CODEN IEJMAT *Internet Electronic Journal of Molecular Design* **2007**, *6*, 96–105 ISSN 1538–6414
BioChem Press http://www.biochempress.com

Inter*net* Electronic Journal of Molecular Design

April 2007, Volume 6, Number 4, Pages 96–105

Editor: Ovidiu Ivanciuc

Special issue dedicated to Professor Lemont B. Kier on the occasion of the 75th birthday

Theoretical Study on the Inclusion of Allergens with Partially Methylated Crystallized β–Cyclodextrin and Hydroxypropyl β–Cyclodextrin

Georgiana G. Surpateanu,[1] Gautier Decock,[1] Sophie Fourmentin,[1] David Landy,[1] Paul Ionut Dron,[1] and Gheorghe Surpateanu [1]

[1] Laboratoire de Synthèse Organique et Environnement, EA 2599 Université du Littoral – Côte d'Opale, MREI, 145 avenue Maurice Schuman, 59140 Dunkerque, France

Received: October 3, 2006; Accepted: December 17, 2006; Published: April 30, 2007

Citation of the article:

G. G. Surpateanu, G. Decock, S. Fourmentin, D. Landy, P. I. Dron, and G. Surpateanu, Theoretical Study on the Inclusion of Allergens with Partially Methylated Crystallized β–Cyclodextrin and Hydroxypropyl β–Cyclodextrin, *Internet Electron. J. Mol. Des.* **2007**, *6*, 96–105, http://www.biochempress.com.

Copyright © 2007 BioChem Press

Inter*net* Electronic Journal of Molecular Design

BioChem Press
http://www.biochempress.com

Theoretical Study on the Inclusion of Allergens with Partially Methylated Crystallized β–Cyclodextrin and Hydroxypropyl β–Cyclodextrin

Georgiana G. Surpateanu,[1,*] Gautier Decock,[1] Sophie Fourmentin,[1] David Landy,[1] Paul Ionut Dron,[1] and Gheorghe Surpateanu [1]

[1] Laboratoire de Synthèse Organique et Environnement, EA 2599 Université du Littoral – Côte d'Opale, MREI, 145 avenue Maurice Schuman, 59140 Dunkerque, France

Received: October 3, 2006; Accepted: December 17, 2006; Published: April 30, 2007

Internet Electron. J. Mol. Des. **2007**, *6* (4), 96–105

Abstract

Motivation. Several compounds used in fragrance are suspected to be allergens and thus has to be extracted and analyzed. Cyclodextrins are well known to form inclusion complexes with a wide range of organic compounds. This is why we investigated, by a theoretical study, the interactions that occur between two modified cyclodextrins and 21 compounds suspected to be allergens.

Method. The computed complexation energies, ΔE, have been calculated for the inclusion of 21 allergens with hydroxyl–propyl–β–cyclodextrin (HPBCD) and partially methylated crystallized β–cyclodextrin (CRYSMEB). Our docking strategy involves three dummy atoms, two variable parameters and two regiochemical ways using MM3 method.

Results. The ΔE energies measured for the formation and stabilization of the inclusion complexes and the salvation energies calculated by AM1 (COSMO solvent field) allows the definition of the most probable structure in each pair of regioconformers, even if both forms may exist in solution in most cases. The complexation behaviors of HPBCD and CRYSMEB are analogous, but a notable greater stabilization is generally obtained with HPBCD. A better recognition is also generally observed for cyclic allergens than for acyclic ones.

Conclusions. The computed complexation energies ΔE calculated by the MM3 method could be considered as a measure of the inclusion ability of allergens in CRYSMEB and HPBCD. The filling of the inner cyclodextrin cavity with allergens could be taken into consideration with complexation energy. The solvation energy in water permits the choice of the most stable regioconformer in each pair of conformers. In respect to β–cyclodextrin, the hydroxypropyl β–cyclodextrin (HPBCD) seems to be the most interesting in the fixation of allergens. The specific affinities cyclodextrin–allergen could be explored from experimental point of view.

Keywords. Cyclodextrins; inclusion compounds; allergens; docking; MM3; AM1.

Abbreviations and notations

βCD, β–cyclodextrin	HPBCD, hydroxypropyl–β–cyclodextrin
CRYSMEB, partially methylated crystallized β–cyclodextrin	RAMEB, randomly methylated β–cyclodextrin

Dedicated to Professor Lemont B. Kier on the occasion of the 75th birthday.

* Correspondence author; E–mail: surpatea@univ-littoral.fr.

