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Journal of Agroalimentary Processes and Technologies 2009, *15*(2), 273-282

Journal of Agroalimentary Processes and Technologies

Molecular modeling and docking studies on Compositae biocompounds – cyclodextrin interactions

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Abstract

The paper presents a molecular modeling and docking studies on the interactions between natural α- and β-cyclodextrin and the main biocompounds from Compositae family plants. Both vacuum and water periodic box conditions were used for the docking experiments. A comparative study on the formation and stability of complex obtained with non-oxidized/oxidized forms of biocompounds was performed. The best interactions (maximum biocompound/cyclodextrin interaction energy) were obtained with the non-oxidated forms of α-bisabolol and caryophyllene, as well as with the sesquiterpene camazulene. The results were in good concordance with the hydrophobicity of biocompounds.

Keywords: cyclodextrins, host-guest interaction, Compositae family, bisabolol, bisabolol-oxid, camazulene, molecular modeling, docking experiments

1. Introduction

In order to obtain a higher bioavailability of bioactive compounds various carriers from synthetic, natural, or hybrid polymers [1-4], some of them as intelligent molecular devices with targeting possibilities [5], were used; this field is named nanomedicine [6]. A series of drug carriers belong to natural and modified cyclodextrins [7,8], which are cyclic oligosaccharides with toroidal structure, containing 6-8 glucopyranoside units, with the capacity to form inclusion compounds and which conduct to hydrosolubilization and increased bioavailability, protection against degradative factors, and controlled release of biomolecules. Various natural or modified cyclodextrin-containing complexes with drugs [9-11], genotherapeutic agents or biocompounds with anticarcinogenic activity [2,12], as well as essential oils biocompounds or biosystems with food and pharmaceutical applications were obtained [8,9].

Molecular modeling in terpenoide class was used in order to evaluate the main structural parameters which were correlated with the gas chromatography retention index by using genetic algorithm for the variable selection and multiple linear regression (MLR), partial least squares (PLS and poly-PLS), and support vector machine (SVM) to obtain QSRRs (quantitative structure-retention relationships) [13]. In the class of terpenoids (like essential oils) many models were obtained for the hydrodistillation and supercritical fluid extraction processes [14-16].

Some molecular modeling and docking studies were performed in order to evaluate the complexation capacity of cyclodextrins. The *tert*butylbenzene was used as guest model in the interaction with β-cyclodextrin and was demonstrated that the complex formation is stabilized by dispersive or van der Waals forces and not electrostatic (dipole-dipole or hydrogen bonding) forces [17]. Studies on the molecular surface area changes with docking guests in

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cyclodextrin host molecules, especially for natural cyclodextrins as hosts and aliphatic and aromatic guests molecules by using methods which allow to calculate the ΔS values [18], single-coordinate-driving (SCD) method [19], or by genetic algorithm and empirical binding free energy function [20], were performed. The results can be applied also for protein-ligand systems.

The stability of the host-guest complex was also investigated by using stochastic methods and molecular dynamic simulations. Cyclodextrins were used as molecular hosts and the main guests studied were model drugs like anti-inflammatory agents (naproxen, ketoprofen, ibuprofen, and ibuproxam [21]), antidepressants and antipsychotic agents [22], or salicylates [23].

Some docking experiments in cyclodextrins were performed for biocompounds from essential oils, like pinenes. The stability of the α-pinene enantiomers/α-cyclodextrin complexes was evaluated by using NMR spectroscopy and molecular dynamic simulations [24,25].

Our earlier studies on host-guest interactions by using natural cyclodextrins revealed that the bioactive compounds with hydrophobic moieties interact very well with the inner cavity of cyclodextrin, but also the oxy or hydroxyl groups can stabilize the complex, especially in the case of fatty acids [26-30]; the complexation and stability of organic sulfur compounds from *Allium* species were also molecular modeled and experimentally studied [31].

In the present paper the encapsulation capacity of α- and β-cyclodextrin with the main biocompounds from Compositae family plants was evaluated by using molecular modeling and docking experiments, both in vacuum and in water periodic box.

2. Materials and Method

Molecular modeling. α- and β-Cyclodextrin structures used for the molecular encapsulation of the main biocompounds from Compositae family plants were molecular modeled by using the MM+ molecular mechanics program from HyperChem package [32]. The starting conformations for cyclodextrins were builded by knowing the X-ray structures in crystals [33].

