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Theoretical examination of paroxetine HCl, the active ingredient of the drug marketed as Paxil, used in antidepressant treatment, using the DFT method

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Paroxetine HCl (PA) is a non-steroidal anti-inflammatory drug active ingredient, marketed as Paxil, a selective serotonin reuptake inhibitor antidepressant. In this study, PA was theoretically examined according to this pharmaceutical effect, that is, treatment group and site of action. Selected molecule is used for therapeutic purposes, but their fate in nature is not taken seriously when it is eliminated from the body or become waste when it is not used. The aim of this study is to theoretically explain the traces of both the molecule and its hydroxylated fractions in nature, which are included in the natural cycle via wastewater as a result of the unused Paroxetine HCl molecule being thrown into the garbage and therefore into nature.

In order to theoretically determine the degradation mechanism of the selected molecule, geometric optimizations were performed on the DFT/B3LYP/6-31G(d) basic DFT set. Mulliken charges of electronegative atoms in the molecule, arrangement of atoms, double and single bonds, calculated energy values, bond lengths and bond angles between atoms were effective in selecting all the parts that would determine the degradation mechanism. As a result of examining the reactions of molecules with the OH radical in air or water, the degradation paths they would follow in nature were determined.

Keywords: Paroxetine HCl, Paxil, DFT, antidepressant, OH radical, drug

INTRODUCTION

In this study, Paroxetine HCl (PA), one of the five molecules investigated in the scientific research project titled "Investigation of Theoretical Degradation Mechanisms of Selected Pharmaceutical Product Active Ingredients", is examined.

PA is a non-steroidal antidepressant drug active ingredient, marketed as Paxil, a selective serotonin reuptake inhibitor antidepressant. It is used to treat major depression, obsessive compulsive disorder, panic disorder, social anxiety disorder, post-traumatic stress disorder, generalized anxiety disorder, and night sweats associated with menopause. Treatment is stopped by gradually reducing the dose over several weeks to months. It has been observed to cause an increase in suicidal thoughts in depressed children and adolescents. It also has temporary side effects such as nausea, diarrhea, constipation, dry mouth, drowsiness, insomnia, headache, blurred vision, irritability, dizziness, tremors, and sexual dysfunction [1-6]. PA, which is an odorless off-white powder with a molecular formula of $C_{19}H_{20}FNO_3$ and a molecular weight of 329.4 g/mol, has a melting point of 120-138 °C, a melting point of solid PA of 147-150 °C, a boiling point of 451.7 °C, and water solubility of 1.131 mg/L at 25 °C [7].

In this study, PA was theoretically examined according to its pharmaceutical effect, that is, treatment group and site of action. Selected molecule is used for therapeutic purposes, but its fate in nature is not taken seriously when it is eliminated from the body or becomes waste when it is not used. The aim of this study is to theoretically elucidate the fate of both the main molecule and its hydroxylated fragments in nature as they enter the natural cycle by mixing with wastewater.

PA is a biomolecule with hydroxylation ability, in other words, it can interact with OH radicals. Radical attack on an aromatic ring can result in the formation of a new fragment that can be much more harmful than the starting molecule. Therefore, it is very important to know the degradation mechanism of the molecule [8]. Organic compounds undergo photolysis by reacting with the OH radical, and this reaction is the main cause of decomposition reactions in the atmosphere. In reactions between hydroxyl radicals and organic molecules, the OH

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radical acts as an electrophile and the O radical acts as a nucleophile. Therefore, the OH radical easily binds to unsaturated bonds, while the O radical cannot interact with them. In addition, in the presence of an aliphatic side chain attached to an aromatic molecule, the OH radical prefers to bind to the aromatic ring [8-15].

This study examines the possibility of obtaining more hazardous substances through hydroxylation of the PA molecule, whether it is released into the atmosphere in the gas phase or into the water cycle *via* wastewater. As we mentioned in the article of the first researched molecule of our project, what is ignored or not given much importance when pharmaceutical products are launched on the market is the question of what would happen if the product used for treatment mixes with nature [16].

