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Theoretical DFT study of stereoselective hydrolysis of enantiomers of naproxen

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RESEARCH ARTICLE

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ABSTRACT

Ester hydrolysis is a common and important reaction in organic chemistry. It is catalyzed by acid or base. This phenomenon becomes very interesting when it attains enantioselectivity. Its most common example is the enantioselective hydrolysis of the S-naproxen ester. When the hydrolysis of R/S-naproxen ester is performed, only the S-naproxen ester takes part in the hydrolysis, but the R-naproxen ester does not. Because of this, the hydrolysis of R/S naproxen ester is used to gain pharmaceutically and biologically active S-naproxen. The data in the literature does not describe why the hydrolysis of only the S-naproxen ester is possible, while that of the R-naproxen ester is not. Furthermore, another notable question is the acid-catalyzed nature alone, while simple ester hydrolysis is an acid-base-catalyzed phenomenon. The theoretical DFT study answers these complicated questions. In the presented article, different parameters of the ester group (-COO-) constituents of the simple ester as well as the R/S naproxen ester in water were theoretically studied. These parameters were the same between the S-naproxen ester and the simple ester after DFT calculation in water. On the other hand, the R-naproxen ester did not show similarities to that of simple ester in water.

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1. Introduction

The acid/base-catalysed hydrolysis of ester is a widespread phenomenon. Its most common example is the hydrolysis of methyl propionate. Methyl propionate (Figure 1a) is a simple ester. When the hydrolysis of the ester is carried out in a basic medium, the attack of the nucleophile (a nucleus-seeking agent, for example, water or hydroxyl ion) on the carbonyl carbon of the ester occurs [1-3]. On the other hand, the formation of a protonated carbonyl group occurs in an acidic medium, leading to a much easier nucleophilic attack [1-3]. After hydrolysis of ester in both mediums, products with carboxylic acid and alcoholic groups are obtained [1-3]. The literature data do not explain the actual chemistry background of the reaction that occurs in both mediums. Therefore, a gap has made its position for the same. Also, no description at the atomic level was found to explain the reason for not only the protonation of the carbonyl group but also the nucleophilic attack on the carbonyl group in acidic and basic medium, respectively. The presented theoretical DFT calculation for the hydrolysis of simple ester describes it deeply.

Unlike simple hydrolysis reactions, the enantioselective hydrolytic reaction has also gained the attention of scientists. This makes the hydrolysis phenomenon in chiral chemistry more mysterious. Its most common example is racemic (R/S)-naproxen ester, whose only S-isomeric ester hydrolyses, while that of the R-isomer does not [4]. Therefore, esters of both enantiomeric forms (Figure 1c) show variations in the hydrolytic reaction, which is also termed enantioselective hydrolysis. We know that there is only one chiral carbon in the naproxen structure, because it exists in two enantiomeric forms, that is, R and S (Figure 1b). In these two enantiomeric forms, only S-naproxen is biologically important because naproxen belongs to non-steroidal anti-inflammatory drugs, but its only S-isomer ((S)-(+)2-[6-methoxy-2-naphthyl] propionic acid) gives a biological response [5]. Therefore, S-naproxen is considered to be a biologically active isomer. This makes the separation of naproxen essential, which is why S-naproxen is separated from its racemic mixture, *i.e.* R/S-naproxen. Ester hydrolysis is the most common method for enantiomeric separation of naproxen just because of the participation of only S-naproxen ester in hydrolytic reaction [6-8]. For enantiomeric separation of naproxen, its enantiomers are converted into their esters (Figure 1c) through the esterification reaction [9]. After that, the pharmaceutically active S-naproxen is obtained by hydrolysis because only the S-naproxen ester participates in the hydrolysis to give pure S-naproxen, while the R-naproxen ester does not. By doing so, S-naproxen has been made available to be sold as a single enantiomer [5,9,10]. Although the lipase enzyme has also been

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Table 1. The DFT calculation-based variation in the parameters of the ester group.