The biocompounds belong to the Compositae family plants which are selected for molecular modeling and cyclodextrin docking studies were: α-bisabolol, bisabolol-oxides A and B, caryophyllene, and its epoxide, and camazulene.

In the MM+ Molecular Mechanics approach a 0.01 kcal/mole RMS gradient and the Polak-Ribiere algorithm were used in order to obtain the stable conformations of cyclodextrins or biocompounds.

Conformational analysis. In order to obtain the most stable conformations of biocompounds (with minimum internal energy), conformational studies for all structures were conducted by using the Conformational Search program from HyperChem package. The following steps were run over: (1) for the biocompound structure in a random conformation, but with defined bond length and angles, all flexible bonds and rings were set up and used in the conformational analysis; (2) a random values of these torsion angles were used for every starting conformation; (3) the minimizing of conformation energy was conducted until the RMS gradient was lower than 0.01 kcal/mole; (4) all conformations with energy of maximum 4 kcal/mole above the minimal energy obtained (the most stable conformation) were retained for the docking studies. The conformational search parameters were: variation of the flexible torsion angles of ±60º - ±180º, acceptance energy criterion 4 kcal/mol above best, duplicate structure if the energy was within the range of 0.05 kcal/mole, skip of the structures which have atoms closer than 0.5 Å and torsion within 15º; the optimization program was MM+, with the Polak-Ribiere algorithm, and RMS gradient of 0.01 kcal/mole; the hydrogen atoms were ignored. The maximum number

of iterations and optimizations were set up to 500, and no more than 50 conformations were retained.

Docking experiments. The docking of the more stable conformations of selected biocompounds from Compositae family plants in α- or β-cyclodextrin was realized by using the molecular mechanics interactions of the host-guest molecules in vacuum or in the water periodic box. The biocompound and α- or β-cyclodextrin structures in minimal energy conformations were set up at distances of ~8Å between the gravity centres of the host-guest molecules, and the biocompound structure was oriented with both main moieties in front of the primary (A) or secondary (B) face of cyclodextrin (the principal axis corresponding to the biocompound was perpendicular to the A or B plan of cyclodextrin). The complex was modeled in absence of water molecules or in water periodic box by using the same MM+ program and the interaction was stopped when the RMS gradient was lower than 0.01 kcal/mole. The biocompound-cyclodextrin interaction energy was evaluated as the difference between the the overall energies of these two molecules and the complex energy.

3. Results and Discussion

In order to evaluate the molecular encapsulation capacity of α- and β-cyclodextrin for main biocompounds from Compositae family plants (α-bisabolol, bisabolol-oxid A and B, camazulene, caryophyllene, caryophyllen-oxid, Figure 1) the molecular modeling and docking experiments were performed by using molecular mechanics calculations (the AM1 and PM3 semi-empirical methods did not conduct to relevant results in comparison with MM+ molecular mechanics analysis).

Molecular modeling of α- and β-cyclodextrin was achieved by MM+ molecular mechanics by using the cyclic start conformation of the glucopyranose moieties (α-(1→4)-glucosidic bonds) in which the interglucosidic bond angles were strained at 127º for α-cyclodextrin and 119º for β-cyclodextrin. The stable conformations (optimized by MM+ molecular mechanics) of cyclodextrins, in vacuum (in absence of water molecules), are presented in Figure 2.

