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Theoretical and experimental investigations on miconazole/cyclodextrin/acid complexes: Molecular modeling studies

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Abstract

The inclusion of miconazole into cyclodextrin cavity has been demonstrated by different authors. Preliminary studies have shown which fragment of the molecule is involved in the inclusion. In the present study, AM1 approximate molecular orbital calculations have been performed on several cyclodextrins complexes (βCD, HPβCD and HPγCD) with miconazole and acidic compounds (maleic, fumaric and L-tartaric acids) as partners. For all the binary complexes, the inclusion of the dichlorobenzene–CH_2–O-group leads to the most stable complex. For the ternary complexes, depending on their conformation and/or their structures, the acids can either stabilize or destabilize the complex. All the theoretical results were in good agreement with experimental data of miconazole inclusion yields into cyclodextrins. This work clearly demonstrates that the structure of both cyclodextrin and acid plays a key-role in the formation of inclusion complexes.

Keywords: Miconazole; Cyclodextrins; Molecular modeling; Complex structure; Multicomponent complex; AM1 calculations; Supercritical carbon dioxide

1. Introduction

Cyclodextrins (CDs) are used for many years to increase the water solubility of sparingly soluble drugs (Loftsson and Brewster, 1996). However, the solubility of natural CDs is limited and chemically modified CDs which present higher water solubility have been synthesized. An other approach consists in the use of a ternary agent. In the case of a basic drug, such as miconazole, the acidic ternary agent, for instance a hydroxyacid, promotes the solubilisation of the guest molecule both by forming a salt and by increasing the stability constant of the complex (Redenti et al., 2000).

Miconazole is an antifungal drug which presents poor water solubility. Many authors have shown that CDs can enhance the miconazole solubility by means of formation of inclusion complexes (Tenjarla et al., 1998; Mura et al., 1992). The interactions of miconazole and CDs have been characterized by spectroscopic techniques like ^{1}H NMR (Piel et al., 1998) and also by quantum chemical method at the AM1 level (Piel et al., 2001).

Recently, we have clearly shown that supercritical carbon dioxide allows the production of genuine miconazole/CD complexes (Barillaro et al., 2004). Firstly, binary miconazole/CD complexes have been produced and the influence of CD type on the miconazole inclusion yield has been evaluated. Secondly, ternary miconazole/CD/acid complexes have been produced by adding an acidic ternary compound. Experimental data have shown that organic acids, in function of their structure, are able to promote the miconazole inclusion yield by the formation of ternary complexes. The formation of such complexes has been shown by a differential solubility method, a dissolution test and a Fourier transform infrared analysis. Then, organic acids demonstrated that they were able to promote the miconazole inclusion as it can be observed in solubility diagram. Eventually,

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the complexes produced by supercritical fluid exhibited interesting pharmaceutical properties such as higher dissolution rate and better oral bioavailability when administered to pigs (Barillaro et al., 2004; Barillaro et al., 2005).

One of the great advantages of theoretical computational chemistry is that it can reproduce and predict physical properties of organic molecules such as geometries, relative energies, spectroscopic properties, with reasonable accuracy. The application of computational chemistry to the study of large systems as CD has been discussed by Lipkowitz (1998). Amato et al. demonstrated that molecular modeling methods are valuable tools for driving information on the geometry and interaction energy of the inclusion compounds (Amato et al., 1992). Austin Model 1, developed by Dewar et al. (1985), has been chosen to study the host–guest interactions between miconazole, CDs and acids. Due to the size of molecular systems, this approximate method can be currently applied regarding the time demand of the calculation.

In this study, the geometries of the ternary miconazole/CD/acid complexes were fully optimized and the interactions between the compounds were analyzed. The theoretical results were compared to experimental miconazole inclusion yields. The aim of this work is to show how the organic acids promote the miconazole inclusion into CD cavity and to point out a structure–activity relationship.

2. Materials and methods

2.1. Materials

Miconazole ((1-2-((2,4-dichlorophenyl)-2-(2,4-dichlorophenyl)-methoxy)ethyl)-1-imidazole) was obtained from Janssen Pharmaceutica (Beerse, Belgium). βCD (Eur. Ph. 4th Edition, 7.58% H_2O) was kindly provided by Roquette (Lestrem, France). Three grades of hydroxypropylβCD (HPβCD) were used: the first two grades were kindly supplied by Roquette with an average molar substitution (MS) of 0.63 at 0.99, respectively (water content of 5.46 and 4.90%, respectively); the third HPβCD with MS of 0.43 (water content 4.98%) was purchased from Cyclolab (Budapest, Hungary). HydroxypropylγCD (HPγCD) (Cavasol® W8 HP, MS 0.58, 1.62% H_2O) was obtained from Wacker Chemie GmbH (Munich, Germany). Fumaric acid was from Fluka (Buchs, Switzerland), maleic acid and D-tartaric acid from Acros (New Jersey, USA) and L-tartaric acid (Eur. Ph. 4th Edition) from Merck (Damstadt, Germany). CO_2 was of N48 quality (99.998%) from Air Liquide (Liège, Belgium). All the products were used as received.