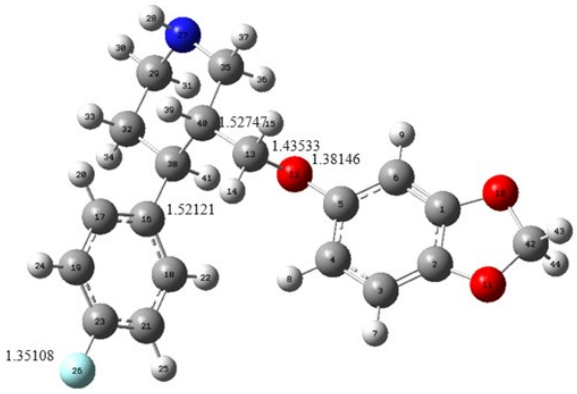
MATERIALS

Theoretically, geometric optimizations were performed in the DFT/B3LYP/6-31G(d) basis set of Quantum Mechanical Density Functional Theory, one of the electronic structure methods, to determine the degradation pathways of PA. Geometric optimizations for all parts were performed using Gauss View 5.0.8 molecular representation program. 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 reaction energy between PA and OH radical [17].

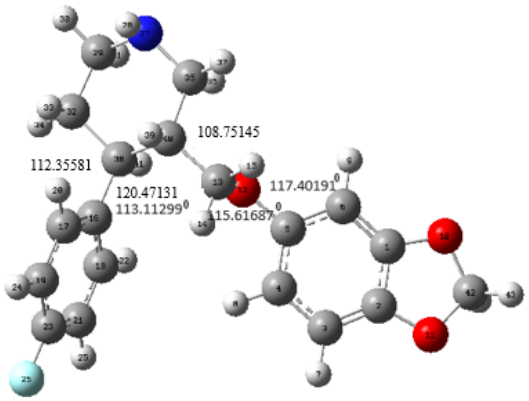
RESULTS AND DISCUSSION

When theoretical chemists look at a molecule they are studying, they think about where it will start to break apart. To avoid any doubt, they start by breaking off the atoms at the ends of the molecule one by one and examine the consequences of each separation. In order to make a decision, firstly the geometric optimization of the molecule under study, that is, its three-dimensional appearance, then the bond lengths and bond angles between atoms, the Mulliken charges of electronegative atoms and most importantly the energy values of each fragment are examined [16, 18, 19].

Although it is predicted that the longest bond and the widest bond angle between atoms in any molecule will break first, the decision is made by examining the multivalent charges of electronegative atoms and the energy values of each fragment. It should be kept in mind that double-bonded or closed-ring structures are more stable than others and that if fragmentation occurs, the breakage from these stable structures will be at the last stage, in other words, the single bonds at the end of the molecule will tend to separate from the molecule more easily [16, 18, 19].



PA(a)



PA(b)

Figure1. The bond lengths between atoms in the PA molecule are shown in PA(a) and the bond angles in PA(b) (C atom is represented in grey, O atom in red, N atom in dark blue, F atom in blue and H atom in white).

According to PA (a) in Figure 1, it is predicted that the bond breaking will be first around the bond length of $C_{13}C_{40}$ and $C_{16}C_{38}$, respectively; and when we look at PA (b) in Figure 1, it is predicted that the bond breaking will be first around the bond angle of $C_{38}C_{16}C_{18}$.

According to the Mulliken charges of the PA molecule presented in Table 1, the electronegative atoms are O_{12}, O_{11}, O_{10}, F_{26}, N_{27}, respectively. Since O_{11}, O_{10} and N_{27} are in a closed ring, the first degradation is not expected to occur here. We can say that O_{12} is the most electronegative atom and one of the degradation paths starts with breaking away from here. Although F_{26} is the 4th electronegative atom, it is located at the end of the molecule. In molecules, the terminal parts are the first parts to be separated in the fragmentation path, unless there are any special conditions (closed ring, double bonded atom, etc.).

The energy values of the possible reaction paths for the studied molecule PA and all its fragments

were calculated both in the gas phase and in the water phase. Every fragment that may be formed because of the interaction of the PA with the OH radical was included in the study. As clearly seen in Table 2: PA1, PA3 and PA2 fragments are the most stable fragments and, respectively, have the lowest energy.