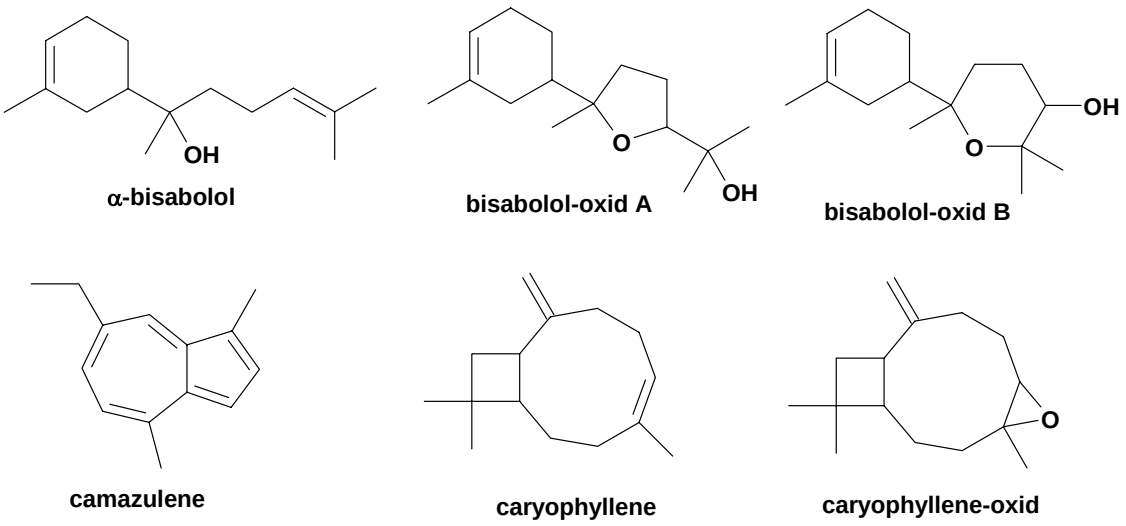


Figure 1. The main biocompounds from Compositae family plants used in molecular modeling and cyclodextrin docking experiments

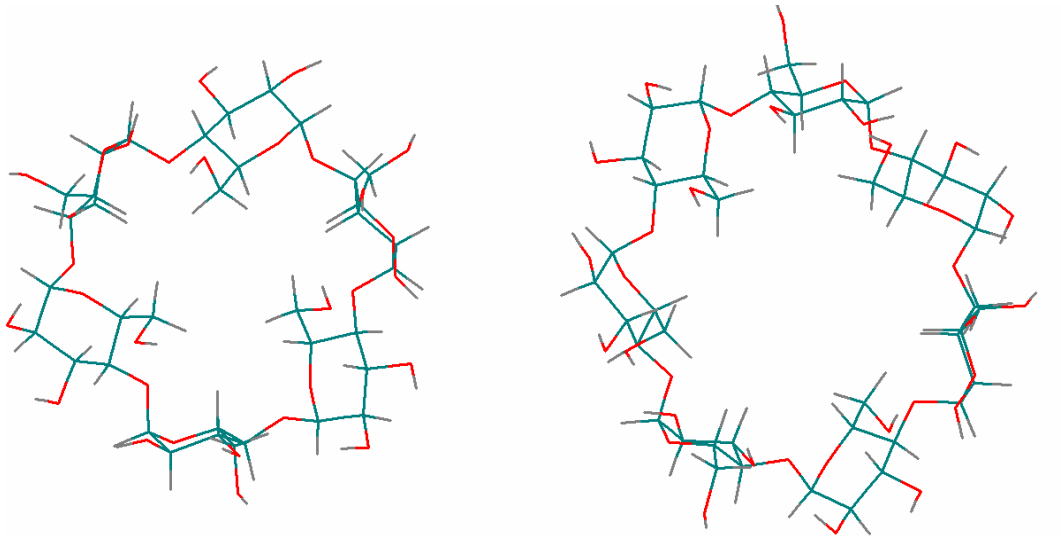


Figure 2. Most stable conformations of α- and β-cyclodextrin

The selected biocompounds from Compositae family plants were conformationally analyzed by using the same MM+ program and the most stable conformations (with the minimum internal energy) were retained and used in the docking experiments.

By molecular modeling studies on the interaction between selected biocompound/cyclodextrins, in vacuum (in absence of water molecules), the minimum energy conformations of biomolecules were used, with the main axis biomolecule perpendicular to the primary (side A, where the primary hydroxyl groups of the C^6 glucose moieties are positioned) and secondary (side B, with the C^2 and C^3 secondary hydroxyl groups of the glucose moieties) side plans of the cyclodextrins. The biomolecules were oriented with both sides along to the main axis of the molecule and only the best interaction with cyclodextrin was considered. The energies of the best conformations for these biomolecules were: 13.2 kcal/mole for α-bisabolol, 25.5 and 22 kcal/mole for bisabolol-oxides A and B, respectively, 11.2 kcal/mole for camazulene, and 53 kcal/mole for caryophyllene; the energy value for the oxidation product of caryophyllene (caryophyllene-oxid) was much higher (Table 1).

