Inclusion of Adamantanol on Fluorescent β-cyclodextrine Derivatives. Theoretical Study by Molecular Mechanics and Quantum Semi-empirical Methods.

François Delattre, Patrice Woisel, Francine Cazier, Patrick Decock and

Gheorghe Surpateanu[*]

*Laboratoire de Synthèse Organique et Environnement, EA 2599, MREI, 145 Avenue

Maurice Schumann, 59140 Dunkerque, France

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 toroidal cavity of β-CD fragments of fluorescent β-CDs 1b-e studied by AM1 method recommends 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, 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 an fluorescent indolizine fragment linked in C-6 position of the β-CD.

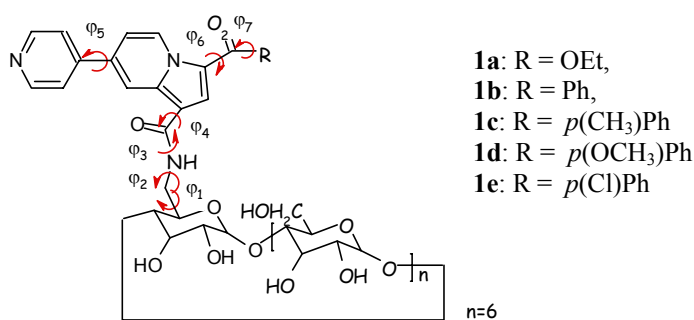[*] Correspondence authors; E-mail: surpatea@univ-littoral.fr.

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 maxima. 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 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**; *ea* φ_1-φ_7. Only the minimum obtained by MM3 method has been tacken 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

*a) Conformational analysis of fluorescent β-CDs **1a-e** by MM3, AM1 and PM3 procedure methods.*

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**.
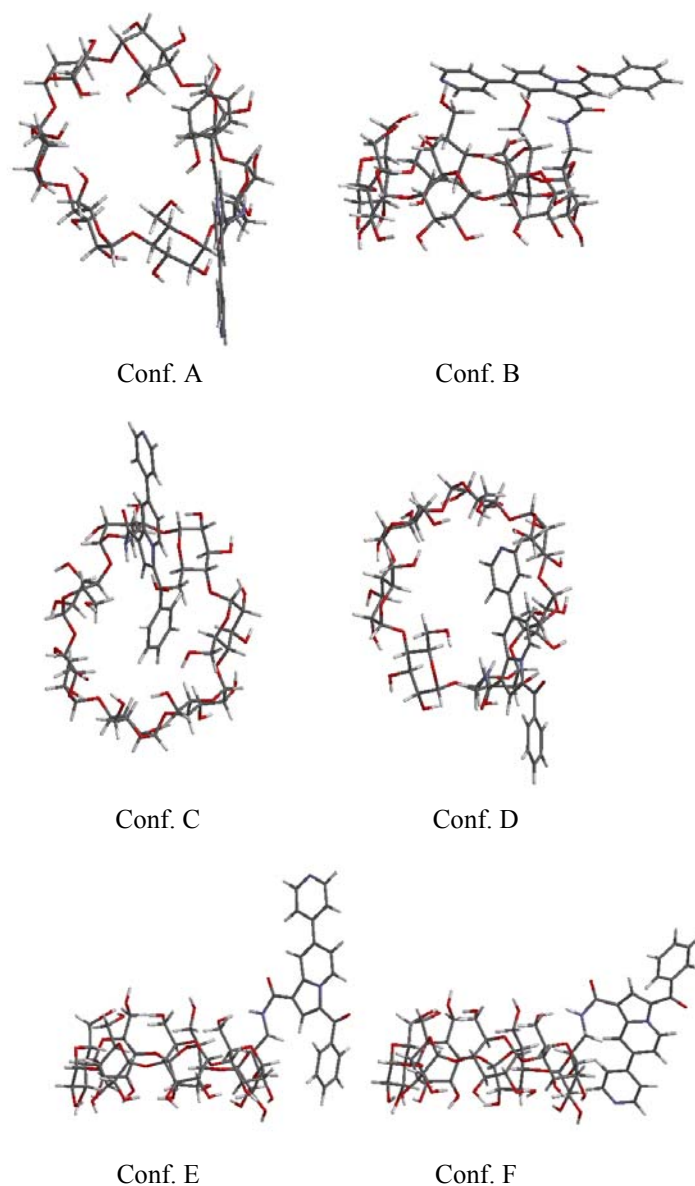

Conf. A   Conf. B

Conf. C   Conf. D

Conf. E   Conf. F

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 minimisation 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 works monomolecularly. It seems to others type of sensors [10-15] reported in literature.