1 INTRODUCTION

The European legislation requires to evaluate fragrances for the content of 25 components suspected to be allergens. Among them some compounds are considered to be involved in skin irritation observed by consumers [1]. Thus their identification and their subsequent quantification remains an important target [2,3]. The use of cyclodextrins (CDs) as extracting agents and some research regarding their use in perfume and cosmetic industry have been reported [4]. The most frequently used are β–cyclodextrins due to their ability to protect efficiently aroma components against thermal or chemical degradation and especially against oxidation [5]. However, aroma components in liquors are very important to their sensory qualities but they are volatiles and tend to vanish from liquors by evaporation. Therefore, it is necessary to stabilize these components and thus retain the aroma in liquor. β–Cyclodextrin, the most common cyclodextrin composed by seven α–1,4 linked glucopyranose subunits and produced from starch by enzymatic degradation [6] is the most accessible at low price. Some chemically modified β–cyclodextrins, more soluble in water or in organic solvents, are commercially available like randomly methylated β–cyclodextrin (RAMEB), hydroxyl–propyl–β–cyclodextrin (HPBCD) and partially methylated crystallized β–cyclodextrin (CRYSMEB). In a previous paper [7] we reported our experimental and theoretical results concerning the inclusion of eugenol, isoeugenol, benzyl alcohol and anisyl alcohol with the four cyclodextrins mentioned above. A good agreement between the experimental and theoretical formation constants has been observed. As a consequence we extended the theoretical study [8] on the inclusion of the 21 others allergens with β–CD and RAMEB. To complete our studies, in this paper we present our complete results concerning the inclusion of the 21 others allergens with CRYSMEB and HPBCD.

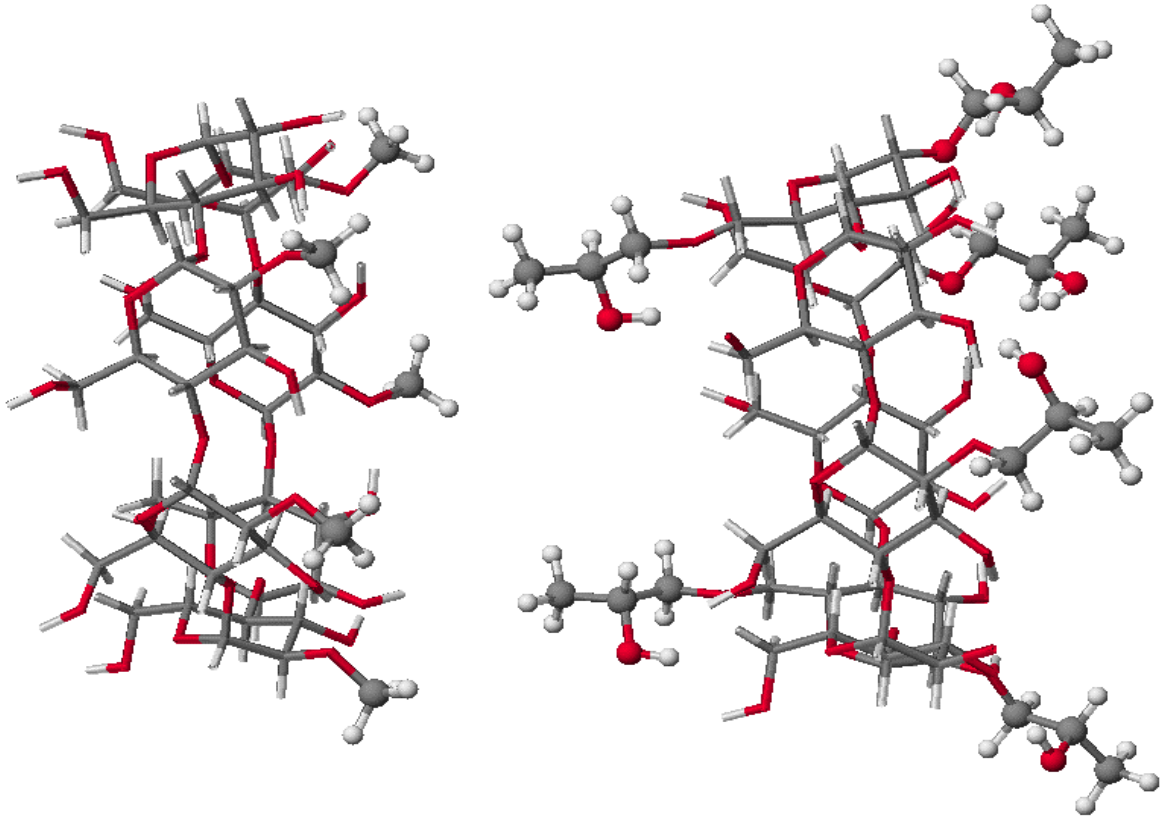
2 MATERIALS AND METHODS

2.1 Structure of Cyclodextrins

The model of CRYSMEB (Figure 1.a) was built from β–CD at which 5 methyl groups, replacing hydroxyl hydrogen's, have been attached at secondary positions. Otherwise, the model of HPBCD (Figure 1.b) was built also from β–CD at which 6 hydroxypropyl groups, replacing hydroxyl hydrogen's, have been attached as follow: two at primary positions and four at secondary positions. Both commercially products are not homogeneous compounds and thus, these two models respond only qualitatively to the reality. In both cases the most stable structure obtained by MM3 search have been minimized without imposition of any restrictions on the basis of AM1 Hamiltonian in gas and aqueous (COSMO solvent field) phase.