Table 1. Compositae biocompounds (B-bisabolol, BoA and B-bisabolol-oxides, Cz-camazulene, Cr-caryophyllene, Cro-caryophyllene-oxid) / cyclodextrin (aCD and bCD) interaction energies calculated with MM+ molecular mechanics program

No	Code	E (CD) (kcal/mole)	E (Biocmpd) (kcal/mole)	E (CD+Biocmpd) (kcal/mole)	E (Biocmpd/CD) (kcal/mole)	$E_{interaction}$ (kcal/mole)
1	aCD-B	71.49	13.19	84.68	70.31	14.37
2	aCD-BoA	71.49	25.50	96.99	83.73	13.26
3	aCD-BoB	71.49	22.00	93.49	78.80	14.69
4	aCD-Cz	71.49	11.15	82.64	66.47	16.17
5	aCD-Cr	71.49	53.05	124.54	105.09	19.45
6	aCD-Cro	71.49	205.82	277.31	262.53	14.78
7	bCD-B	82.70	13.19	95.89	73.07	22.82
8	bCD-BoA	82.70	25.50	108.20	88.57	19.63
9	bCD-BoB	82.70	22.00	104.70	83.38	21.32
10	bCD-Cz	82.70	11.15	93.85	76.68	17.17
11	bCD-Cr	82.70	53.05	135.75	115.18	20.57
12	bCD-Cro	82.70	205.82	288.52	267.96	20.56

The studied biocompounds seems to accommodate better in the β-cyclodextrin cavity than in α-cyclodextrin, as it can be see from the MM+ molecular mechanics forcefileld docking experiments.

For the α-bisabolol and its oxides the molecular encapsulation in α-cyclodextrin revealed a hydrophobic interaction (*i.e.* van der Waals interaction) between the hydrophobic moiety of the biocompound and the inner cavity of cyclodextrin. The interaction energy (evaluated as difference between the minimal energy conformations of biocompound and cyclodextrin and the energy of the complex, in vacuum or in water periodic box) was in the range of 13-19.5 kcal/mole. All values are presented in Table 1. The best interaction seems to be for α-bisabolol (Figure 3), but also with bisabolol-oxid B, comparatively for the interaction of α-cyclodextrin with bisabolol-oxid A. This can be due to the smaller moiety of tetrahydrofurane for bisabolol-oxid B, comparatively with the tetrahydropyrane moiety of the corresponding oxid A.

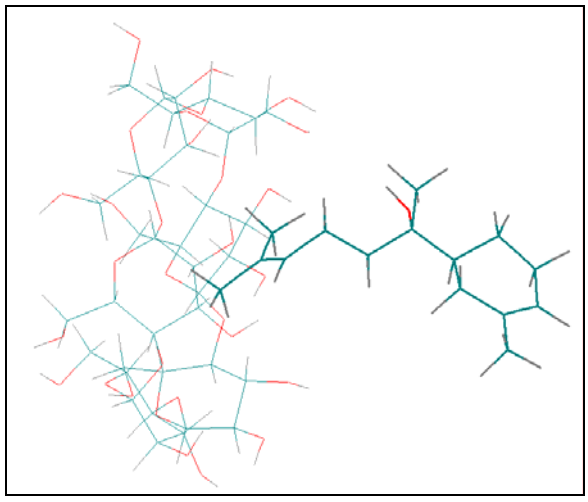


Figure 3. α-Bisabolol/α-cyclodextrine complex

The best interaction of α-bisabolol is obtained with β-cyclodextrin (22.8 kcal/mole), but in aqueous media this interaction is reduced by the presence of water molecules (hydrophyllic interactions between OH groups of bisabolol and water molecules) (Figure 4). The formation of the complex has comparable ratios for α-bisabolol, as well as for bisabolol-oxides (Figure 5), both in the case of α- and β-cyclodextrin complexes, although the rate of complex formation seems to be lower for β-cyclodextrin.

