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Adamantanol Inclusion in Fluorescent β–cyclodextrin Derivatives. Theoretical Study by Molecular Mechanics and Quantum Semi–empirical Methods [#]

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Abstract

The more stable conformers of fluorescent β–CDs **1a–e** have been established by MM3, AM1 and PM3 procedure methods. The inclusion of 1–adamantanol into the toroidal cavity of β–CD fragments of fluorescent β–CDs **1b–e** was studied by the AM1 method and indicates that the internal closed complex **1** as more probable. The calculated results are in good agreement with the experimental data obtained by fluorescence spectroscopy.

Keywords. Fluorescent β–cyclodextrins; conformers; inclusion compounds; MM3; semi–empirical methods.

1 INTRODUCTION

Cyclodextrins (CDs) are cyclic oligomers of D–glucose and named α, β and γ–CD for hexamer, heptamer and octamer, respectively [1]. They are a toroidal cyclic structure with secondary hydroxyls glucose C–2 and C–3 on their more open face and the primary C–6 hydroxyl on the opposite secondary face [2]. Their ability to bind organic molecules in the hydrophobic central cavity has provided a basis for the construction of models for receptor [3]. It is widely accepted that the binding forces involved in the inclusion complex formation are van der Waals interactions, hydrophobic interactions, hydrogen bonding and electrostatic interactions between charged part of the guest molecule and CDs [4].

In previous paper [5], we reported the synthesis of some fluorescent β–cyclodextrin derivatives as chemosensors for molecular detection. These compounds have in their structure a fluorescent indolizine fragment linked in C–6 position of the β–CD (Figure 1).

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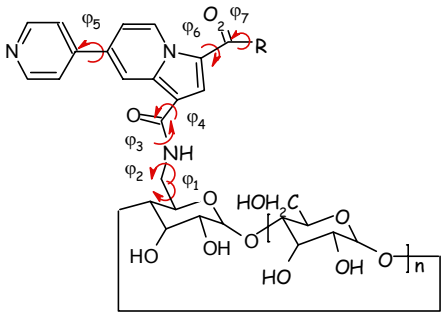

1a: R = OEt
1b: R = Ph
1c: R = *p*(CH_3)Ph
1d: R = *p*(OCH_3)Ph
1e: R = *p*(Cl)Ph

Figure 1. Fluorescent β–CDs.

Briefly, this new class of fluorescent β–Cds has been performed by 1,3–dipolar cycloaddition reaction of bipyridinium ylides with electrodeficient propynamido–β–cyclodextrin. Dominantly, their structures have been established by 2D–NMR spectra, also as their fluorescent spectra by absorption and emission maxims. The quantum yield of each fluorescent derivatives has also been calculated. In this paper, we describe the conformational analysis of these fluorescent β–CDs and we present our results concerning the inclusion of 1–adamantanol as model guest of others organic molecules.

2 MATERIALS AND METHODS

The molecular mechanics MM3 and semi–empirical RH AM1 and PM3 calculations were performed using PC–Spartan O2 Package [6]. A general procedure of multiconformational search has been used only for MM3 procedure method [7–9]. That consists in studying the ΔE, potential energy variation, by automatic sequential procedure according to the variation of the dihedral angle by rotational increments of 15°. The minimum value of ΔE is chosen according to the curve scribing. The analysis was developed tacking in account all single bonds composing the five studied fluorescent β–CDs **1a–e**, namely φ_1–φ_7. Only the minimum obtained by MM3 method has been taken in consideration for the next semi–empirical AM1 and PM3 procedure methods. The barrier rotation corresponding to dihedral angles φ_1 and φ_2 are excessively due to their proximity to toroidal cycle of β–CD. On the other hand, the torsions according to φ_5, φ_6 and φ_7 are not involved directly on the position of fluorescent fragment in respect to primary face of β–CD. The R group is automatically placed in a suitable position by all employed methods. That is why we considered as more important in our study the rotations assigned to angles φ_3 and φ_4.

3 RESULTS AND DISCUSSION

3.1 Conformational analysis of fluorescent β–CDs 1a–e by MM3, AM1 and PM3

All energy minimisations in MM3 were performed by using successively steepest descent, conjugate gradient and Newton–Raphson algorithms, with final convergence fixed to 0.001 kcal/mol. Next, we present graphically only our results of the study on **1b**.

