

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

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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.

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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 activity 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

[14]. From the geometry of the enantiomers, we can see that to achieve chiral transfer of enantiomer from S-type to R-type, the migration must be done from 32H out of paper to the position 12C inside the paper. According to the basic molecular structure theory and empirical studies, we can presume that the chiral transitional process is: Firstly, 33H transfers to the 31O; Then 32H transfers to 30O; Finally, 32H or 33H transfers to the other side of 12C. Accompanied the process, the isomerization of carbon skeleton (4C-12C-17C, 11C-13C-14C-15C), the rotational isomerization of 11C, 14C, 15C, 16C, etc., the rotational isomerization of C ring plane around 11C, 1C, 4C and 12C, as well as the isomerization of the bond angle of 32H-12C-16O will happen. Thus, the chiral transition of enantiomers completes.

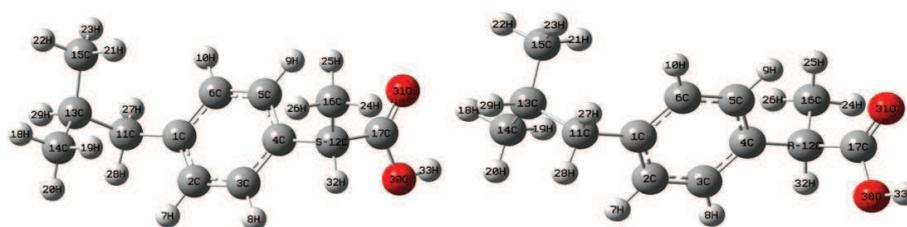


Figure 1: The geometries of S-type and R-type ibuprofen molecule in B3LYP/6-31+g(d,p) level.

3.2 The calculation of intermediates in the transitional path of chiral ibuprofen molecular and the exploration to the transition state

According to above analysis, we get the transitional process of chiral ibuprofen molecules: Firstly, S-ibuprofen achieved the transfer from 33H to 31O through the transitional state TS1, to form an intermediate INT1. Then 32H transfers to 30O through the transitional state TS2, to form an intermediate INT2. 33H or 32H then transfers to the other side of 12C. The former is that INT2 directly forms into R ibuprofen molecules via transitional state TS3. The latter is that INT2 forms into transitional state INT4 via an intermediate TS4 and INT4 achieves the process from 33H moved back to 30O via transitional state TS5 to obtain the isomerization of R-type ibuprofen.

3.2.1 The Structural properties of intermediates in the transfer path of chiral ibuprofen molecules

In this thesis, we need make geometry optimization to every intermediate, as well as calculate singlet lowest single-point energy, frequencies of vibrational infrared and frontier molecular orbit in B3LYP/6-31+g(d,p) level.

The structure of INT1 shown in Fig. 2 has no imaginary frequency. Frontier molecular orbit shown in Fig. 2 is mainly from the contribution of carbon atom on the benzene ring skeleton and p electron on the oxygen atom. The *pi* key effect occurs among carbon atom in benzene ring, between 1C and 11C, between 12C and 16C. The local characteristic is

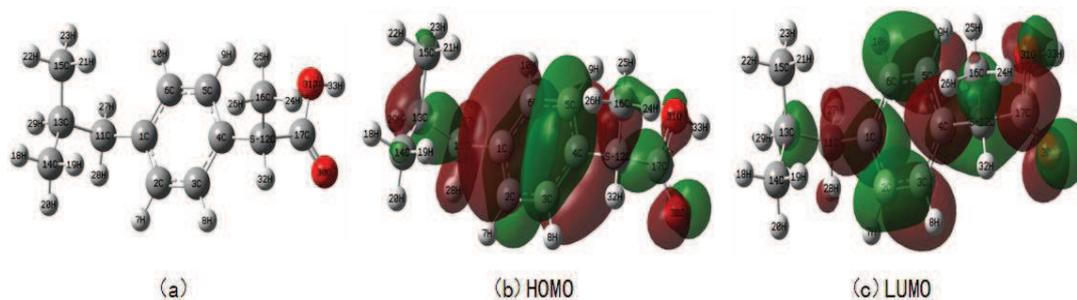


Figure 2: The geometry (a), frontier molecular orbitals (b) and (c) of INT1 in B3LYP/6-31+g(d,p) level.

also shown in other p electrons. Non-key property is shown between 32H or 33H and adjacent backbone atoms.

