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Theoretical study of possible reaction pathways with the OH radical of the Apranax (AP) molecule with naproxen sodium (NS) as an active ingredient

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In this study, Apranax (AP) with active ingredient naproxen sodium (NS) was examined. Geometric optimizations of the fragments were made on the DFT/B3LYP/6-31G(d) basic set of the Quantum Mechanical Density Functional Theory to theoretically determine all possible reaction pathways of AP with the OH radical. Since the reaction of the molecule with the OH radical is important for both water purification and atmospheric chemistry, calculations were performed both in the gas phase and in the water phase, modeled with CPCM in the COSMO (conductor-like screening solvation model) solvent model. The degradation mechanism was clarified by examining the energy values for all fragments, the bond lengths of the atoms in the fragments, the bond angles, and the Mulliken charges.

Keywords: Apranax, naproxen sodium, DFT, OH radical, Gaussian 09

INTRODUCTION

In this study, the degradation mechanism and fate of the Apranax (AP) molecule in nature of one of the five molecules we investigated in our current scientific research project entitled. "Examining the theoretical degradation mechanisms of selected pharmaceutical product active ingredients" were examined. It is estimated that, the molecules selected within the scope of the project are either excreted from the body through faeces after being used for treatment purposes or it will be mixed into wastewater through the natural cycle as domestic waste without being used at all. When pharmaceutical products, popularly called medicines, are excreted from the body, or are not used and thrown away as waste, their fate in nature has not been investigated yet. The main purpose of this study is to theoretically elucidate the fate of the AP molecule and its hydroxylated parts during degradation in nature.

Naproxen or naproxen sodium (NS) is available and is safely and effectively used worldwide.

Almost one in every five prescriptions for non-steroidal anti-inflammatory drugs contains this active ingredient, such as Apranax fort and Apranax (AP), which are mainly orally administered. Apranax is one of the drugs widely used for the relief of mild to moderate pain, such as headache, toothache, muscle pain, backache, or cold, as well as for medicinal purpose as a treatment of pain for those who suffer from rheumatic diseases such as strains, sprains, menstrual pain, osteoarthritis, rheumatoid arthritis, or other conditions. AP may cause nausea, diarrhoea, and vomiting. It has side effects such as abdominal pain and skin rash, and its half-life is short. NA is a white crystalline substance used as an analgesic. It is soluble in water; pH of the aqueous solution is 6 or above [1-6].

AP is a hydroxyl scavenger biomolecule. It is also a detector of hydroxyl radicals due to its hydroxylation ability. Attack of any hydroxyl radical on an aromatic compound results in the formation of a new hydroxylated product which can be much more harmful than the original molecule at the beginning of the process. Knowing the degradation mechanism is very important for monitoring the products [7]. Organic compounds undergo photolysis. They react with the OH radical and this reaction causes decomposition reactions in the atmosphere. The OH radical acts as an electrophile in its reaction with any organic molecule and therefore, it easily binds to unsaturated bonds, whereas the O radical is a nucleophile and therefore cannot interact with bonds. If an aliphatic side chain is attached to an aromatic molecule, the OH radical prefers binding to the aromatic ring [8-14]. This study examines the probability of obtaining more dangerous substances through hydroxylation of the AP molecule on its mixing with nature. Of course, all necessary research experiments are carried out before pharmaceutical products are placed on the market, all possible side effects are determined, after which the product is used for the treatment of people. The issue that is ignored or not given much importance is "*What would happen if many pharmaceutical products used for therapeutic purposes mix with nature?*".