2.2. Experimental details

2.2.1. Preparation of the inclusion complexes by means of supercritical fluids

The inclusion complexes were produced using supercritical carbon dioxide following a method and an experimental set-up previously described (Barillaro et al., 2004). Miconazole-CD 1:1 (mol:mol) and miconazole-CD-acid 1:1:1 physical mixtures were processed by supercritical carbon dioxide in a static mode at 30 MPa, 125 °C during 60 min.

2.2.2. Determination of the inclusion yields

The inclusion yields were determined using the differential solubility method whose principle has been described by Van Hees et al. (2002) and which has been successfully applied to miconazole and validated in a previous study (Barillaro et al., 2004).

2.2.3. Computational details: docking study

The geometry optimisation was performed with the Gaussian 98 software package (Frisch et al., 1998) by using semiempirical AM1 method (Dewar et al., 1985). The geometries were fully optimized without any constraint by minimisation of the analytical gradient. The nature of the located critical points is determined by vibrational frequency calculation derived from the second derivative matrix. When all the eigenvalues of this Hessian matrix are positive, the energy is minimum in each direction associated to the variables. For each equilibrium structure, the thermochemistry data are derived from the analytical frequency calculation at 298.15 K and 1 atm. (MC Quarrie, 1973).

Two types of complexes were considered depending on the part of miconazole which could interact with the CD cavity: the dichlorobenzene group directly linked to the asymmetric carbon and the dichlorobenzene–CH_2–O-group (Fig. 1). These complexes are, respectively noted dock1 and dock2. In these inclusion modes, the imidazole group remains outside the CD cavity and thus can interact with the acid. As the miconazole structure presents an asymmetric carbon, we focused our investigations on the S form. Moreover, in previous study, the S isomer

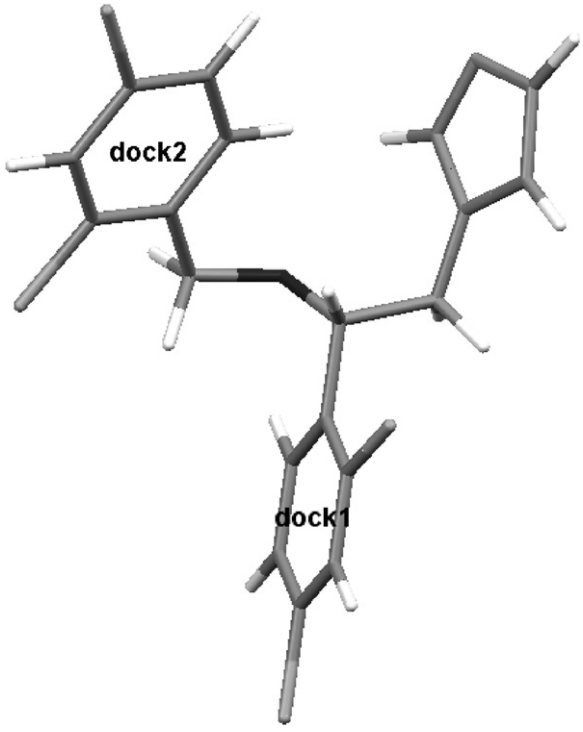

Fig. 1. AM1 optimized geometry of miconazole.

Table 1
Complexation, deformation and interaction energies in kJ/mol (ΔS in J/mol K) with the reference to both reoptimized βCD and miconazole(/acid)[a]

CD/acid model	βCD[b] (a)		βCD/maleic acid (b)		βCD/fumaric acid (c)		βCD/L-tartaric acid (d)	
	Dock1	Dock2	Dock1	Dock2	Dock1	Dock2	Dock1	Dock2
Complexation energy								
ΔE	21.48	−8.23	−6.98	−35.61	−21.69	−26.83	−15.23	−52.68
ΔH	29.81	1.01	−0.48	−30.18	−13.87	−19.40	−8.59	−34.91
ΔS	−174.47	−193.43	−197.20	−255.72	−245.89	−255.91	−189.29	−270.26
ΔG	81.83	58.68	56.04	46.07	59.45	56.90	47.84	45.67
Deformation energy								
Miconazole(/acid)	−3.24	−15.31	−15.18	−20.73	−2.93	−18.54	−11.25	−12.36
CD	−37.30	−4.99	−36.73	−10.78	−3.49	−13.48	−33.02	−5.01
Interaction energy	−19.06	−28.53	−58.89	−67.11	−28.10	−58.86	−59.50	−70.06

Model (a) refers to miconazole/βCD complex, model (b) to miconazole/βCD/maleic acid complex, model (c) to miconazole/βCD/fumaric acid complex and model (d) to miconazole/βCD/tartaric acid complex.

