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Diastereomeric β-cyclodextrin Complexes With Cizolirtine and Its Carbinol. A Molecular Dynamics Study

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The enantiodifferentiation observed in the complexation of cizolirtine and its parent carbinol with β-cyclodextrin is due to differences in the average structure of each diastereomeric complex, as deduced from molecular dynamics simulations. Bimodal complexation is possible for all these molecules; both computations and experiments indicate the inclusion of the phenyl group. Two distinct inclusion orientations of this group were considered; although the preferred orientation was determined, the other one may contribute to the final average structure depending on the enantiomeric guest molecule.

Keywords: β-cyclodextrin; Host–guest; Enantiodifferentiation; Molecular dynamics and MM/PBSA

INTRODUCTION

Complexation of cyclodextrins with racemic mixtures yields enantiodifferentiation [1,2]. However, few theoretical studies have been carried out to elucidate the enantiodifferentiation process. An outstanding report describes the host–guest interaction in gas phase using molecular dynamics (MD) simulations where the "principle of maximum chiral discrimination" [3] is developed, and reports that the macrocyclic cavity is the most enantiodiscriminating domain.

The key role of the cavity is thus well established, but the forces responsible for the subtle differences at bimodal complexations are not fully understood. Moreover, the experimental data seldom suffice to obtain the 3D structure for the host–guest complexes, and computations may be of great help in this respect. Four cyclodextrins have been used as NMR chiral solvating agents to resolve the enantiomers of the analgesic (±)-cizolirtine, **2**, and its chemical precursor ((±)-carbinol, **1**) [4]. The preparation of stable cyclodextrin complexes offers great potential for pharmaceutical formulations that improve the solubility and bioavailability of the active drug. Concerning optical resolution, the most accurate enantiodiscrimination occurs when the natural β-cyclodextrin (β-CyD) is used (Figs. 1 and 2). No geometrical differences between the two diastereomeric complexes formed by a cyclodextrin and a racemic substrate were detected through nuclear Overhauser effect (NOE) studies [5]. The magnetic non-equivalence induced on guest protons by the enantioselective binding may thus result from subtle disparities in the orientation and/or of the conformation of the complexed enantiomers.

Here, we study the 3D structures for the diastereomeric complexes formed between β-CyD and racemic mixtures of *1* and **2** by means of MD simulations. The AMBER program (version 5) [6] was used because it reproduces the experimental

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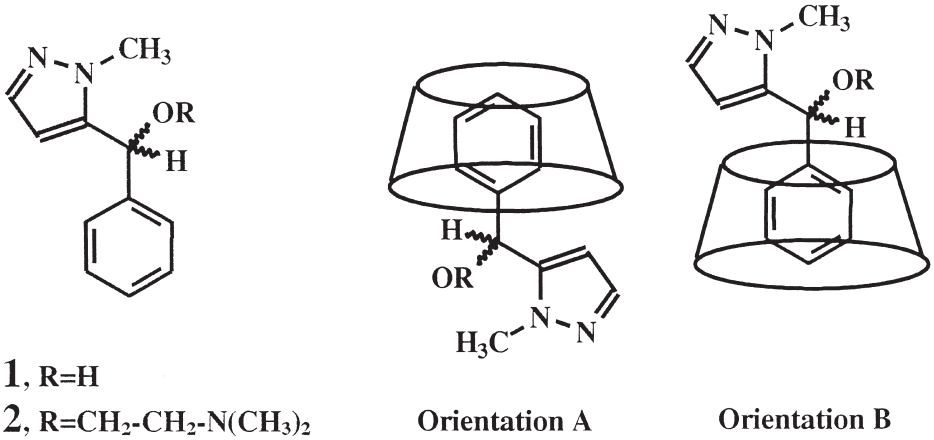

FIGURE 1 Guest molecules studied, **1** and **2** and the two possible inclusion orientations.

conditions (298 K and water solution). The solute–solvent electrostatic interactions were evaluated using *ab initio* atomic charges and explicit water molecules.

EXPERIMENTAL

NMR experiments: All NMR data have been reported elsewhere [4].