Table 1. Bond lengths and bond angles between atoms in the PA molecule and Mulliken atom charges of the PA molecule

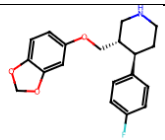
	Bond lengths	(A^0)	Bond angles	(^{0})	Mulliken atom charges	
	C_5O_{12}	1.38146	$C_5O_{12}C_{13}$	115.61687	C_3	-0.044557
	$C_{13}O_{12}$	1.43533	$O_{12}C_{13}C_{40}$	108.75145	C_4	-0.049626
	$C_{13}C_{40}$	1.52747	$C_{32}C_{38}C_{16}$	112.35581	C_6	-0.084981
	$C_{16}C_{38}$	1.52121	$C_{38}C_{16}C_{18}$	120.47131	O_{10}	-0.532583
	$C_{23}F_{26}$	1.35108	$C_{40}C_{38}C_{16}$	113.11299	O_{11}	-0.533305
					O_{12}	-0.551004
					C_{17}	-0.055576
					C_{18}	-0.051571
					C_{19}	-0.052870
					C_{21}	-0.052294
					F_{26}	-0.299715
					N_{27}	-0.241867
					C_{32}	-0.007642
					C_{38}	-0.027975
					C_{40}	-0.007487

Table 2. ΔE (energy), ΔH (enthalpy) and ΔG (Gibbs free energy) values of PA molecule and its fragments in gas and water phases

(Au)	PA	PA1	PA2	PA3
ΔE	-1115.901943	-1016.661385	-696.425937	-785.699939
ΔH	-1115.900999	-1016.660441	-696.424993	-785.698994
ΔG	-1115.974133	-1016.732302	-696.480191	-785.757346
		-1016.671934	-696.435342	-785.708994
Water phase		-1016.670990	-696.434398	-785.708050
		-1016.742818	-696.489460	-785.766289
	PA4	PA41	PA42	PA5
	-621.228352	-521.987682	-581.943520	-535.139137
Gas phase	-621.227408	-521.986738	-581.942575	-535.138193
	-621.279685	-522.036912	-581.992043	-535.182765
	-621.234407	-521.993481	-581.949644	-535.145383
Water phase	-621.233463	-521.992537	-581.948699	-535.144439
	-621.285699	-522.042637	-581.998093	-535.189027
	PA6	PA7		
	-495.863539	-420.655009		
Gas phase	-495.862594	-420.654065		
	-495.902120	-420.690901		
	-495.871824	-420.659593		
Water phase	-495.870880	-420.658649		
	-495.910451	-420.695505		

The C_{23}-F_{26}, C_{16}-C_{38} and O_{12}-C_5 bonds in Figure 1 were broken, resulting in the formation of PA1, PA3 and PA2 fragments. As we clearly observe in Table 2, these three fragments have the lowest energy values, meaning that they participate in the fragmentation process voluntarily (no external energy is required). According to the broken C_{23}-F_{26}, C_{16}-C_{38} and O_{12}-C_5 bonds in Figure 1, PA1, PA3 and

PA2 are formed, respectively, as shown in the degradation mechanism in Figure 2. The bond length of C_{16}-C_{38} has already been stated in Table 1 as the second-longest bond length, 1.52121 Å. Although C_{23}-F_{26} has the shortest bond length with a value of 1.35108, it is ready to break at the very end of the molecule. Since the lowest Mulliken charge in Table 1 is -0.551004 (O_{12}), this is reason enough to pay attention to the arrangement of this electronegative atom and its surrounding atoms. For each atom in the PA molecule, the Mulliken charges in Table 1, stable double bonds, weak single bonds at the end of the molecule, the calculated energies given in Table 2, the bond angles and lengths between the atoms shown in Figure 1 and Table 1 were considered as a whole. All these data helped us to determine the parts in the degradation mechanism. PA1, PA2 and PA3 parts were determined, and it was also clarified which of the three branches the degradation would start from. After this, the degradation up to the stable rings or carbon dioxide and water molecules that will be formed with their degradation can be written with similar thinking. In this study, the sample degradation prediction is shown in Figure 2.