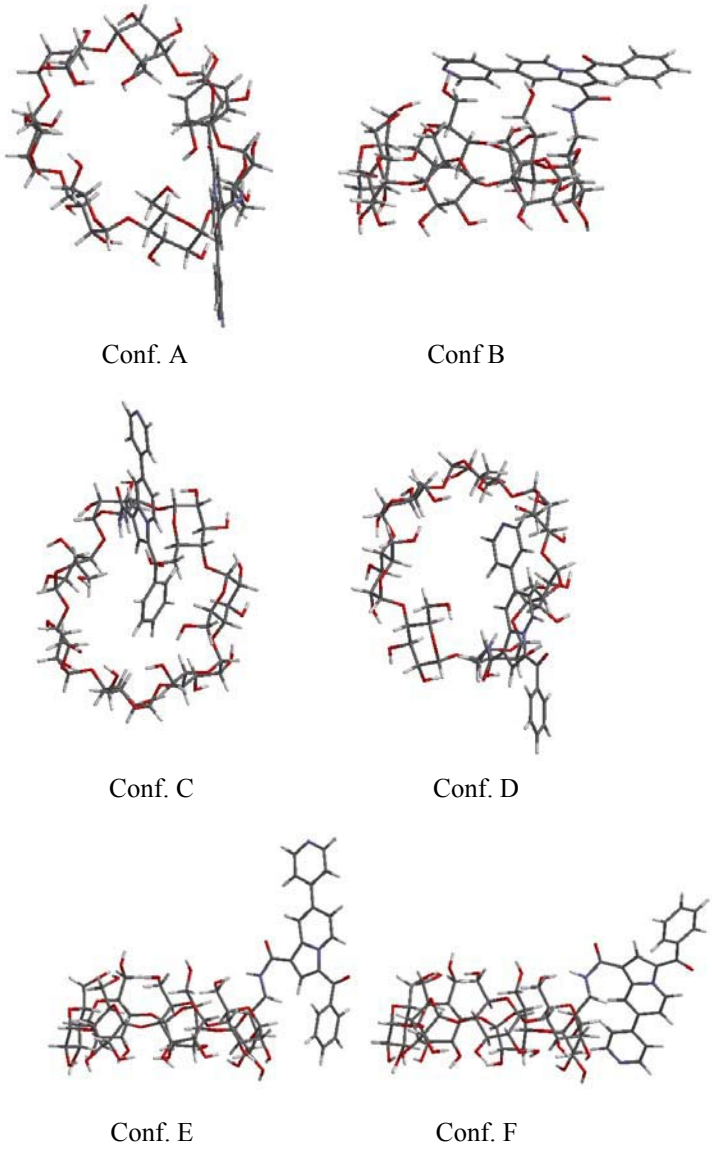

Figure 2. Conformations of fluorescent β–CD **1b**.

Survey of surfaces of potential energies for all five conformers of **1b**, we extracted six more stable conformations, depicted as A, B, C, D and E and F (Figure 2). Always, every minimal energy conformation was resubmitted to a final minimization and only these corresponding numerical data are given in Table 1. Generally, by semi–empirical calculations of enthalpies of formation the conformers of the type B could be considered as more stable. That corresponds to a spatial shape in which the pyridinoindolizinic arm covers as a cap the primary face of β–CDs. We consider these structures as a novel host–guest sensory system which would work monomolecularly. These investigations are relevant to others type of sensors [10–15] reported in literature.

Table 1. Potential energy (MM3) and Enthalpy of formation (AM1 and PM3) of six conformations of **1a–e** (kcal/mol)

		Conformers					
compound	Methods	A	B	C	D	E	F
1a	MM3	335.78	341.05	340.14	338.15	346.73	349.12
	AM1	–1617.09	–1621.77	–1620.19	–1618.56	–1610.32	–1609.92
	PM3	–1451.83	–1459.85	–1449.27	–1451.66	–1444.93	–1446.89
1b	MM3	348.56	362.37	357.97	355.25	360.52	363.72
	AM1	–1535.21	–1537.30	–1533.75	–1531.33	–1529.27	–1528.70
	PM3	–1369.80	–1376.08	–1370.74	–1374.98	–1367.81	–1372.52
1c	MM3	347.84	358.07	351.35	361.35	353.15	359.88
	AM1	–1539.66	–1539.06	–1542.01	–1538.02	–1534.66	–1534.29
	PM3	–1382.82	–1381.00	–1382.90	–1580.20	–1379.63	–1375.76
1d	MM3	344.95	346.99	343.44	349.61	350.71	359.62
	AM1	–1570.25	–1580.58	–1572.61	–1565.19	–1569.57	–1564.53
	PM3	–1411.35	–1415.37	–1410.12	–1407.53	–1405.67	–1399.78
1e	MM3	346.46	355.15	351.47	352.84	352.33	356.54
	AM1	–1537.97	–1543.08	–1537.78	–1540.46	–1533.64	–1532.33
	PM3	–1379.31	–1379.24	–1376.93	–1379.65	–1379.14	–1373.39