Computational methodology: Six conformations for **1** and **2**, and the X-ray structure for the β-CyD, were optimized under the Gaussian-94 program [7] using the STO-3G basis set. Molecular electrostatic potentials were calculated at HF/6-31G* level, and atomic charges were derived with the RESP methodology [8,9]. Additional parameters (bond lengths and constants, angle widths and constants, and torsion constants) for these molecules were derived from *ab initio* calculations or by comparison with other parameters in parm94 [10] force field. For the simulations in water, molecules were solvated by a cubic box of TIP3P [11] water molecules. Periodic boundary conditions, 8 Å for the primary cutoff and 13 Å for the secondary cutoff were applied to non-bonded interactions. For all systems, the energy was initially minimized and temperature was increased to 300 K at three 50 ps intervals. Once the systems were equilibrated, 500 ps data collection runs were performed saving trajectories every 1 ps (500 snapshots were collected). The 2 fs time step was used at constant temperature and pressure.

The MM/PBSA methodology [12] was also applied to estimate the free energies of binding ($\Delta G_{\text{binding}}$) from the absolute energies in the gas phase (E_{gas}) and the solvation free energies ($G_{\text{PB}} + G_{\text{non-polar}}$) for the complex, guest (**1** or **2**) and host (β-cyclodextrin). This procedure can be summarize as follows:

$$\Delta G_{\text{binding}} = \Delta G_{\text{water}}(\text{complex}) - [\Delta G_{\text{water}}(\text{guest}) + \Delta G_{\text{water}}(\text{host})]$$

The free energies, ΔG_{water}, for each species were evaluated by the following scheme:

$$\Delta G_{\text{water}} = E_{\text{gas}} + \Delta G_{\text{solvation}}$$

$$G_{solvation} = G_{\text{PB}} + G_{\text{non-polar}}$$

$$E_{\text{gas}} = E_{\text{internal}}(\text{bond, angle, torsion}) + E_{\text{electrostatic}} + E_{\text{vdW}}$$

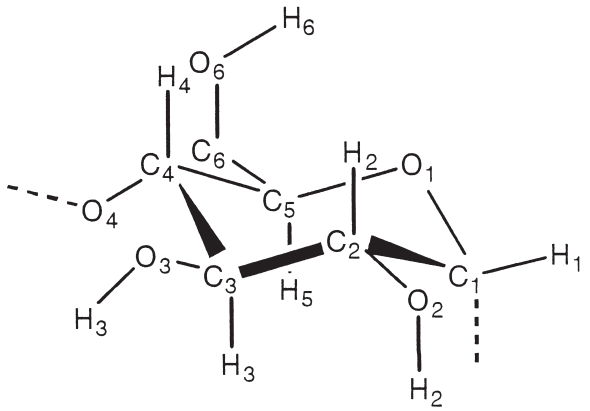

FIGURE 2 Fragment of the chemical structure, and atomic numbering used for β-CyD.

RESULTS AND DISCUSSION

Molecular Dynamics Simulations

Experimental results [4,5] confirm that the phenyl group is included in the β-CyD cavity. Two inclusion orientations are possible for each enantiomer of the guest molecule (Fig. 1), but no clear conclusion can

TABLE I MD average energies (total energy, E_{tot}, kinetic energy, EK_{tot}, and potential energy, Ep_{tot}, in kcal/mol) of the orientations studied for the **1**/β-CyD complex, as well as the energy terms for the potential energy (stretching, E_{bond}, bending, E_{ang}, torsional, E_{dih}, 1–4 non-bonded, $E_{1-4\ NB}$, 1–4 electrostatic, $E_{1-4\ el}$, van der Waals, E_{vdW}, and electrostatic, E_{elec}, also in kcal/mol as obtained with the AMBER force field