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

compound	Methods	Conformers					
		A	B	C	D	E	F
1a	MM3	335.78	341.05	340.14	338.15	346.73	349.12
	AM1	-1621.77	-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	-1537.30	-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	-1539.06	-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	-1539.06	-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	-1543.08	-1543.08	-1537.78	-1540.46	-1533.64	-1532.33
	PM3	-1379.31	-1379.24	-1376.93	-1379.65	-1379.14	-1373.39

b) *inclusion of adamantanol on fluorescent β-CDs, **1b-e**, by semi-empirical AM1 method.*

Normally, the approach of 1-adamantanol on the secondary face of fluorescent β-CD as B conformer has been explored in two different ways *.ea.* with hydroxy group in upper and bass position (Figure.3).
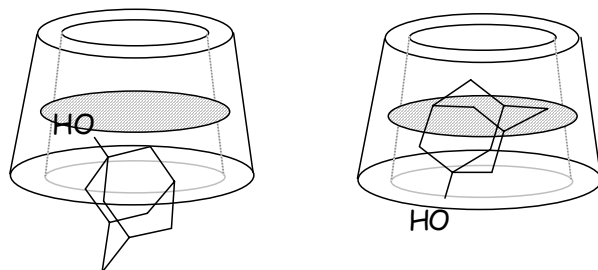

Figure 3. The approach of 1-adamantanol

In order to obtain desired distances between adamantanol and a central plane of toroidal cycle of β-CD, some constraints have been imposed. Always, at the equilibrium position a final supplementary minimisation has been performed.

In all cases we obtained analogous curves as that depicted in Figure 4 for the complex **1b**/1-adamantanol.

The approach of upper adamantanol to fluorescent β–CD **1b** leads to a complex 1 (Figure 5) as more stable structure. It is very interesting to observe that during deplacement the adamantanol undergoes an inversion of its initial position. The hydroxyl group in adamantanol comes into bass position. Indeed, as explanation we could accept that in the first part of deplacement 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).

In accordance with our strategy, starting in complex 1, the deplacement 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 **1a** has been simulated (2 in figure 4). This time a less stable complex 2 (Figure 6) 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 formation of a more stable complex 1 depicted in figure5.
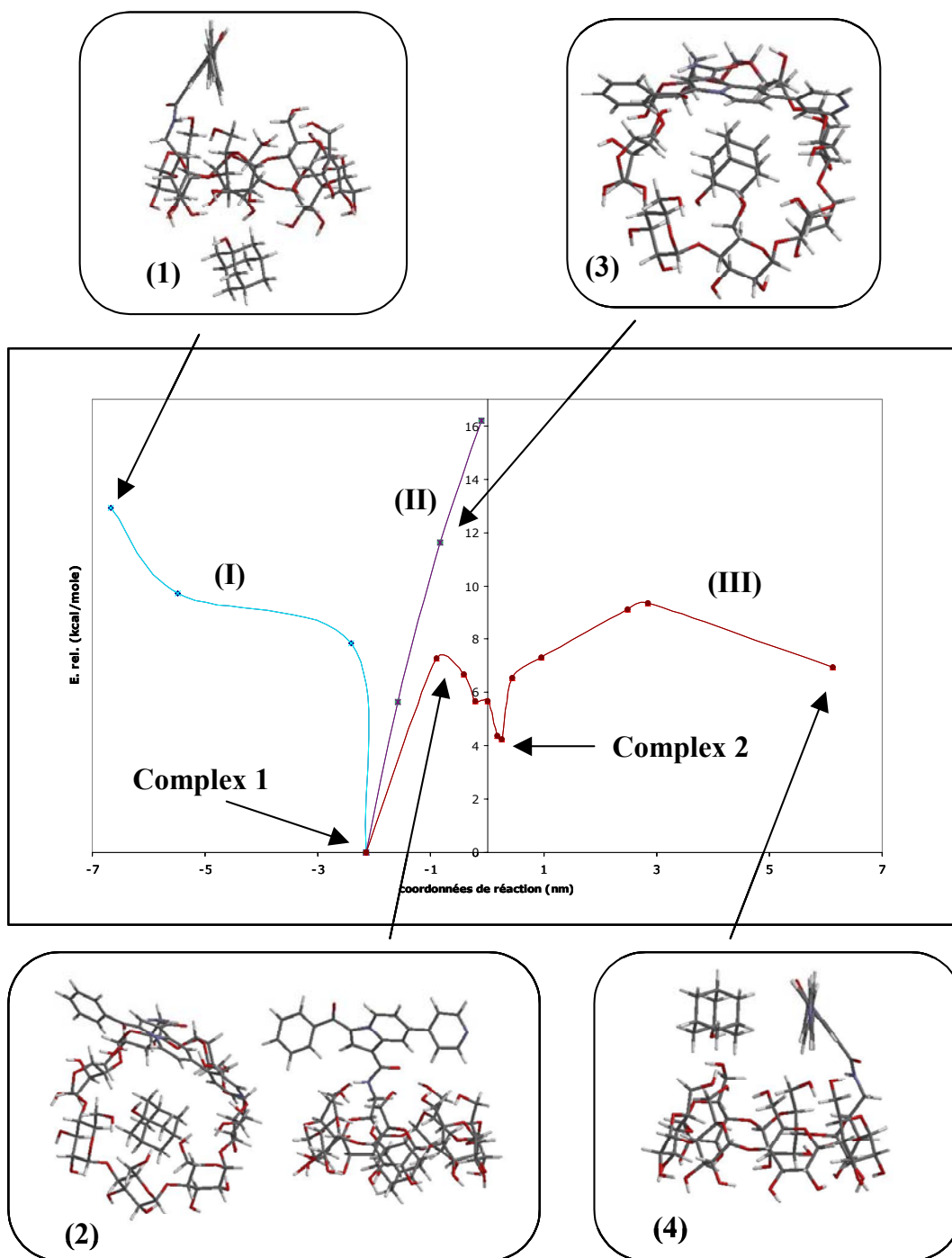
Figure 4. Variation of formation enthalpy, ΔH, during complexation of **1b**/1-adamantanol