Moreover, the guest molecules were initially retrieved from the data provided by the structural Database System of the Cambridge Crystallographic Data Centre and then energy minimized with MM3 force field and AM1 procedure method. Secondary headings are numbered, font size 14,

centered, bold, and with the first letter of each main word capitalized.



a *b*

Figure 1. Structure of CRYSMEB (*a*) and HPBCD (b).

2.2 Conformation of Inclusion Compounds

The docking of each guest into CRYSMEB and HPBCD cavity has been performed using three dummy atoms (D1, D2 and D3) placed as shown in Figure 2.

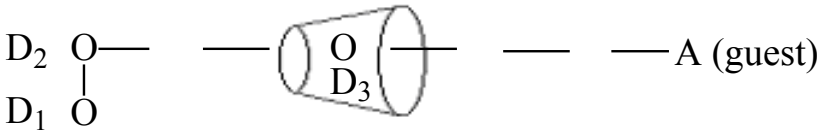


Figure 2. Representation of the dummy atoms in respect to the cyclodextrin fragment and the guest.

These dummy atoms are connected to each guest through one of its atom, designed by A. Concretely, with two variable parameters, the length A–D2 and the dihedral angle D1–D2–D3–A, it is possible to cross and cover all inner cavity of cyclodextrin fragment. Moreover, in order to examine all possible conformations during the docking guest–cyclodextrin, two general ways noted by E1 and E2 in Figure 3 have been considered to take into account the asymmetric structure (A–B)

of the guest molecule.

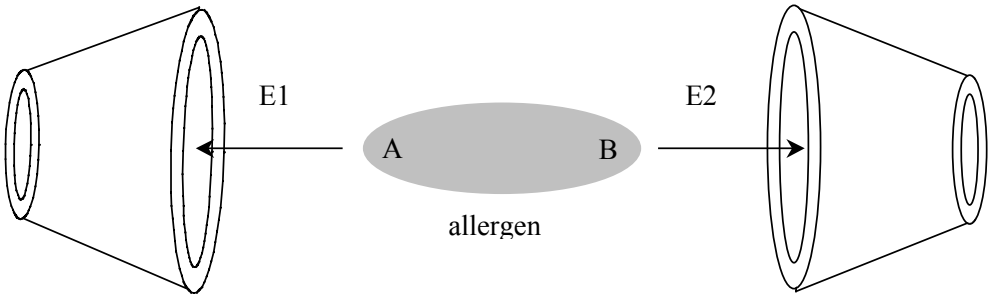
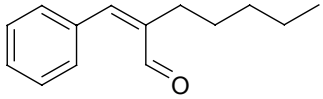
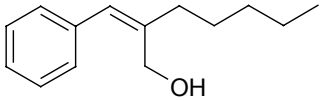
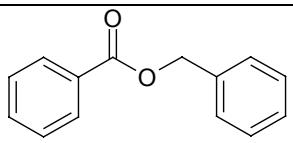
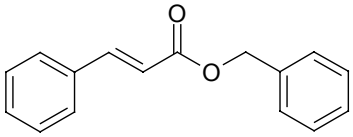
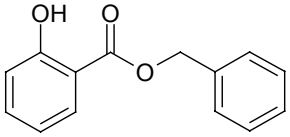
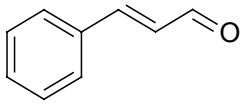
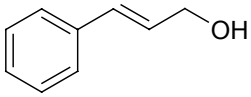
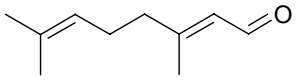
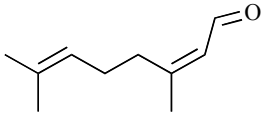
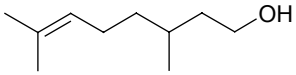
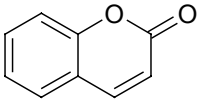
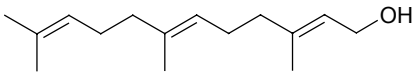
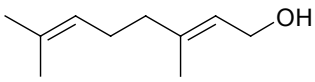
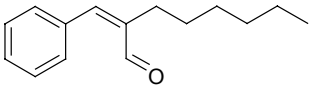
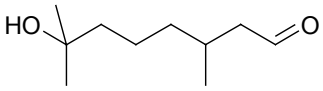
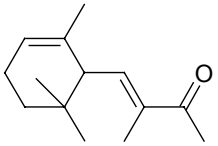
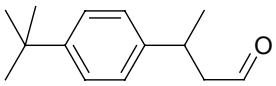
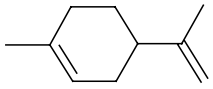
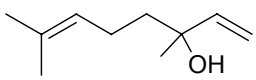
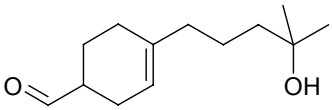
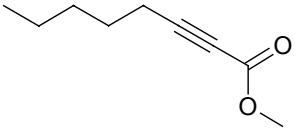