*Complex**	E_{tot}	EK_{tot}	EP_{tot}	E_{bond}	E_{ang}	E_{dih}	$E_{1-4\ NB}$	$E_{1-4\ el}$	E_{vdW}	E_{elec}
*R*phA	−6456.7	1692.5	−7849.1	39.0	107.0	95.5	55.0	855.2	1118.2	−10119.0
*R*phB	−6154.8	1692.7	−7847.5	38.9	106.2	95.9	54.7	855.8	1120.1	−10119.0
*S*phA	−6124.5	1684.3	−7808.8	39.0	105.8	100.3	54.5	858.4	1116.0	−10082.9
*S*phB	−6166.3	1691.6	−7857.9	39.5	109.2	88.9	53.7	857.3	1124.0	−10130.4
*R*pyA	−6093.5	1675.6	−7769.2	38.6	106.4	100.5	54.7	850.7	1104.5	−10024.6
*R*pyB	−5815.5	1611.3	−7426.7	39.4	107.8	94.5	54.3	850.9	1054.5	−9628.1

*First character of the name indicates the chirality (*R*, *S*), second and third the group being included (ph: phenyl, py: five-membered ring), and the last the orientation considered (**A**, **B**).

be made drawn of experimental values [4]. MD simulations were carried out considering the inclusion of both the phenyl and the pyrazole rings on orientations **A** and **B** for each molecule studied. As the experimental results point to the phenyl inclusion, the five-membered ring inclusion was exclusively simulated for one enantiomer of each molecule: the *R* isomer. Tables I and II show the energy values corresponding to the **1**/β-CyD and **2**/β-CyD inclusion complexes, respectively. MD simulations indicate that both orientations are very similar in energy when the phenyl ring is included, and that the inclusion of the five-membered ring is energetically unfavorable, in agreement with the experimental data.

The contributions of the energy terms to the total energy are very similar, so we cannot establish orientations and enantiomeric preferences. Hydrogen bond analysis was carried out, with the CARNAL module of AMBER to identify the interactions responsible for complex formation.

In both complexes, **1**/β-CyD and **2**/β-CyD, the inclusion of the five-membered ring (py) is less stable than the inclusion of the phenyl group (ph). Guests are more constrained and less deeply included inside the β-CyD cavity in this orientation owing to the py methyl group (*R*pyA and *R*pyB complexes in Figs. 3 and 4). Moreover, the sp^2 nitrogen of the py group interacts much better with water than with the low polar β-CyD cavity. However, MD simulations indicate that the complex can be formed, and that it is stabilized by intermolecular hydrogen bond interactions between the polar groups of the guest and the β-CyD hydroxyl groups. The ph inclusion showed higher stability than the py inclusion, and was further supported by experimental evidence. We thus focused on this inclusion, hereafter referred to as ph inclusion.

For **1**/β-CyD complexes, the guest molecule is more included in orientation **A** (Fig. 3), which shows more intermolecular hydrogen bonds (both the O and H from the carbinol hydroxyl group and the sp^2 N, with the β-CyD secondary hydroxyls) than in