[a] Interaction energy: energy of the complex − sum of the energy of each partner at the complex geometry. Deformation energy: energy of the partner − energy of the partner in the complex. Complexation energy: energy of the complex − sum energy of each part in their respective equilibrium geometry. ΔG is calculated at 298.15 K.

[b] Results taken from Piel et al. (2001).

gives rise to more stable complexes than the R one (Piel et al., 2001). The fully optimized structure of miconazole at the AM1 level is given in Fig. 1.

The atomic coordinates of the βCD molecule (refcode POBRON of the Cambridge Structural Database (CSD)) has been selected as starting geometry for a complete optimisation of the isolated βCD (Steiner and Koellner, 1994). The HPβCD derivative was built-up by adding to βCD four hydroxypropyl groups (MS 0.6). Three are located on secondary hydroxyl groups and one on a primary hydroxyl group. In the same way, the HPγCD derivative was built-up by adding to γCD, referenced as CIWMIE in the CSD (Harata, 1987), five hydroxypropyl groups (MS 0.6), three being located on secondary groups and two on primary hydroxyl group. The configuration of the asymmetric carbon of this side chain is assumed to be S. Only one pattern of substituent distribution was examined for each βCD and γCD derivatives, since authors have described no statistically significant differences in docking energy values by varying the relative position of the substituents using CVFF force field (Mura et al., 1995).

The optimization procedure is following: starting from the optimized geometry of each ternary complex, miconazole/acid and the CD were re-optimized separately. The same procedure has been applied to the study of miconazole binary inclusion complexes (Piel et al., 2001).

3. Results and discussion

3.1. Molecular modeling of miconazole inclusion complexes

The results are presented as energetic outcomes expressed as complexation, deformation and interaction energies.[2] In order to emphasize a structure–activity relationship, three organic acids were tested: maleic, fumaric and L-tartaric acid. As mentioned in Section 2, starting form the optimised geometry of miconazole/βCD complex, these acids were added and the structure was reoptimized.

3.1.1. Docking of miconazole into βCD

As observed for all the studied complexes, the difference of free energy (ΔG) is positive indicating that a contribution of energy is necessary to form these complexes (Table 1).

For the two computed inclusion forms of miconazole with βCD and maleic acid (b) (Fig. 2), the interaction energies are high (<59 kJ/mol) whatever the relative orientation of miconazole is. For the miconazole/acid dimer, the deformation energy is similar for both inclusion modes while the βCD deformation energy is higher for the b_dock1 mode than the b_dock2 value. Finally, the b_dock2 complexation energy is much higher than the b_dock1 value. According to these results, it seems that the inclusion of the dichlorobenzene–CH_2–O (dock2) is more favourable ($\Delta E < 0$) than the inclusion of the inclusion of the dichlorobenzene directly linked to the asymmetric carbone (dock1). The acid generates hydrogen bonds with the imidazole ring of the miconazole, on one end, and with the βCD on the other end (Fig. 2).

Concerning the miconazole/βCD/fumaric complex (c) (Fig. 2), for the dock2 inclusion mode, the interaction and deformation energies of both βCD and miconazole/acid dimer are the highest (Table 1). The complexation energies are stabilizing for both systems. As for the previous ternary complex

[2] The complexation energy is the difference between the energy of the complex and the sum of both partners (miconazole/acid and CD) in their respective equilibrium geometry which is obtained by reoptimisation of the one found in the complex. Each geometries significantly vary depending on the type of the dimer which has been optimized. The deformation energy is determined by the difference between the energy of the partners at their respective equilibrium geometry and their energy at the complex geometry. The interaction energy is defined as the difference between the energy of the complex and the sum of the energies of both partners at their complex geometry.

