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Theoretical Study on the Inclusion of Allergens with β–Cyclodextrin and Randomly–Methylated–β–Cyclodextrin

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Theoretical Study on the Inclusion of Allergens with β–Cyclodextrin and Randomly–Methylated–β–Cyclodextrin

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Abstract

Motivation. Some compounds used in fragrance are suspected to be allergens and thus has to be extracted and analyzed. Since cyclodextrins are known to form inclusion complexes with a large variety of organic compounds, we have investigated the interactions occurring between two cyclodextrins and 21 compounds suspected to be allergens by a theoretical study.

Method. The computed complexation energies, ΔE, have been calculated for the inclusion of 21 allergens with β–cyclodextrin (βCD) and Randomly Methylated β–cyclodextrin (RAMEB). Our docking strategy involves four 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 solvation 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 βCD and RAMEB are analogous, but a slightly greater stabilization is generally obtained with RAMEB. A better recognition is also generally observed for cyclic allergens than for acyclic ones.

Conclusions. The use of complexation and solvation energies as computed by the MM3 and AM1–COSMO methods could be considered as a measure of the inclusion ability of allergens in βCD and RAMEB, and allows the determination of the most stable conformer. The filling of the inner cyclodextrin cavity with the allergens seems to be a key factor for the recognition. According to the restrained range of stabilization that have been observed, it seems that all allergens could be complexed and thus extracted by cyclodextrins, especially the cyclic allergens and preferably with RAMEB.

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.

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1 INTRODUCTION

The European legislation requires that fragranced products are evaluated for their content in 24 compounds that are suspected to be skin sensitizers, according to the Scientific Committee on Cosmetic Products [1]. Thus, their identification and their subsequent quantification remains an important target [2,3]. To this end, cyclodextrins (CDs) could be used as extracting agents, and some researches regarding the use of these macrocycles in perfume and cosmetic industry have been reported [4–8].

Cyclodextrins are macrocyclic carbohydrates composed of α–1,4 linked glucopyranose subunit, produced from starch by enzymatic degradation [9–10]. Among CDs, the β–cyclodextrin (βCD) is the most used due to its inclusion ability and low price. In addition, some chemically modified βCD which are more soluble in water or in organic solvents are commercially available like randomly methylated β–cyclodextrin (RAMEB), hydroxypropyl–β–cyclodextrin (HPBCD) and partially methylated crystallized β–cyclodextrin (CRYSMEB). β–Cyclodextrin and its derivatives can form host–guest complexes with a large variety of solid, liquid and gaseous organic compounds by a phenomenon of molecular complexation [10,12]. As a consequence, the use of cyclodextrins could be proposed to enhance the solubility of allergens, which thus could be extracted, before their quantification or to increase the retention of these products in solutions.

In a previous paper [13], we reported our experimental and theoretical results concerning the inclusion of eugenol (EUG), isoeugenol (IEUG), benzyl alcohol (AB) and anisyl alcohol (AA) on βCD, RAMEB, HPBCD and CRYSMEB. A good agreement between the experimental and theoretical formation constants has been observed. As a consequence, we extended the theoretical study on the inclusion of 21 other substances, most frequently linked to allergic reactions to fragrances, into βCD and RAMEB. The resulting data are presented in this paper.

