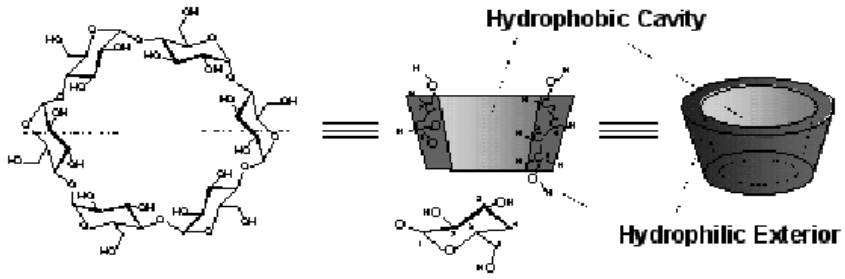


Fig. 1. Structure and topology of the β-cyclodextrin

We have already reported a theoretical study of some nitrososulfa-mayol (CENS), compounds with antitumor activity. It was shown experimentally that these compounds are instable and have a low solubility in water. But their inclusion in β-cyclodextrin increases their stabilities. The majority of investigations carried out recently are focused on the inclusion process between β-CyDs and several anticancer active principles[5-8].

In this article, a theoretical study of the inclusion of CENS in β-cyclodextrin is presented with the aim of determining the more stable conformers of the inclusion complexes, their stabilities and the geometry of CENS molecule in cyclodextrin cavity.

## RESULTS AND DISCUSSION

All simulations were run out in vacuum on PIII 233 PC using MM+ force field implemented in Hyperchem 6.0 software[16]. The initial structure of β CyDs was constructed by connecting seven units of α-D-glucopyranose by α -1, 4- bonding and this was fully minimized. The conformational search of the four CENS were performed by simulated annealing molecular dynamics-full energy minimization strategy and the lowest energy conformation of CENS were used as starting conformation for docking and molecular dynamics simulations. The conformations of the CENS molecules are depicted in Fig. 2.

The CENS molecule can be introduced in the β CyDs cavity by two different orientations[9]. In order to determine which of the two orientations is preferred. The inclusion complex was obtained by docking the CENS structure into β CyDs cavity (which was positioned parallel to xy plane) and the guest molecule was aligned with the z axis, rotated around x, y and z by step of 10° and translated with x, y and z by step of 1 Å to locate the minimum position[10,11]. No cut-off was imposed on the non bonded interactions calculation. The geometry optimization was carried out by using the

Polak-Ribiere algorithm to a maximum energy gradient of 0.01 kcal/mol.

The following nomenclature will be used in order to interpret computational results obtained in the present work. There are two different orientations in which CENS structure can be introduced into β-CD cavity.

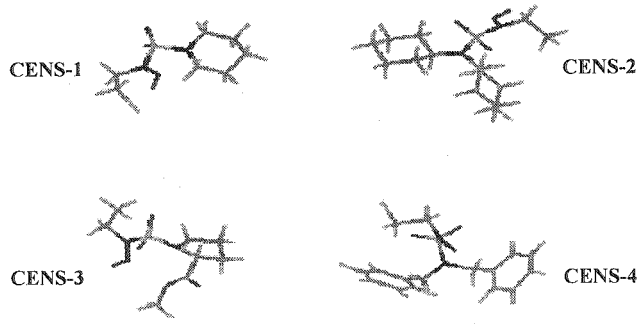


Fig. 2. Lowest energy conformation of the four CENS, CENS-1: N-Nitroso, N-(2-Chloroethyl), N'-sulfamoylpiperidyne, CENS-2: N-Nitroso, N-(2-Chloroethyl), N'-dicyclohexylsulfamoyl, CENS-3: N-Nitroso, N-(2-Chloroethyl), N'-sulfamoylprolinate, CENS-4: N-Nitroso, N-(2-Chloroethyl), N'-dibenzylsulfamoyl

Table-1 summarized the results of different operations of the CENS docking in β CyDs.