The structure of INT2 shown in Fig. 3 has no imaginary frequency. Frontier molecular orbit shown in Fig. 3, is mainly from the contribution of the p atoms in the backbone atoms get rid of 14C and 15C, which shows the π bond effect. The p atoms in 17C atoms show the local characteristics. LUMO orbit shows non-key properties of the 32H, 33H and O atoms.

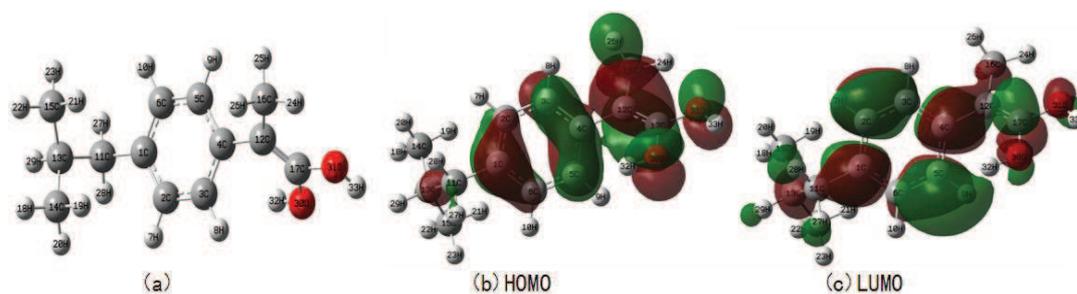


Figure 3: The geometry (a), frontier molecular orbitals (b) and (c) of INT2 in B3LYP/6-31+g(d,p) level.

The first case is that the product resulting from 33H in INT2 migrates to 12C is optimized to get the structure shown in Fig. 4. By comparing the bond length, bond angle, and dihedral angle of R-ibuprofen molecule in Fig. 1 and Fig. 4, we find the same data (the difference changes between 0.010 and 0.10, which is even smaller). The resulting structure is indeed proved to be chiral enantiomers R of S-molecules ibuprofen.

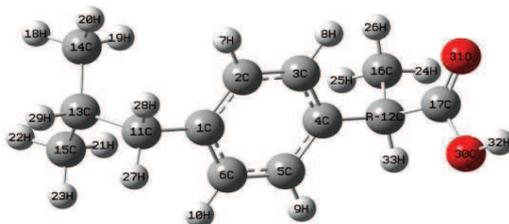


Figure 4: The geometry of R-type ibuprofen molecule.

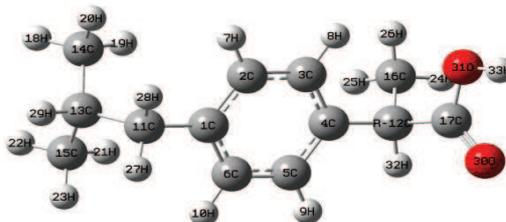


Figure 5: The geometry of INT4.

The second case is that intermediate product INT4 forms from the migration from 32H to 12C, and then product R forms from the move from 33H back to 30O. The structure of INT4 is shown in Fig. 5, which has the same energy with INT1. Frontier molecular orbit shown in Fig. 6, is mainly from the contribution of the p atoms in the backbone atoms get rid of 11C, 14C and 15C, which shows the *pi* bond effect. The p atoms in 30O atoms show the local characteristics. LUMO orbit shows non-key properties of the 33H and O atoms.