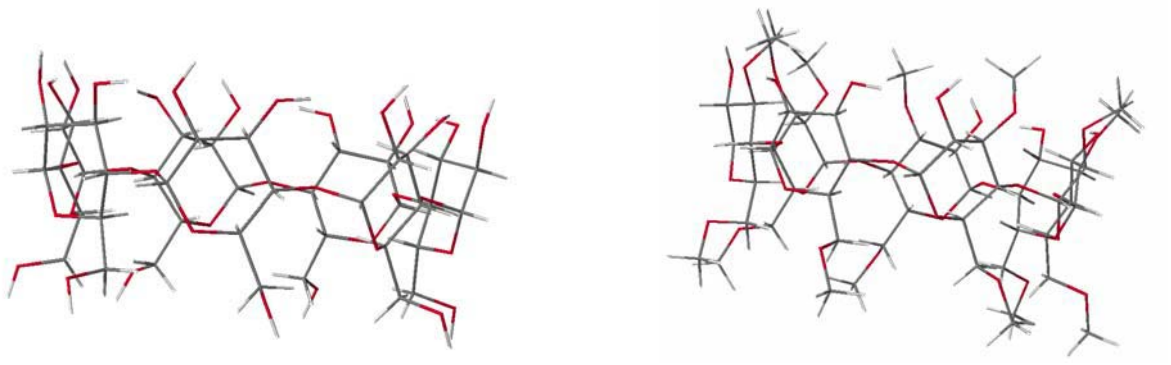
2 MATERIALS AND METHODS

2.1 Structures of Cyclodextrins

The βCD structure was built from data provided by the structural Data Base System of the Cambridge Crystallographic Data Center. The calculations were made using the CAChe library [14]. The most stable conformer of βCD obtained by MM3 method is showed in Figure 1.

The model of RAMEB (Figure 1) was built starting from βCD at which 14 methyl groups replacing hydroxyl hydrogen's have been attached as follow: 7 at primary positions and 7 at secondary positions. Both βCD and RAMEB most stable structures obtained by MM3 search have been minimized without imposing any restrictions on the basis of AM1 hamiltonian in gas and aqueous (COSMO solvent field [15]) phase. Moreover, the guest molecules were initially retrieved

from the data provided by the structural Data Base System and their energy minimized with MM3 force field and AM1 procedure method.



βCD RAMEB

Figure 1. Structure of βCD and RAMEB.

2.2 Inclusion Compounds Conformation

The docking of each guest into βCD and RAMEB cavity has been performed using four dummy atoms (D1, D2, D3 and D4) placed as shown in Figure 2. These dummy atoms are connected to each guest trough one of its atom, designed by "G1". Obviously, it is possible to cross and cover all inner cavity of the studied cyclodextrin with two variable parameters, the D2–D3 length and the D1–D2–D3–D4 dihedral angle.

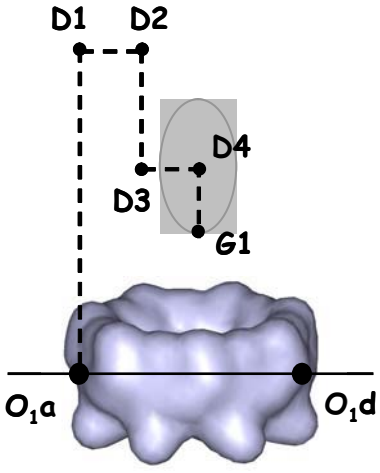


Figure 2. Representation of the dummy atoms (D1, D2, D3 and D4) according to the position of the cyclodextrin and the guest (first atom of which is referred as G1). The D3–D4 distance is nearly equal to 0.

Moreover, in order to examine all possible conformations during the docking, two general ways of inclusion noted by E1 and E2 (Figure 3) have been considered to take into account the asymmetric structure of the guest molecule. Then, a multiconformational search integrated in CAChe has been employed with the MM3 force field. During this search, the cyclodextrin host is

kept rigid, while the guest freedom if freely allowed (indeed, and contrary to the structure of the studied guests, the cyclodextrin conformation is controlled by many geometric parameters so that random variations may be observed during the search if the cyclodextrin geometry is not locked).