In Table 2 are given the enthalpie of formation of complexes 1 and 2 (Figure 4) of all four fluorescent $\beta-$CDs with 1-adamantanol ΔH_1 and ΔH_2, respectively, also as the energetic difference between them ΔE_1 and corresponding barriers ΔE_2.

Table 2. Enthalpie of formation ΔH_1 and ΔH_2 (kcal/mol) of complexes 1 and 2. Difference energies ΔE_1 (kcal/mol) and barrier energies 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

Indeed, in all simulated complexations the inclusion complex of the type 1 (Figure 5) is energetically favorized.
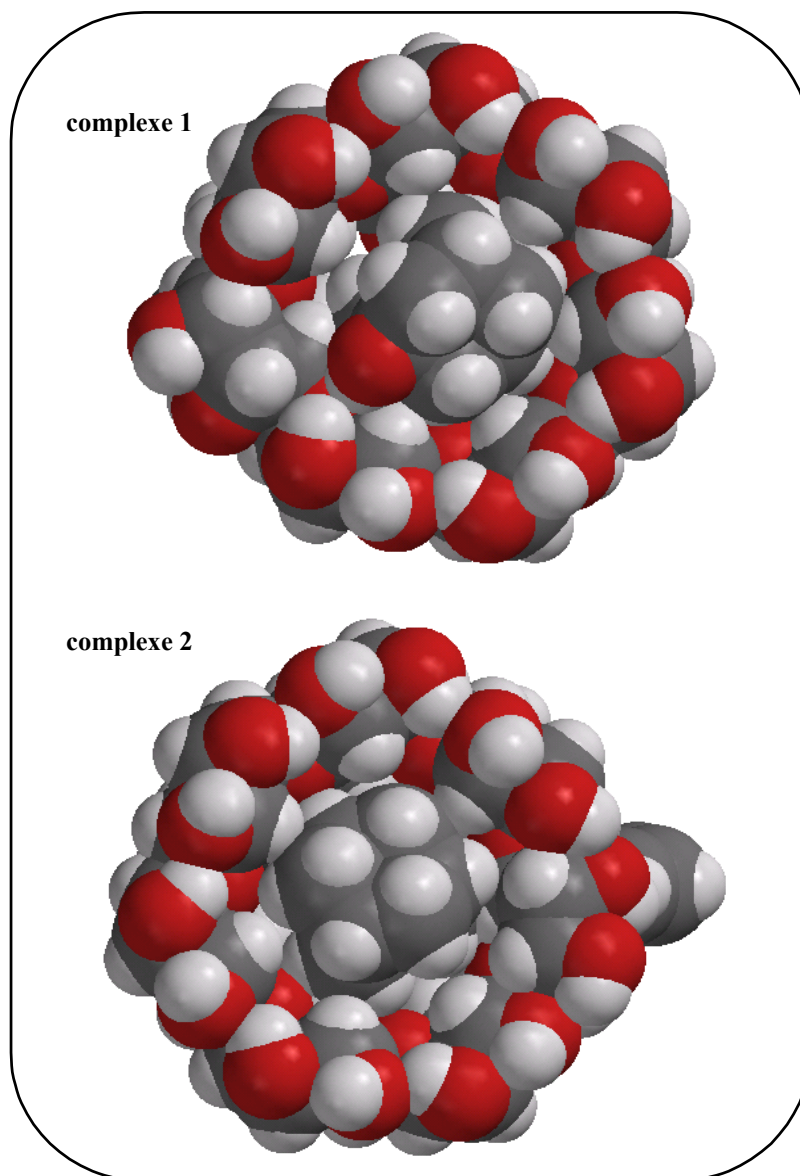