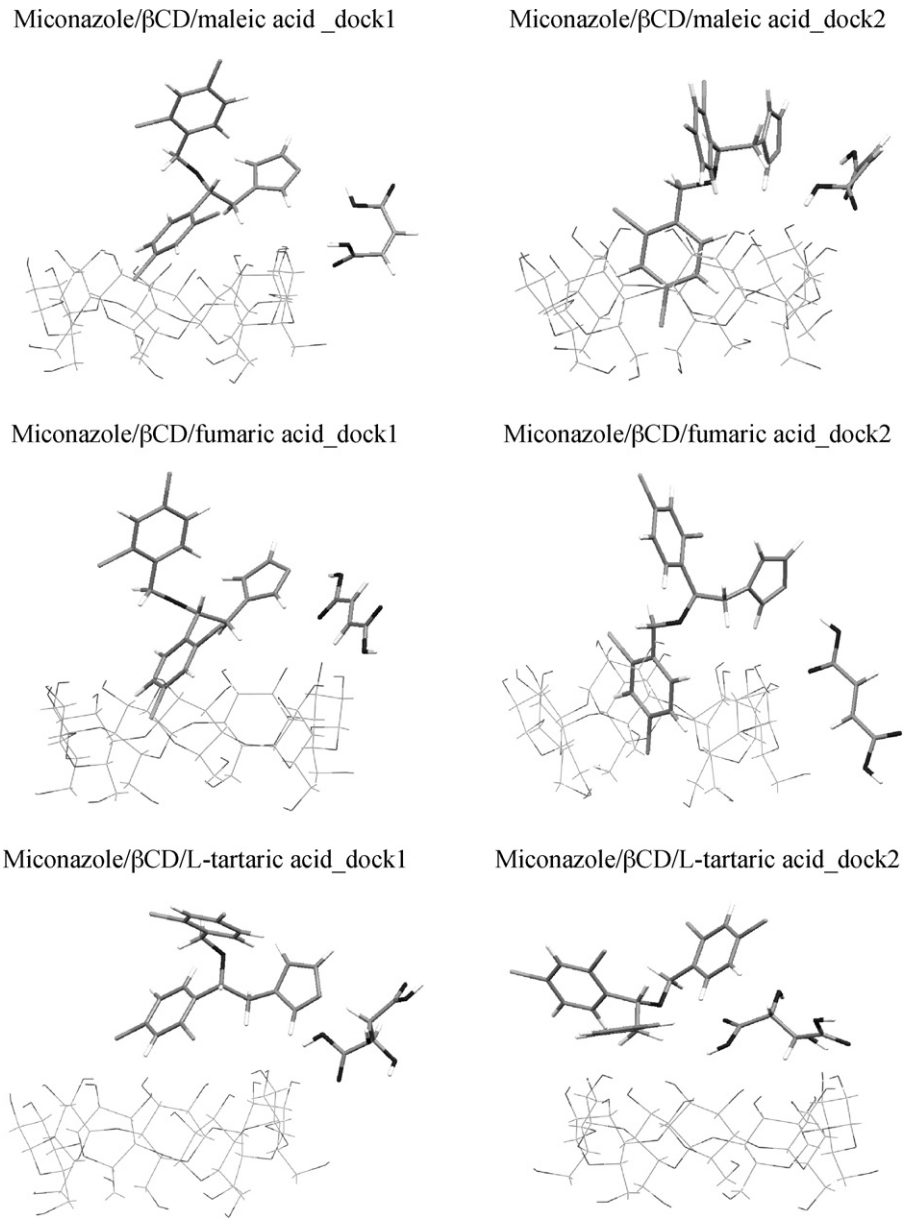

Fig. 2. AM1 optimized structures of the miconazole/βCD/acids complexes in both inclusion modes: dock1 and dock2.

with βCD and maleic acid, it seems that the inclusion of the dichlorobenzene–CH_2–O (dock2) is the most favourable.

Fig. 2 shows that fumaric acid interacts with miconazole and the βCD by means of hydrogen bonds. In the c_dock2 mode, fumaric acid forms hydrogen bonds with the secondary and the primary face of the CD. In contrast to maleic acid, the *trans* conformation of the double bond of fumaric modifies its interactions with miconazole and βCD and the ternary complex adopts a less compact shape by comparison with the complexes with maleic acid.

So, acids play a key-role in the structures of the complexes and also in their stabilization. The conformation of the double bond obviously affects the structure of the complex. In contrast to fumaric acid, the *cis* conformation of maleic acid allows the establishment of close interactions between the compounds and seems to present the best shape to form and to stabilize the multicomponent complex. The interaction energies present this following trend: b_dock2 > b_dock1 > c_dock2 > c_dock1. Moreover, if we compare the most stable conformations of the complexes, i.e. b_dock2 and c_dock2, the complexation and interaction energies of the b_dock2 complex are the highest, the deformation energy lying in the same magnitude. So, the efficiency of maleic acid in the formation and the stabilization of the ternary complex is superior to the one of fumaric acid.

Surprisingly, as observed in Fig. 2, the optimized structures with L-tartaric acid are non-inclusive complexes. Starting from the optimized geometry of the binary complex, L-tartaric acid 'extracts' miconazole from the CD cavity to form a ternary entity where miconazole is no more included.

The complexation energies are stabilizing ($\Delta E < 0$), the one concerning the d_dock2 is very high ($\Delta E = -52.68$ kJ/mol) (Table 1). The miconazole/L-tartaric acid energy of deformation

Table 2
Complexation, deformation and interaction energies in kJ/mol (ΔS in J/mol K) with the reference to both reoptimized HPβCD and miconazole(/L-tartaric acid[a]

CD/acid model	HPβCD (e)		HPβCD/L-tartaric acid (f)		
	Dock1	Dock2	Dock1_I	Dock1_II	Dock2
Complexation energy					
ΔE	−7.99	−17.52	−27.63	−23.43	−47.30
ΔH	−1.87	−11.41	−23.17	−17.44	−38.23
ΔS	−193.06	−221.94	−271.18	−225.94	−255.25
ΔG	55.68	54.76	60.18	49.93	37.87
Deformation energy					
Miconazole(/acid)	−3.71	−5.88	−8.28	−19.82	−16.67
CD	−8.63	−16.46	−0.75	−14.52	−18.88
Interaction energy	−20.33	−39.87	−49.20	−57.76	−82.84

Model (e) refers to miconazole/HPβCD complex and model (f) to miconazole/HPβCD/L-tartaric acid complex. The two stable conformations of this last complex in the dock1 mode are noted I and II.