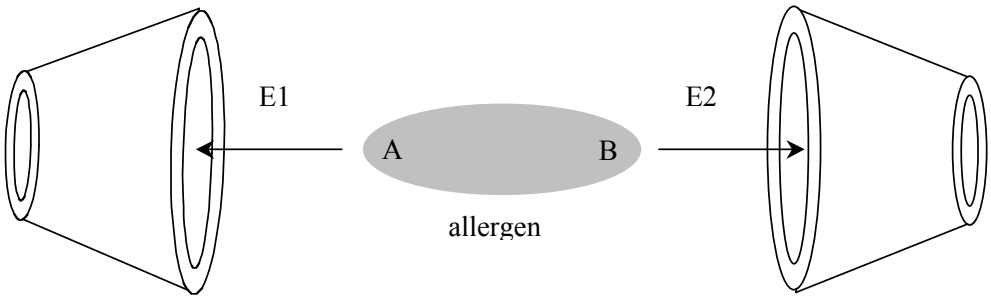
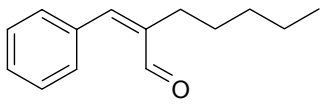
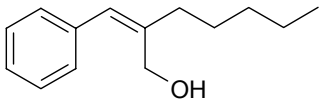
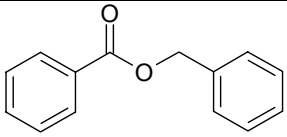
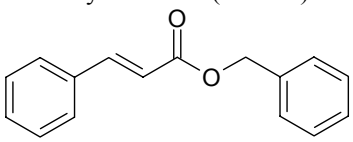
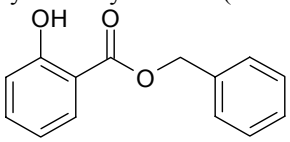
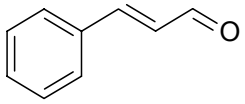
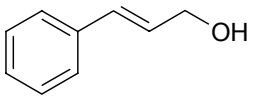
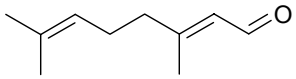
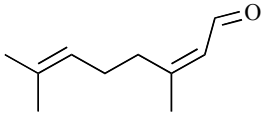
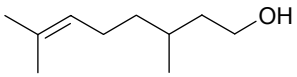
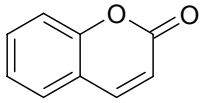
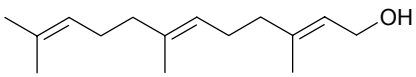
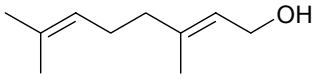
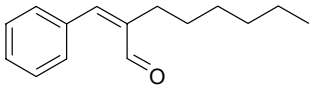
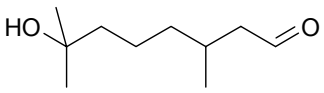
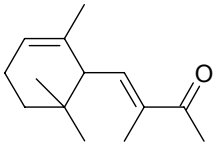
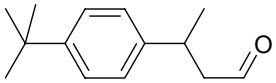
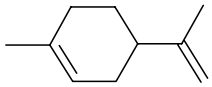
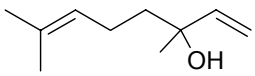
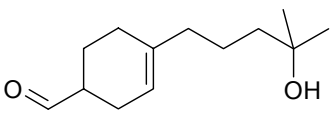
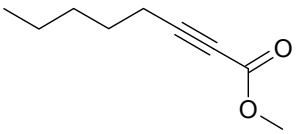


Figure 3. Docking strategy.

Table 1. Representation of the 21 Allergens

 Amylcinnamal (AMCO)	 Amylcinnamyl alcohol (AMOH)	 Benzyl benzoate (BEBE)
 Benzyl cinnamate (BECI)	 Benzyl salicylate (BESA)	 Cinnamal (CACO)
 Cinnamic alcohol (CAOH)	 Citral geranial (CIGE)	 Citral neral (CINE)
 β–citronellol (CITR)	 Coumarin (COUM)	 Farnesol (FARN)
 Geraniol (GERA)	 Hexyl cinnamaldehyde (HCCO)	 Hydroxycitronellal (HCNA)
 Isomethyl α–ionone (IMIO)	 Lilial (LILI)	 Limonene (LIMO)
 Linalool (LINA)	 Lyral (LYRA)	 Methyl heptine carbonate (MOCT)

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). The difference (ΔE, kcal/mol) between total energy of the inclusion complex and the sum of their individual component in their optimized ground states was then used as theoretical parameter to evaluate the inclusion capacity of the cyclodextrin host. The 21 allergens are presented in Table 1. The simplified identifications of all products used in this paper are mentioned in bracket. The docking involves the allergen in its structure described in Table 1 and thus both regiochemical ways E1 and E2 have been investigated.