Figure 5. Representation of complexes 1 and 2

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 sonly will be published [16]].
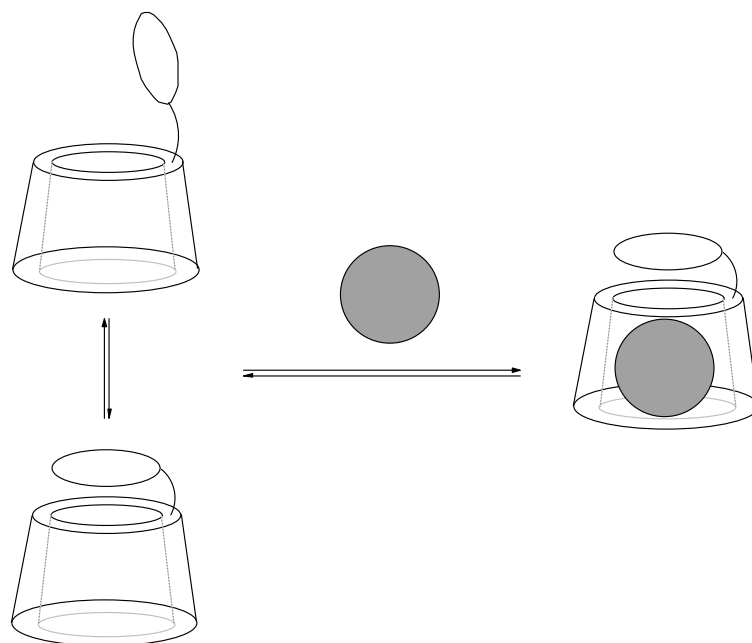

Figure 6. Representative schema of inclusion of sensors **1a-e**

4 CONCLUSIONS

1. Conformationnal search by MM3, AM1 and PM3 procedure methods recommends the conformers A and B as possible structures of fluorescent β-CDs.

2. Inclusion of adamantanol by AM1 method, starting of conformers A and B of fluorescent β-CDs **1b-e** offers a complex of closed structure.

3. The closed final conformer is in good agreement with the fluorescence behaviour of **1b-e** observed experimentally in the presence of 1-adamantanol.

5 REFERENCES

[1]   J. Szeytli, *Cyclodextrin Technology*, Kluwer Academic Publishers, Dordrecht, **1988**.
[2]   Y. Cao, X. Xiao, R. Lu and Q. Guo, *J. Mol. Struct*. **2003**, 660, 73.
[3]   S. Li and W. C. Purdy, *Chem. Rev.* **1992**, 92, 1457.
[4]   J. Szeytli, *Chem. Rev.* **1998**, 98, 1743.
[5]   F. Delattre, P. Woisel, G. Surpateanu, M. Bria, F. Cazier and Patrick Decock, *Tetrahedron* **2003** (in press).
[6]   Spartan, wave function, Inc. 2001.

[7]   G. G. Surpateanu, G.   Vergoten and G. Surpateanu, *J. Mol. Struct*. **2000**, 526, 143.

[8]   G. G. Surpateanu, G. Vergoten and G. Surpateanu, *J. Mol. Struct*. **2001**, 559, 263.

[9]   G. G. Surpateanu, F. Delattre, P. Woisel G. Vergoten and G. Surpateanu, *J. Mol. Struct*. **2003**, 645, 29.

[10]   A. Ueno and R. Breslow, *Tetrahedron Letters* **1982**, 23, 345.

[11]   A; Ueno, F. Moriwaki and T. Osa *Tetrahedron Letters* **1987**, 23, 1571.

[12]   T. Kuwahara, A. Matsushita, A. Nakamura, A. Ueno and F. Toda, *Chemistry Letters* **1993**, 2081.

[13]   S; Pagliari, R. Corradini, G. Galvarena, S. Sfortza, A. Dossena and R. Marcheli, *Tetrahedron Letters* **2000**, 41, 3691.

[14]   I. Suzuki, Y. Kato, Y. Egawa, J. Anzai, M. Vadamori, H. Yokomizo and K. Takahashi, *J. Mol. Struct*. **2002**, 602-603, 223.

[15]   T. Tanabe, K. Toume, H. Hamasaki and A. Ueno, *Anal. Chem*. **2001**, 73, 126.

[16]   Unpublished fluorescence data.