Figure 3. The docking strategy.

Table 1. Representation of the 21 Allergens

 α–Amylcinnamal (AMCO)	 Amyl cinnamyl alcohol (AMOH)	 Benzyl benzoate (BEBE)
 Benzyl cinnamate (BECI)	 Benzyl salycilate (BESA)	 Cinnamal (CACO)
 Cinnamyl alcohol (CAOH)	 Citral geranial (CIGE)	 Citral neral (CINE)
 β–Citronellol (CITR)	 Coumarine (COUM)	 Farnesol (FARN)
 Geraniol (GERA)	 Hexyl cinnamaldehyde (HCCO)	 Hydroxy citronellal (HCNA)
 Isomethyl α–ionone (IMIO)	 Lilial (LILI)	 Limonene (LIMO)
 Linalool (LINA)	 Lyral (LYRA)	 Methyl heptine carbonate (MOCT)

Next, a multiconformationnal search integrated in CAChe library [9] has been employed with the MM3 force field. During this search, the cyclodextrin host is kept rigid, while the guest freedom if

freely allowed. The most stable structures obtained by this procedure are then energy minimized without any constraint, not only with MM3 force field but also with AM1 Hamiltonian in absence and in presence of the COSMO simulation of water.

Table 2. Computed Energies of Allergens–CRYSMEB Complexes

N°	Complex	ΔE (kcal/mol)	Rank	ΔΔE (kcal/mol)	$\Delta\Delta E_S$ (kcal/mol)	$\Delta\Delta E_T$ (kcal/mol)	Conformers
1	CRYSMEB – AMCO – E1	–13.3	6	–0.2	+0.2	0.0	E1 & E2
	CRYSMEB – AMCO – E2	–13.1					
2	CRYSMEB – AMOH – E1	–15.0	2	–2.4	–1.5	–3.9	E1
	CRYSMEB – AMOH – E2	–12.6					
3	CRYSMEB – BEBE – E1	–14.5	3	–0.7	+1.7	+1.0	E2
	CRYSMEB – BEBE – E2	–13.8					
4	CRYSMEB – BECI – E1	–14.5	3	–0.3	+1.8	+1.5	E2
	CRYSMEB – BECI – E2	–13.8					
5	CRYSMEB – BESA – E1	–12.6	1	+3.1	+2.5	+5.6	E2
	CRYSMEB – BESA – E2	–15.7					
6	CRYSMEB – CACO – E1	–10.0	11	+0.8	–1.9	–1.1	E1
	CRYSMEB – CACO – E2	–10.8					
7	CRYSMEB – CAOH – E1	–13.9	4	–1.6	+0.1	–1.5	E1
	CRYSMEB – CAOH – E2	–12.3					
8	CRYSMEB – CIGE – E1	–10.6	12	–0.9	–2.0	–2.9	E1
	CRYSMEB – CIGE – E2	–9.7					
9	CRYSMEB – CINE – E1	–9.7	13	+0.5	+0.3	+0.8	E2
	CRYSMEB – CINE – E2	–10.2					
10	CRYSMEB – CITR – E1	–9.1	9	+2.6	–1.1	+1.5	E2
	CRYSMEB – CITR – E2	–11.7					
11	CRYSMEB – COUM – E1	–12.2	8	–1.7	–2.1	–3.8	E1
	CRYSMEB – COUM – E2	–10.5					
12	CRYSMEB – FARN – E1	–13.7	5	–3.8	+1.8	–2.0	E1
	CRYSMEB – FARN – E2	–9.9					
13	CRYSMEB – GERA – E1	–11.2	10	–1.6	–1.7	–3.3	E1
	CRYSMEB – GERA – E2	–9.6					
14	CRYSMEB – HCCO – E1	–13.9	4	–2.3	–0.2	–2.5	E1
	CRYSMEB – HCCO – E2	–11.6					
15	CRYSMEB – HCNA – E1	–9.6	14	+0.2	+1.3	+1.5	E2
	CRYSMEB – HCNA – E2	–9.8					
16	CRYSMEB – IMIO – E1	–5.1	14	+4.7	+1.6	+6.3	E2
	CRYSMEB – IMIO – E2	–9.8					
17	CRYSMEB – BPMP – E1	–13.3	6	–0.2	–0.6	–0.8	E1
	CRYSMEB – BPMP – E2	–13.1					
18	CRYSMEB – LIMO – E1	–9.5	15	+0.2	+0.2	+0.4	E2
	CRYSMEB – LIMO – E2	–9.7					
19	CRYSMEB – LINA – E1	–12.3	7	+0.2	+0.7	+0.9	E2
	CRYSMEB – LINA – E2	–12.5					
20	CRYSMEB – HCCA – E1	–11.6	9	+0.1	–0.6	–0.5	E1
	CRYSMEB – HCCA – E2	–11.7					
21	CRYSMEB – MOCT – E1	–6.6	16	+1.4	–2.2	–0.8	E1
	CRYSMEB – MOCT – E2	–8.0					