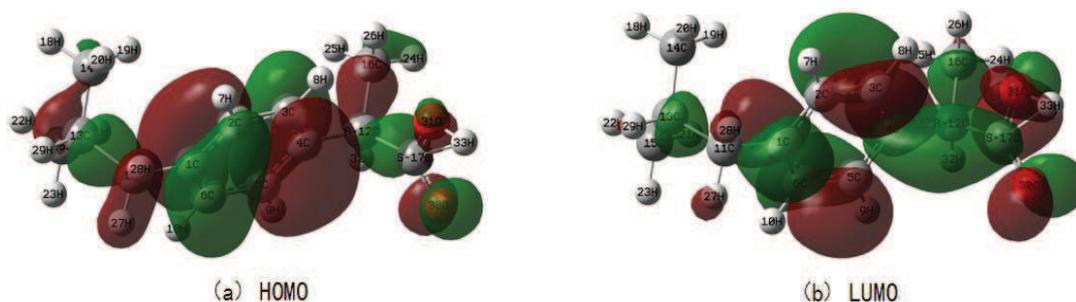


Figure 6: The frontier molecular orbitals (a) and (b) of INT4 in B3LYP/6-31+g(d,p) level.

The optimized structure of the product got from the process that 33H in INT4 migrates back to the 30O via TS5 is same with R-type ibuprofen in Fig. 1. By comparing the bond length, bond angle, and dihedral angle of R-ibuprofen molecule, we find the same data (the difference changes between 0.010 and 0.10, which is even smaller). Energy of each stable point is shown in Table 1.

3.2.2 The Structural properties of the transitional state in the transformational process of chiral ibuprofen molecules

In this thesis, the transition state TS1, TS2, TS3, TS4 and TS5 are explored in B3LYP/6-31+g(d,p) level to get their geometries, frontier molecular orbitals and vibration mode under imaginary frequency which are shown in Figs. 7-11 (The frontier molecular orbitals of TS2 and TS4 are identical with that of TS3 and TS5 respectively, omitted here).

All transitional states are proved to be correct by optimizing the structure of the transition state, respectively, corresponding to each reactant and product. The optimization is

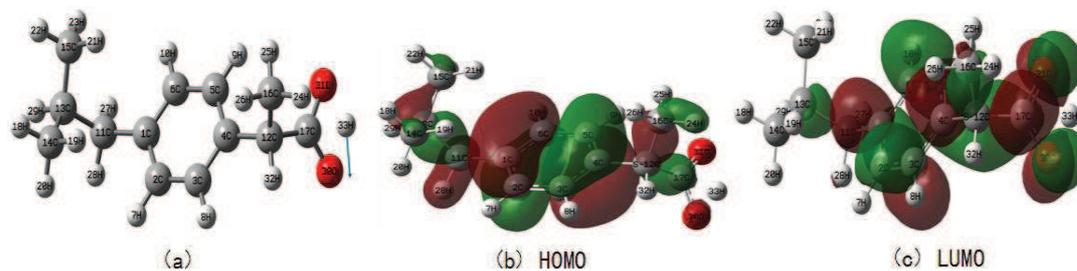


Figure 7: The geometry vibration modes (a) under imaginary frequency and frontier molecular orbitals (b) and (c) of TS1.

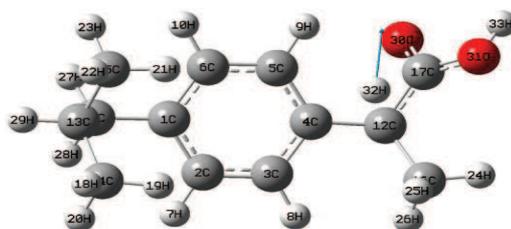


Figure 8: The geometry and vibration modes under imaginary frequency of TS2.

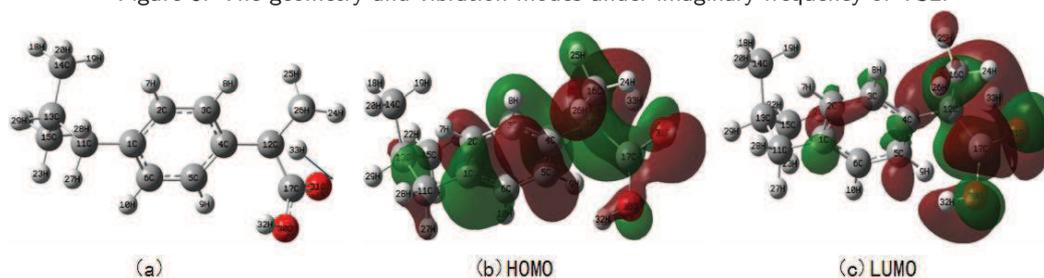


Figure 9: The geometry, vibration modes (a) under imaginary frequency and frontier molecular orbitals (b) and (c) of TS3.

