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A Study of a Molecular Mechanics Field Used in Simulating Enantiorecognition

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Abstract: A molecular mechanics field, Alchemy II, was utilized to model the chiral recognition between S-N-acetyl-α-methyl-l-naphthylamine and (R, S)-N-(3, 5-dinitrophenyl)-α-methyl-benzeneacetamide and between β-cyclodextrin and (R, S)-fenoprofen. Some preliminary results have been obtained to sustain the three-point action models and the induce-fit action in enantiorecognition.

Keywords: Molecular mechanics; simulating; enantiorecognition.

Enantiorecognition is a measure of the discrimination ability between enantiomeric molecules. It is of fundamental significance in many areas of the chemical and biological sciences, it also plays an important role in separation of enantiomers by chromatography. Although the intermolecular forces (hydrogen bonding, multipolar association, dispersion forces, charge transfer complexation, hydrophobic association, *etc*.) have been thoroughly studied and are well documented, but how these forces precisely work in concert to promote intermolecular action is not clear yet[1]. The method of computational chemistry allows us not only to determine which forces are at play, but also to obtain their quantitative relationship in molecular interaction, shows promise in enantiorecognition recently.

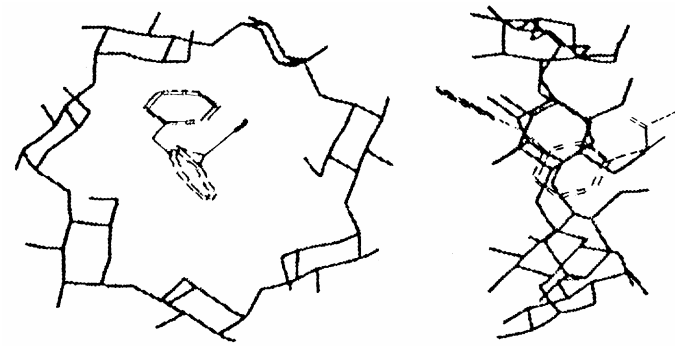
Molecular Mechanics and Simulating Methods

Molecular mechanics, a recipe for reproducing a molecule's potential energy surface, is a non-quantum mechanical method of computing structures, energies and some properties of molecules. Here a molecule is viewed as a collection of particles (nuclei) held together by elastic forces (electrons). These forces are defined in term of potential energy functions of internal coordinates such as bond lengths, bond angles and torsion angels. Once all the potential functions and associated force constants are determined, the internal energy is minimized by moving the particles toward their equilibrium positions (geometry optimization). Since an empirical force field, for example Alchemy II force field, treats electrons implicitly rather than explicitly, molecular mechanics is a much faster computation method than quantum mechanics. Factually, the potential energy function of a polyatomic molecular model usually has the local

optimal values. In order to obtain its reasonable optimizing result, it is important to calculate many more random original model modes and treat their optimums with statistical mechanics theory[2]. This is hard work for a single personal computer. However, if the original models come from the confirmed tests (*e. g.* X-ray diffraction techniques), it is possible to gain some reasonable calculus from small amounts of reasonable original models, and then it is possible to reach some useful conclusions on a few models.

In this work, the original models of the inclusion complexes of β-cyclodextrin and (R, S)-fenoprofen (for short (R, S)-CD-FF) were built on the basis of their crystal structures determined by X-ray diffraction techniques[3], so do the model of the complexes of S-N-acetyl-α-methyl-l-naphthylamine and (R, S)-N-(3,5-dinitrophenyl)-α-methyl-benzeneacetamide (for short (R, S)-AMN-DMB)[4]. For a rapid optimizing-calculation, all the hydrogen atoms in the inclusive complex model (R, S)-CD-FF have been omitted (**Figure 1**). In the mixed crystals of S-N-acetyl-α-methyl-l-naphthylamine and S-N-(3,5-dinitrophenyl)-α-methyl-benzeneacetamide, there are two complex conformations rather than only a dominant one[4], so two models of S-AMN-DMB, represented by S-AMN-DMB1 and S-AMN-DMB2, have been studied. In the optimizing-calculations, when the deviation of two iterative values is not more than 0.02 kJ/mol, the computer stops these processes at once and the geometry optimizations of these complex models are obtained.