Table 3. Computed Energies of Allergens–HPBCD Complexes

N°	Complex	ΔE (kcal/mol)	Rank	ΔΔE (kcal/mol)	$\Delta\Delta E_S$ (kcal/mol)	$\Delta\Delta E_T$ (kcal/mol)	Conformers
1	HPBCD – AMCO – E1	–16.8	5	–3.1	+0.3	–2.8	E1
	HPBCD – AMCO – E2	–13.7					
2	HPBCD – AMOH – E1	–17.7	2	–2.8	–3.3	–6.1	E1
	HPBCD – AMOH – E2	–14.9					
3	HPBCD – BEBE – E1	–16.2	7	–3.1	–0.8	–3.9	E1
	HPBCD – BEBE – E2	–13.1					
4	HPBCD – BECI – E1	–16.2	7	–0.4	+6.3	+5.9	E2
	HPBCD – BECI – E2	–15.8					
5	HPBCD – BESA – E1	–18.0	1	–2.2	–1.9	–4.1	E1
	HPBCD – BESA – E2	–15.8					
6	HPBCD – CACO – E1	–12.2	16	–0.7	–1.3	–2.0	E1
	HPBCD – CACO – E2	–11.5					
7	HPBCD – CAOH – E1	–16.5	3	+1.1	–1.3	–0.2	E1
	HPBCD – CAOH – E2	–17.6					
8	HPBCD – CIGE – E1	–13.5	13	–2.4	+0.1	–2.3	E1
	HPBCD – CIGE – E2	–11.1					
9	HPBCD – CINE – E1	–13.6	12	+0.1	–2.5	–2.4	E1
	HPBCD – CINE – E2	–13.7					
10	HPBCD – CITR – E1	–12.5	11	+1.9	–5.7	–3.8	E1
	HPBCD – CITR – E2	–14.4					
11	HPBCD – COUM – E1	–12.8	15	+0.4	–7.5	–7.1	E1
	HPBCD – COUM – E2	–13.2					
12	HPBCD – FARN – E1	–12.2	4	+5.3	+0.1	+5.2	E2
	HPBCD – FARN – E2	–17.5					
13	HPBCD – GERA – E1	–13.5	6	+2.9	–0.8	+2.1	E2
	HPBCD – GERA – E2	–16.4					
14	HPBCD – HCCO – E1	–13.4	14	–0.6	+1.3	+0.7	E2
	HPBCD – HCCO – E2	–12.8					
15	HPBCD – HCNA – E1	–15.3	9	–3.4	+5.1	+1.7	E2
	HPBCD – HCNA – E2	–11.9					
16	HPBCD – IMIO – E1	–10.2	17	+1.2	–0.1	+1.1	E2
	HPBCD – IMIO – E2	–11.4					
17	HPBCD – BPMP – E1	–15.2	10	–3.1	–4.9	–8.0	E1
	HPBCD – BPMP – E2	–12.1					
18	HPBCD – LIMO – E1	–10.9	19	–0.3	–4.9	–5.2	E1
	HPBCD – LIMO – E2	–10.6					
19	HPBCD – LINA – E1	–15.2	8	+0.4	+1.5	+1.9	E2
	HPBCD – LINA – E2	–15.6					
20	HPBCD – HCCA – E1	–13.4	2	+4.3	–2.0	+2.3	E2
	HPBCD – HCCA – E2	–17.7					
21	HPBCD – MOCT – E1	–10.5	18	+0.5	+0.5	+1.0	E2
	HPBCD – MOCT – E2	–11.0					