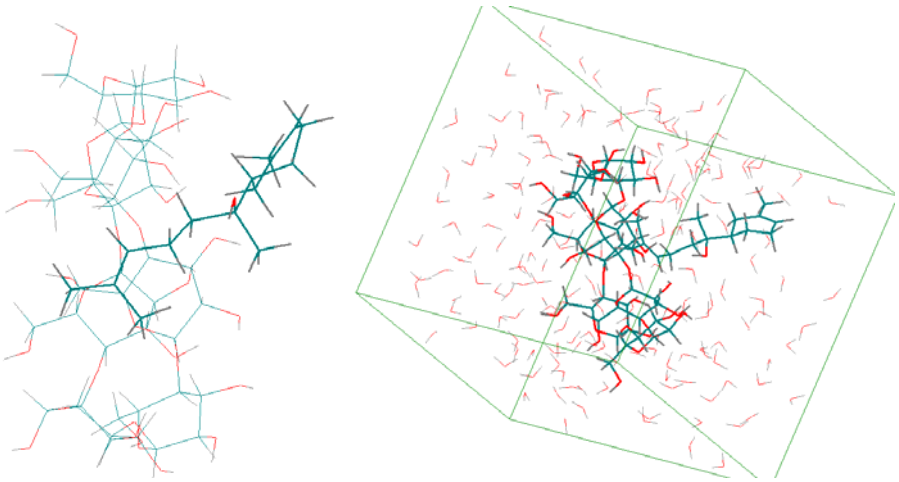
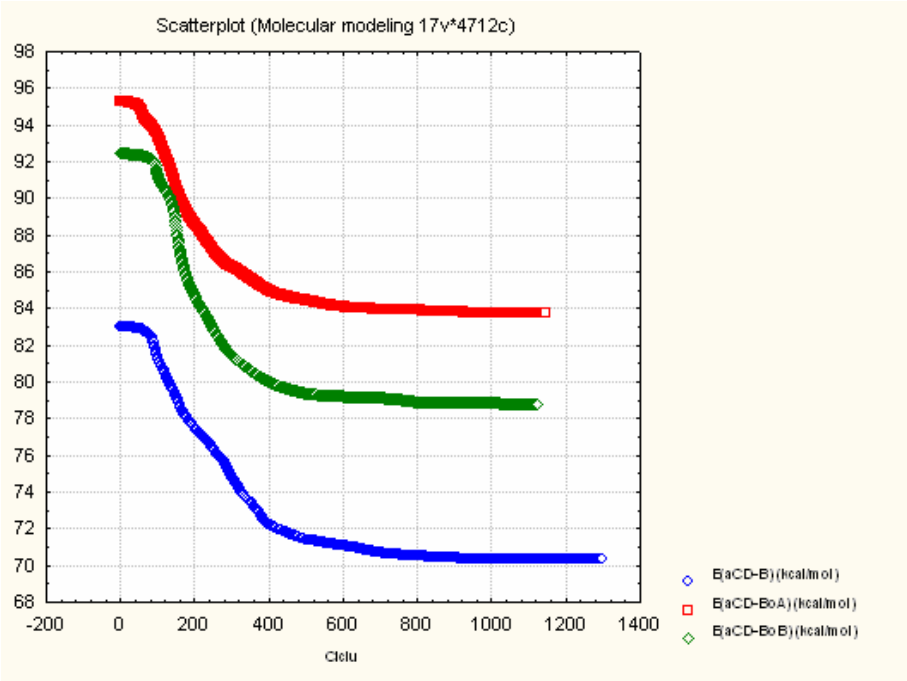


Figure 4. α-Bisabolol/β-cyclodextrin complex in vacuum (left) and in water periodic box (right)