3 RESULTS AND DISCUSSION

According to our docking strategy, we found the most stable conformer for each inclusion compound. The corresponding complexation energies with βCD and RAMEB are presented respectively in Table 2 and Table 3. In those two tables, ΔE values correspond to the energetic difference between the complex (for a given regioselectivity of inclusion) and the free species, as 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 (ΔΔEs) between the two regioconformers is calculated by AM1–COSMO method. The resulting total difference (ΔΔE+ΔΔEs) is expressed as $\Delta\Delta E_T$.

Since a good agreement between experimental and theoretical results has been observed in a previous study for the complexation of other allergens [13], the numerical values of the computed complexation energy ΔE could be used as a parameter describing the stability of the complexes between the cyclodextrins and all the 25 allergens considered in our studies.

In the case of the complexation with βCD, the highest value of ΔE (–14.9 kcal/mol) is observed for the complexation of amylcinnamyl alcohol with β–cyclodextrin in the regiocomplexation type E1, noticed in Table 1 as βCD/AMOH–E1, rank 1. At the opposite, the lowest value of ΔE (–6.4 kcal/mol) is observed for the complexation of methyl heptine carbonate with β–cyclodextrin in the regiocomplexation type E2, noticed in table 1 as βCD/MOCT–E2, rank 21. Similar remarks could be made for the complexation of the two allergens benzyl salicylate and methyl heptine carbonate with RAMEB, that is to say the highest value of ΔE (–16.0 kcal/mol) for RAMEB/BESA–E1, rank 1 and the lowest value of ΔE (–9.1 kcal/mol) for RAMEB/MOCT–E2, rank 21. It is interesting to note that, for both cyclodextrins, a better recognition is generally observed for the allergens with cyclic structures than for the acyclic ones.

Table 2. Computed Energy of Allergens Complexation with βCD

N°	Complex	ΔE (Kcal/mol)	Rank	ΔΔE (Kcal/mol)	ΔΔEs (Kcal/mol)	$\Delta\Delta E_T$ (Kcal/mol)	Most stable conformer
1	βCD/AMCO – E1	–12.3	8	–3.0	0.3	–2.7	E1
	βCD/AMCO – E2	–9.3					
2	βCD/AMOH – E1	–14.9	1	–2.0	1.1	–0.9	E1
	βCD/AMOH – E2	–12.9					
3*	βCD/BEBE – E1	–12.7	5	0.5	2.1	2.6	E2
	βCD/BEBE – E2	–13.2					
4*	βCD/BECI – E1	–12.2	7	0.6	1.2	1.8	E2
	βCD/BECI – E2	–12.8					
5	βCD/BESA – E1	–14.5	2	–1.7	3.1	1.4	E2
	βCD/BESA – E2	–12.8					
6	βCD/CACO – E1	–10.6	9	1.0	–0.7	0.3	E2
	βCD/CACO – E2	–11.6					
7	βCD/CAOH – E1	–14.3	3	–4.0	0.9	–3.1	E1
	βCD/CAOH – E2	–10.3					
8	βCD/CIGE – E1	–9.7	17	0.1	–1.0	–0.9	E1
	βCD/CIGE – E2	–9.8					
9*	βCD/CINE – E1	–9.8	14	0.6	2.1	2.7	E2
	βCD/CINE – E2	–10.4					
10	βCD/CITR – E1	–8.7	19	0.6	–0.7	–0.1	E1
	βCD/CITR – E2	–9.3					
11	βCD/COUM – E1	–10.2	12	0.8	–2.3	–1.5	E1
	βCD/COUM – E2	–11.0					
12	βCD/FARN – E1	–9.9	16	–0.5	–0.2	–0.7	E1
	βCD/FARN – E2	–9.4					
13	βCD/GERA – E1	–8.8	20	0.3	–0.4	–0.1	E1
	βCD/GERA – E2	–9.1					
14	βCD/HCCO – E1	–9.2	15	1.1	–2.3	–1.2	E1
	βCD/HCCO – E2	–10.3					
15	βCD/HCNA – E1	–9.5	18	–0.3	0.6	0.3	E2
	βCD/HCNA – E2	–9.2					
16	βCD/IMIO – E1	–8.5	10	3.0	–3.2	–0.2	E1
	βCD/IMIO – E2	–11.5					
17	βCD/LILI– E1	–13.4	4	–0.4	–3.6	–4.0	E1
	βCD/LILI– E2	–13.0					
18	βCD/LIMO – E1	–13.1	6	–0.3	–2.5	–2.8	E1
	βCD/LIMO – E2	–12.8					
19	βCD/LINA – E1	–11.4	11	–0.5	–3.6	–4.1	E1
	βCD/LINA – E2	–10.9					
20	βCD/LYRA – E1	–10.5	13	–0.2	–0.1	–0.3	E1
	βCD/LYRA – E2	–10.3					
21	βCD/MOCT – E1	–6.4	21	2.2	–2.8	–0.6	E1
	βCD/MOCT – E2	–8.6					

