Bulgarian Chemical Communications, Volume 48, Special C (pp. 5–8) 2016

Investigation of possible degradation reactions of amoxicillin molecule

T. Tekpetek, Y.Y. Gurkan*

Namik Kemal University, