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Monte Carlo simulations of the chiral recognition of fenoprofen enantiomers by cyclomaltoheptaose (β-cyclodextrin)

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Abstract

Differential complexation of fenoprofen enantiomers by cyclomaltoheptaose (β-cyclodextrin) was investigated by Monte Carlo docking simulations. The chiral discrimination of (*R*)- and (*S*)-fenoprofen by β-cyclodextrin was discussed in terms of the difference in the interaction energies and the patterns of molecular interactions. The interaction energies between each enantiomer of fenoprofen and β-cyclodextrin were consistent with the reported experimental results that showed that the S isomer interacted preferentially with β-cyclodextrin and was retained longer in a separation process than the R isomer. The thermodynamic preference of inclusion complex formation of (*S*)-fenoprofen could be explained by the orientation of the phenyl group attached to the chiral carbon, which provided closer contact and thus more favorable intermolecular interactions between the host and guest molecule. The results presented here would be very useful for the prediction of chiral recognition ability of β-cyclodextrin.

Keywords: Monte Carlo simulation; Chiral recognition; Fenoprofen; β-Cyclodextrin

1. Introduction

Chiral discrimination has been a subject of great interest in the development, use, and action of pharmaceutical agents. Different stereoisomers of drugs often cause different physiological responses, so the use of pure isomers can elicit more exacting therapeutic effects. Numerous examples exist where the undesired effects of one isomer limit the overall effectiveness of the active species [1].

This problem can be illustrated by fenoprofen, 2-(3-phenoxyphenyl)propionic acid or α - methyl - 3 - phenoxyphenyl)propionic acid, which is a nonsteroidal anti-inflammatory, antipyretic, analgesic drug and belongs to the group commonly called the 2-arylpropionic acids [2]. It has a chiral carbon atom, resulting in two enantiomers, R-(−) and S-(+). Of the two enantiomers, the S isomer is about 35 times more potent than the R isomer [3], so the chiral discrimination of this molecule is of interest.

β-Cyclodextrin (β-CD) has been a powerful tool for the chromatographic separation of enantiomers [4]. β-CD is a bucket-shaped

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macrocyclic molecule formed by α-(1→4)-glycosidic links between seven D-glucose monomeric units. β-CD has a hydrophobic inner cavity with a diameter 6.5 ~ 8.0 Å and shows remarkable ability to form inclusion complexes with a variety of molecules that fit inside its cavity [5,6]. It has been used as bonded chiral phases in liquid chromatography (LC) or as chiral mobile phase additives in LC and capillary electrophoresis (CE) for the enantiomeric separation of racemic molecules [7,8].

In this study, the inclusion complexes formed between β-CD and both (*R*)- and (*S*)-fenoprofen were modeled and refined by Monte Carlo (MC) docking simulations to rationalize the chiral discrimination ability of β-CD. The interaction energies and configurations of the β-CD complexes of (*R*)- and (*S*)-fenoprofen were compared. We suggest a computational approach for the understanding and prediction of chiral recognition by β-CD.

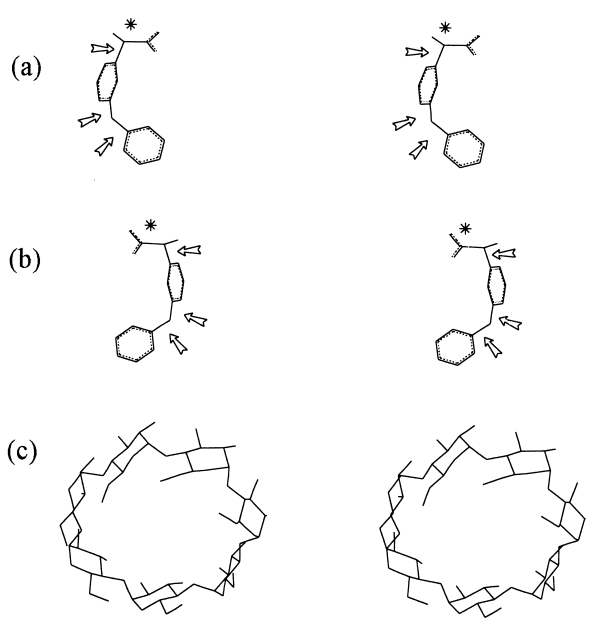

Fig. 1. Stereoview of molecular models used in the MC simulations. (a) (*R*)-fenoprofen, (b) (*S*)-fenoprofen, and (c) β-CD. The single bonds of fenoprofen, which were allowed to rotate in the MC runs are indicated by arrows and the chiral carbons are indicated by asterisks.