Table 3. Computed Energy of Allergens Complexation with RAMEB

N°	Complex	ΔE (Kcal/mol)	Rank	ΔΔE (Kcal/mol)	ΔΔEs (Kcal/mol)	$\Delta\Delta E_T$ (Kcal/mol)	Most stable conformer
1	RAMEB/AMCO – E1	–8.8	8	3.4	–3.7	–0.3	E1
	RAMEB/AMCO – E2	–12.2					
2	RAMEB/AMOH – E1	–15.9	2	–2.1	1.9	–0.2	E1
	RAMEB/AMOH – E2	–13.8					
3	RAMEB/BEBE – E1	–14.4	3	0.2	–1.0	–0.8	E1
	RAMEB/BEBE – E2	–14.6					
4	RAMEB/BECI – E1	–12.6	6	0.6	0.7	1.3	E2
	RAMEB/BECI – E2	–13.2					
5	RAMEB/BESA – E1	–16.0	1	–1.0	2.9	1.9	E2
	RAMEB/BESA – E2	–15.0					
6	RAMEB/CACO – E1	–11.5	12	–1.3	–0.8	–2.1	E1
	RAMEB/CACO – E2	–10.2					
7	RAMEB/CAOH – E1	–11.5	12	–0.1	1.0	0.9	E2
	RAMEB/CAOH – E2	–11.4					
8	RAMEB/CIGE – E1	–10.3	17	0.5	–1.3	–0.8	E1
	RAMEB/CIGE – E2	–10.8					
9	RAMEB/CINE – E1	–10.5	18	–0.7	–0.2	–0.9	E1
	RAMEB/CINE – E2	–9.8					
10	RAMEB/CITR – E1	–9.8	19	0.4	–1.8	–1.4	E1
	RAMEB/CITR – E2	–10.2					
11	RAMEB/COUM – E1	–10.6	11	1.2	–2.6	–1.4	E1
	RAMEB/COUM – E2	–11.8					
12	RAMEB/FARN – E1	–11.0	12	0.5	0.7	1.2	E2
	RAMEB/FARN – E2	–11.5					
13	RAMEB/GERA – E1	–10.9	16	–1.1	–0.8	–1.9	E1
	RAMEB/GERA – E2	–9.8					
14	RAMEB/HCCO – E1	–13.5	5	–1.4	–2.4	–3.8	E1
	RAMEB/HCCO – E2	–12.1					
15	RAMEB/HCNA – E1	–10.1	20	–0.7	–2.4	–3.1	E1
	RAMEB/HCNA – E2	–9.4					
16	RAMEB/IMIO – E1	–6.2	10	5.7	–0.9	4.8	E2
	RAMEB/IMIO – E2	–11.9					
17	RAMEB/LILI– E1	–14.1	4	–0.3	–0.2	–0.5	E1
	RAMEB/LILI– E2	–13.8					
18	RAMEB/LIMO – E1	–12.4	7	0.1	0.8	0.9	E2
	RAMEB/LIMO – E2	–12.5					
19	RAMEB/LINA – E1	–12.1	9	0.0	0.5	0.5	E2
	RAMEB/LINA – E2	–12.1					
20	RAMEB/LYRA – E1	–11.5	12	–0.4	–0.3	–0.7	E1
	RAMEB/LYRA – E2	–11.1					
21	RAMEB/MOCT – E1	–7.7	21	1.4	–2.3	–0.9	E1
	RAMEB/MOCT – E2	–9.1					