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MATERIALS

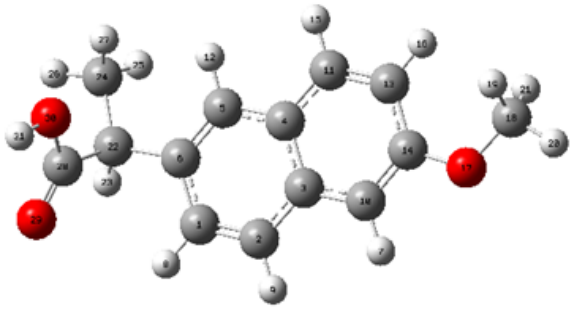
Theoretically, to determine all possible reaction paths of AP, geometric optimizations were made on the DFT/B3LYP/6-31G(d) basis set of the Quantum Mechanical Density Functional Theory (DFT), one of the methods for studying electronic structure. For all fragments, energy values were calculated, and geometric optimizations were made using the Gauss View 5.0.8 molecular representation program and the Gaussian 09 program in orbital calculations. With Gaussian 09 program the energies of atoms and molecules can be calculated, geometric optimizations can be made and vibration frequencies, force constants and dipole moments depending on energy can be calculated. Gauss View 5.0.8 Preparing input files for Gaussian package programs is a graphical interface designed to visualize the outputs. Gaussian views molecules, visualizes them, allowing us to rotate and move them as we wish, and it allows us to make changes. Moreover, even for complex calculations, it can be easily entered to prepare the files. It allows us to examine a graphical display of the results calculated by the Gaussian program [15]. The fragmentation reaction energy is affected by the water molecules in the aqueous environment. In addition, geometry stretching in solutions is induced by H_2O. In other words, the presence of a dielectric medium such as H_2O causes relaxation in the geometry of the solute and has a stabilizing effect, reducing the energy for this mechanism [7]. Therefore, in this study, CPCM in the COSMO (conductor-like screening solvation model) solvent model in the Gaussian 09 package program was used to explain the solvent effect of H_2O on the AP + ·OH reaction energy [15].

RESULTS AND DISCUSSION

For any molecule, the subseqquent steps should be considered in order to determine the fragmentation path. Even though it is known that that the longest bond and the widest bond angles of atoms will be fragmented first, monitoring the energy values and environments of the electronegative atoms is the determining factor for the fragmentation. It is essential that double-bonded or closed-ring structures are more stable than others, and if fragmentation occurs, breaking away of these stable structures will be at the last stage [16].

As given in Table 1, the energy values of all possible reaction pathways for each fragment were calculated in both the gaseous and aqueous phases. Every fragment that could be formed after the interaction of the main molecule AP with the OH radical was included in the study. Since the digits after the comma are close to each other when converting the results to SI units, which also leads to a difficulty in observing the energy difference between the fragments, the energy values are given in atomic mass units (AU).

When the Mulliken charges of the AP molecule (see Table 2) are examined, the electronegative atom s are O_{30}, O_{17}, O_{29}, C_{24}, C_{22}, C_{18}, respectively. In Fig. 1, O_{29} is stable because it makes a double bond with C_{28}, and although O_{29} is the third electronegative atom according to Table 2, this bond is not expected to be broken.



AP

Fig. 1. In the geometric structure of the Apranax (AP) molecule optimized by the DFT method, the C atom is represented in grey, the O atom in red, and the H atom in white.

According to Table 1, the A_1 fragment of the molecule is the fragment with the lowest energy (in atomic mass units-Au) of -728.065048 Au, it is the most stable. This fragment is formed by breaking the O_{17}-C_{18} bond with a length of 1.41818 Å according to Fig. 2 (a) and removing the methyl group from the molecule. This bond length is not the longest bond length in the molecule, but the bond angle of C_{14}-O_{17}-C_{18} is the widest bond angle at 118.76650^0 according to Fig. 2 (b).

The O_{17} atom is the second electronegative atom with a value of -0.510088 (Table 2). The OH radical is a selective organic molecule scavenger. As a result of examining the molecule in terms of its reaction with OH radicals in air or water, this part of the molecule is the first to react.

Table 1. ΔE (energy), ΔH (enthalpy) and ΔG (Gibbs free energy) values of the AP molecule and its fragments in gas and water phases.

(AU)	AP	A_1	A_2	A_3
ΔE	-767.340690	-728.065048	-728.058301	-692.097954
Gas phase ΔH	-767.339746	-728.064104	-728.057357	-692.097009
ΔG	-767.399548	-728.120317	-728.114497	-692.154919
Water phase	-767.351790	-728.078283	-728.069433	-692.107155
	-767.350846	-728.077339	-728.068489	-692.106210
	-767.410901	-728.133929	-728.125993	-692.164391
	A_4	A_5	A_6	A_7
	-652.854532	-688.782675	-652.814627	613.572178
Gas phase	-652.853588	-688.781731	-652.813683	-613.571234
	-652.907137	-688.835296	-652.868863	-613.622106
	-652.863690	-688.795917	-652.823952	-613.581316
Water phase	-652.862746	-688.794973	-652.823008	-613.580372
	-652.916915	-688.849045	-652.878269	-613.631589
	A_8	A_9	A_{10}	A_{11}
	-500.224176	-539.513017	-538.328373	-425.027148
Gas phase	-500.223232	-539.512073	-538.327429	-425.026204
	-500.268414	539.561234	-538.376379	-425.069205
	-500.229842	-539.518748	-538.335816	-425.030971
Water phase	-500.228898	-539.517804	-538.334872	-425.030027
	-500.274103	-539.566972	-538.384073	-425.073003
	A_{12}	A_{13}		
	-460.949586	-385.738101		
Gas phase	-460.948642	-385.737157		
	-460.990157	-385.776091		
	-460.957008	-385.741854		
Water phase	-460.956063	-385.740910		
	-460.997569	-385.779854		