TABLE-1
ENERGIES, WITH AND WITHOUT OF WATER, OF THE FOUR COMPLEXES CENS-β CyDs IN TWO POSSIBLE ORIENTATIONS (A OR B), AS CALCULATED BY MM+

| | In vacuum (kcal/mol) | | | In water (kcal/mol) | | |
|---|---|---|---|---|---|---|
| | Orientation A | Orientation B | Difference | Orientation A | Orientation B | Difference |
| Complex-1 | | | | | | |
| E total | 74.15 | 82.70 | 8.55 | 2.72 | 25.26 | 22.54 |
| Complex-2 | | | | | | |
| E total | 60.04 | 83.01 | 22.97 | -9.50 | 26.03 | 35.03 |
| Complex-3 | | | | | | |
| E total | 86.94 | 96.24 | 9.30 | 38.01 | 34.05 | -3.95 |
| Complex-4 | | | | | | |
| E total | 83.57 | 85.59 | 2.02 | 2.54 | 31.04 | 28.50 |

We consider the two orientations in which the alkyl group (A orientation) or the N-sulfamoyl groups (B orientation) are introduced respectively into β CyDs cavity. The first calculations were conducted to determine which of the two orientations is preferred without solvent molecules, in vacuum. The molecular mechanics calculations show that A orientation is preferred by 2.02, 8.55, 9.3 and 22.93 kcal /mol with respect to B orientation.

In the complex-1, the CENS molecule adapts well to the CyDs cavity in the two orientations and only the Vdw interactions which give the preference to A orientation. On the other hand in the preferred orientation of complex-3 the proline is totally embedded in cylodextrin cavity and the alkyl group remains in exterior of CyDs cavity. In the preferred orientation of complex-2 and complex-4 only one cyclohexyl group or phenyl ring is completely fitted in CyDs cavity and the most part of CENS molecule is outside the cavity. Similar results were reported by Cabral Marques and Ernesto Estrada[7,12].

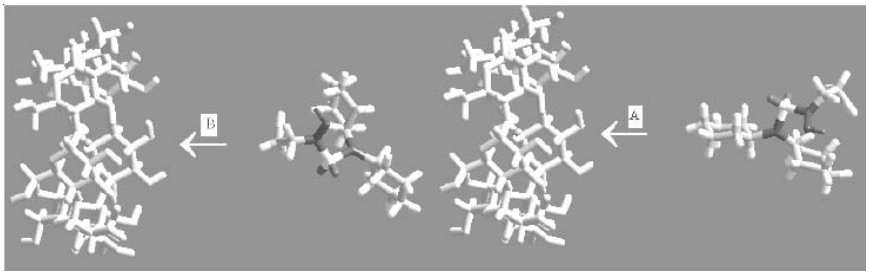


Fig. 3. The two possible orientations of the CENS in the β-cyclodextrin cavity

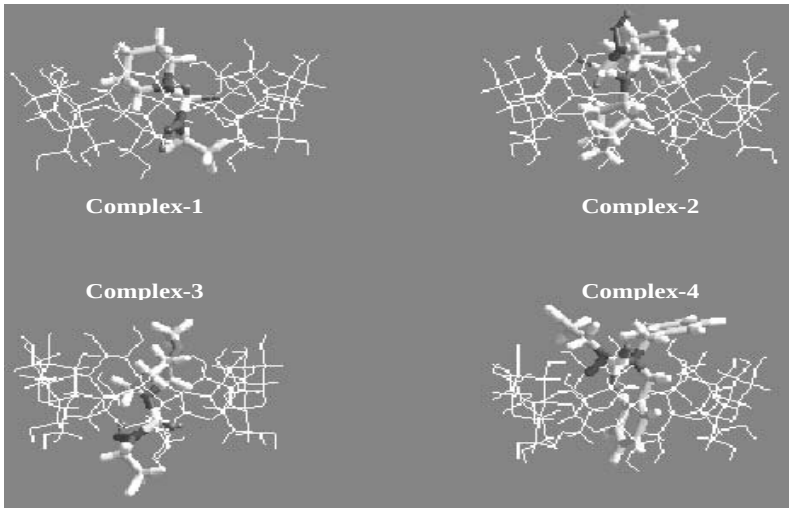


Fig. 4. Energy-minimized structures of the four CENS-β cyclodextrin in the A orientation. The complexation energy was defined as the difference between the sum of the energy of individual host and guest molecule and the inclusion complex energy. Different stoichiometry can be produced according to the size of the invited molecules. 1:1, 1:2 and 2:1

The A orientations becomes more favorable in medium aqueous and the difference between the two orientations exceeds the 20 kcal/mol, except in complex-3. In presence of water molecules, the B orientation of

complex-3 that or the two cyclohexyl group is in cavity exterior, becomes more favorable. This can be explained that in A orientation the cyclohexyl group cannot adopted the most favorable conformation in presence of water molecules.

