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Electron Spin Resonance Spectrum Simulations and DFT Calculations for Possible Radicals of the Ketoprofen Molecule

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Abstract: In this study, the molecular structure of the Ketoprofen molecule, which is the drug's active ingredient, was revealed by using theoretical methods. First of all, conformational space scanning in the Ketoprofen molecule was performed by the Molecular Mechanical Force Field method. Then, the most stable structure, geometry parameters, Nuclear Magnetic Resonance parameters of the ketoprofen molecule was found with the help of the Density Functional Theory method. Further, Possible radicals were modeled using the most stable structure of the ketoprofen molecule. Electron Spin Resonance parameters of these possible radicals were also calculated with the Density Functions Theory method. Finally, using these parameters theoretical Electron Spin Resonance spectra of possible radicals were obtained by simulation program.

Ketoprofen Molekülünün Olası Radikalleri İçin Elektron Spin Rezonans Spektrum Simülasyonları ve DFT Hesaplamaları

Anahtar Kelimeler
Elektron Spin Rezoanans, Yoğunluk Fonksiyonelleri Teorisi, Ketoprofen, Radikal simülasyonları

Öz: Bu çalışmada ilaç etken maddesi olan Ketoprofen molekülünün moleküler yapısı teorik yöntemler kullanılarak açığa çıkarılmıştır. Öncelikle Ketoprofen molekülünün konformasyonel uzay taraması Moleküler Mekanik Kuvvet Alanları metodu kullanılarak gerçekleştirilmiştir. Daha sonra ketoprofen molekülünün en kararlı yapısı, geometri parametreleri, Nükleer Manyetik Rezonans parametreleri Yoğunluk Fonksiyonel Teorisi yöntemi yardımıyla bulunmuştur. Ayrıca ketoprofen molekülünün en kararlı yapısı kullanılarak olası radikaller modellendi. Son olarak, bu parametreler kullanılarak olası radikallerin teorik Elektron Spin Rezonans spektrumları simülasyon program ile elde edilmiştir.

1. INTRODUCTION

Ketoprofen is a kind of non-steroid anti-inflammatory drugs (NSAID) which are widely used around the world due to their pain and inflammation-reducing properties. Ketoprofen is a benzophenone derivative, especially used in the treatment of moderate pain [1-6]. Since it is a drug active ingredient, it is important to reveal the structure of the Ketoprofen molecule correctly. The electronic properties (energy, dipole moment etc.) of a molecule are closely related to its molecular structure. If the molecular structure is correctly detected, other electronic properties of the molecule can also be accurately detected. The molecular structure of a molecule may be revealed by X-ray study or by spectroscopic methods such as Nuclear Magnetic Resonance (NMR) spectroscopy. NMR spectroscopy provides information about molecular structure and is a frequently used method to explain molecular structure [7-9]. The Density Functional Theory (DFT) method is a very successful theoretical method in revealing the molecular structures of molecules and calculating NMR parameters [10-14]. Drugs may be exposed to radiation for sterilization purposes or accidentally. As a result of drug interaction with radiation, radicals may form in the drug [15, 16]. Electron Spin Resonance (ESR) technique is one of the commonly used methods to detect the radical formed in the drug [17,18]. ESR technique can detect even a very small amount of paramagnetic center,

namely radical, in the sample [19-21]. The g and hyperfine coupling constant (hfcc) parameters obtained from the ESR spectrum give us important information about the paramagnetic center. However, it is often not easy to analyze an ESR spectrum and accurately determine the ESR parameters from that spectrum. The DFT method can help analysis of ESR spectra [22-25].

2. MATERIAL AND METHOD

The theoretical calculation of the Ketoprofen molecule started with conformation analysis. The conformation analysis of the Ketoprofen molecule was carried out using the Molecular Mechanical Force Fields (MMFF) method by the Spartan08 program [26]. As a result of the conformation analysis, 19 conformations of the Ketoprofen molecule were obtained. The most stable conformation of the Ketoprofen molecule was determined by optimization and frequency calculation for each conformer using the B3LYP/6-311++G(d,p) method basis set combination [27,28]. As a result of optimization and frequency calculations, the most stable structure and its geometry parameters were determined. Nuclear Magnetic Resonance parameters (^{1}H and ^{13}C chemical shift values) of the Ketoprofen molecule were calculated using the B3LYP/6-311++G(d,p) method-basis set combination. Seven possible radicals of the Ketoprofen molecule were modeled using the B3LYP/6-311++G(d,p) method basis set combination. ESR parameters (g value and hfcc values) of seven possible radicals were also calculated using the same method and basis set. All calculations except the conformation analysis were performed using the Gaussian03 program [29]. ESR spectrum patterns of possible radicals were obtained by using the calculated ESR parameters of possible radicals in the JEOL IsoSimu/ Fa Version 2.2.0 simulation program.