[a] Interaction energy: energy of the complex − sum of the energy of each partner at the complex geometry. Deformation energy: energy of the partner − energy of the partner in the complex. Complexation energy: energy of the complex − sum energy of each part in their respective equilibrium geometry. ΔG is calculated at 298.15 K.

lies in the same order in both cases but, for the βCD, its deformation energy in the d_dock1 conformation is higher than the one in the d_dock2 conformation. Lastly, the interaction energies seem to be higher for the d_dock2 'complex'. L-tartaric acid forms hydrogen bonds between the βCD and the miconazole. So, the d_dock2 conformation seems to be the most energetically favourable.

3.1.2. Docking of miconazole into βCD and γCD hydroxypropyled derivatives

With regard to our experimental data concerning the miconazole inclusion yields into hydroxypropyled CDs, our investigations were conducted on two modified CDs: HPβCD and HPγCD. Moreover, as L-tartaric acid plays a particular role in the miconazole/βCD, we would like to study the influence of this acid on the miconazole/HPCD complexes which experimentally exhibits the best results in terms of inclusion yields (Barillaro et al., 2004).

3.1.2.1. Docking of miconazole into HPβCD, effect of L-tartaric acid. Concerning the miconazole/HPβCD complex (e), in both cases, the complexation energy is stabilizing ($\Delta E < 0$), but, again, the e_dock2 complex presents a complexation energy higher than e_dock1 (Table 2), the optimized geometries are depicted in Fig. 3. The deformation energies of miconazole and HPβCD are higher in the e_dock2 conformation leading to a higher interaction. Hydrogen bond takes place between the miconazole and a hydroxyl group of an HP-substituent in order to stabilize the complex. These observations suggest that the e_dock2 complex can exist with the highest probability.

By comparison with the results obtained by Piel et al. concerning the miconazole/βCD complexes (Piel et al., 2001), the role of the HP-substituent on the complexation can be estimated. Indeed, the presence of HP-substituents dramatically modifies the energy outcomes of the complexes. The complexation and the interaction energies are higher for the miconazole/HPβCD complexes, indicating that these complexes are the most stable thermodynamically.

The energy outcomes for the miconazole/HPβCD/L-tartaric systems (f) are presented in Table 2. After the optimization run, for the f_dock1 docking mode, two different conformations are located as local minima on the potential energy hypersurface: f_dock1_I and f_dock1_II. The optimised geometries are depicted in Fig. 4. These two conformers are stable and significantly differ

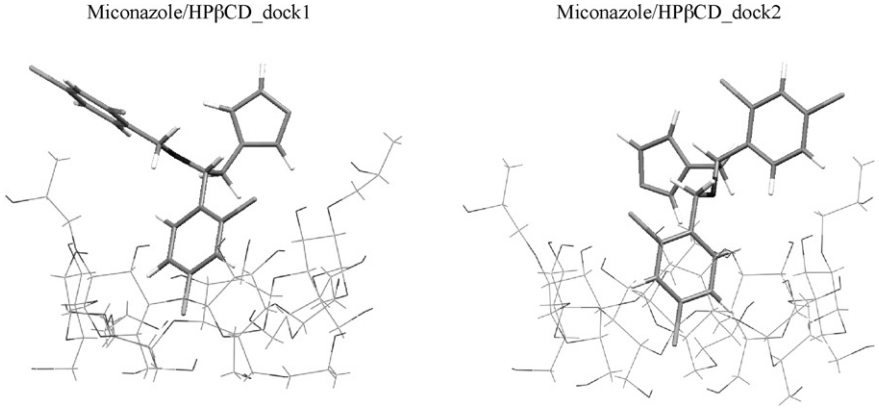

Fig. 3. AM1 optimized structures of the miconazole/HPβCD complexes in both inclusion modes: dock1 and dock2.