2. Methods

Molecular mechanics calculations were performed with the InsightII/Discover program (version 97.0, Molecular Simulations, USA) using consistent valence force field (CVFF) [9] on a SGI R4600 platform (Silicon Graphics, USA).

The molecular model of β-CD was obtained from the crystallographic geometry [10]. The conformational searches of (*R*)- and (*S*)-fenoprofen were performed by simulated annealing molecular dynamics–full energy minimization strategy [11], and the lowest energy conformation of each enantiomer was selected for the MC docking simulations. These molecular models were fully energy minimized before MC runs. The conformations of these molecules are depicted in Fig. 1.

The chiral recognition process is intended to involve a 1:1 interaction between β-CD and fenoprofen in the MC docking simulations [12]. The host and guest molecule were positioned in the neighborhood with a distance of ~ 12 Å. MC docking simulation started by conjugate gradient energy minimization of this initial configuration for 50 iterations and accepted it as the first frame. Trials to a new configuration were accomplished by changing the position, orientation and/or conformation of fenoprofen. In this process, fenoprofen could take translational movement to the *x*, *y*, and *z* axes (maximum 7 Å) and rotation around the *x*, *y*, and *z* axes (maximum 180°). The three dihedral angles of fenoprofen could rotate (maximum 180°) for conformational flexibility. Nine degrees of freedom were present for this system (3 translational, 3 rotational, and 3 dihedral). Each cycle began with a random change of up to 5 degrees of freedom among them. If the energy of the resulting configuration was within 1000 kcal/mol from the last accepted one, it was subjected to the 50 iterations of conjugate gradient energy minimization. The energy tolerance of 1000 kcal/mol was imposed to avoid significant overlap of van der Waals radii in the random search. After the energy minimization, acceptance was determined by the following two criteria. (a) An energy check with the Metropolis criteria at 300 K [13], and (b) a

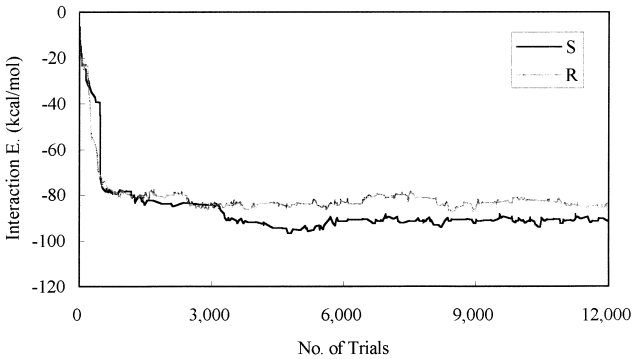

Fig. 2. Energy profile of the Metropolis Monte Carlo docking simulations. The interaction energy was defined as the difference between the sum of independently calculated energy of each host–guest molecule and the energy of each configuration in the process of MC docking simulations.

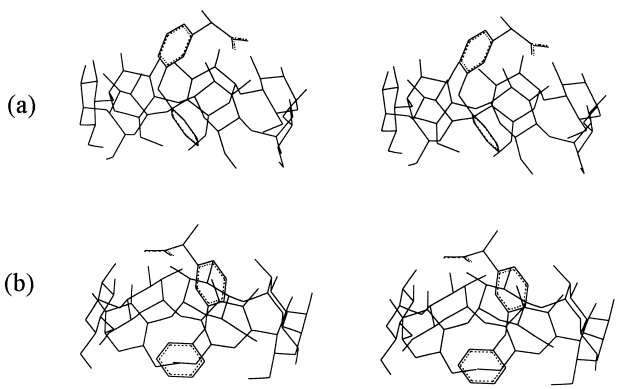

Fig. 3. Stereoview of representative configurations of the inclusion complexes of both enantiomers of fenoprofen and β-CD. (a) (*R*)-fenoprofen–β-CD complex, (b) (*S*)-fenoprofen–β-CD complex. (*S*)-fenoprofen is more deeply embedded in the cavity of β-CD than (*R*)-fenoprofen.