Ester	Mulliken's charges in ester group			Bond length b/w carbonyl carbon and alkoxy oxygen (Å)	Electron density (eV)	
	Carbonyl carbon	Alkoxy oxygen	Carbonyl oxygen		Minimum	Maximum
Methyl propionate in a gaseous state	-0.192	-0.033	-0.516	1.389	-5.790×10^{-2}	5.790×10^{-2}
Methyl propionate in water	-0.134	-0.060	-0.598	1.383	-6.826×10^{-2}	6.826×10^{-2}
R-naproxen in water	-0.559	0.055	-0.564	1.380	-6.386×10^{-2}	6.386×10^{-2}
S-naproxen in water	-0.890	0.054	-0.587	1.381	-7.778×10^{-2}	7.778×10^{-2}

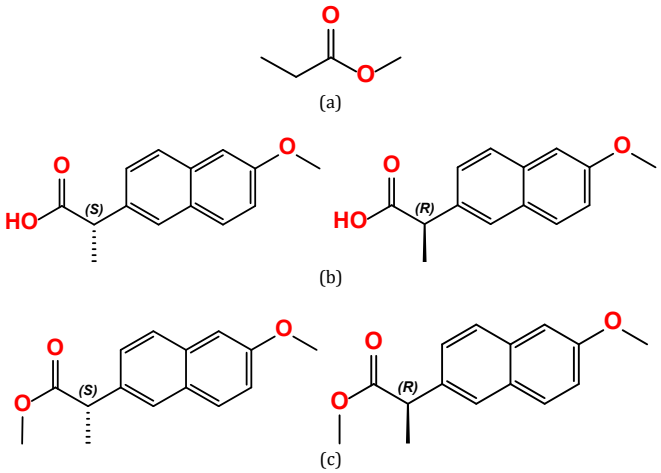


Figure 1. Structures of (a) simple ester, (b) R/S-naproxen, and (c) R/S-naproxen ester.

used to prepare optically pure naproxen by enantioselective hydrolysis of its racemic esters [5,9,10], the question of why hydrolysis of only the S-naproxen ester occurs remains constant. Furthermore, the most important and notable question is the occurrence of the hydrolysis of the S-naproxen ester in an acid medium (pH < 7) only [11], while simple ester hydrolysis can occur in both mediums (acidic or basic). The real and deep chemistry background of these secretive facts at the atomic level has been unknown to us till now. Hence, a theoretical DFT calculation was performed to evaluate these mysterious points. In addition, all variations occurring at the atomic level of a simple and enantiomeric ester were studied in water with the help of DFT calculation. This is because ester hydrolysis is carried out in water. The theoretical results based on DFT calculations answered all complicated points associated with not only enantioselective hydrolysis but also simple hydrolysis.

2. The density functional theory studies

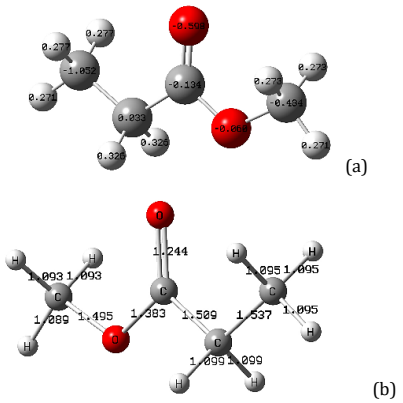
Of course, simulation studies have played an important role in the reaction mechanism [12], chiral separation [13-16], isolation of the most active gradient from the plant [17], and biological chemistry [18-25], but this is the first time that the computational method has been applied to know the quantum background of enantioselective hydrolysis. This is because DFT calculations have already been done on both enantiomers of naproxen [26], but no one evaluated such parameters that enhance the participation in hydrolysis. In the presented work, the different atomic parameters of the constituent of the group (-COO-) of the R / S-naproxen ester were studied by the DFT method in the ground state using the Gaussian(R) 03 program [27]. Because the hydrolysis of any organic ester occurs in water, the enantiomeric structures of naproxen ester were optimized in the same. For this purpose, the basis set used was B3LYP/3-21+G* using Becke's three-parameter hybrid functionals [28] with Lee, Yang, and Parr correlation functional methods (B3LYP) [29]. The same DFT method was also applied to optimize the structure of a simple ester in a gaseous state as well as in water. The calculated results were visualized using GaussView 6.0 [30]. After that, a comparative study including the variation at the atomic level between the simple ester and the R/S naproxen ester in water was done. Additionally, the torsion angle was also evaluated at the bond formed between the carbonyl carbon and alkoxy ether, i.e. the ester bond. This is because only ester group (-COO-) dissociation takes part in the hydrolysis reaction. For the angle torsion study, Discovery Studio Visualizer 2019 (v19.1.0.18287) [31] was used. The result interpretation was found able to explain the questionable points mentioned in the introductory part of the current article.