3. RESULTS AND DISCUSSION

The structure of the most stable conformer of the Ketoprofen molecule is shown Figure 1.

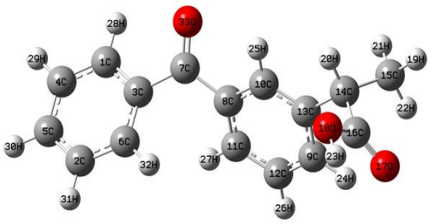

Figure 1. The most stable structure of Ketoprofen molecule

The geometry parameters of the optimized structure are given in Table 1. It is seen that the geometry parameters given in Table 1 of the most stable structure of the Ketoprofen molecule are compatible with the experimental and theoretical studies previously studied in the literature [3,6]. One of the methods used to determine the molecular structure is the NMR spectroscopy method. Experimental NMR parameters of Ketoprofen molecule (^{1}H and ^{13}C chemical shift values) are available in the literature [30].

NMR parameters (^{1}H and ^{13}C chemical shift values) calculated using the B3LYP/6-311++G(d,p) method basis set combination of the Ketoprofen molecule are given in Table 2. Defining the molecular structure correctly will increase the accuracy of the calculation to be made using that molecular structure. As can be seen from Table 2, the experimental and calculated chemical shift values are compatible for the Ketoprofen molecule. The fact that the theoretical and experimental NMR parameters are compatible with each other is a situation that shows the accuracy of the theoretically found molecular structure.

Table 1. The calculated and experimental geometry parameter of the Ketoprofen molecule

	Bond Lenghts (Aº)			**Bond Angles (degree)**	
	Experimental [6]	**Calculated**		**Experimental [6]**	**Calculated**
C1-C3	1.388	1.402	C2-C6-C3	120.3	120.3
C3-C6	1.393	1.400	C6-C3-C7	122.5	122.6
C6-C2	1.382	1.393	C1-C3-C7	118.9	118.1
C2-C5	1.374	1.399	C3-C7-O33	119.0	119.9
C5-C4	1.367	1.396	C3-C7-C8	121.4	120.1
C4-C1	1.378	1.389	C7-C8-C11	121.5	122.7
C3-C7	1.487	1.500	C7-C8-C10	118.6	117.9
C7-O33	1.218	1.221	C8-C10-C13	121.4	121.3
C7-C8	1.488	1.501	C10-C13-C9	118.6	118.8
C8-C11	1.395	1.399	C13-C9-C12	121.1	120.5
C11-C12	1.381	1.394	C9-C12-C11	120.1	120.4
C12-C9	1.392	1.392	C12-C11-C8	119.1	119.9
C9-C13	1.385	1.402	C11-C8-C10	119.8	119.2
C13-C10	1.367	1.392	C13-C14-C15	112.4	112.3
C13-C14	1.532	1.528	C13-C14-C16	110.3	109.4
C14-C15	1.518	1.537	C15-C14-C16	110.0	110.7
C14-C16	1.515	1.523	C18-C16-O17	123.3	122.5
C16-O17	1.248	1.206		**Dihedral Angles (degree)**	
C16-O18	1.254	1.355	C6-C3-C7-C8	-36.0	32.9
	Bond Angles (degree)		C8-C7-C3-C1	147.5	-150.8
C4-C1-C3	120.4	120.4	C3-C7-C8-C11	-25.3	31.4
C1-C4-C5	120.6	120.0	C10-C8-C7-C3	159.3	-152.6
C4-C5-C2	119.9	119.9	C13-C14-C16-O17	-107.3	90.0
C5-C2-C6	120.2	120.1	C13-C14-C16-O17	72.2	88.8
C6-C3-C1	118.5	119.2	C9-C13-C14-C16	-67.6	-58.5
			C10-C13-C14-C16	116.0	123.3

Table 2. Experimental and Theoretical ^{1}H Chemical Shift values of Ketoprofen molecule in ppm