The ranges of complexation energy are thus similar for βCD and RAMEB. Besides, the complexation behaviors seem to be close between the two cyclodextrins (taking into account the most significant complexation energies corresponding to a pair of complexes involving the same allergen). Indeed, if we plot the complexation energy obtained for RAMEB in function of the

corresponding one for βCD, a linear trend is mainly observed (Figure 4). The exclusion of the two outlier (some specific affinities for βCD with cinnamic alcohol and for RAMEB with hexyl cinnamaldehyde can be pointed out) leads to a correlation coefficient equal to 0.945.

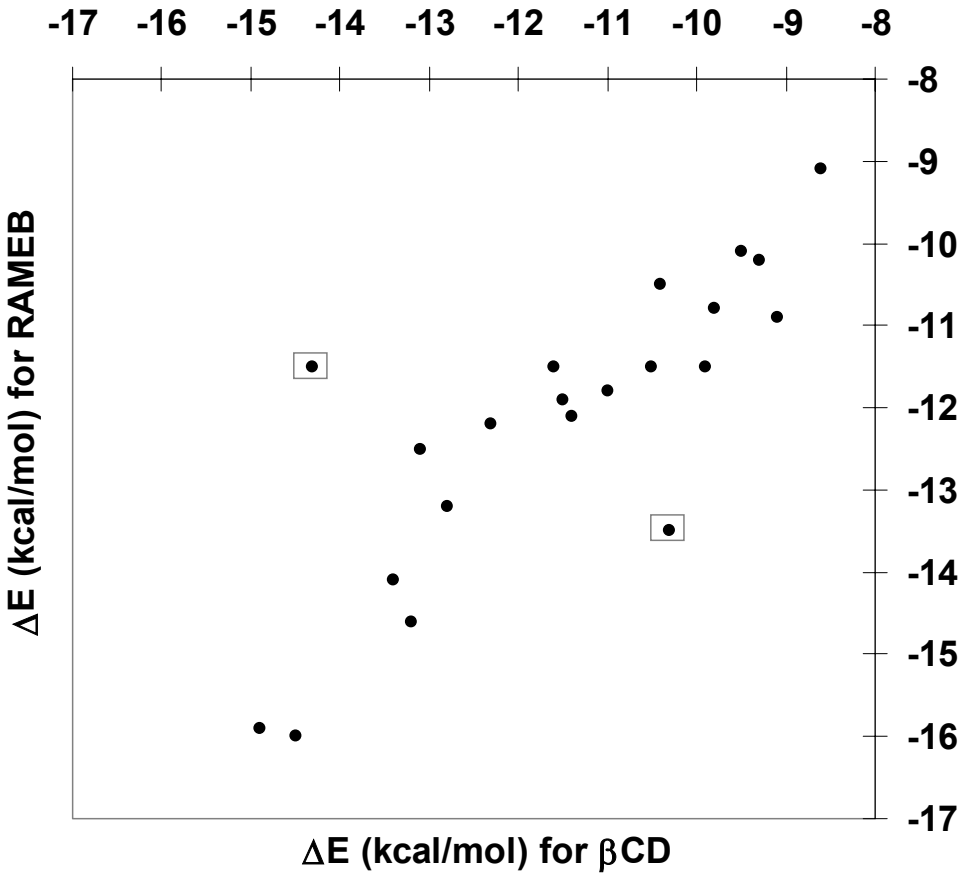
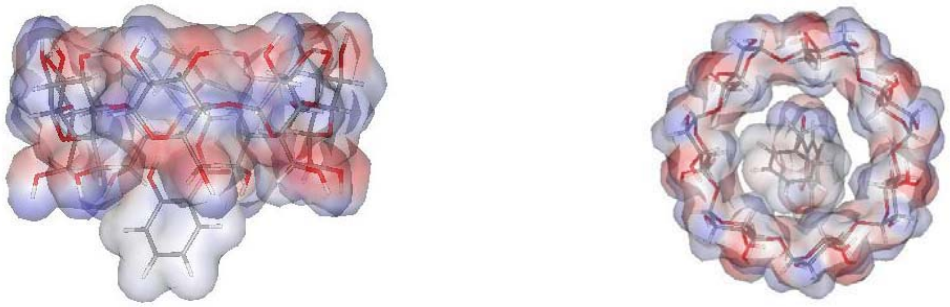
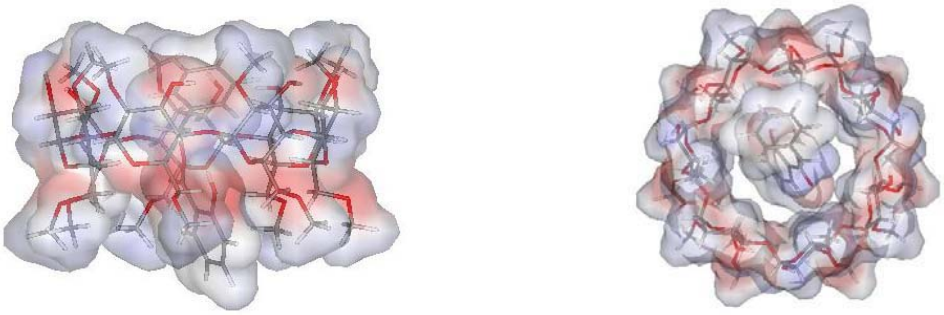