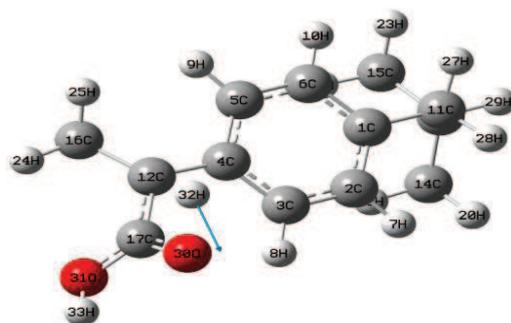


Figure 10: The geometry and vibration modes under imaginary frequency of TS4.

mainly to fine-tuning the structure along the vibratory direction of related atoms under imaginary frequency.

The frontier molecular orbits of the five transitional states have common traits. Only

Table 1: The energies of various stability points and transition states, the virtual frequencies of transition states, energy differences between transition states and intermediates, as well as reactants and products in the reaction path of B3LYP/6-31+g(d,p) level.

Structures	E(hartree)	ΔE (hartree)	ΔE (Kcal/mol)	Imaginary (cm^{-1})
S	-656.7565	0.0000	0.00	
TS1	-656.7017	0.0548	34.53	-1906.23
INT1	-656.7551	0.0014	0.88	
TS2	-656.6384	0.1181	74.42	-2087.92
INT2	-656.7204	0.0361	22.75	
TS3	-656.6384	0.1181	74.42	-2087.92
TS4	-656.6400	0.1165	73.41	-2006.49
INT4	-656.7551	0.0014	0.88	
TS5	-656.7017	0.0548	34.53	-1906.23
R	-656.7565	0.0000	0.00	

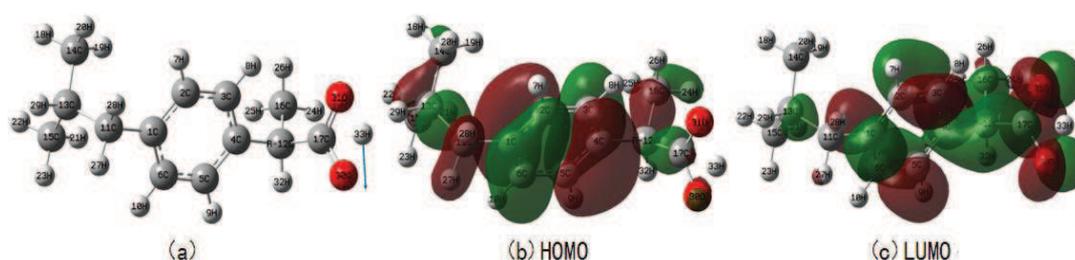


Figure 11: The geometry, vibration modes (a) under imaginary frequency and frontier molecular orbitals (b) and (c) of TS5.

the representative frontier molecular orbits of TS1, TS3 and TS5 are given in Fig. 7, Fig. 9, and Fig. 11 for the limited space. The electron p in 30O and 31O atoms and electron S in 33H atom together contributes to the HOMO orbit of TS1 which has obvious anti-bonding characteristics. At the same time, the electron p in 31O atom and electron S in 33H atom together contributes to the LUMO orbit of TS1 which has bonding characteristics. The frontier molecular orbits of TS3 and TS5 also reflect the anti-bonding characteristics of transitional state. Specific analysis omits.

The energies and imaginary frequencies of transitional states after full optimization in the B3LYP/6-31+g(d,p) level are shown in Table 1.