	CH_3 peak value	CH peak value	Phenyl peak values
Experimental [23]	1.377	3.771	7.436-7.639
This study	1.422	4.112	7.842-8.274

Defining the molecular structure correctly will increase the accuracy of the calculation to be made using that molecular structure. As can be seen from Table 2, the experimental and calculated chemical shift values are compatible for the Ketoprofen molecule. The fact that the theoretical and experimental NMR parameters are compatible with each other is a situation that shows the accuracy of the theoretically found molecular structure. Katusin-Razem et al., mentioned that a radical was formed in the sample in their study in 2005 years for the sterilization of the Ketoprofen molecule. In this study, Katusin-Razem et al. discussed possible radicals for the ketoprofen molecule [31]. Spin trapping EPR studies of the Ketoprofen molecule are also available in the literature [32]. However, there is no definition in the literature of the radical(s) that will occur due to the irradiation of Ketoprofen. Six possible radicals were modeled using the B3LYP/6-311++G(d, p) method basis set combination considering the studies in the literature for the Ketoprofen molecule. The radicals were named as Rad1, Rad2, Rad3,…,Rad6. H23 atom for Rad1 radical ($RCCH_3C\dot{O}O$), H23 and O18 atoms for Rad2 radical ($RCH_3\dot{C}O$), H20 atom for Rad3 radical ($R\dot{C}CH_3COOH$), H19 atom for Rad4 radical ($RC\dot{C}H_2COOH$), C15-H19-H21-H22 atoms for Rad5 radical ($R\dot{C}COOH$) were modeled by removing them from the Ketoprofen molecule. The Ketoprofen molecule is modeled anionic for Rad 6 radical $(RCCH_3COOH)^-$. Possible radicals modeled are shown in Figure 2.

ESR parameters (g and hfcc values) of the modeled radicals were calculated using the same method and basis set. The calculated isotropic ESR parameters of the modeled radicals are given in Table 3.

ESR spectra may not be easily resolved due to overlaps. In such cases, spectra can be analyzed with simulations. Values such as g and hfcc values of the radical(s) that are assumed to occur are needed for simulation. The g and hfcc values required for simulation can be obtained from theoretical calculations. More than one radical can form in the molecule, in which case the analysis of the spectrum will become more complicated. Theoretical calculations can be used to analyze such complex spectra, and the success of the DFT method in calculating ESR parameters is known from previous studies [33,34].