root-mean-squared displacement (RMSD) check, which compared the RMSD of the new configuration against those accepted so far. Configurations within 0.1 Å RMSD of pre-existing ones were discarded to avoid accepting similar configurations. The MC docking simulations continued until the complete energy convergence. No cutoff was imposed on the calculation of non-bonded interactions, and the dielectric constant was set to 1.

3. Data and results

The pathways of MC docking simulations showed general tendencies of inclusion complex formation and lowering interaction energies for both enantiomers of fenoprofen with β-CD. The interaction energy was defined as the difference between the sum of independently calculated energy of each host–guest molecule and the energy of each configuration in the process of MC docking simulations [14]. Fig. 2 compares the interaction energies in the MC runs for both complexes. For each enantiomer, the MC process could be divided into three phases: the initial, middle and equilibrium phase. In the initial phase (from trial 1 to 1000), the interaction energies decreased rapidly, and the host got close and in contact with the host. In the middle phase (from trial 1000 to 4000), the interaction energies decreased more slowly, and the guest searched for stable conformations in the cavity of the host. In the equilibrium phase (from trial 4000 to the end), the interaction energies reached its equilibrium value and fluctuated around it in a stable manner. The interaction energies of both (*R*)- and (*S*)-fenoprofen with β-CD were almost parallel to each other. The average interaction energy of the (*S*)-fenoprofen–β-CD complex was -91.3 ± 1.5 kcal/mol, whereas that of the (*R*)-fenoprofen–β-CD complex was -83.2 ± 1.8 kcal/mol in the equilibrium phase. The lower interaction energy of the (*S*)-fenoprofen–β-CD complex could indicate the formation of thermodynamically more stable inclusion complexes. This result is consistent with reported experimental results that the S isomer preferentially interacted with β-CD [6] and was retained longer in the separation process [15] than the R isomer. We have tried several MC runs from different initial configurations for each enantiomer, and obtained similar results.

Armstrong et al. suggested that there were a number of requirements for chiral recognition by β-CD. For example, an inclusion complex must be formed, and there must be a relatively tight fit between the complexed moiety and the β-CD. In addition, the chiral center, or one substituent of the chiral center must be near and interact with the mouth of the β-CD cavity. The unidirectional 2- and 3-hydroxyl groups located at the mouth of the β-CD cavity were thought to be particularly important in chiral recognition [1]. These requirements could be used for the explanation of preferential binding of (*S*)-fenoprofen with β-CD.

Fig. 3 shows representative configurations of inclusion complexes of (*R*)- and (*S*)-fenoprofen with β-CD. The lowest energy configurations were selected for the representative ones, as the configurations in the equilibrium phase are not much different. When all the configurations in the equilibrium phase were superimposed by least-squares fitting, the RMSD calculated all over non-hydrogen atoms were only of the order of 1 Å. Thus, the lowest energy configurations could safely represent the overall features of inclusion complexes. The configuration of inclusion complexes with (*S*)-fenoprofen in the equilibrium phase were consistent with the model of the (*S*)-fenoprofen–β-CD inclusion complex on the basis of the solution NMR data [12], which suggested that (*S*)-fenoprofen penetrated deeply into the cavity from the larger-diameter side with one hydrogen atom at the end of the phenoxyphenyl ring extruded form the smaller diameter side, and the methyl group remained external to the larger side of the β-CD [12]. Both enantiomers of fenoprofen were tightly fitted in the cavity of β-CD and oriented in a similar manner (Fig. 3). The carboxyl groups attached to the chiral carbon of fenoprofen in both the R and S isomers were placed to 2- and 3-hydroxyl groups of the β-CD for hydrogen-bonding. However, important differences were observed between the complexes of the R and S isomers with respect to the orientation of phenyl rings attached to the chiral carbon. The phenyl ring of (*S*)-fenoprofen was more perpendicular to the least-squares plane of β-CD than that of (*R*)-fenoprofen. The methyl group attached to the chiral carbon seemed to play an important role on the orientation of the phenyl ring in the β-CD cavity. The tilt angle between the aromatic plane of the phenyl ring and the least-squares plane of β-CD was $72.7 \pm 4.1°$ for (*S*)-fenoprofen and $43.6 \pm 2.6°$ for (*R*)-fenoprofen (Fig. 4). This could be an explanation of the thermodynamic preferences of (*S*)-fenoprofen for the inclusion complex formation with β-CD.