3.3 Ibuprofen molecule chiral transition path

To sum up the analysis and research above, we can confirm that there are two paths to realize the chiral transition or ibuprofen molecules from S-type to R-type. Path 1: S \rightarrow TS1 \rightarrow INT1 \rightarrow TS2 \rightarrow INT2 \rightarrow TS3 \rightarrow R. The geometry of the local minimum points during the process are shown in Figs. 1-4. The structures of transitional states are shown in Figs. 7-9. Path 2: S \rightarrow TS1 \rightarrow INT1 \rightarrow TS2 \rightarrow INT2 \rightarrow TS4 \rightarrow INT4 \rightarrow TS5 \rightarrow R. The

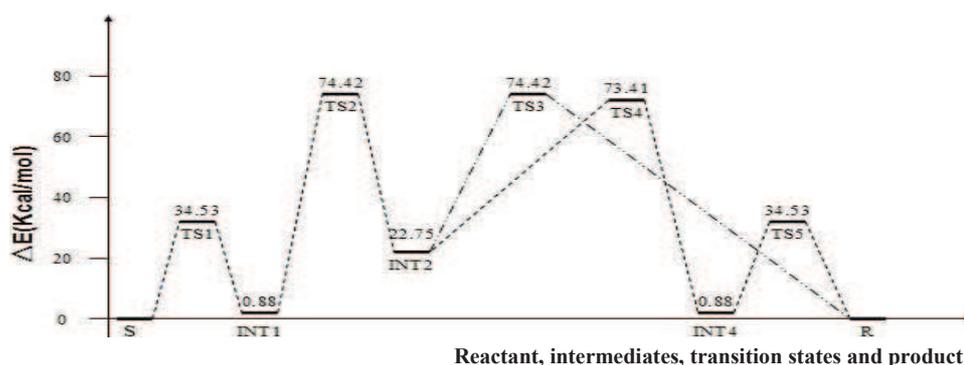


Figure 12: The schematic of potential energy surface during the process of chiral transitional in B3LYP/6-31+g(d,p) level.

geometry of the local minimum points during the process are shown in Figs. 1-3, and Fig. 5. The structures of transitional states are shown in Fig. 7, Fig. 8, Fig. 10 and Fig. 11.

According to the datas in Table 1, the schematic of potential energy surface in path 1 and path 2 during the process of chiral transition are drawn in Fig. 12, to visually describe the various energies of intermediates, transitional states, reactants and products during reactive process, which makes the reactive process more clearly.

We can see two processes from Fig. 12. For the Path 1: S needs to cross the energy barrier 34.53 Kcal/mol, to form INT1 via TS1. INT1 needs to across energy barrier 73.54Kcal/mol to transfer to INT2 via TS2. INT2 needs to across energy barrier 51.67 Kcal/mol to transfer to R via TS3. For Path 2: S needs the same process with path 1 to transfer to INT2. INT2 then crosses energy barrier 50.66 Kcal/mol to form INT4 viaTS4. INT4 finally crosses energy barrier 33.65 Kcal/mol to transfer to R-type ibuprofen via TS5. The main geometric parameters of the reactants, intermediates, transitional states and products in path1 and path2 are respectively shown in Table 2 and Table 3.

Table 2: The main geometric parameters of various stability points and transitive states in the reaction path 1 of B3LYP/6-31+g(d,p) level. α : 4C-12C-16C-17C; β : 17C-12C-15C-24H; γ : 4C-32H-12C-17C; δ : 14C-11C-13C-15C; θ : 1C-11C-28H-13C; ω : 6C-2C-1C-11C.

Structures	α	β	γ	δ	θ	ω
S	-122.88	-60.398	-117.39	126.26	127.12	179.46
TS1	-123.45	-179.20	-119.79	126.63	127.18	179.21
INT1	-125.72	-179.53	-119.46	126.66	127.12	179.49
TS2	-150.15	-173.12	-118.73	126.49	127.31	179.72
INT2	-178.17	-178.98	-120.47	126.51	127.19	179.89
TS3	150.15	173.12	121.11	-126.49	-127.32	-179.72
R	122.88	60.398	117.39	-126.62	-127.12	-179.45

The datum in Table 2 show the change in the main dihedral angle of reactants, intermediates, transitional states and products, during the process of S-type ibuprofen

Table 3: The main geometric parameters of various stability points and transitive states in the reaction path 2 of B3LYP/6-31+g(d,p) level. α : 4C-12C-16C-17C; β : 17C-12C-16C-24H; γ : 14C-11C-13C-15C; δ : 1C-11C-28H-13C; θ : 6C-2C-1C-11C; ω : 4C-32H-12C-17C.