Table 2. Mulliken atomic charges of the AP molecule

	AP	A_1	A_2	A_3
	O_{17} -0.510088	O_{17} -0.644225	C_{18} -0.214859	C_{18} -0.215461
Mulliken	C_{18} -0.214741	C_{18} -0.227769	C_{22} -0.411621	C_{22} -0.219371
atomic charges	C_{22} -0.227955	C_{20} -0.464094	C_{24} 0.575113	C_{24} -0.473059
	C_{24} -0.463800	C_{24} 0.587793	O_{25} -0.457604	C_{28} 0.266246
	O_{29} -0.468068	O_{25} -0.467892	O_{26} -0.560323	O_{29} -0.388433
	O_{30} -0.565811	O_{26} -0.565833		
	A_4	A_5	A_6	A_7
	C_{17} -0.228769	O_{17} -0.643993	O_{17} -0.509248	C_{17} -0.412000
	C_{19} -0.464121	C_{18} -0.411896	C_{18} -0.215717	C_{19} 0.575202
	C_{23} 0.587811	C_{20} 0.575225	C_{22} -0.416238	O_{20} -0.456608
	O_{24} -0.467005	O_{21} -0.457244	C_{24} 0.263829	O_{21} -0.559514
	O_{25} -0.565016	O_{22} -0.560294	O_{25} -0.382001	
	A_8	A_9	A_{10}	A_{11}
	O_{17} -0.510468	O_{17} -0.511301	C_{17} -0.417131	C_{17} -0.532257
	C_{18} -0.214254	C_{18} -0.213556	C_{19} 0.263685	
		C_{22} -0.531819	O_{20} - 0.380335	
	A_{12}	A_{13}		
	C_{13} -0.156415	C_1 -0.134946		
	C_{14} 0.354987	C_2 -0.190872		
	O_{17} -0.644507	C_5 -0.190768		
		C_6 -0.135011		
		C_{10} -0.190765		
		C_{11} -0.190866		
		C_{13} -0.134947		
		C_{14} -0.135010		

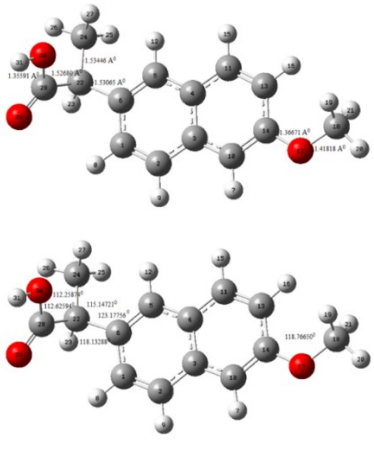


Fig. 2. Bond lengths (a) and bond angles (b) between the atoms connected to the closed ring in the AP molecule (C atom is represented in grey, O atom in red and H atom in white).

O_{30} is the most electronegative atom according to Table 2. When the methyl groups of C_{18} and C_{24} at the ends of the AP molecule and the OH group of O_{30} are removed from the molecule, the A_1, A_2 and A_3 fragments formed are low-energy fragments with values of -728.065048 A^0, -728.058301 A^0, and -692.097954 A^0, respectively. By comparing with the energy values of all other fragments, three different separation methods were assumed from these three fragments.

After determining the three main fragmentation pathways of the AP molecule, all possible fragments of each pathway were created by removing atoms from the ends of the A_1, A_2, and A_3 fragments. We already know that the OH radical acts as an electrophile and the O radical acts as a nucleophile [8-14]. Thus, we identified all hydroxylation products of the AP molecule. In order to prevent any incompleteness, all fragments, which were fragmented from around different atoms of MA molecule, were investigated in terms of their optimized figure, electrochemical values, bond lengths and angles, and the most stable fragments were chosen accordingly.