3. Results

The main purpose of the presented study was to evaluate the variation in the atomic properties of the (-COO-) group of the ester in water. It is because only the (-COO-) group dissociates in hydrolysis and plays an important role. The interpretation of the results helped to remove the curtain from the ester hydrolysis and stereoselective hydrolysis of the S-naproxen ester. Therefore, the variation in ester group constituents such as carbonyl carbon, carbonyl oxygen, and alkoxy oxygen was studied in depth. Although the DFT calculation-based results obtained in water are described below, the most significant data for not only interpretation, but also the reader's sake are given in Table 1.

3.1. Ester group constituents with Mulliken's charges in water

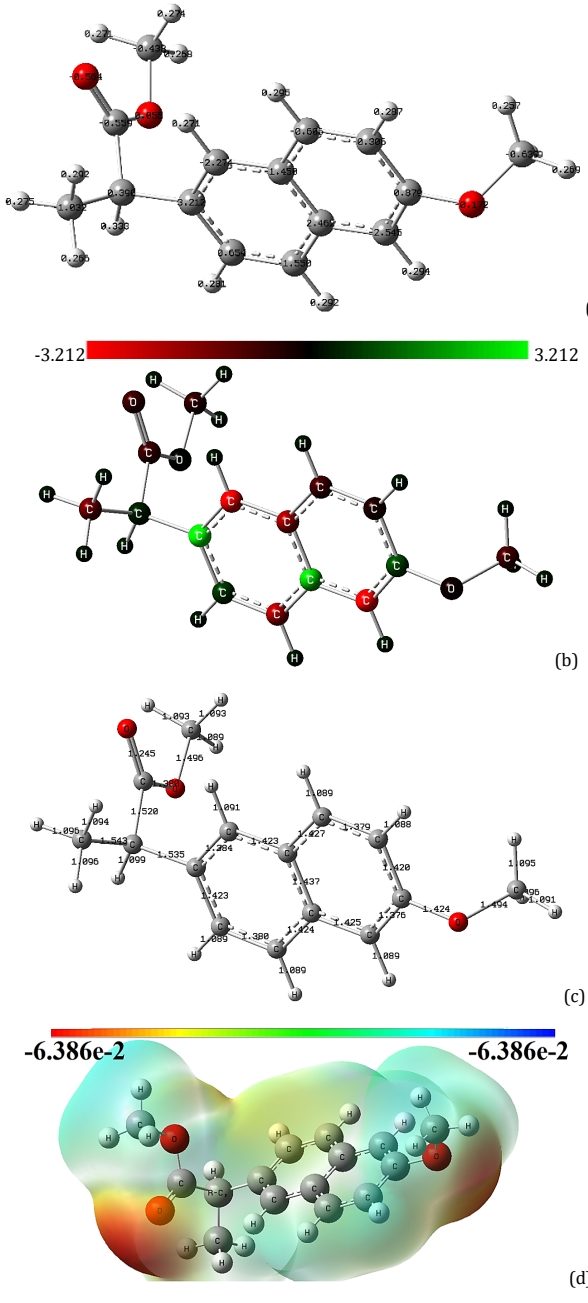
According to DFT calculations, Mulliken's charges were -0.134, -0.060 and -0.598 on the carbonyl carbon, alkoxy oxygen, and carbonyl oxygen, respectively, in simple ester, *i.e.*, methyl propionate (Figure 2a). Furthermore, the length of the bond between the carbonyl carbon and alkoxy oxygen of the simple ester group was 1.383 (Figure 2b). In water, the DFT calculation-based results were found to be very different between R-naproxen ester and S-naproxen ester, but are enough to know the ambiguities described in the Introduction part of the presented paper. In the case of R-naproxen ester (Figure 3), Mulliken's charges were -0.559, 0.055, and -0.564 on