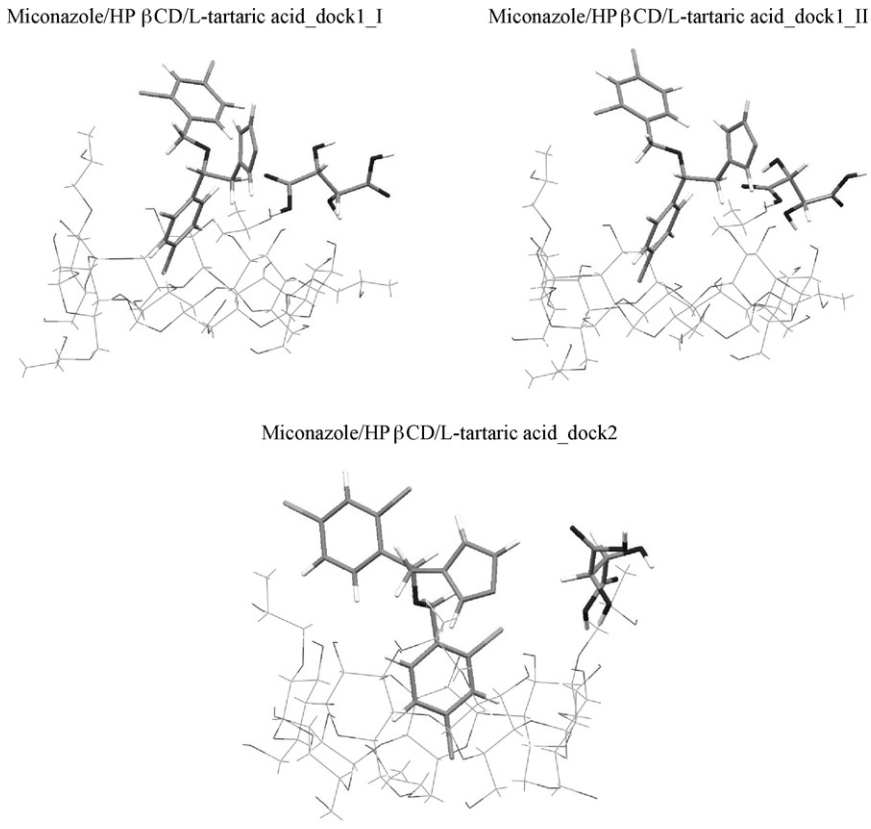

Fig. 4. AM1 optimized structures of the miconazole/HPβCD/L-tartaric acid complexes in both inclusion modes: dock1 and dock2.

in their energy outcomes. For all the miconazole/HPβCD/L-tartaric acid complexes, the complexation energy is stabilizing ($\Delta E < 0$). The comparison between the two conformers of the f_dock1 mode shows that the interaction energy is higher for the f_dock1_II and that the deformation energies for the partners are also higher for this inclusion mode. This last conformer is the more stable conformer for the dock1 inclusion mode. Again, the dock2 inclusion mode presents the highest complexation and interaction energies and the deformation energies are small.

In contrast to the miconazole/βCD/L-tartaric acid complexes, there is not a direct interaction between L-tartaric acid and miconazole. L-tartaric acid preferentially interacts with the CD structure. This kind of behaviour was previously observed with the miconazole/βCD/L-tartaric acid.

3.1.2.2. Docking of miconazole into HPγCD, effect of L-tartaric acid. The results obtained after optimisation of the miconazole/HPγCD systems (g) are listed in Table 3 and show that the complexation energies are stabilizing and the dock2 complexation value is the highest. Due to the size of the molecular system, the deformation energies are very weak for both partners. So, it appears that HPγCD does not need much energy to fit miconazole. Consequently, the interaction energies are weak (−6.20 kJ/mol for the g_dock1 mode and −16.11 kJ/mol for the g_dock2 mode). The optimized structures of both complexes are depicted in Fig. 5.

The results for the optimisation of the miconazole/HPγCD/L-tartaric acid complex (h) are listed in Table 3. Both inclusion modes give rise to thermodynamically stable complexes with respect to their respective complexation energy ($\Delta E < 0$) that is higher for the h_dock2 mode. The deformation energy of miconazole/L-tartaric acid dimer is higher for the h_dock1 mode, but the one of HPγCD is higher for the h_dock2 mode. Moreover, the interaction energy and the entropy are higher for the

Table 3
Complexation, deformation and interaction energies in kJ/mol (ΔS in J/mol K) with the reference to both reoptimized HPγCD and miconazole(/acid)[a]

CD/acid model	HPγCD (g)		HPγCD/L-tartaric acid (h)	
	Dock1	Dock2	Dock1	Dock2
Complexation energy				
ΔE	−5.77	−11.66	−7.38	−45.10
ΔH	1.61	−4.63	0.71	−37.19
ΔS	−156.24	−196.44	−172.36	−299.63
ΔG	48.19	53.94	52.10	52.23
Deformation energy				
Miconazole(/acid)	−0.26	−2.31	−18.53	−4.90
CD	−0.17	−2.13	−2.75	−13.59
Interaction energy	−6.20	−16.11	−28.66	−63.60

Model (g) refers to miconazole/HPγCD complex and model (f) to miconazole/HPγCD/L-tartaric acid complex.