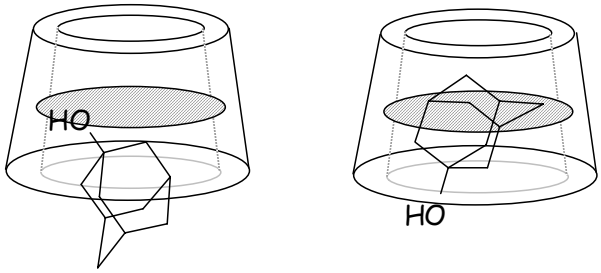

Figure 3. The approach of 1–adamantanol.

3.2 Inclusion of adamantanol on fluorescent β–CDs, 1b–e, by AM1

Normally, the approach of 1–adamantanol on the secondary face of fluorescent β–CD as B conformer has been explored in two different approach, namely with the hydroxyl group in upper and bass position (Figure 3) by using semi–empirical AM1 method. The complexation pathway according to the coordinate's reactions has been carried out by simulating the approach of the guest compared to the central plane of toroidal cycle of β–CD which some constraints have been imposed and then finally removed to allow a better calculation of enthalpic energy. Always, at the equilibrium position a final supplementary minimization has been performed.

In all cases we obtained analogous curves as that depicted in Figure 4 for the complex **1b**/1–adamantanol. The two approach of adamantanol to fluorescent β–CD **1b** lead to a complex **1** (Figure 5) as more stable structure (right in Figure 3). It is very interesting to observe that during displacement the adamantanol undergoes an inversion of its initial position. The hydroxyl group in adamantanol comes into lower position. Indeed, as explanation we could accept that in the first part

of displacement the formation of hydrogen bonds between the hydroxyl of adamantanol and those of the border of the secondary face of β–CD (curve I, Figure 4).