Recently it was shown that the stoichiometry of the inclusion the CENS molecule in β CyDs is 1:1 and the complexation energy have been calculated by the relation[13]:

$$\Delta E = [E_{CENS/BCD} - (E_{BCD}) - (E_{CENS})]$$

Table-1 reports the computed complexation energies and the individual contribution of the non-bonded energy components. The lowest energy conformation of the four CENS considered in A orientation, should give inclusion complex with β CyDs in the vacuum and in presence of water molecules. The calculation of the complexation energy was given in Table-1.

The consideration of aqueous solvent in the calculation was done by considering a box of water molecules with the following dimension 12.12.12 Å. The minimum distance between solvent and solute atoms was 2.3 Å. We included the complex in the box water (35 water molecules). Full geometry optimizations of the host/guest complexes into the water box were carried by using MM+ force field. The energy of system is reoptimized in order to reorganize water molecules around complexes. The energy of each complex is determined at starting from the optimal geometry obtained in system complex / solvent and after elimination of all the water molecules.

TABLE-2
DETAILS OF ENERGY OF THE FOUR COMPLEXES OF CENS-β CyDs: COLUMN 1 IN VACUUM, COLUMN 2 IN WATER (kcal/mol)

| | Complex-1 (kcal/mol) | | Complex-2 (kcal/mol) | | Complex-3 (kcal/mol) | | Complex-4 (kcal/mol) | |
|---|---|---|---|---|---|---|---|---|
| Bond length (Å) | 05.75 | 05.99 | 05.76 | 06.37 | 06.96 | 07.56 | 06.42 | 06.43 |
| Angle (°) | 34.41 | 35.21 | 33.33 | 35.51 | 37.10 | 38.63 | 41.59 | 42.53 |
| Dihedral | 24.49 | 25.02 | 12.57 | 12.87 | 31.58 | 31.12 | 26.64 | 28.29 |
| Van der waals | 20.78 | 32.22 | 19.67 | 20.62 | 21.35 | 30.72 | 19.38 | 35.08 |
| Str. bend | 01.42 | 01.46 | 01.39 | 01.58 | 01.81 | 01.94 | 01.41 | 01.46 |
| Electrostatic | -13.76 | -66.23 | -13.75 | -99.37 | -13.35 | -85.76 | -12.38 | -63.28 |
| Total | 73.43 | 34.53 | 60.04 | -21.45 | 86.94 | 25.81 | 83.57 | 52.02 |
| Complexation energy | 29.67 | -62.56 | -43.82 | -106.32 | -22.52 | -83.65 | -20.99 | -52.53 |

According to the computation results of the negative complexation energy values that proves that the complexes of inclusion of the CENS in the β CyDs are stable and that the adaptation which is done best is that of the biphenyl. The presence in water increases the stability of these complexes and does not constitute a gene.

Semi-empirical calculation, PM3, of orientation A of the complexes CENS-β CyDs, is made of a system of 464 orbital which put with our Pentium 3 more the 48 h in best of the cases to optimize the structure. It should be known that the structure of the complexes minimized using MM+ are taken as initial structure for calculations with PM3. The Polak-Ribiere algorithm to a maximum energy gradient of 0.05 kcal/mol.

Table-3 summarizes the results of PM3 calculation of the four complexes and the CENS only. The negative value of the binding energy of the four complexes suggested the strong reduction in the binding energy while passing from the CENS to the inclusion complex CENS-β CyDs. Thus, these complexes of inclusion have a very strong stability, while comparing with the only CENS.

