

Molecular Mechanics Calculations on the Differentiation of Diastereomeric Complexes of *cis*-Decalin with β -Cyclodextrin

FRÉDÉRIC FOTIADU, MOHAMED FATHALLAH, and CARLOS JAIME*
Department de Química, Facultat de Ciències, Universitat Autònoma de Barcelona, 08193
Bellaterra (Barcelona), Spain.

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Abstract. Molecular mechanics calculations with the latest available version of Allinger's MM2 force field (MM2(91)) on the diastereomeric complexes of both enantiomeric conformations of *cis*-decalin with β -cyclodextrin show a small preference (1.67 kJ mol^{-1}) for one of them, in agreement with the available ^{13}C -NMR results. Calculations were found to be sensitive to the procedure used.

Key words: β -Cyclodextrin, molecular mechanics, decalin, inclusion compounds.

1. Introduction

A large number of successful practical applications of cyclodextrins (CDs) to chiral recognition have been carried out [1]. In spite of the enormous literature existing on CD inclusion complexes, the mechanism of the complex formation remains unclear. Several hypotheses have been invoked [2] but in the case of complexes with nonpolar molecules the sum of many weak attractive van der Waals interactions may act as the driving force in the complexation process.

Some β -CD complexes with hydrocarbons have been prepared (e.g., adamantane [3], and decalins [4]). The β -CD/adamantane complex does not show any interesting properties due to the high symmetry of the guest (point group: T_d). In contrast, the β -CD/decalin complex does present interesting properties. Decalin can be either in *cis* or *trans* configurations and both complexes seem to be formed due to the separation of both decalins using β -CD in a chromatographic column [4a]. The β -CD/*cis*-decalin complex has been obtained in crystalline form [5] and its 125.76 MHz ^{13}C -NMR spectrum recorded in dimethylformamide solution at low temperature (233 K) shows the splitting of several signals indicating the existence of two diastereomeric complexes which should correspond to each of the two enantiomers of *cis*-decalin, **1a** and **1b**. The almost equal intensity in the split signals seems to be an indirect proof of a small energy difference between the two complexes.

* Author for correspondence

Theoretical studies of CD complexation processes have been carried out either with semiempirical MO or with MM calculations as a consequence of the larger number of atoms involved. Recently, we published some articles [6] on the MM2 [7] calculations of the geometry and energy involved in the formation of inclusion complexes with CDs. Following the same work, we wish to present here the MM2(91) calculations [8] on the diastereomeric complexes of both enantiomers of *cis*-decalin, **1a** and **1b**, with β -CD, **2**.

2. Methodology

The previously published method [3b, 6a] was followed. The β -CD molecule was oriented so as to have the glycosidic oxygens in the *xy* plane and the geometric center of the almost regular heptagon formed by them was placed at the origin of the coordinate axes. No restrictions were imposed on the optimization of the host geometry. The narrower entrance of the β -CD toroidal cavity was placed in the positive region of the *z*-axis. The guests, **1a** and **1b**, were oriented in two different arrangements, trying to represent the most reasonable fit between the guest and the host cavity. These two orientations were:

- (i) For molecule **1a** the C2 and C6 atoms were placed on the *z* axis, while for **1b** the C3 and C7 atoms were placed on the *z* axis (hereinafter called the vertex orientation) (Figure 1a)
- (ii) The middle points of the C2–C10 and C6–C9 segments of **1a** were placed on the *z* axis, while for **1b** the middle points of the C3–C9 and C7–C10 segments (hereinafter called the center orientation) (Figure 1b).

Since the internal diameter of the CD cavity is large enough to locate the *cis*-decalin in its larger dimension, a third orientation was also considered. The middle point of the C9–C10 bond was placed on the *z* axis, and the average plane formed by C4, C10, C9 and C8 atoms of **1a**, or alternatively C1, C9, C10 and C5 atoms of **1b**, was kept parallel to the *xy* plane (hereinafter called the planar orientation) (Figure 1c).