[a] Interaction energy: energy of the complex − sum of the energy of each partner at the complex geometry. Deformation energy: energy of the partner in the complex − energy of the partner. Complexation energy: energy of the complex − sum energy of each part in their respective equilibrium geometry. ΔG is calculated at 298.15 K.

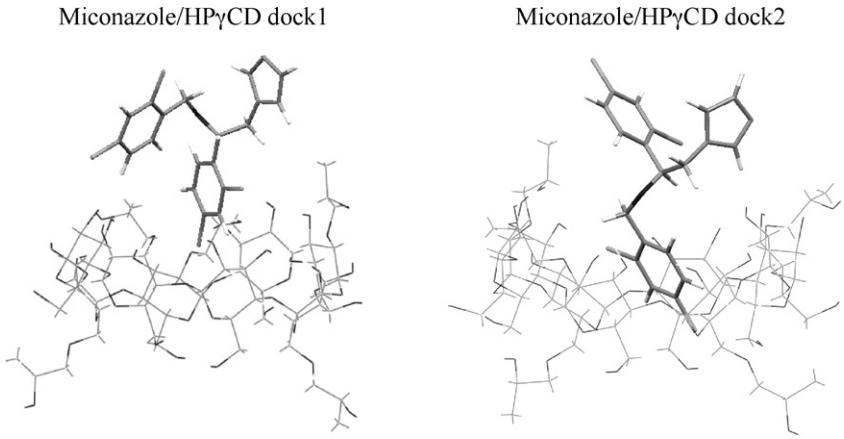

Fig. 5. AM1 optimized structures of the miconazole/HPγCD complexes in both inclusion modes: dock1 and dock2.

h_dock2 mode. Thus, in regards to the energetic outcomes, the h_dock2 mode seems to be the most thermodynamically stable complex.

In h_dock1 mode, miconazole is not deeply included in the HPγCD cavity, as seen for the miconazole/βCD/tartaric acid complex (Fig. 6) but miconazole forms a hydrogen bond between an aromatic hydrogen and an hydroxyl group of the cyclodextrin. In both complexes, the conformation allows the formation of H-bonds between the acid and, on one hand, the HPγCD and, on the other hand, miconazole.

3.2. Experimental miconazole inclusion yield

The miconazole inclusion yields in several systems obtained by means of supercritical carbon dioxide treatment are listed in Table 4. In binary combination with βCD, miconazole presents a poor inclusion yield and acids allow to increase the inclusion yields. Compared to binary systems, maleic and fumaric acids promote the miconazole inclusion but the increase with maleic acid lies at about 11% and is higher than the inclusion yield with fumaric acid (about 9%). The influence of tartaric acids on miconazole inclusion is very low. The two enantiomers of tartaric acid (L- and D-tartaric acid) have the same macroscopic effects on the miconazole inclusion into βCD probably because racemic miconazole was tested during the inclusion experiments.

With HPβCD, the miconazole inclusion yields increase with its substitution degree. The use of HP-CD dramatically modifies the inclusion of miconazole. The CD hydroxypropyl substitution modifies the complexation properties: the cavity seems to be enlarged and new host–guest interactions can occur in order to increase the stability of the complex (Zia et al., 2001). HPγCD gives the highest inclusion yield for the binary systems and lies about 40%. L-tartaric acid dramatically modifies the miconazole inclusion yield for both HPβCD and HPγCD and gives inclusion yields around 90%. As observed with βCD, the enantiomers of tartaric acid increase the miconazole inclusion yield in the same magnitude.

3.3. Comparison between experimental data and docking simulations

There is a relatively good agreement between the theoretical and the experimental approaches about the interaction of miconazole with CD. The relatively poor inclusion of miconazole into βCD is reflected in the energy outcome of the binary

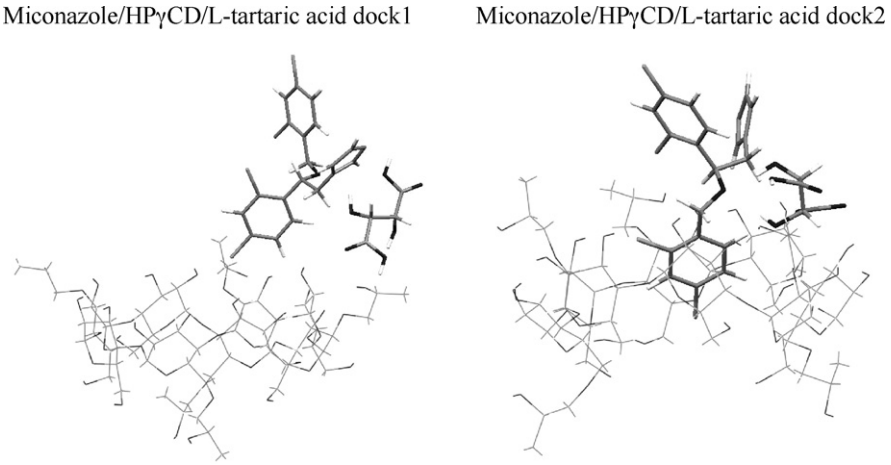

Fig. 6. AM1 optimized structures of the miconazole/HPγCD/L-tartaric acid complexes in both inclusion modes: dock1 and dock2.