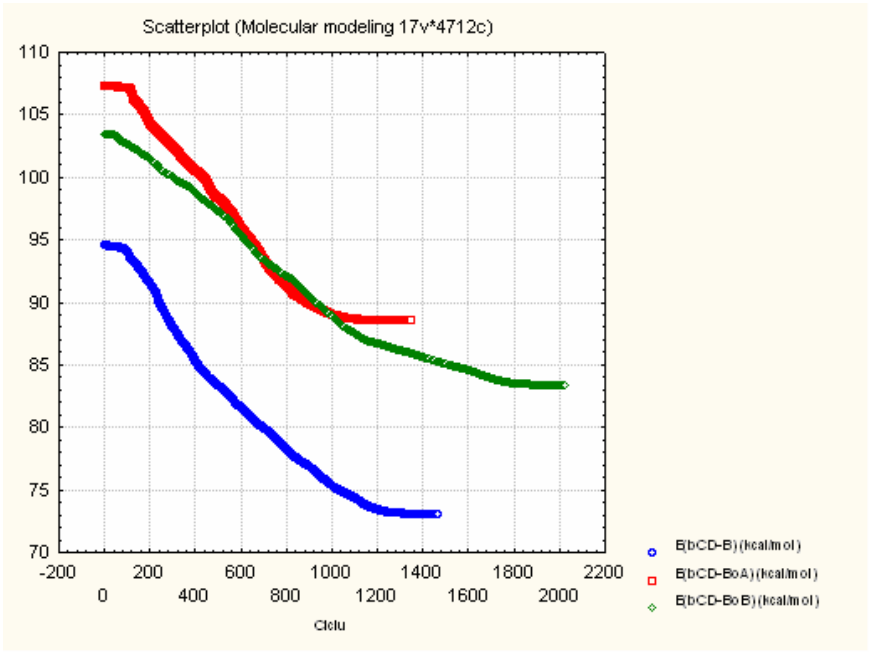


Figure 5. Energy variation (kcal/mole) of complex formation in the case of α-bisabolol (B), bisabolol-oxid A (BoA) and B (BoB) with α-cyclodextrin (up) and β-cyclodextrin (down)

Camazulene and caryophyllene allow a more efficient encapsulation, especially with the moiety with minimal steric hindrance (cyclopentane ring for camazulene and cyclobutane ring for caryophyllene), even in the presence of water molecules (water periodic box). The best interaction was obtained with caryophyllene (~20 kcal/mole) for both cyclodextrins. The interaction energy was much higher in the case of caryophyllene/ α-cyclodextrin comparatively with the corresponding caryophyllene-oxid, but in the case of β-cyclodextrin complexes the interaction energies were more closely; this

suggest that the α-cyclodextrin is more selective for this sesquiterpene than β-cyclodextrin (Figures 6 and 7). The rate of complex formation in these cases is relatively low and the stability of complexes can be evaluate from the energy variation of the complex, when the best stability seems to be for camazulene and caryophyllene complexes, comparatively with the poor stability of caryophyllene-oxid complex (Figure 8).

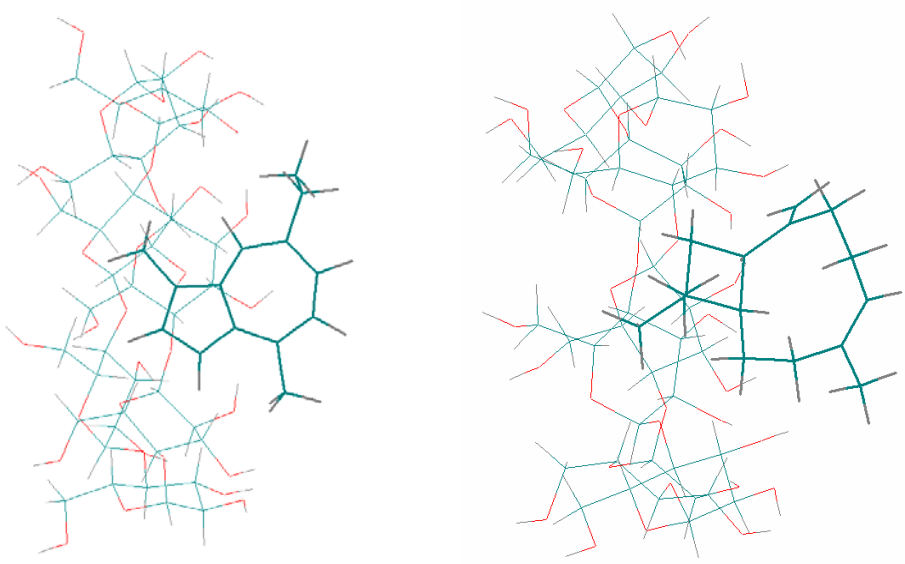


Figure 6. Camazulene/β-cyclodextrin (left) and caryophyllene/β-cyclodextrin (right) complexes