Furthermore, due to the pseudo- C_7 symmetry of CD, the guest was rotated into a variation domain of $360/7$ degrees from an arbitrary starting position with a step of 10.3° (a total of six points were thus generated). The systematic variation of these two parameters (*z* coordinate and rotation angle) produces one energy surface for each complexation process studied (a total of six surfaces, two in each orientation, were obtained).

3. Vertex Orientation

The guests were initially located far from the host having the nearest C atom at a *z* coordinate of -14 \AA and they were forced to pass through the host cavity until they had crossed it completely. The scanning of the translation along the *z* axis was

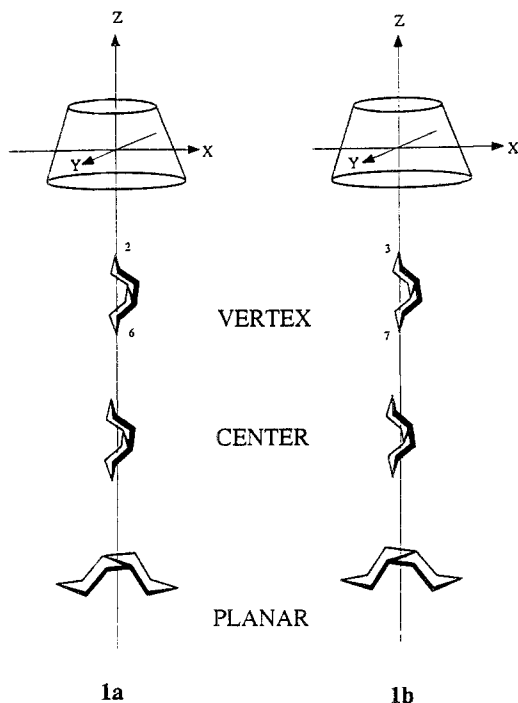


Fig. 1. Schematic representation of the three orientations used in the calculations of the diastereometric complexes of *cis*-decalin. (a) Vertex orientation; (b) center orientation; (c) planar orientation.

performed using 2 Å steps from -14 to -6 Å and +6 to +14 Å, while a 1 Å step was used for the central domain.

When the total energy of the supermolecule was plotted against the z coordinate for the C2 atom of **1a** or for the C3 atom of **1b** on the one hand and the rotation angle on the other hand, smoothed surfaces having only one energy minimum were obtained. Figure 2 shows the surface corresponding to the complexation of **1a** as an example. As stated before, it can be seen that the computed variation domain of the rotation angle represents a single unit of the whole periodic surface. The structures corresponding to both energy minima were then re-optimized, removing all the movement restrictions and the global minima were found at 2.99 Å for **1a** and 3.16 Å for **1b**. Figure 3a shows the final geometries of the global energy minima for this orientation. The **2/1a** complex was 3.93 kJ mol⁻¹ more stable than the **2/1b** complex.

4. Center Orientation

The guests were now located with the geometric center of the cyclohexane ring nearest to the β -CD at a z coordinate of -14 Å. The plot of the surfaces obtained when the guests passed through the host cavity had a shape similar to that for