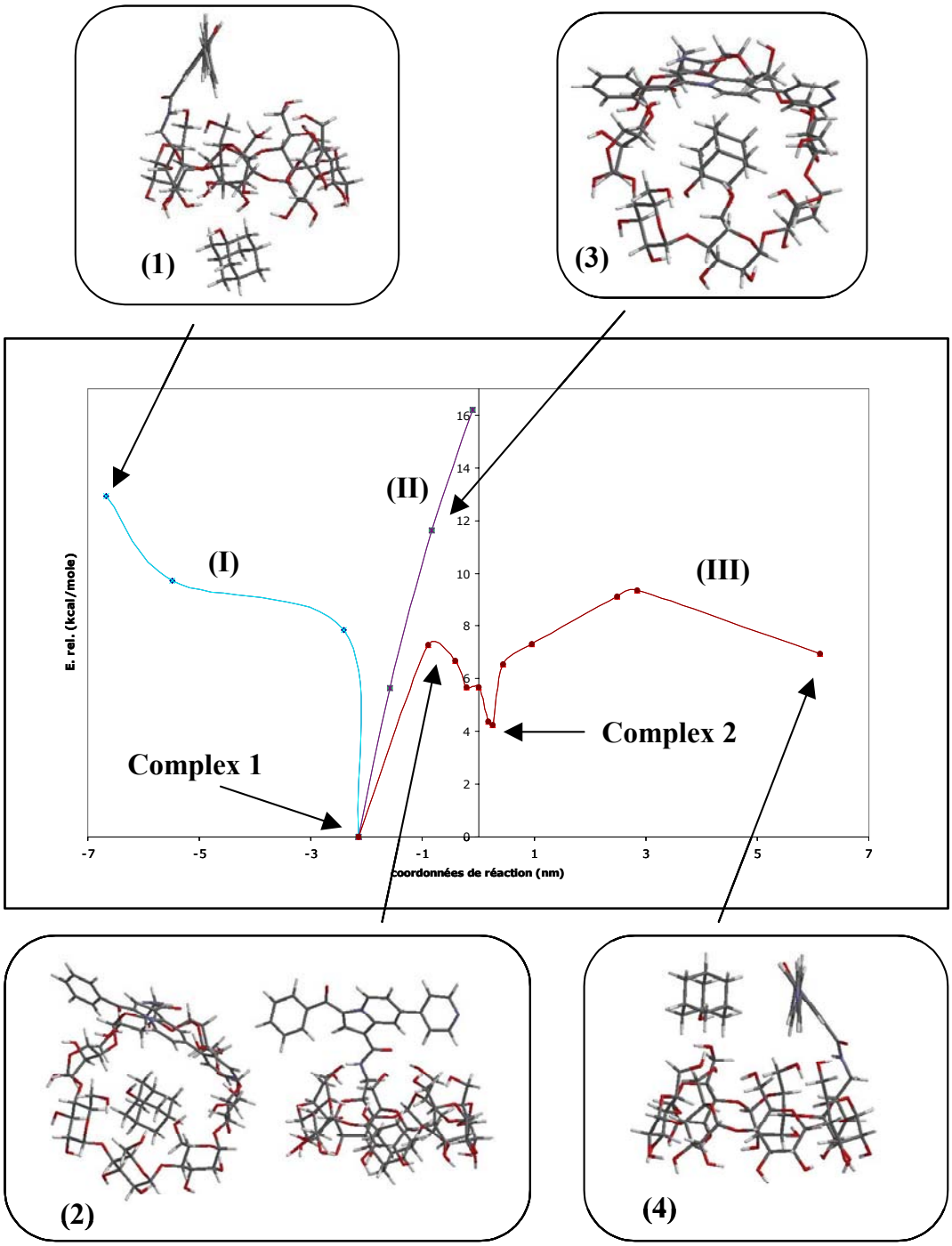

Figure 4. Variation of formation enthalpy ΔH during complexation of **1b**/1–adamantanol according to the reaction coordinates (nm).

In accordance with our strategy, starting in complex 1, the displacement of adamantanol proceeds up to primary face of β–CD fragment (**3** in Figure 4). That corresponds to high relative energies, yielding this sterical way as an improbable process.

Normally, the imposed inclusion of upper adamantanol into **1b** has been simulated (**2** in Figure 4). This time a less stable complex **2** (left in Figures 3 and 5) has been obtained. Also, the exit of adamantanol in this complex (**4** in Figure 4) is depicted (curve III, Figure 4). Otherwise, the inclusion of adamantanol into fluorescent β–CD **1b** succeeds with the formation of a more stable complex **1** depicted in Figure 5.

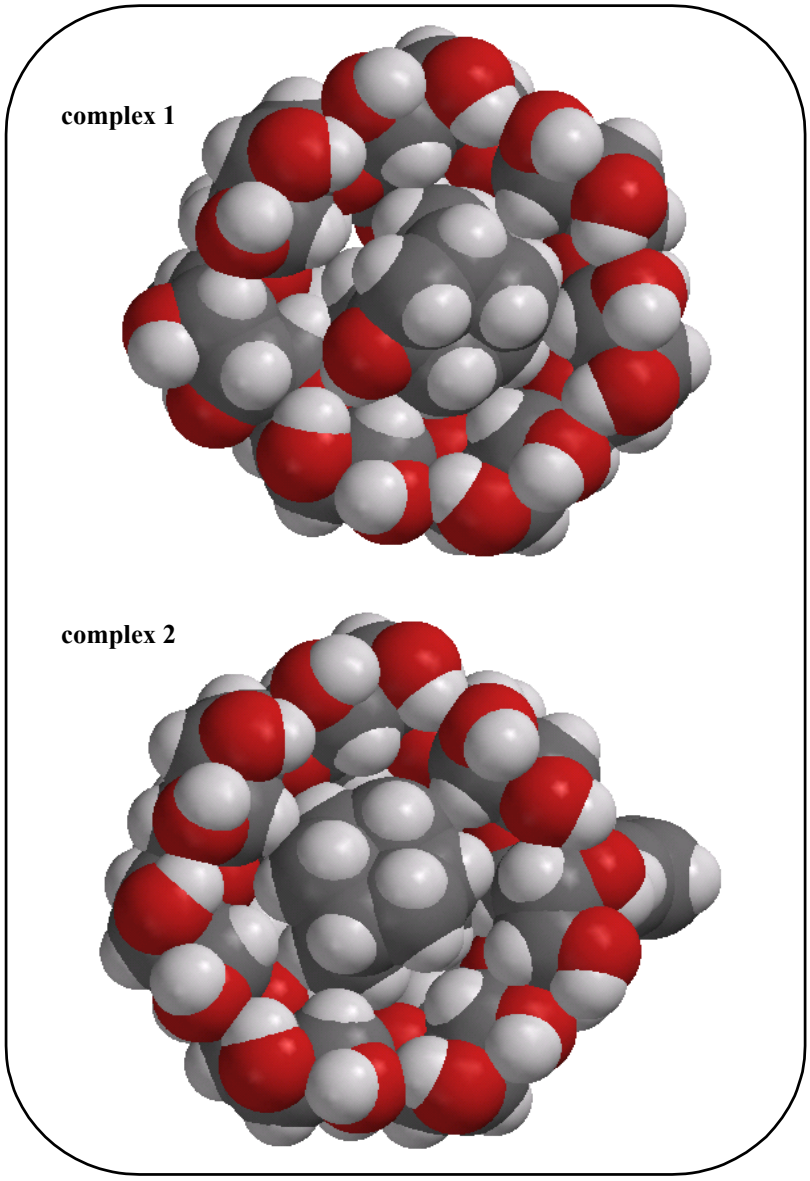

Figure 5. Representation of complexes **1** and **2** by a visualization of the secondary face of the β–cyclodextrin.