(a)

(b)

Figure 2. Methyl propionate with (a) Mulliken's charge distribution and (b) bond length in water.



(a)

(b)

(c)

(d)

Figure 3. DFT calculation-based (a) Mulliken's charges, (b) atoms colored by charge (-3.212 to 3.212), (c) bond length, and (d) electron density from total SCF density of R-Naproxen ester in water.

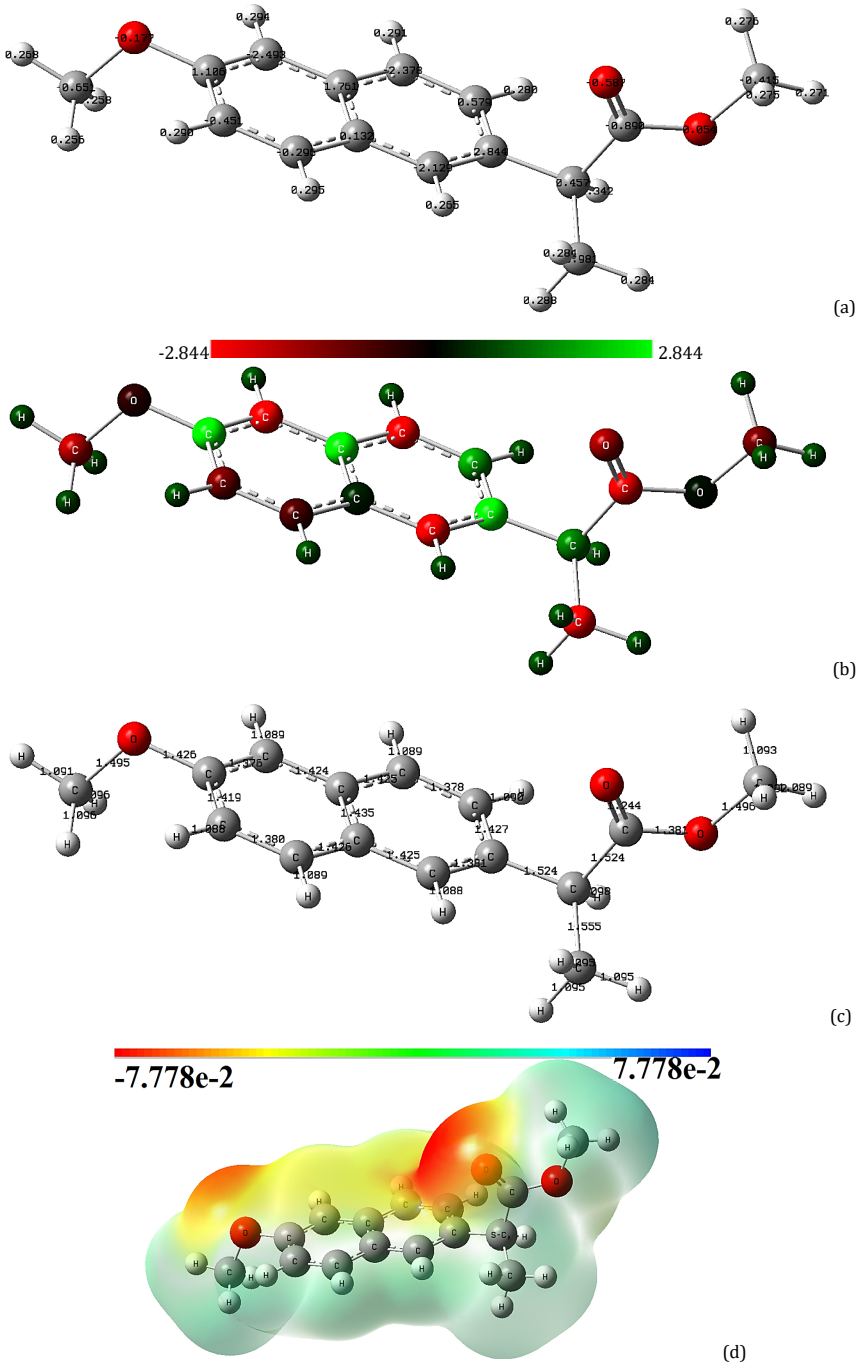


Figure 4. DFT calculation-based (a) Mulliken's charges, (b) atoms colored by charge (-2.844 to 2.844), (c) bond length, and (d) electron density from the total SCF density of the S-Naproxen ester in water.

the carbonyl carbon, alkoxy oxygen, and carbonyl oxygen respectively. In addition, the bond length between the carbonyl carbon and alkoxy oxygen of the (-COO-) group of R-naproxen ester was 1.380. On the other hand, Mulliken's charges in the S-naproxen ester group were -0.890, 0.054, and -0.587 in carbonyl carbon, alkoxy oxygen, and carbonyl oxygen, respectively (Figure 4). Additionally, a bond length of 1.389 Å was found between the carbonyl carbon and the alkoxy oxygen of the ester group (-COO-) of the S-enantiomer.

When the bond torsion in the (-COO-) group of esters taken in the present study was evaluated, the main fact supporting the core findings of the current study was observed. A comparative study for the bond