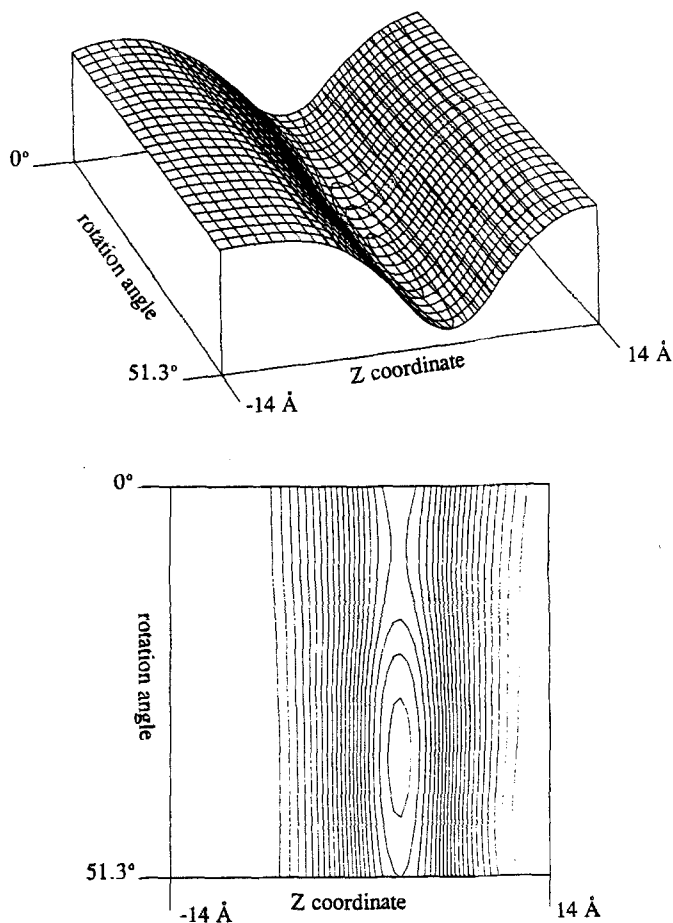


Fig. 2. Energy surface obtained for the complexation of **1a** with **2** in the vertex orientation.

the vertex orientation. Figure 3b shows the final geometries of the complexes of **2** with **1a** and **1b** in this orientation. The complex **2/1b** is now more stable than the **2/1a** by only 1.67 kJ mol^{-1} . Although such a small energy difference must be considered with caution, the relative order of stability of the two complexes was confirmed by several calculations performed on fixed points located in the vicinity of the previously found minima: in all the cases, it appeared that the **2/1b** species were less energetic than the **2/1a** ones.

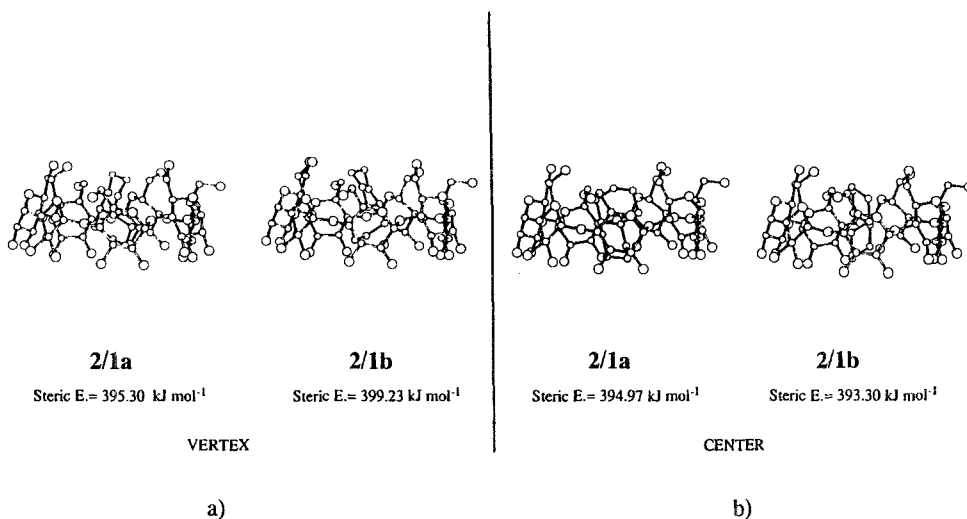


Fig. 3. Drawings of the energy minima obtained in the MM2(91) calculations of the diastereomeric complexes of *cis*-decalin (hydrogen atoms have been removed for clarity). (a) vertex orientation; (b) center orientation.

5. Planar Orientation

Finally, the guests were located with the geometric center of the C9–C10 bond at a z coordinate of -14 \AA . The energy surfaces obtained for this orientation clearly denote the existence of severe non-bonding repulsive interactions between host and guest. Each surface shows two valleys separated by a high barrier. Figure 4 contains the graphical representation for the surface obtained for the **2/1a** complexation. The energy values corresponding to these valleys (around 435 and 460 kJ mol^{-1} respectively) were at least 40 kJ mol^{-1} above the global minima located in the two preceding orientations, and allow us to discard them as stable complexes. Indeed, further optimizations without any restricted motion were performed on various points lying on the bottom of these two valleys. The resulting geometries exhibited dramatic changes in the orientation of the guest. The decalin molecules have moved from horizontal to roughly vertical positions (where the C2 and C6 atoms in **1a** or C3, C7 in **1b**, were nearly parallel to the z axis), closely related to those obtained with the center orientation.

