J. At. Mol. Sci.
doi: 10.4208/jams.022514.031414a

Vol. **5**, No. 4, pp. 289-300
November 2014

The theoretical research on the chiral transition of ibuprofen molecules under isolated conditions

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Received 25 February 2014; Accepted (in revised version) 14 March 2014
Published Online 29 October 2014

Abstract. In this article, we do a research on the chiral shift process of the isolated alpha alanine molecule using the basis set of 6-31+g(d,p), which is based on density functional theory B3LYP. Furthermore, the chiral transition path reaction potential energy surface of ibuprofen molecule is drawn by looking for the extreme value point structure including the transition state and intermediate. Finally, the geometry and electronic structure properties of extreme value point are also analyzed. The results show that there are two achieve reaction paths of ibuprofen from S-type to R-type. Path 1 consists of three transition states and two intermediate states. Path 2 includes four transition states and three intermediate states. On the reaction path, the greatest barrier which is from the transfer of hydrogen in chiral carbon to oxygen in carboxyl, is 73.54 Kcal/mol. The research provides a theoretical reference to further realize some important application value over the chiral transition reaction control of point chiral molecule.

PACS: 36.40.-c; 31.15.E-

Key words: Chiral; Ibuprofen; Density functional theory; Transition state

1 Introduction

Ibuprofen (MF: C13H18O2) which has a series of effects such as anti-inflammatory, analgesic and antipyretic, always been used for the treatment of rheumatic arthritis, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and neuritis. Plenty of researches

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related on Ibuprofen have been reported. The simulation and experiment on kinetic resolution of racemic ibuprofen have been done by Bhatia *et al.* [1]. Qing *et al.* have found that the pharmacological activify of ibuprofen is mainly from dextroisomer, which is superior than racemic ibuprofen in efficacy, safety and pharmacokinetic characteristics [2]. Lin reported that activity of dextral body is 160 times of, as well as 1.6 times of the racemate, which can achieve the slow transition in vivo from L-body to dextral body [3]. However, the chiral shift mechanism of ibuprofen has not been reported.

Generally, all we got are the racemates, which results the most of commercially available products are racemates [4]. Therefore, looking for a more efficient way becomes particularly important which transfer the ”bad isomers” in existing racemic ibuprofen drugs into an effective single isomer ”excellent isomers”. In this thesis, we hope to get the reactive mechanism of chiral shift through the research on barrier which needs to overcome during the transition path and the reaction of ibuprofen in isolated condition. The research makes a necessary preparation on the theoretical study on the slow change of ibuprofen in vivo, as well as provides a new way of obtaining optically pure ibuprofen experimentally in the theory.

2 Methods of research and calculation

The thesis is based on the B3LYP [5, 6] density functional theory, in which d polarization function is added to carbon, oxygen atoms, as well as p polarization function is added to hydrogen atoms by using double split methyl. That’s to say, the minimum of single potential energy surface, frequencies of vibrational infrared and frontier molecular orbit are needed to theoretically calculated by using of 6-31+g(d,p) basis set. Then make the S-ibuprofen molecule as a reactant, to find the transitional states and intermediates of R ibuprofen molecules [7-9]. What’s more, do an analysis of the extreme points including the transitional states of frontier molecular orbit to obtain the key characteristics of the molecule. Finally, connect the extreme points of the reactants, transitional state, intermediate, reaction products, etc., to ensure the determined path. In order to verify the reliability of the transitional state, an intrinsic reaction coordinate (IRC) analysis [10-13] is done on the transition states. In this thesis, theoretical calculations and graphics of molecular structure, etc. are done by software program of Gaussian03/GaussView3.0.

3 Results and discussion

3.1 The structure and analysis of the enantiomer of chiral ibuprofen molecular

The enantiomer’s structure of a chiral ibuprofen obtained in B3LYP/6-31+g(d,p) level is shown in Fig. 1. According to the existing reports, the transferred process of hydrogen is the best shift reaction pathway to the transfer of chiral molecules’ enantiomers