torsion clearly showed that the bond torsion in the (-COO-) group of the S-naproxen ester was very close to that of the simple ester. On the other hand, the R-naproxen ester did not show a bond-torsion-based similarity with the simple ester when the same parameter was studied between the R-naproxen ester and the simple ester (Figure 5).

4. Discussion

Based on the DFT calculation results, it becomes very easy to explain (i) how the hydrolysis of the simple ester is possible in both conditions (acidic and basic), (ii) why the S-naproxen ester gets hydrolysed only in acidic medium, and (iii) the R-naproxen ester does not get hydrolysed in any medium. In the case of methyl propionate, a decrease in negative charge on the carbonyl carbon was observed when its optimized gaseous state was compared with the state optimized in water (Table 1).

Table 2. The DFT calculation-based electronegativity difference in ester group constituents.

Ester in water	Carbonyl carbon	Alkoxy oxygen	Electronegativity difference	Ionic character in ester group
Methyl propionate	-0.134	-0.068	0.074	Less ionic
R-Naproxen	-0.559	0.055	0.614	
S-Naproxen	-0.890	0.054	0.944	R < S

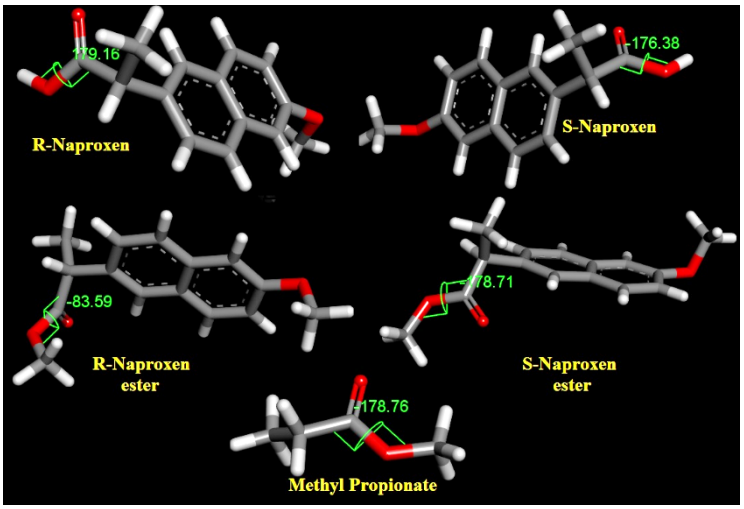


Figure 5. Bond torsion between the carbonyl carbon and the alkoxy oxygen in the taken molecules.