6. Discussion

The total steric energies shown in Figure 3 for the different complexes with diverse orientations clearly denote the difficulty involved in the computer modeling of the complexation process. The stability order is reversed when the orientation is changed, even under full geometry optimization of the guest inside the host with total allowance of both to move freely. This fact is a clear indication of either a very

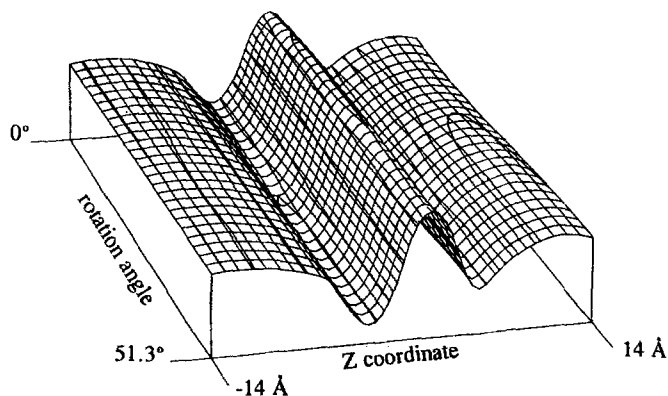


Fig. 4. Energy surface obtained for the complexation of **1a** with **2** in the planar orientation.

flat energy hyper surface or the incapacity of the block-diagonal algorithm used in the MM2 minimization scheme to push the molecule downhill to reach the deepest global minimum. A single test carried out decreasing the energy convergence criteria ten times from the MM2 default value, resulted in prohibitive computation time and, moreover, it was unable to push the guest down from the -6 \AA point to the minimum previously found (see Figure 2). However, it seems likely that a gradient minimization algorithm would allow a fall down to a local minimum corresponding to an inclusion complex, starting from dissociated species of higher energy. Unfortunately, this molecule has too many atoms for study with the latest version of the MM3 program [9], which performs full matrix optimizations.

Nevertheless, if we consider only the two most stable situations we have obtained in this work, the complex of enantiomer **1b** is only 1.67 kJ mol^{-1} more stable than that of enantiomer **1a**, in good agreement with the ^{13}C -NMR observations [4b]. This center orientation, revealed to be the most favorable, may be due to the minor deformations induced by the guest on the host geometry, whereas the vertex approach imposes a dissymmetric, elliptic opening of the CD cavity, as in the case of adamantane [3b]. Even more striking distortions of the CD are observed in the case of the planar orientation of decalin. Despite the infinity of starting points that can be retained for each orientation, varying the position of the translation axis in the host cavity, the present results suggest that only some of them may correspond to acceptable inclusion processes: those that do not affect the CD geometry to a large extent. Since small deviations from the centered position induce significant structural and energetic changes as illustrated by the vertex orientation, it can be suggested that most of the possible minima are located nearby those obtained for the center orientation. Exhaustive explorations of the potential energy hyper surface being precluded by the size of the molecular system, the proposed strategy seems to provide a satisfactory alternative.

7. Conclusions

The methodology used in this work has been found to be sensitive to the orientation utilized. The MM2 force field seems to behave properly in reproducing the experimentally available data in the host-guest β -CD chemistry. The molecular mechanics study of the diastereomeric complexation of the two enantiomers of *cis*-decalin agrees well with the ^{13}C -NMR observations and allows one to suggest that the most stable β -CD complex of *cis*-decalin is that of the stereoisomer **1b**. Whatever effect the complexation has on the chemical shifts for one specific C atom, it should be clear that the greater the stability of the complex the bigger the induced chemical shifts. Consequently, and according to these MM2(91) calculations, the complex **2/1b** should have all its signals as far as possible from those belonging to a fast equilibrium with the free *cis*-decalin.

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