Figure 4. Correlation between the complexation energies observed for βCD and RAMEB. The points inside squares correspond to the outliers.

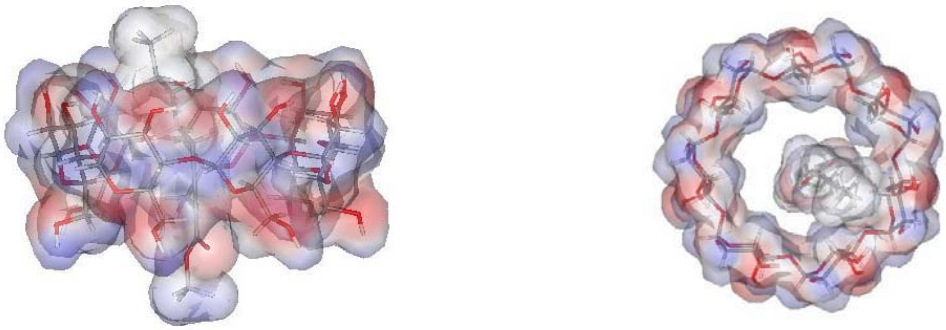
Nevertheless, a slightly greater stabilization is observed for RAMEB, with a mean value for the 21 allergens of –11.6 kcal/mol against –10.9 kcal/mol for βCD. It has to be mentioned that, on an experimental point of view, RAMEB is known to lead generally to higher formation constants than genuine βCD. Such result is in agreement with the increase of van der Waals interactions due to the presence of methyl groups on this modified cyclodextrin. For instance, the βCD/BESA–E1 complex is stabilized with a ΔE value of –14.5 kcal/mol, against –16.0 kcal/mol for the RAMEB/BESA–E1 complex. The stabilization due to van der Waals interactions, electrostatic interactions and hydrogen bonds are respectively of –12.9 kcal/mol, –1.1 kcal/mol and –0.5 kcal/mol for βCD/BESA–E1 and of –14.4 kcal/mol, –1.2 kcal/mol and –0.5 kcal/mol for RAMEB/BESA–E1. The strength of binding is thus mainly driven by the van der Waals interactions, while electrostatic interactions and hydrogen bonds contribute positively, but weakly, to the inclusion.