TABLE-3
BINDING ENERGY, HEAT OF FORMATION, ELECTRONIC ENERGY, NUCLEAR ENERGY, DIPOLE AND THE TOTAL ENERGY OF THE COMPLEXES CENS-β CyDs AND CENS ONLY OF PM3 CALCULATIONS (kcal/mol)

| | Complex-1 | Complex-2 | Complex-3 | Complex-4 |
|---|---|---|---|---|
| Binding energy | -16985.08 | -18804.040 | -17322.82 | -18760.23 |
| Heat of formation | -1537.26 | -1536.853 | -1585.82 | -1566.02 |
| Total energy | -443956.90 | -467349.100 | -460204.80 | -470023.70 |

## Conclusion

The calculations carried out by molecular mechanics and semi empirical method (PM3) shows that the inclusion complexes of the CENS molecules in the β CyDs are stable and they confirm experimental observations. During this theoretical study at the inclusion of CENS molecule in cyclodextrin cavity in accordance two processes A and B. Molecular mechanics predicts a favorable A orientation in the two complexes. In this orientation the phenyl ring or the cyclohexyl group are totally embedded in cyclodextrin cavity. On the other hand the use of PM3 semi-empirical method confirms this result for three complexes and gives the B orientation favorable in complex-2. The obtained result is contrary with that obtained by molecular mechanic. Finally, we observed that the preference of A orientation increases in aqueous medium except in the complex-2.

## REFERENCES

1. W. Saengers, *Angew. Chem. Int. Ed. Engl.*, **19**, 344 (1980).
2. P. Perly, F. Djedaîni-Pilard and P. Berthault, New Trends in Cyclodextrins and Derivatives, Ch. 6 (1990).
3. M.E. Amato, F. Djedaîni-Pilard, P. Perly and G. Scarlata, *J. Pharm. Sci.*, **81**, 1151 (1992).
4. K.H. Frômming and J. Szejtli, Cyclodextrins in Pharmacy, Kluwer Academic Press, Dordrecht (1998).

5. M. Fermeglia, M. Ferrone, A. Lodi and S. Priel, *Carboxyhyd. Polym.*, **53**, 15 (2003).
6. S. Alcaro, D. Buttaglia and F. Ortuso, *Arkivoc*, **107**, 117 (2004).
7. E. Estrada, L. Pedromo-Lopez and J.J.T. Labandeira, *J. Org. Chem.*, **65**, 8510 (2000).
8. K. Hyunmyung, J. Karpjoo, L. Sangsan and J. Seunho, *Bull. Korean. Chem. Soc.*, **24**, 95 (2003).
9. D.B. Ledium and B.A. Teicher, Cancer Therapeutics, Experimental and Clinical Agents, Humana Press, New Jersey, p. 81, 92 (1997).
10. M. Abdaoui, G. Dewynter, N.E. Aouf and G.L. Montero, *Phosphorus Sulfur Silicon Rel. Elem.*, **118**, 39 (1996).
11. M. Abdaoui, G. Dewynter, L. Tropet and G.L. Montero, *Tetrahedron*, **56**, 2427 (2000).
12. M. Abdaoui, G. Dewynter, N.E. Aouf, G.L. Montero, G. Favre and A. Morere, *Bioorg. Med. Chem.*, **4**, 1227 (1996).
13. M. Abdaoui, G. Dewynter and G.L. Montero, *Tetrahedron Lett.*, **37**, 5695 (1996).
14. M. Abdaoui, G. Dewynter, Z. Regainia and G.L. Montero, *Tetrahedron*, **52**, 14217 (1996).
15. M. Abdaoui, N.E. Aouf, G. Dewynter, Z. Regainia and G.L. Montero, *Tetrahedron*, **56**, 381 (2000).
16. HyperChem, Release 6.03 for Windows, Hypercube, Inc. (2000).
17. M.Y. Nie, L.M. Zhou, Q.H. Wang and D.Q. Zhu, *Acta Chim. Sinica*, **59**, 268 (2001).
18. M.Y. Nie, L.M. Zhou, Q.H. Wang and D.Q. Zhu, *Chem. Lett.*, **11**, 347 (2000).
19. W. Chuanzhong, G. Qiago and H. Jianbin, *Langmuir*, **19**, 3757 (2003).
20. H.M.C. Marques, J. Hadgraf, I. Kellaway and W.J. Pugh, *Int. J. Pharm.*, **63**, 267 (1990).
21. M. Kadri, N. Dhaoui, M. Abdaoui, J.Y. Winium and J.L. Montero, *Eur. J. Med. Chem.*, **39**, 79 (2004).

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