Table 4
Miconazole inclusion yield determined by differential solubility in function of CD and acid types ($n = 3$; mean ± S.D.)

	Total miconazole content (%, wt/wt)	Free miconazole content (%, wt/wt)	Inclusion yield (%)
βCD[a]	22.06 ± 0.51	21.95 ± 1.07	2.91 ± 2.66
βCD/maleic acid[a]	20.88 ± 0.61	18.61 ± 0.84	10.84 ± 2.46
βCD/fumaric acid[a]	22.69 ± 0.10	20.74 ± 0.05	8.59 ± 0.61
βCD/L-tartaric acid[a]	22.58 ± 0.01	21.69 ± 0.27	3.96 ± 1.20
βCD/D-tartaric acid	21.56 ± 0.34	20.63 ± 0.34	4.34 ± 1.46
HPβCD (0.43)	23.31 ± 0.45	23.76 ± 0.16	−1.96 ± 1.69
HPβCD (0.63)[a]	23.13 ± 0.13	22.09 ± 0.35	4.53 ± 1.90
HPβCD (0.99)	21.05 ± 0.25	6.60 ± 0.17	68.67 ± 3.74
HPβCD(0.63)/L-tartaric acid[a]	21.39 ± 0.69	2.11 ± 0.05	90.15 ± 2.43
HPβCD (0.63)/D-tartaric acid	18.03 ± 2.92	2.37 ± 0.03	86.88 ± 2.02
HPγCD[a]	18.88 ± 1.15	11.93 ± 0.65	36.81 ± 0.98
HPγCD/L-tartaric acid[a]	19.42 ± 0.18	1.92 ± 0.01	90.13 ± 0.44
HPγCD/D-tartaric acid	18.91 ± 0.31	1.51 ± 0.02	92.00 ± 2.64

[a] Results taken from Barillaro et al. (2004).

complex in which the interaction and the complexation energies are weak (Table 1). With βCD, the conformation of the acid obviously influences the formation of the complex. Maleic acid seems to present the best conformation in order to form a ternary complex. So, the inclusion yields with this acid are higher than those in which fumaric acid is used. In the same way, in particular for the dock2 mode, higher complexation and interaction energies are obtained with maleic acid by comparison with fumaric acid. Lastly, L-tartaric acid, as its enantiomer, does not affect the miconazole inclusion yield with βCD. As revealed in the theoretical study, L-tartaric acid seems to have more affinity for the CD cavity and thus to "extract" miconazole from its inclusion mode observed in the binary complex.

The case of CD derivatives is particular. Indeed, the presence of HP-substituent modifies the complexing ability of the CD. So, the interaction and complexation energies for HPβCD are higher than those of the native one. Moreover, experimentally, miconazole inclusion is promoted by the substitution degree of the HPβCD, confirming that these substituents can interact with miconazole to stabilize the binary complex. For HPγCD, the energies of complexation, deformation and interaction are very weak, due to the large cavity that prevents a good fit between the host and the guest. Nevertheless, this CD derivative experimentally produces the best inclusion yield for the binary complexes.

By opposite to the miconazole/βCD/L-tartaric acid complexes, L-tartaric acid stabilizes the complexes with HP-CD derivatives, increases the interaction and complexation energies and finally promotes the miconazole inclusion. The experimental miconazole inclusion yield lies around 90% for both HPβCD and HPγCD with both L- and D-tartaric acids. It is interesting to note that L-tartaric acid does not interact with the imidazole ring of the miconazole, as maleic and fumaric acid do. It is the CD itself that forms hydrogen bond between the imidazole and HP-substituent. Finally, in the ternary complexes with HPγCD, molecular modeling reveals an interaction between L-tartaric acid and miconazole by means of its aromatic protons.

4. Conclusion

In conclusion, with the use of theoretical methods, the present work unambiguously determined the characteristics of the interaction between miconazole, CD and acid. Interaction models for miconazole with both CDs and acids were built at the AM1 level. The models which probably represent the predominant solution and solid-state structures indicate that the inclusion of the dichlorobenzene–O–CH_2 moiety into CD occurs. Maleic and fumaric acids establish electrostatic interactions with the imidazole ring and hydrogen bonds with 2- and/or 3-hydroxyl group of the βCD. L-tartaric acid induces a non-inclusive complex with βCD. Also, the results show that HP-substituents modify the complexation ability of the native CD for binary and ternary complexes (with L-tartaric acid). The results are also consistent with the miconazole inclusion yields experimentally obtained. In conclusion, the structure of both the CD (ring size, presence or not of substituent) and the ternary agent nature appears to be the key element for the stabilization of the inclusion complex.

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