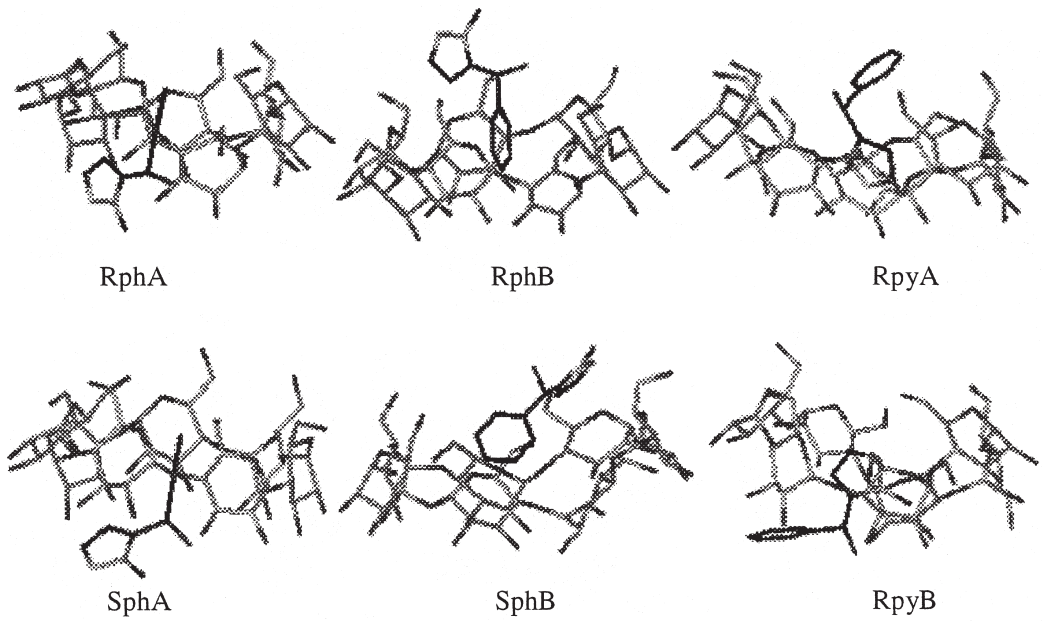

FIGURE 3 Average structures for **1**/β-CyD complexes.

TABLE II MD average energies (total energy, E_{tot}, kinetic energy, EK_{tot}, and potential energy, Ep_{tot}, in kcal/mol) of the orientations studied for the **2**/β-CyD complex, as well as the energy terms for the potential energy (stretching, E_{bond}, bending, E_{ang}, torsional, E_{dih}, 1–4 non-bonded, $E_{1-4\ NB}$, 1–4 electrostatic, $E_{1-4\ el}$, van der Waals, E_{vdW}, and electrostatic, E_{elec}, also in kcal/mol as obtained with the AMBER force field

*Complex**	E_{tot}	EK_{tot}	EP_{tot}	E_{bond}	E_{ang}	E_{dih}	$E_{1-4\ NB}$	$E_{1-4\ el}$	E_{vdW}	E_{elec}
*R*phA	−6382.7	1754.1	−8136.8	41.0	116.4	89.6	57.4	823.5	1150.9	−10415.6
*R*phB	−6015.1	1668.0	−7683.1	41.2	117.4	90.5	56.3	818.9	1089.0	−9896.2
*S*phA	−6540.3	1793.5	−8333.8	40.2	112.3	102.7	57.8	825.7	1179.1	−10651.5
*S*phB	−6541.5	1793.8	−8335.4	40.7	112.9	102.6	57.8	825.9	1186.2	−10661.4
*R*pyA	−6064.0	1681.0	−7744.9	40.8	112.8	100.2	56.7	815.0	1095.9	−9965.9
*R*pyB	−5921.0	1647.7	−7568.7	40.4	114.4	96.1	57.6	818.2	1068.5	−9763.8

*First character of the name indicates the chirality (*R*, *S*), second and third the group being included (ph: phenyl, py: five-membered ring), and the last the orientation considered (**A**, **B**).

orientation **B** (only the hydroxylic H of carbinol forms an intermolecular H-bond with the primary hydroxyls). Therefore, the guest molecule forms more hydrogen bond interactions with water molecules in orientation **B** than in orientation **A**.

The energetic terms for the complexation of **2** with β-CyD (Table II) show higher differentiation between *R* and *S* complexes than in the carbinol **1**; β-CyD complexes with *S*-cizolirtine are more stable than with *R* isomer. Stabilization results from the favorable electrostatic energy that overcomes the unfavorable dihedral, 1–4 electrostatic, and van der Waals terms. The MD average structures for each complex indicate that the *S*-cizolirtine is more included than the *R* isomer (Fig. 4) which explains the unfavorable terms. As for **1**, there are more intermolecular hydrogen bonds in orientation **A** than in **B**. In both complexes, the hydrogen bonds are formed preferentially with the secondary hydroxyls of the β-CyD. As for **1**, the guest forms more hydrogen bond interactions with water in orientation **B**. The electrostatic term enhances the stability of *S* complexes, but these show less intermolecular H-bonds than in *R* complexes, and so the stabilization of the β-CyD/*S*-cizolirtine complex is due to electrostatic interactions other than H-bond interactions.

Cizolirtine complexes have less intermolecular H-bond interactions with water than carbinol complexes. This is consistent with the experimental results, which show that cizolirtine, in particular *R*-cizolirtine, is less soluble and can thus form more intermolecular H-bonds with cyclodextrin.