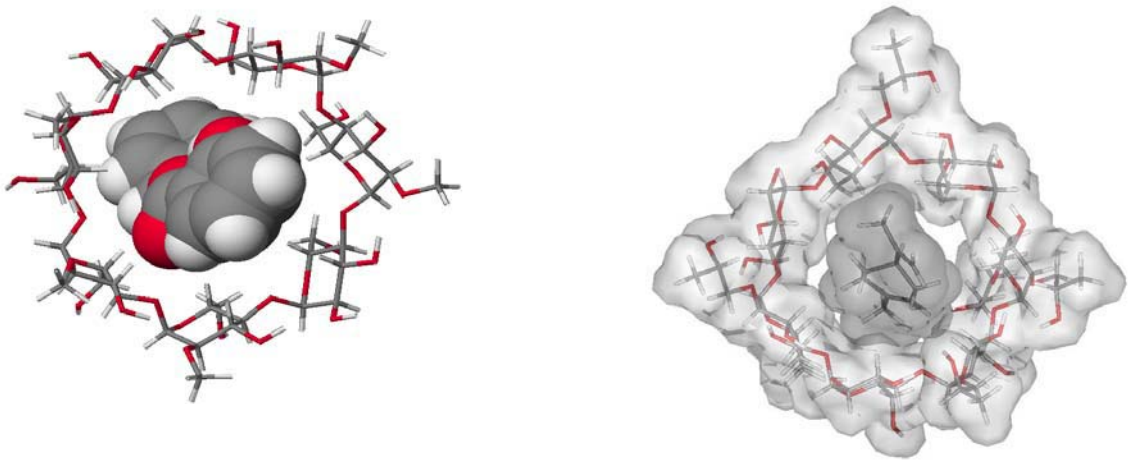
The difference (MM3, ΔE, kcal/mol) between potential energy of the inclusion complex and the sum of their potential individual component in their optimized ground states was then used as theoretical parameter to evaluate the inclusion capacity of the cyclodextrin host. Indeed to recommend and to use this simplified docking strategy, with reduced time consuming, a complete

study concerning both unlocked eugenol and β–CD partners has been performed. The random variations may be observed during the search if the cyclodextrin geometry is not locked. Even if the potential energies of two more stable inclusion complexes involving unlocked eugenol with unlocked β–cyclodextrin and unlocked eugenol with locked β–cyclodextrin are totally different, the difference in their complexation energies ΔE, is only of 1.27 kcal/mol. The 21 allergens are presented in Table 1. The simplified identifications of all products used in this paper are mentioned in parenthesis. We note that the beginning of the docking involves the allergen in its regiostructure described in Table 1 and thus both regiochemical ways E1 and E2 have been investigated.

3 RESULTS AND DISCUSSION

By our docking strategy, we found the most stable conformer for each inclusion compound. In Tables 2 and 3 are given the nature of the complex for both regiochemical ways E1 and E2. In those tables ΔE values represent the nature of the computed complexation energies calculated by MM3. ΔΔE is the difference between the two regioselective forms of inclusion, in such a way that a negative value is obtained if the E1 complex is more stable than the E2 one. The difference of solvation energy ($\Delta\Delta E_S$) between the two regioconformers is calculated by AM1–COSMO method. In order to identify the more stable regiocomplex in each pair a resulting total difference ($\Delta\Delta E + \Delta\Delta E_S$) is expressed as $\Delta\Delta E_T$.

The data presented in Tables 2 and 3 enable us to point out some conclusions. For the complexation of benzyl salycilate (BESA) with both studied cyclodextrins, the highest values of ΔE (–15.7 and –18.0 kcal/mol) have been calculated for CRYSMEB/BESA–E2 and HPBCD/BESA–E1 respectively, whereas the lowest values of ΔE (–8.0 and –10.9 kcal/mol) have been obtained for CRYSMEB/MOCT–E2 and HPBCD/LIMO–E1, respectively (Figure 4).



a

Figure 4. Models of the complexes: (*a*) CRYSMEB/BESA–E2.