On the other hand, the same comparative study clearly showed an increase in negative charge on carbonyl oxygen of methyl propionate (Table 1). According to the relationship between Milliken's charges and electronegativity, the larger the negative value of Milliken's charges, the higher the electronegativity of an atom [32]. It evidently means that the decrease in negative charge on the carbonyl carbon atom indicates a decrease in its electronegativity. In addition, it is also an indication of the probability of nucleophilic attack, i.e. the attack of the OH^- group on the less electronegative carbonyl carbon of the (-COO-) group in the water. This shows why the ester hydrolysis reaction can occur in a basic medium having an excess of OH^- ions. However, the increase in negative charge on the carbonyl oxygen atom of methyl propionate indicates an increase in its electronegativity according to the relationship between Milliken's charges and electronegativity [32]. Therefore, the increased negative charge on the carbonyl oxygen of methyl propionate is also an indication of the probability of electrophilic attack, i.e. the attack of the H^+ ion on the carbonyl oxygen of (-COO-) group in water. This shows why the ester hydrolysis reaction can also occur in an acidic medium having an excess of H^+. Therefore, the results based on DFT calculations resolved the question of how hydrolysis of the simple ester is possible under both conditions (acidic and basic).

The DFT calculation-based results of the enantiomeric hydrolysis were also found to be very helpful for understanding why the hydrolysis of only S-naproxen ester is possible, but that of the R-naproxen ester is not, in water. Based on the results obtained after optimization of the R/S naproxen esters, a difference in electronegativity was also evaluated between carbonyl carbon and alkoxy oxygen in the ester bond. This electronegativity difference was found in the S-naproxen ester to be higher than that in the R-naproxen ester (Table 2). According to data from the literature [33], the difference in electro-negativities between two atoms determines the nature of the chemical bond, i.e. ionic or covalent. Hence, a large electronegativity difference between carbonyl carbon and alkoxy oxygen in the S-naproxen ester (Table 2) makes the ester bond ionic in water. Because of its ionic nature, the ester bond in S-naproxen ester becomes dissociative in water. This is because the bond-dissociation in water is a common thing found in compounds containing ionic character [34]. The bond length between carbonyl carbon and alkoxy oxygen in the S-naproxen ester was slightly higher than that in the R-naproxen ester (Table 1). This also supports the dissociative nature of the ester bond in the S-naproxen ester since the longer bond length shows a dissociative nature with low energy [35,36]. Therefore, because of its ionic nature and more dissociative nature, the (-COO-) group of S-naproxen ester takes part in hydrolysis. On the other hand, R-naproxen does not do so, because of the covalent nature of its ester group caused by the shorter bond length with less electronegativity difference between the carbonyl carbon and alkoxy oxygen. Hence, the covalent or less ionic nature in water, the bond dissociation between the carbonyl carbon and alkoxy oxygen of the R-naproxen ester becomes very difficult. In this way, the DFT calculation-based results resolved the question of why the hydrolysis of only S-naproxen ester is possible, but not that of R-naproxen ester, in water. Furthermore, the key points for not only the R / S-naproxen ester but also the simple ester to participate in hydrolysis are shown in Figure 6.

Another factor for the same can be explained through the results based on the bond torsion study. In the case of S-naproxen ester, the bond torsion between the carbonyl carbon and alkoxy oxygen was found similar to that of simple ester (Table 3). This indicates that the bond torsion between carbonyl carbon and alkoxy oxygen favours the participation of the S-naproxen ester in a hydrolysis reaction like that of a simple ester. On the other hand, the bond torsion between carbonyl carbon and alkoxy oxygen in R-naproxen ester was not found to be similar to that in a normal ester. It indicates that the bond torsion between the carbonyl carbon and alkoxy oxygen does not favour the participation of the R-naproxen ester in the hydrolysis reaction.