Geometry Considerations

We aimed to confirm the preference for the phenyl inclusion over the five-membered ring inclusion, as indicated by the energetic preference of the ph inclusion, and by intermolecular rotating-frame

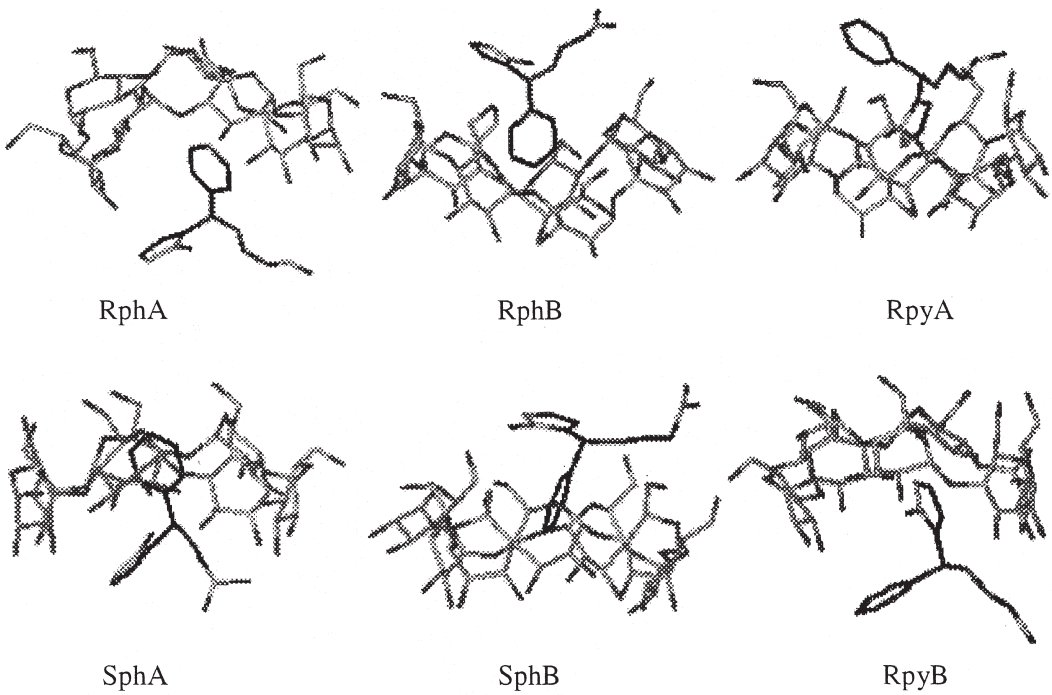

FIGURE 4 Average structures for **2**/β-CyD complexes.

TABLE III Average distances between the phenyl group protons (*ortho*, *meta* and *para*) of guest molecules **1** and **2**, and the inner protons of β-CyD (H3 and H5), in each complex simulation

	1/β-CyD			**2**/β-CyD		
	ortho	*meta*	*para*	*ortho*	*meta*	*para*
*R*phA-H3	3.212	3.827	3.695	3.720	3.236	3.853
*R*phA-H5	3.471	3.185	3.620	5.220	3.316	2.903
*R*phB-H3	4.311	3.237	3.288	5.034	3.211	3.100
*R*phB-H5	3.117	3.380	4.106	3.136	3.088	4.070
*S*phA-H3	3.613	3.247	3.501	3.162	4.428	5.761
*S*phA-H5	3.440	3.570	3.248	3.349	3.139	3.774
*S*phA-H3	4.121	3.467	3.463	4.514	3.465	3.629
*S*phB-H5	3.274	3.410	3.211	3.329	3.386	3.748

nuclear Overhauser effect (ROE) experiments. The average distances (Table III) between the phenyl guest protons and the inner host protons (Fig. 5) also confirm the inclusion of the phenyl group. Results from ROE experiments may be explained by either of the orientations (**A** or **B**) (distances lower than 4 Å). This fact provides evidence for the inclusion of the phenyl group but does not shed any light on the orientation preference.