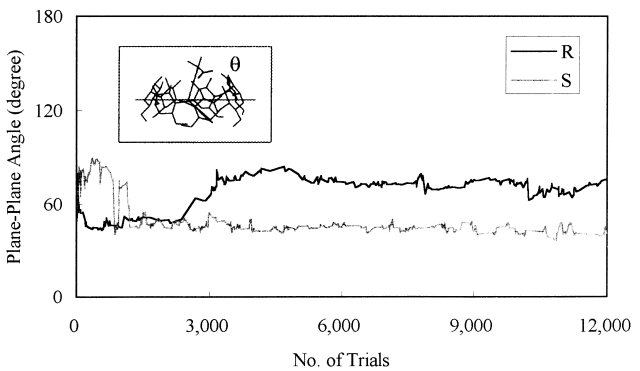

Fig. 4. Tilt angle between the aromatic plane of the phenyl ring attached to the chiral carbon of fenoprofen and the least-squares plane of β-CD. The plane–plane tilt angle of (*S*)-fenoprofen–β-CD complex is closer to 90° than that of the (*R*)-fenoprofen–β-CD complex, which means that the phenyl ring of (*S*)-fenoprofen is inserted more vertically into the β-CD cavity than that of the (*R*)-fenoprofen. (Inset: definition of the plane–plane tilt angle.)

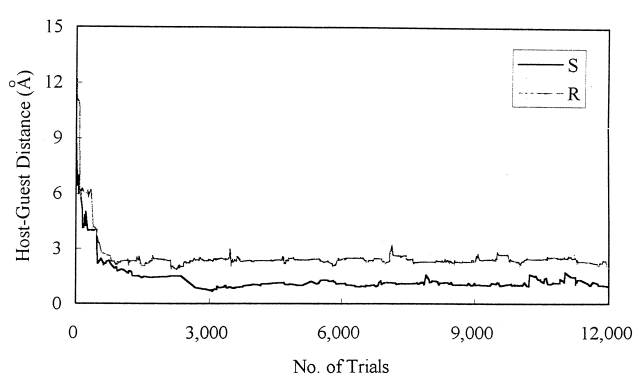

Fig. 5. Center-of-mass distance fluctuations between the host and guest molecule in the MC simulations. In the equilibrium phases, the center-of-mass distance between (*S*)-fenoprofen and β-CD is shorter than that of (*R*)-fenoprofen, indicating that β-CD holds (*S*)-fenoprofen more closely inside the cavity than (*R*)-fenoprofen.

This orientation allowed the phenoxyphenyl group of (*S*)-fenoprofen to be inserted more deeply in the cavity of β-CD than (*R*)-fenoprofen. It could be illustrated by the shorter center-of-mass distance between host and guest molecule (Fig. 5). The average distance between the center-of-mass of host and guest was 1.15 ± 0.15 Å for (*S*)-fenoprofen and 2.38 ± 0.17 Å for (*R*)-fenoprofen. The orientation of the phenoxyphenyl group adjacent to the chiral carbon for (*S*)-fenoprofen provided closer contact and thus more favorable van der Waals interactions between the host and guest molecule.

In this study, we investigated the molecular models of chiral discrimination by β-CD through the differences in the interaction energies and configuration of inclusion complexes by MC docking simulations. The prediction and understanding of chiral discrimination

abilities will be valuable for the evaluation of chiral separation systems. The results presented here would be very useful for the prediction of chromatographic behavior of chiral molecules, and evaluation of chiral separation systems. We believe that this method is applicable for a variety of other chiral separation systems.

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