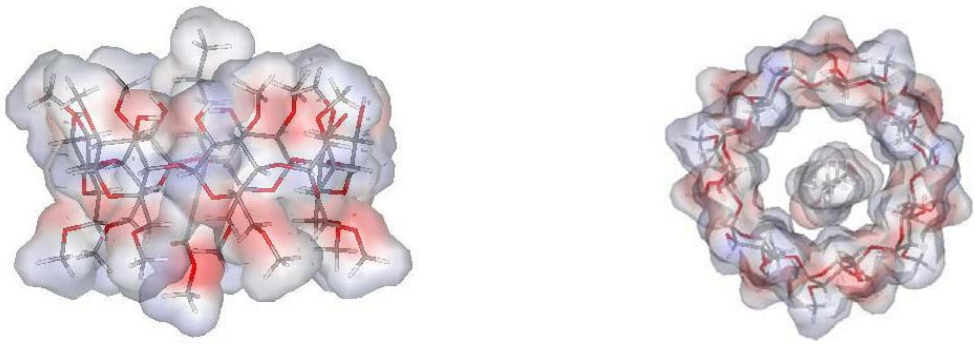
BCD/BESA–E1



RAMEB/BESA–E1



BCD/MOCT–E2



RAMEB/MOCT–E2

Figure 5. Van der Waals surfaces of βCD and RAMEB complexes with benzyl salicylate and methyl heptine carbonate.

As a consequence, the filling of the inner cavity of cyclodextrins should be a crucial factor ordering the stability of the cyclodextrin/allergen complexes, and the inclusion compounds illustrated in Figure 5 seem to prove this assumption. The complexes with benzyl salicylate

(βCD/BESA–E1 and RAMEB/BESA–E1) are presented since they have the highest values of complexation energy ΔE with βCD and RAMEB, while, at the opposite, the lowest values of complexation energy ΔE were obtained for methyl heptine carbonate with βCD and RAMEB (βCD/MOCT–E2 and RAMEB/MOCT–E2).

In addition to the filling of the cavity, the solvation is another factor known to affect the complexation phenomena for cyclodextrins. Thus, we have calculated the solvation energy for all the inclusion compounds of this study (AM1–COSMO method). First of all, we have to mention that these solvation energies are systematically higher for the βCD complexes (53 to 62 kcal/mol) than for analogous complexes involving RAMEB (41 to 50 kcal/mol). The higher number of hydrogen bonds that could occur between water and βCD can explain this observation. Nevertheless, no additional stabilization of the genuine cyclodextrin complexes is observed, since these hydrogen bonds also exist when βCD is not complexed with the allergens. On the other hand, the solvation may modify the regioselectivity of complexation: thus, we have calculated the difference of solvation energies (ΔΔEs) for each pair of complex. $\Delta\Delta E_T$, the sum of ΔΔE and ΔΔEs, may then be considered as the factor governing the regioselectivity of inclusion; the most stable complexes in each pair of regioconformers E1 and E2 appear in Tables 1 and 2. It has to be underlined that $\Delta\Delta E_T$ absolute values are not really high, since 74% of 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.

Finally, we recommend the use of the theoretical results in this paper as qualitative comparable parameters in respect to experimental data. As we are interested in the development of the fixation of perfumes with cyclodextrin, we will use those data to develop experimental studies.

4 CONCLUSIONS

The computed complexation energies ΔE calculated by the MM3 method could be considered as a measure of the inclusion ability of allergens in βCD and RAMEB. Among other parameters, the filling of the inner cyclodextrin cavity with allergens could be taken into consideration in connection with complexation energy. The use of computed complexation and solvation energies permit the determination of the most stable conformer, even if the two forms coexist for a great number of complexes. If some specific affinities concerning the inclusion of allergens with βCD and RAMEB could be observed, the ranges of stabilization are not very wide and the complexation behaviors are quite close from one cyclodextrin to the other.

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