Enantiodifferentiation is observed (signal splitting) in the guest protons H3′ and H4′ (Fig. 5). It is clearer with **2**/β-CyD complexes than with **1**/β-CyD ones. The energy analysis of MD simulations indicates that both orientations are possible and coexist. We can conclude that enantiodifferentiation results from the geometrical differences between *R* and *S* complexes, and that distinct chemical environments surround the differentiated protons, especially in **2**/β-CyD complexes, in which *S* molecules are more deeply included in the CyD cavity than the *R* ones (Fig. 4). However, this geometrical dissimilarity is too slight to be observed in **1**/β-CyD complexes (Fig. 3).

MM/PBSA Results

Comparison of molecular dynamics energies revealed the preference of the phenyl group inclusion over the pyrazole ring in the complexation of **1** and **2** with β-CyD. However, the energies of the complexes for **1** and **2** cannot be directly compared because they contain a different number and arrangement of atoms. Various orientations of the same complex can usually be compared if the number of water molecules surrounding the complexes is the same. A thorough MM/PBSA analysis is required to compare the energies between all the orientations and complexes studied.

The total free energy for the complexation process is the complex energy minus the guest and the host energies. We considered the guest energy as the average energy of each guest (molecules **1** and **2**), and the host energy as the average energy of the β-CyD in all the simulations, to avoid deviations of these energies in each simulation. The results for **1**/β-CyD and **2**/β-CyD complexes are shown in Table IV.

The total energy of **1**/β-CyD complexes shows a clear preference for orientation **B** in both enantiomers (*R*phB, *S*phB). This preference results from the polar contribution of the solvation energy, E(PB), although the electrostatic and van der Waals terms show a preference for orientation **A**, which is stabilized by more intermolecular hydrogen bonds, as explained in the MD analysis. The energy in the gas phase, E(gas), shows higher stabilization of the complexes with the *R* enantiomer (electrostatic and van der Waals terms favoring these complexes), but addition of solvation terms favors the complexes with the *S* enantiomer. The non-polar contribution of the solvent, E(np), shows no significant differences between complexes.

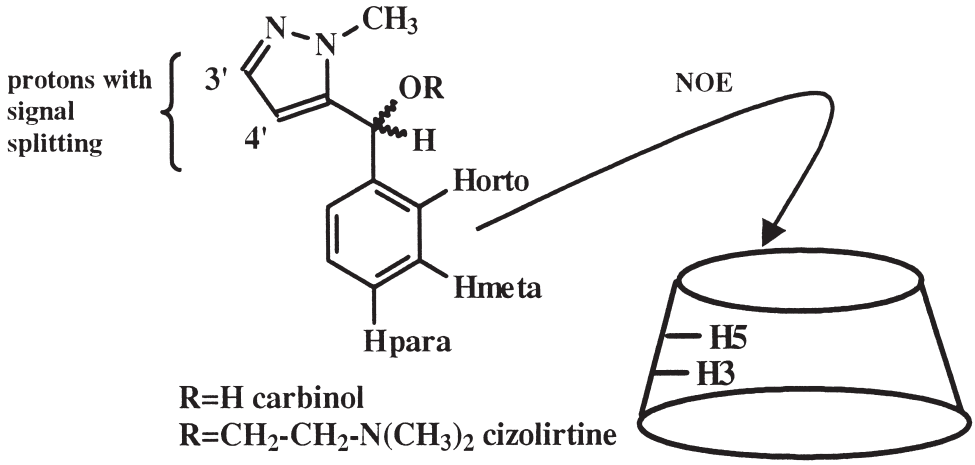

FIGURE 5 Guest protons showing signal splitting (H3′ and H4′) and guest protons showing NOE (phenyl group protons) with the cyclodextrin inner protons (H5 and H3) in the ^{1}H-NMR and intermolecular ROE experiments (see [4] for more details).