Figure 1. The geometry optimization of S-CD-FF (the orthogonal graphs on Y-axis and all hydrogen atoms are omitted, the dotted lines represent S-fenoprofen)



Results and Discussion

The optimized models' results have been listed in **Table 1**. For the (R, S)-AMN-DMB models, the calculated total energy (E) of the S-complex is more negative than the two R-complexes, this result corresponds with the objective reality which the X-ray diffraction and HPLC have been given in literature (S-N-(3, 5-dinitrophenyl)-α-methyl-benzeneacetamide has a longer retaining time on the stationary phase of S-N-acetyl-α-methyl-l-naphthylamine than its R-enantiomer)[4]. In

the same way, the calculation values show that S-conformation CD-FF has a much higher stability than R-conformation and this difference between them has been verified in the literature (crystallizing the racemic fenoprofen and β-cyclodextrin, more S-conformation CD-FF is obtained than R-conformation)[3].

By comparing the contribution of E_{str}, E_{ang}, E_{tor} and E_{vdw} (*cf.* notes of **Table 1**) in the total energy E and analyzing their differences between R, S-enantiomeric complexes, it can be found that van der Waals force plays the most important role in enantiorecognition. It is because the most part of the different energy between R, S-enantiomeric complexes come from van der Waals energy. This maybe supports that there are different action ways implied by three-point action theory and its supplementary modes in enantiorecognition (here all the chiral centers of β-cyclodextrin can be assumed an additive chiral center or cave)[5]. Up to now, the three-point action theory is the most reasonable and direct interpretation of enantiorecognition, but not the satisfied one. The reason is that three-point model is too simple and rough to describe the detailed information of chiral action, for instance, to tell the respective action of four functional groups combined with the same chiral carbon in a molecule. Factully, this detail is very important in understanding the chiral phenomenon of life and the design of chiral drugs. However, this theory tells that because there is mirror difference between the guest molecules of R, S-enantiomers, when the chiral host molecule accesses to and contacts with them, the different interaction occurs. This difference mainly comes from the different site-relationship of non-bonded atoms between the R, S-enantiomers that complex the same host molecule, in other words, this difference is the source of the deviation of van der Waals force between them. Besides the van der Waals forces, the other kinds of forces, especially E_{ang} and E_{tor}, are also important to the combination of molecules in a complex, their roles imply that the induce-fit occurs between host-guest molecules must be considered in enantiorecognition. The induce-fit effect is the result of the flexible (or non-rigid) molecules or every flexible part of a molecule fitting each other. This effect can make the total energy of a complex or compound decrease to the smallest value. But the function of induce-fit in enantiorecognition is not always in concert with van der Waals forces, sometimes with the negative recognizing contribution, this can be inferred from (R, S)-AMN-DMB models. Here this effect reduced the energy difference between R-AMN-DMB and S-AMN-DMB. For the stiffer β-cyclodextrin, there is a reverse result, it is implied by the R-CD-FF and the S-CD-FF models.

Table 1 The optimized results of some enantiorecognition models (calculated by Alchemy II)

	E_{str}	E_{ang}	E_{tor}	E_{vdw}	E
R-AMN-DMB	7.11	16.72	15.88	-150.90	-111.19
S-AMN-DMB1	7.52	14.21	15.47	-136.69	-99.49
S-AMN-DMB2	7.52	16.72	20.06	-155.79	-71.49
R-CD-FF	2.93	43.05	156.75	-713.53	-510.8
S-CD-FF	2.51	42.64	155.08	-719.38	-519.15

Notes: E_{str} is the bonds' stretching vibration energy; E_{ang} is the bond angles' bending vibration energy; E_{tor} is the bond angles' rotating tension energy; E_{vdw} is the van der Waals forces of all the

non-bonding atoms of a complex. All of the units of computing energy are kJ/mol.

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