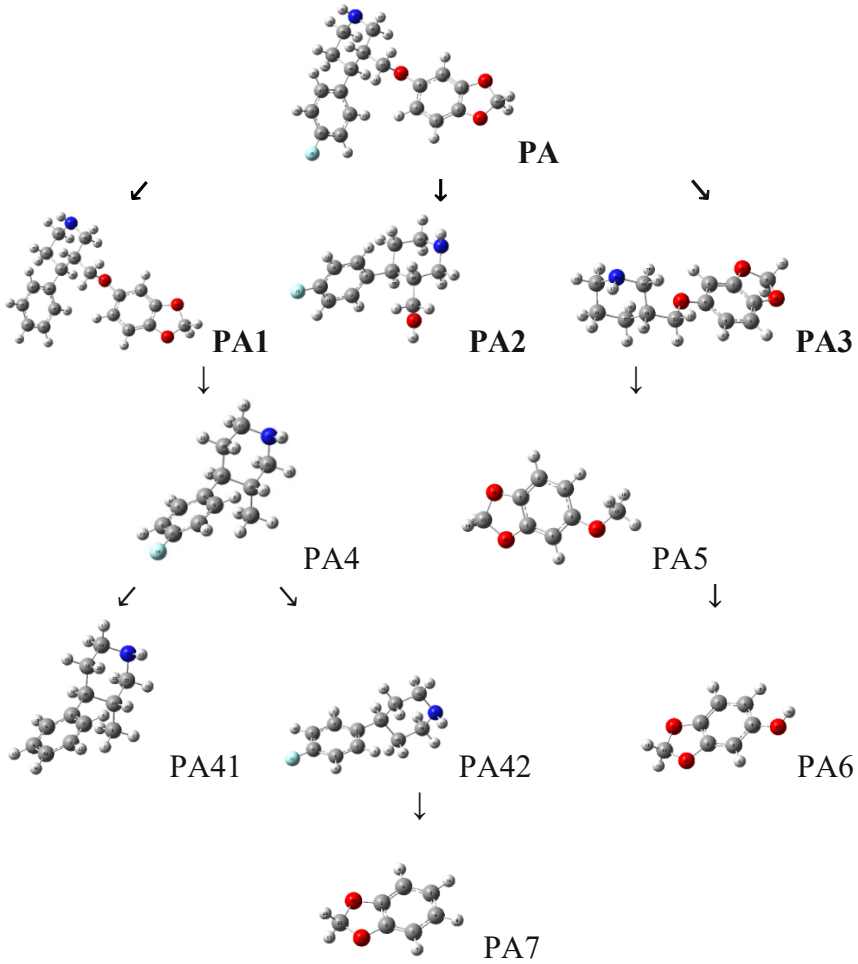


Fig. 2. Pathway of PA molecule (degradation mechanism) (C atom is represented in grey, O atom in red, N atom in dark blue, F atom in blue and H atom in white)

CONCLUSION

The fate of pharmaceutical products, commonly known as drugs, in nature has not yet been investigated when they are used and excreted from the body or when they become waste without being used. PA is one of the molecules selected for our completed project from three different groups, which are effective as anti-inflammatory, antidepressant and calcium channel blocker, according to their pharmaceutical effects (in other words, treatment groups) and effect regions. The degradation mechanism for Apranax (AP), marketed as Naproxen or Naproxen sodium (NS), which has analgesic and anti-inflammatory effects, has been determined and published [16]. The degradation mechanism of Paroxetine HCl (commercial name Paxil), an antidepressant, is shown in Figure 2.

The main purpose of this study is to explain theoretically what will happen to the PA molecule and its hydroxylation products during degradation in nature. The OH radical is a selective organic molecule scavenger. As a result of the reaction of the

PA molecule with hydroxyl radicals in air or water, the mechanism was written starting from the low energy parts. In our study, the path followed by the investigated active pharmaceutical ingredient in nature, water or atmosphere was theoretically examined without using any chemical substance. If desired, when the necessary samples are taken from wastewater and analysed with HPLC, they can be compared with the fragments determined in our fragmentation reactions. Our previous experimental study on the removal of carbamate and organophosphate pesticides from nature using advanced oxidation techniques will also guide researchers who want to use UV in this regard [19].

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