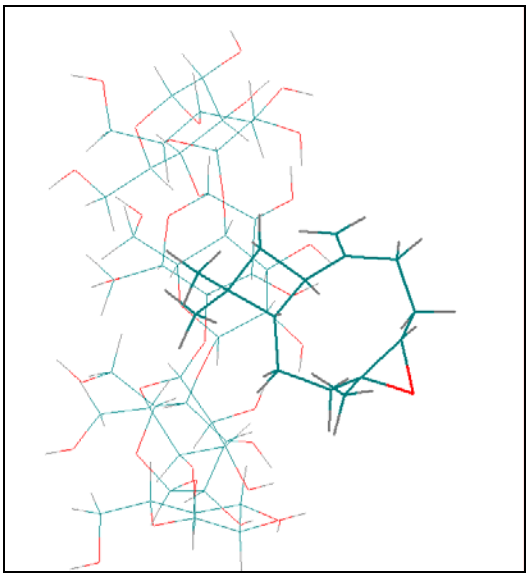


Figure 7. Caryophyllene-oxid/β-cyclodextrin complex

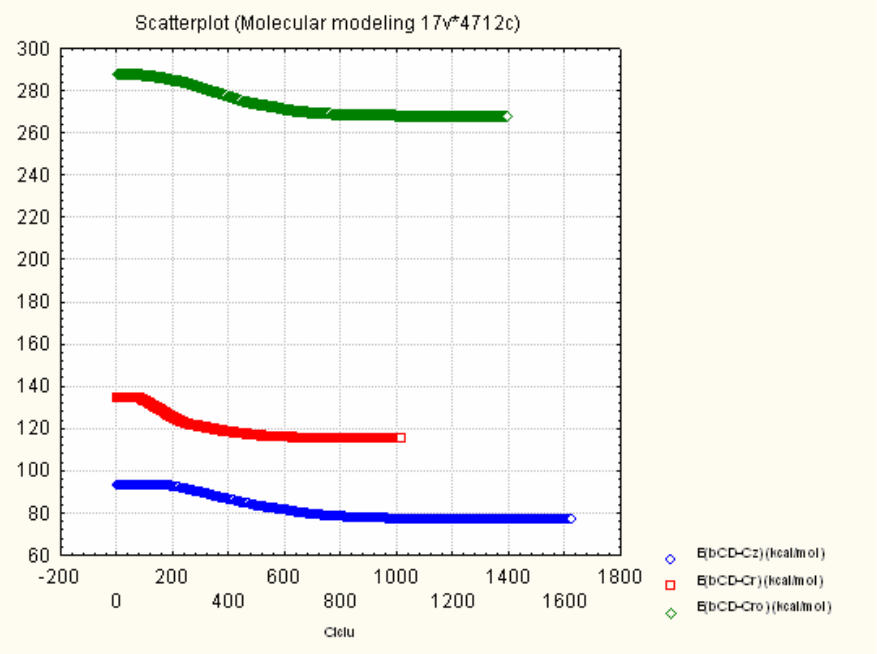


Figure 8. Energy variation (kcal/mole) of complex formation in the case of camazulene (Cz), caryophyllene (Cr) and caryophyllene-oxid (Cro) with β-cyclodextrin

4. Conclusion

The following conclusion can be draw according to the molecular modeling and docking experiments in the Compositae family plants biocompounds/cyclodextrin interactions: (1) the complexes of Compositae biocompounds with β-cyclodextrin seems to be more stable than those with α-cyclodextrin, even the rate of complex formation is lower for the first ones; (2) the best interaction between biocompounds and cyclodextrins is with the more hydrophobic and minimal hindrance moieties of biocompounds on the secondary side of cyclodextrin; (3) among Compositae biocompounds and they oxides, the best interactions are obtained for the first ones (more hydrophobic, with *log*P values – logarithm of the octanol/water partition coefficient, evaluated with the QSAR Properties program from the HyperChem package [32] – of 3.57 for α-bisabolol, 2.53 for camazulene, and 4.32 for caryophyllene), comparatively with the corresponding oxides, where the *log*P was lower (with one order of magnitude; 2.4 for both bisabolol-oxid A and B, and 3.22 for caryophyllene-oxid); (4) α-cyclodextrin seems to be more selective for non-oxidized sesquiterpenes than for the corresponding oxides (*i.e.* carryophyllene/carryophyllene-oxid), but the stability of complexes is higher in β-cyclodextrin cases for such biomolecule pairs; (5) both α- and β-cyclodextrin allow to obtain complexes by molecular inclusion of biocompounds or extracts from Compositae family plants, with improved stability and quality (lower concentration of oxidized compounds) and possibility to use for food and/or pharmaceutical purposes.

Acknowledgements

Authors are grateful to Professor Mircea Mracec, Ph.D. ("Coriolan Drăgulescu" Institute of Chemistry, Timişoara, Romania) for permission to use the HyperChem molecular modeling and statistical packages. This work was supported by Ministry of Education and Research from Romania, CNCSIS A 326 / 2007 Grant.

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