In addition to the interesting facts described above, one more fact associated with the condition for the hydrolysis of the S-naproxen ester was also observed. According to the introduction part of the current article, the hydrolysis of the S-naproxen ester occurs under an acidic condition [11] only, that is, pH < 7. The presented DFT study also resolves the question of why the hydrolysis of S-naproxen ester occurs only under

Table 3. Bond torsion between carbonyl carbon and alkoxy oxygen.

Ester	Bond torsion (°)	Ester dissociation probability	Participation in hydrolysis
Methyl propionate	-178.76	More	Yes
R-Naproxen ester	-83.59	Very Less	No
S-Naproxen ester	-178.71	More	Yes

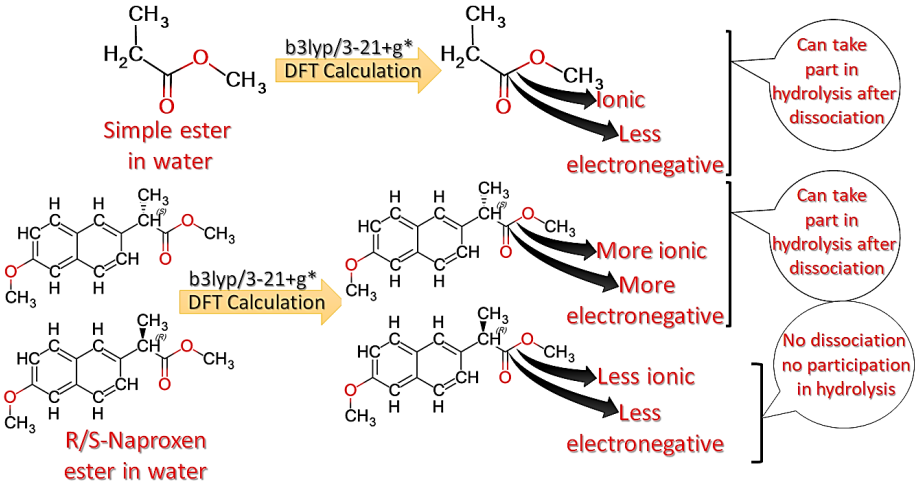


Figure 6. The DFT calculation-based key points responsible for stereoselective hydrolysis of R/S-Naproxen ester.

acidic conditions and mediums. After DFT calculation, the negative charges on the carbonyl carbon of the (-COO-) group of enantiomeric esters, *i.e.*, R/S-naproxen in water, were compared. The negative charge on the carbonyl carbon of the (-COO-) group of the S-naproxen ester was observed to be higher than that of not only the R-naproxen ester, but also simple ester (Table 1). Therefore, the existence of an increased negative charge on the carbonyl carbon atom makes it more electronegative according to the relation between Milliken charges and electronegativity [32]. It also shows no probability for a nucleophilic attack i.e. OH^- ion. It is only because of the repulsion between the more electronegative carbonyl carbon and the OH^- ion. However, the increased negative charge on the oxygen atom indicates an increase in its electronegativity, which is an indication of the probability of the electrophilic attack, i.e. the attack of the H^+ ion on the carbonyl oxygen. Because of this fact, the hydrolysis of the S-naproxen ester occurs in an acidic medium only in which H^+ ions are present. Therefore, the results based on DFT calculations solved the question of why the hydrolysis of the S-naproxen ester occurs in an acid medium, that is, pH < 7

5. Conclusions

After a deep study of the parameters of the ester bond constituent, the presented work resolved all the questions mentioned in the introductory part of the article. In addition, more chirality-based concepts except for the hydrolysis of S-naproxen ester are yet to be described. Only a DFT calculation may help in the evaluation of such chiral-chemistry-based facts. Therefore, by using DFT calculation, the different enantiomeric behaviour of a chiral compound/drug may also be resolved in the future. For this purpose, we have to do DFT calculations in different mediums for different enantiomers of the same chiral drug to know their different behaviour.

Disclosure statement

Conflict of interest: The author declares that he has no conflict of interest.
Ethical approval: All ethical guidelines have been adhered to.

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