TABLE IV MM/PBSA energy differences (E_{total} in kcal/mol) as well as their corresponding energy terms (electrostatic, E_{elec}, van der Waals, E_{vdW}, internal [stretching+bending+torsional] E_{int}, gas [internal+electrostatic+van der Waals] E_{gas}, Poison–Boltzman E_{PB}, and non-polar, $E_{non\text{-}polar}$ also in kcal/mol) of all the orientations studied for the **1**/β-CyD complexes (left) and **2**/β-CyD (right)

	1/β-CyD				**2**/β-CyD			
	*R*phA	*R*phB	*S*phA	*S*phB	*R*phA	*R*phB	*S*phA	*S*phB
E_{elect}	−13.57	−5.06	−4.67	1.37	4.37	4.50	−9.49	−7.83
E_{vdW}	−23.96	−21.38	−20.29	−18.96	−23.26	−21.99	−26.99	−19.72
E_{int}	0.83	0.41	4.69	−2.96	−4.63	−2.10	4.85	6.34
E_{gas}	−36.70	−26.03	−20.28	−20.56	−23.52	−19.59	−31.63	−21.21
E_{PB}	34.64	20.80	22.61	15.71	21.55	14.19	30.01	19.38
$E_{non\text{-}polar}$	−3.46	−3.22	−3.28	−3.21	−3.25	−3.49	−3.68	−3.34
E_{total}	−5.52	−8.45	−0.95	−8.06	−5.22	−8.88	−5.30	−5.17

In the β-CyD complex with *R* cizolirtine, the total energy of complexation also shows a preference for orientation **B**, but no significant preference is observed for the complex with *S*-cizolirtine. The electrostatic and van der Waals terms favor complexes with orientation **A**. The electrostatic energy also favors the complexation with the *S* enantiomer but the internal energy is higher for complexes with the *R* cizolirtine, which are less included than those with the *S*-cizolirtine (which are more included and more restrained, and thus show more electrostatic interactions) (Fig. 4). In the gas phase, orientation **A** is preferred but solvation terms favor orientation **B**.

In general, orientation **B** is preferred because of the polar solvation term. For this orientation, the complexes with the *R* enantiomer, especially the **2**/β-CyD complexes, are energetically more favorable. Energies show that the **2**/β-CyD complex is more stable than **1**/β-CyD.

The solvation terms for **1** (carbinol) are more negative than for **2** (cizolirtine) (Table V), in agreement with water solubility values, which are higher for carbinol.

SUMMARY

The slight differences between *R* and *S* enantiomers are hard to reproduce. Researchers encountered several drawbacks: the simulation time has to be long enough to obtain a converged average structure, and the energetic results are dramatically reversed when solvation terms, which are deduced from a continuum solvation model and can be a source of errors, are included.

Inclusion of carbinol, **1**, and cizorlitine, **2**, in β-CyD was observed experimentally, revealing ROE between the cyclodextrin inner protons and the protons of the guest phenyl group. Our data show that complexes with the phenyl group are more stable than those with the pyrazole ring, and that the two inclusion orientations of the phenyl are possible. Electrostatic and van der Waals forces are responsible for complex formation and stability. Orientation **B** (with the five-membered ring in the narrower rim of the β-CyD) is preferred. The complexation of the *R* enantiomer in this orientation is also energetically more favorable than the *S* complexation.

The distances between the inner cyclodextrin protons and the phenyl group protons are consistent with the ROEs observed. This points to the phenyl inclusion but does not shed any light on orientation. Enantiodifferentiation results from the differences in the average structure for the diastereomeric complexes with *S* and *R* enantiomers, which condition the chemical environment of pyrazole protons. This is clear in **2**/β-CyD where *S* complexes are more deeply included into the host cavity than *R* complexes. Moreover, both orientations of *S* complexes (**A** and **B**) are close in energy and so they coexist; in contrast, those of the *R* enantiomer show one preferred orientation. The average structure is thus different for *R* and *S*. In the case of the parent alcohol, **1**/β-CyD complexes, MD simulations for *R* and *S* complexes show the same preferred inclusion orientation, and the average structures are similar, thus predicting low enantiodifferentiation, in agreement with the experimental results.

TABLE V Total energy for solvation in water (G_{solv}, in kcal/mol), as well as corresponding energy terms (Posion–Boltzman, E_{PB}, and non-polar, $E_{non\text{-}polar}$, also in kcal/mol) for **1** (carbinol) and **2** (cizolirtine), as obtained using the MMPB/SA methodology

Solvation terms	**1**	**2**
E_{PB}	−18.50	−17.57
$E_{non\text{-}polar}$	3.12	3.79
G_{solv}	−15.38	−13.77

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