Structures	α	β	γ	δ	θ	ω
S	-122.88	-60.398	-117.39	126.26	127.12	179.46
TS1	-123.45	-179.20	-119.79	126.63	127.18	179.21
INT1	-125.72	-179.53	-119.46	126.66	127.12	179.49
TS2	-150.15	-173.12	-118.73	126.49	127.31	179.72
INT2	-178.17	-178.98	-120.47	126.51	127.19	179.89
TS4	150.146	161.81	119.65	126.50	127.32	179.72
INT4	125.72	179.53	119.46	-126.66	-127.20	-179.49
TS5	123.45	179.20	118.73	-126.63	-127.18	-179.47
R	122.88	60.398	117.39	-126.62	-127.12	-179.45

molecules transfer to intermediate INT1, INT2 and R-type ibuprofen molecular, via the transitional state TS1, TS2, TS3, respectively. That's to say, S-ibuprofen molecule completes chiral shift via path1, realizing the isomerism to R-ibuprofen molecule.

The datum in Table 3 show the change in the main dihedral angle of reactants, intermediates, transitional states and products, during the process of S-type ibuprofen molecules transfer to intermediate INT1, INT2, INT4 and R-type ibuprofen molecular, via the transitional state TS1, TS2, TS4, TS5, respectively. That's to say, S-ibuprofen molecule completes chiral shift via path2, realizing the isomerism to R-ibuprofen molecule.

3.4 Ibuprofen molecule chiral transition process transition state analysis of IRC

To further verify the reliability of the transitional states, the transitional states are made an IRC calculation in B3LYP/6-31+g(d,p) level. The results are shown in Figs. 13-16. The highest point corresponds to the transition state. The IRC of TS5 is roughly the same with that of TS1, so omitted.

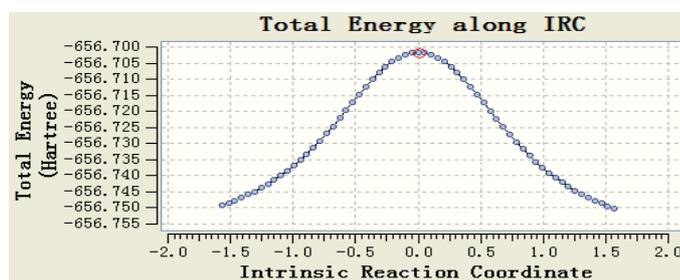


Figure 13: IRC analysis of transitive state TS1. The lowest point: the right side points to S, the left side points to INT1.

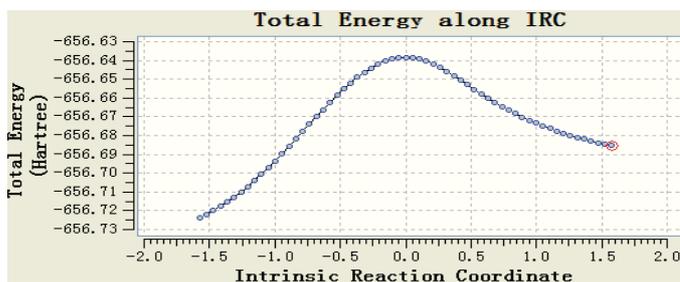


Figure 14: IRC analysis of transitive state TS2. The lowest point: the left side points to INT1, the right side points to INT2.

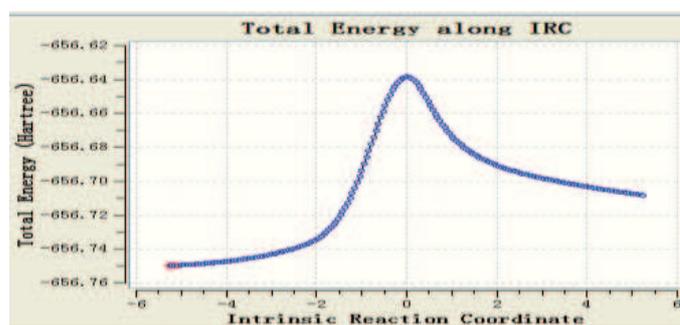


Figure 15: IRC analysis of transitive state TS3. The lowest point: the right side points to INT2, the left side points to R.