Table 2. Enthalpy of formation ΔH_1 and ΔH_2 (kcal/mol) of complexes **1** and **2**. Difference energy ΔE_1 (kcal/mol) and energy barrier ΔE_2 (kcal/mol).

compound	ΔH_1	ΔH_2	ΔE_1	ΔE_2
1b	–1634.74	–1630.49	4.25	7.30
1c	–1642.44	–1632.67	9.77	17.10
1d	–1672.98	–1671.86	1.12	4.80
1e	–1641.80	–1633.26	8.54	17.40

In Table 2 are given the enthalpy of formation of complexes **1** and **2** (Figure 4) of all four fluorescent β–CDs with 1–adamantanol ΔH_1 and ΔH_2, respectively, also as the energetic difference between them ΔE_1 and corresponding barriers ΔE_2. Indeed, in all simulated complexations the inclusion complex of the type **1** (Figure 5) is energetically favored.

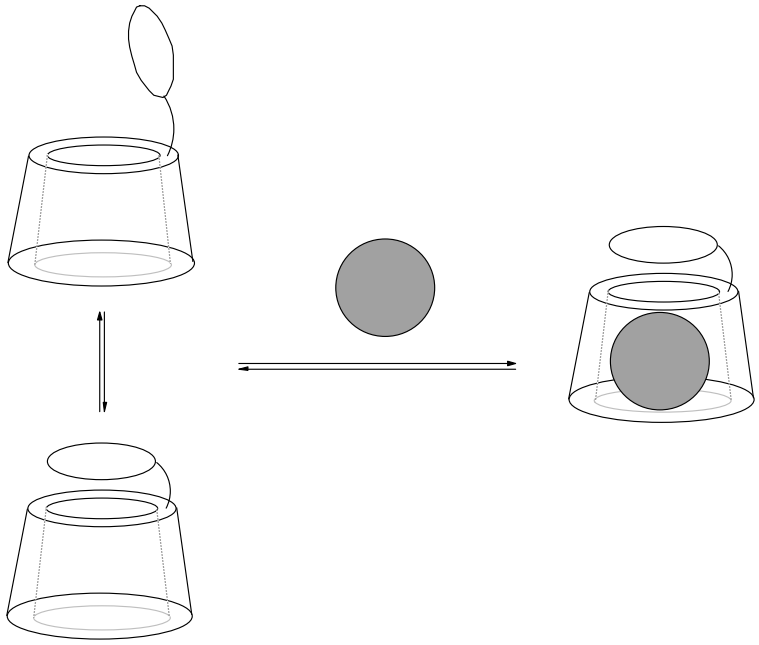

Figure 6. Representative diagram of inclusion of sensors **1a–e**.

All others calculations developed with conformers of the type A recommend the same complex as more probable. Finally, the closed structures depicted in Figure 6 could be obtained, which prove that this new class of sensor must be explored. These results are in good agreement with our experimental data obtained by fluorescent spectroscopy which will be published elswhere [16].

4 CONCLUSIONS

This study represents the first study by semi–empirical calculation of Molecular Energy Potential of modified β–cyclodextrin complexation. In this paper, we have been evaluated the relative pathway complexation between pyridin–4–ylindolizine modified β–cyclodextrin and 1–adamantanol. The results are summarized below:

(1) A conformational search by MM3, AM1 and PM3 methods recommends the conformers A and B as possible structures of fluorescent β–CDs. The results show that it should exist a conformational equilibrium between conformations A and B.

(2) The complexation study shows that the adamantanol can adopt two positions inside the macrocycle with a weak energy difference for sensors **1b** and **1d**.

(3) The AM1 study of the inclusion of adamantanol, giving conformers A and B of fluorescent β–CDs **1b–e**, represents a group of closed structures. Thus, the conformational equilibrium between A and B is displaced towards closed structures.

(4) The closed final conformer is in good agreement with the fluorescence behavior of **1b–e** observed experimentally in the presence of 1–adamantanol.

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