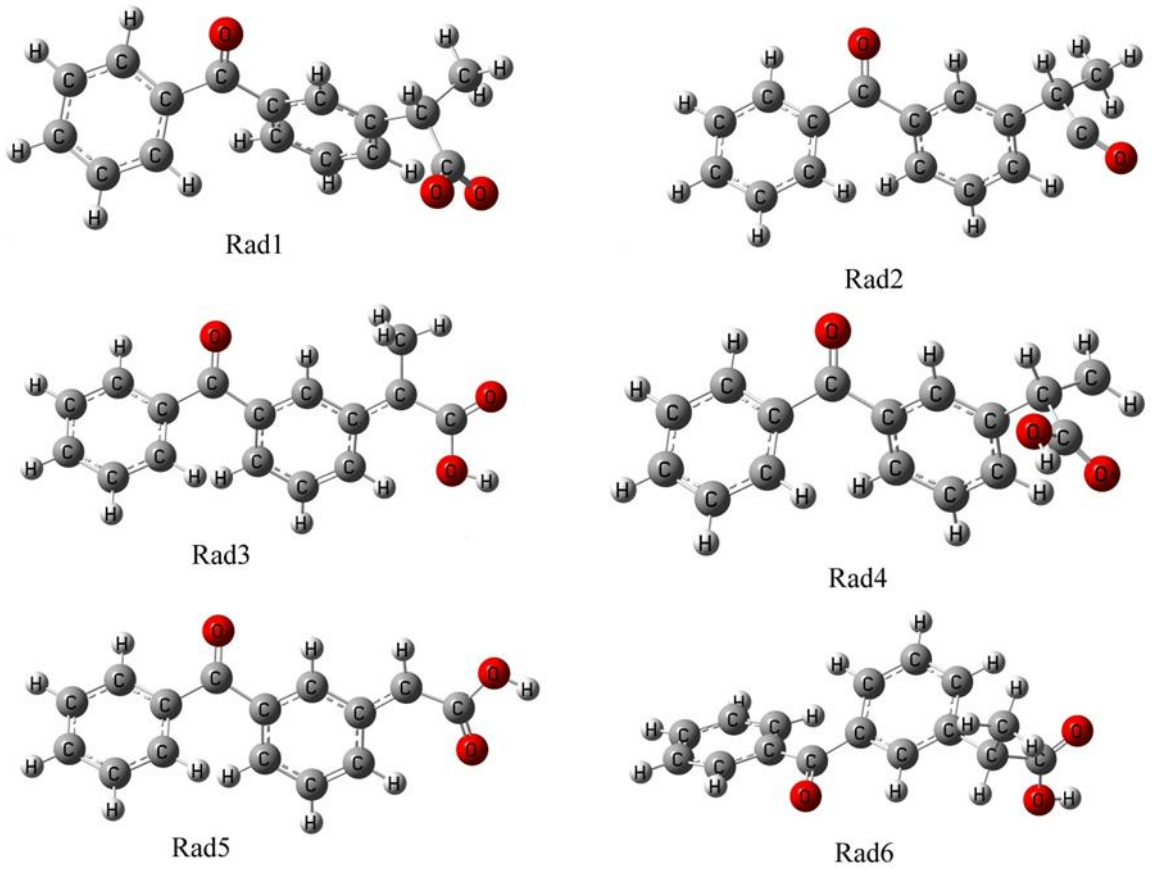

Figure 2. The possible radicals of Ketoprofen molecule

Table 3. The calculated hfcc(in Gauss) and g values of six possible radicals

Atom	Rad1	Rad2	Rad3	Rad4	Rad5	Rad6
H19			2.4			
H20	3.9	1.9		23.0	14.1	
H21	1.5	4.9	28.4	21.5		
H22			16.3	22.4		
H23					1.1	
H24			3.8		4.5	4.1
H25			4.3		4.9	2.6
H26			1.6		1.8	
H27			4.1		5.1	2.0
H28						2.3
H30						3.3
H32						1.7
g_{iso}	2.0096	2.0007	2.0033	2.0026	2.0033	2.0040

For the radical modeled as $RCCH_3COO\dot{}$, the calculation could not be completed with B3LYP/6-311++G(d,p) base set combination. In order to calculate the g and hfcc values of the $RCCH_3COO\dot{}$ radical, the basis set was changed. The isotropic g and hfcc values of $RCCH_3COO\dot{}$ radical were calculated using four different basis set combinations. Thus, the effect of different basis sets on the calculation was also investigated. The isotropic g and hfcc values calculated with different basis sets are given in Table 4 for the $RCCH_3COO\dot{}$ radical.

Table 4. The g and hfcc (in Gauss) values of the Rad1 radical calculated with different basis sets

	Basis Sets			
Atoms	6-31+ (d)	6-311+(d)	6-31+(d,p)	6-311 (d,p)
H20	3.8	4.1	3.8	4.0
H21	1.5	1.4	1.6	1.3
giso	2.0094	2.0098	2.0094	2.0099

When Table 4 is examined, the g value and hfcc values for Rad1 model radical do not change much with the change of the basis set. In other words, the change of the basis set does not affect the calculation results much. Possible ESR spectra were obtained by using the ESR parameters given in Table 2 in the JEOL IsoSimu/Fa Version 2.2.0 simulation program. Spectra with different line widths were simulated for each radical. The simulations were created by taking the average of the isotropic g and hfcc values given in Table 3 for the $RCCH_3COO\dot{}$ radical. The line width of the simulations is indicated on the spectra. The simulated ESR spectra are given in Figure 3.