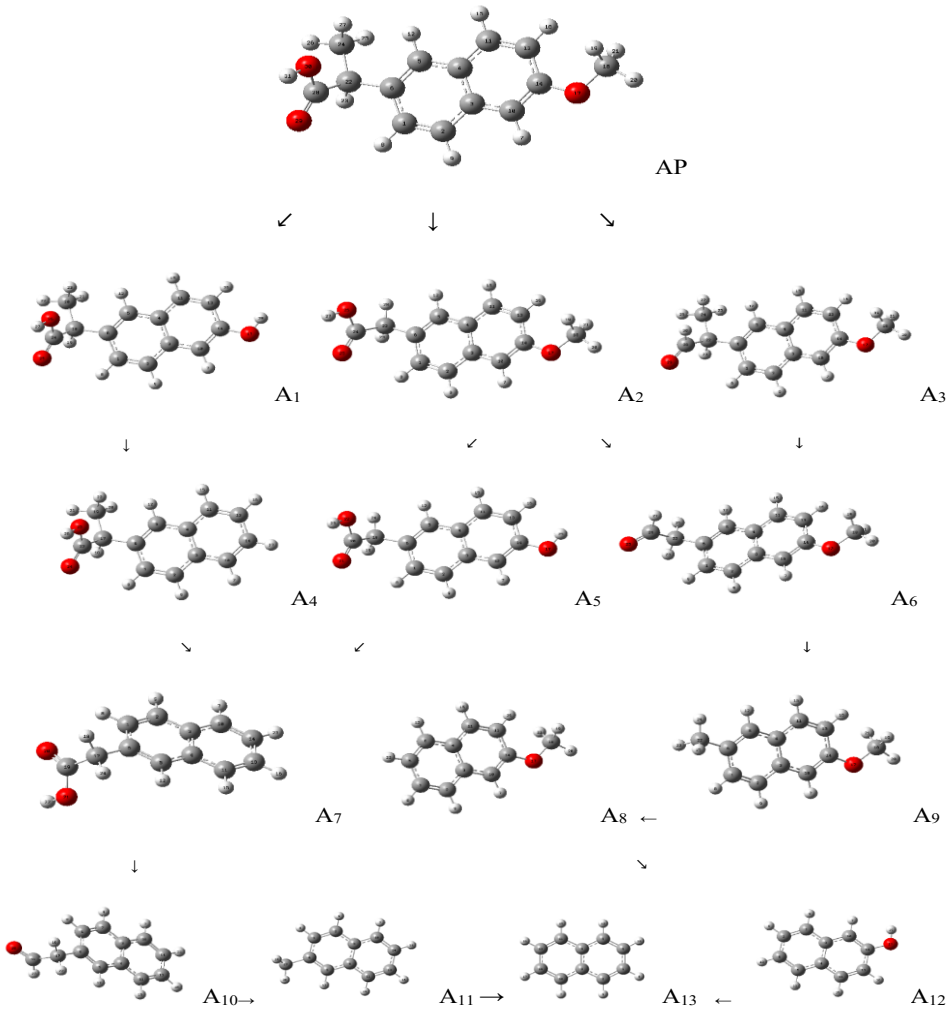


Fig. 3. Degradation pathway (degradation mechanism) of the Apranax (AP) molecule (the C atom in the geometric structures of the AP molecule and in all fragments optimized by the DFT method is represented in grey, the O atom in red and the H atom in white).

CONCLUSION

The Mulliken charges of the atoms in the molecule were examined as described, and the electronegative atoms in the molecule and the arrangement of the atoms around them, stable double bonds, weak bonds at the end of the molecule, calculated energies, bond lengths and bond angles between the atoms helped us to select all the fragments that would determine the degradation mechanism. The degradation pathway of the AP molecule is shown on Fig. 3. The OH radical is a selective organic molecule scavenger. As a result of examining the molecule in terms of its reaction with OH radicals in air or water, the fragmentation reaction of each molecule was written, starting from the low-energy fragments, and its fate in nature could be determined in this way. In our study, the path that the active ingredient of the researched product follows in nature, in water or in the atmosphere, that is, the degradation reactions with OH radicals, was theoretically investigated without using any chemicals. The results obtained can be compared with the fragments we specified in our fragmentation reaction, if desired, when the necessary samples are taken from the wastewater and analyzed by HPLC.

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