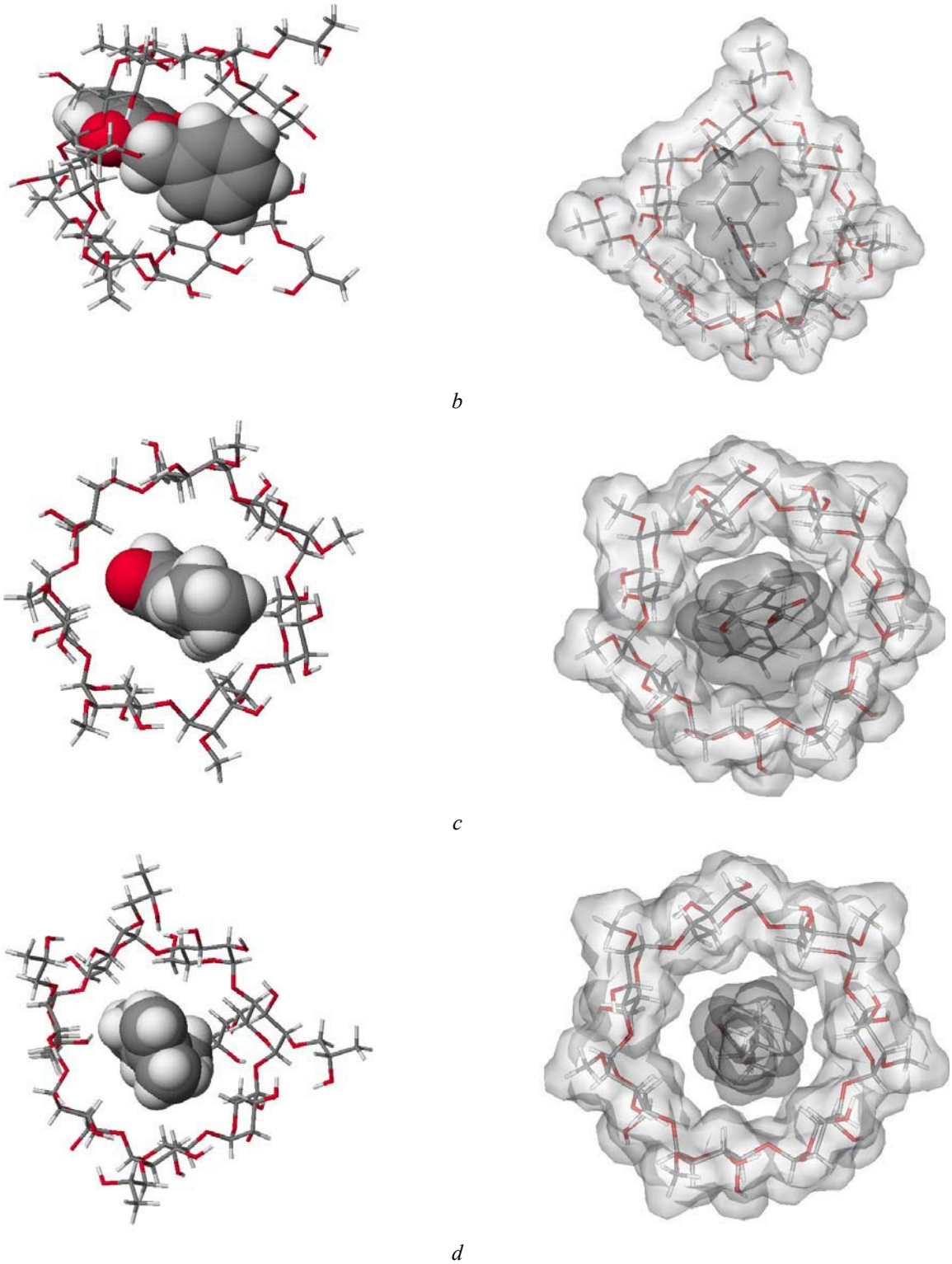


Figure 4. Models of the complexes: (*b*) HPBCD/BESA–E1; (*c*) CRYSMEB/MOCT–E2; (*d*) HPBCD/LIMO–E1.

Considering the importance of van den Waals interactions the filling of the inner cyclodextrin cavity should be a crucial factor ordering the stability of the cyclodextrin–allergen complexes. As a matter of fact, the inclusion compounds illustrated in Figure 4 seem to prove this assumption. The complexes with benzyl salycilate are more stables with highest complexation energies. As we

finished our theoretical studies on all 21 allergens with all four commercially available β–cyclodextrins in Table 4 we summarized our resultants for CRYSMEB and HPBCD together with the others previously published data [7,8] for β–CD and RAMEB.