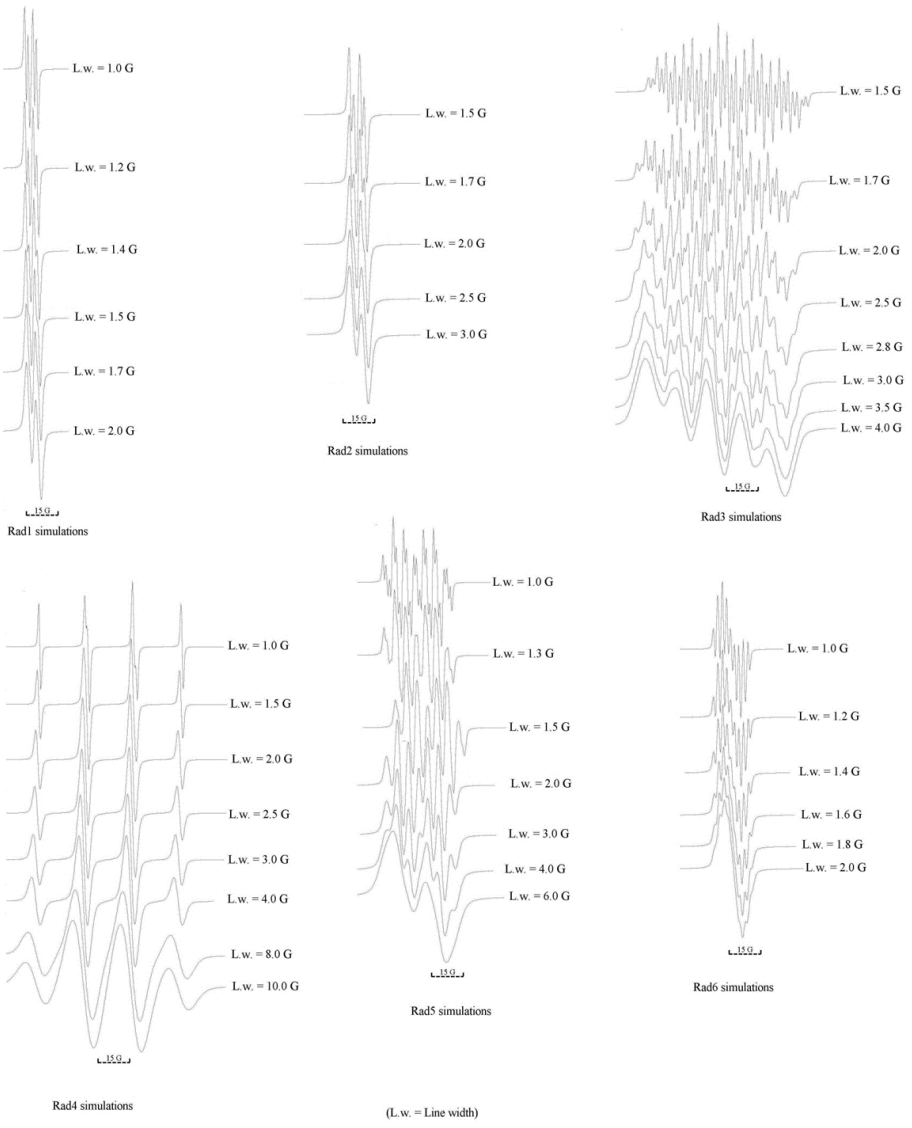

Figure 3. Electron Spin Resonance spectrum simulations of the modeled radicals

It is possible to reproduce the simulations given in Figure 3. When the spectra in Figure 3 are examined, the shape of the spectra changes depending on the line width. Although the line width is kept small when recording the ESR spectrum, the line width will increase due to overlaps. Therefore, the appearance of the spectrum will change. More than one simulation spectra of a radical are given. Since it is not possible to predict what kind of overlap will occur in the experiment. The first thing the experimenter encounters in ESR spectroscopy analysis is the spectrum pattern. It can measure the g and hfcc values from the spectrum after being able to analyze the spectrum pattern. In this sense, spectra created based on theoretical values can guide experimenters. Of course, simulations with the same spectrum patterns can also be seen here. In simulations with similar spectrum patterns, the differences between the theoretical and experimental values of g and hfcc are calculated to decide which radical is formed. For g values, the difference between the experiment and the theoretical calculation should be at most 1000 ppm [35]. For hfcc values, the difference between the experiment and the theoretical calculation should not exceed % 20 [36].

4. CONCLUSIONS

In this study, the molecular structure of the Ketoprofen molecule and the radicals that may occur in the Ketoprofen molecule when exposed to radiation were investigated. Using the ESR parameters of the modeled radicals, theoretical ESR spectra were generated for each radical. The parameters required to construct the ESR spectra of the radical can be derived by theoretical calculation methods. How to use the ESR parameters obtained by theoretical calculations in spectrum simulations is presented to the literature. The values of the ESR parameters of the radical(s) formed by the irradiation of the ketoprofen molecule are not available in the literature. These parameters have been presented in the literature with this study.

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