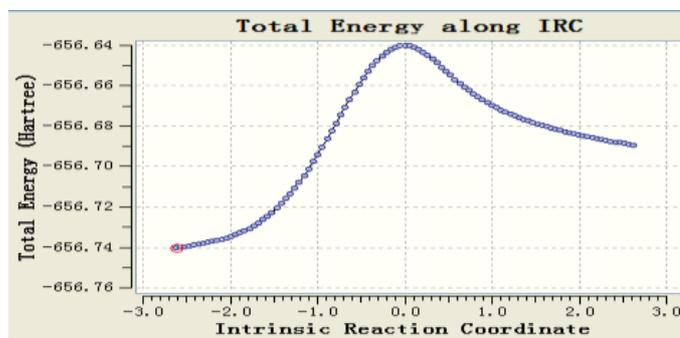


Figure 16: IRC analysis of transitive state TS4. The lowest point: the right side points to INT2, the left side points to INT4.

The optimization of reactants and products on both ends of IRC path verifies the reliability of the various transitional states. Fig. 17 shows several structures of representative points on the IRC path of TS1, which clearly proves the reliability of transitional state TS1 from S turns to INT1. The isomerism on other IRC paths also describe the reliability of corresponding transitional states. Omit here due to limiting space.

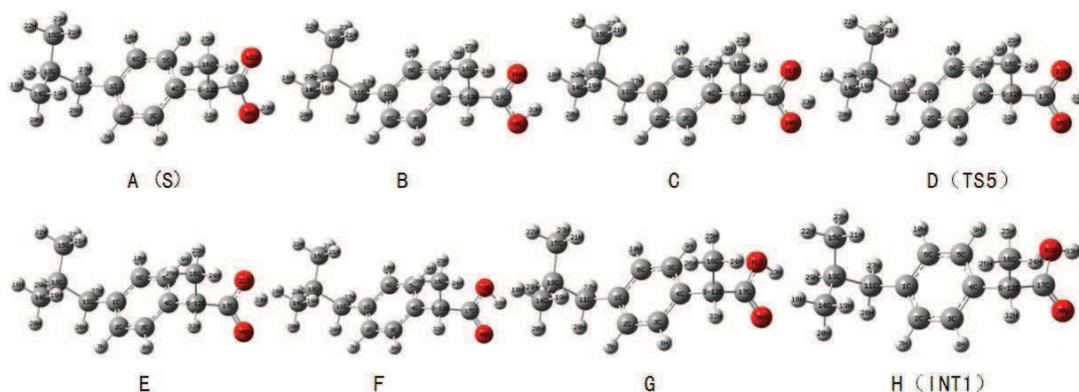


Figure 17: The brief conversion from S-type enantiomer into INT1: A \rightarrow B \rightarrow C \rightarrow D \rightarrow E \rightarrow F \rightarrow G \rightarrow H.

4 Conclusion

In this thesis, we do a research on the shift process of ibuprofen molecules from S-type to R-type by using the basis set of 6-31+g(d,p), which is based on density functional theory B3LYP. The results show that there are two paths during the reaction: The first is S \rightarrow TS1 \rightarrow INT1 \rightarrow TS2 \rightarrow INT2 \rightarrow TS3 \rightarrow R. There are three transitional states and two intermediates in path1, which needs to cross the energy barrier 34.53Kcal/mol, 73.54 Kcal/mol and 51.67 Kcal/mol. The second is S \rightarrow TS1 \rightarrow INT1 \rightarrow TS2 \rightarrow INT2 \rightarrow TS4 \rightarrow INT4 \rightarrow TS5 \rightarrow R. On path2, the process from S to INT2 is the same with path 1. Then INT2 transfers to INT4 via TS4, crossing energy barrier 50.66 Kcal/mol. Finally, INT4 transfers to R via TS5, crossing energy barrier 33.65 Kcal/mol to achieve the transformation of chiral enantiomer. The structure of ibuprofen is stable under normal conditions, since the two paths both have relatively high energy barrier. So the process of chiral transformation can be achieved in certain ambient intervention. All the transitional states are further proved to be reliable by researching the frontier molecular orbitals and IRC calculation of transitional states. This research has a certain reference value on obtaining the pure enantiomer of chiral molecules including ibuprofen and transitional mechanisms in vivo.

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