Table 4. The Complexation of Allergens with β–CD, RAMEB, CRYSMEB and HPBCD

Number	Cyclodextrin	ΔE (range) (kcal/mol)	E_S (range) (kcal/mol)	Ranking
1	B–CD	8.6 – 14.9	53.1 – 62.1	2, 5, 7, 17, … 15, 21
2	RAMEB	9.1 – 16.0	41.0 – 50.1	5, 2, 3, 17, … 15, 21
3	CRYSMEB	8.0 – 15.7	46.8 – 61.1	5, 2, 3, 4, … 18, 21
4	HPBCD	10.9 – 18.0	50.5 – 84.4	5, 2, 7, 12, … 21, 18

Thus we could point out some general theoretical conclusions concerning the use of cyclodextrins as stabilization materials in perfume and cosmetic industries. Concretely, the three modified β–cyclodextrins RAMEB, CRYSMEB and HPBCD by their complexation energies ΔE could be considered as more performed inclusion hosts. If the RAMEB and CRYSMEB, by their ranges ΔE, are not so different in respect to β–CD, in the case of HPBCD the difference is notable. Even as the ranges in solvation energies E_S, in water are comparables we note that in the complexation of allergens with HPBCD nine values of solvation energies are enveloped between 62 – 84 kcal/mol, over the maximum value of 62.1 kcal/mol found for the complexation of β–CD with Lyral. This observation could be explained by the presence of hydroxyl groups in the hydroxypropyl fragments of HPBCD which support the hydrogen bounding with water. The solvation may modify the complexation regioselectivity. That is why the parameters $\Delta\Delta E_S$ and $\Delta\Delta E_T$ have been calculated. Nevertheless, it has to be underlined that ΔΔET absolute values are not really complete if the studied complexes have less than 2 kcal/mol of difference between regioconformers E1 and E2. We thus may reasonably think that, most of the time the two forms of inclusion coexist in solution. In this paper we refer only to the most stable conformer of each pair of regioisomer when we present the numerical data. We think that the data in the last column of Table 4 are very interesting. All computed complexation energies for the inclusion of benzyl salycilate (BESA) and amyl cinnamyl alcohol (AMOH) are mostly probable with HPBCD. Many other affinities, cyclodextrin–allergen, could be explored using numerical data given in Tables 2 and 3. Some of them were experimentally proved and we are interested in the development of the fixation of perfumes with cyclodextrins.

4 CONCLUSIONS

1. The computed complexation energies ΔE calculated by the MM3 method could be considered as a measure of the inclusion ability of allergens in CRYSMEB and HPBCD.

2. The filling of the inner cyclodextrin cavity with allergens could be taken into consideration with complexation energy.

3. The solvation energy in water permits the choice of the most stable regioconformer in each pair of conformers.

4. In respect to β–cyclodextrin, the hydroxypropyl β–cyclodextrin (HPBCD) seems to be the most interesting in the fixation of allergens.

5. The specific affinities cyclodextrin–allergen could be explored from an experimental point of view.

5 REFERENCES

[1] P. L. Scheinman, Am. *J. Contact Dermatitis* **1996**, *7*, 65–76.
[2] R. Sheellie, P. Marniott, A. Chaintreau, *Flavour Fragrance J.* **2004**, *19*, 91–98.
[3] C. Debonneville, A. Chaintreau, *Journal of Chromatography A*. **2004**, *1027*, 109–115.
[4] (a) M. Sing, R. Sharma, U.C. Barnerjee, *Biotechnol*. *Adv*. **2002**, *20*, 325–339; (b) E. M. Martin Del Valle, *Process Biochem.* **2004**, *39*, 1033–1046; (c) C. X. Wang, S. L. Chen, *J. Industrial Textiles* **2005**, *34*, 157–166; (d) V. Sarveiyal, J. F. Templeton, H. A. E. Benson, *J. Incl*. *Phenom*. *Macro*. *Chem*. **2004**, *49*, 275–281; (e) K. Hara, K. Minuki, K. Hara, H. Hashimoto, *J. Incl*. *Phenom*. *Macro*. *Chem*. **2002**, *44*, 241–245.
[5] (a) I. Goubet, C. Dahout, E. Semon, E. Guichard, J. L. Le Quere, A. Voilley, *J. Agric*. *Food Chem*. **2001**, *49*, 5916–5922; (b) G. A. Reineccius, S. J. Risch, *Perfum*. *Flavor*. **1986**, *11*, 3–6.
[6] (a) J. Szejtli, *Cyclodextrin Technology*, Kluwer Academic Publishers, **1988**; (b) K. A. Connors, *Chem*. *Rev*. **1997**, *97*, 1325–1367.
[7] G. Decock, S. Fourmentin, G. G. Surpateanu, D. Landy, P. Decock, G. Surpateanu, *Supramol*. *Chem*. **2006**, *18*, 477–482.
[8] G. Decock, S. Fourmentin, D. Landy, G. Surpateanu, P. Decock, and G. Surpateanu, Theoretical Study on the Inclusion of Allergens with β–Cyclodextrin and Randomly–Methylated–β–Cyclodextrin, *Internet Electron. J. Mol. Des.* **2006**, *5*, 376–386, http://www.biochempress.com.
[9] CAChe Work System, 6.01, 2003.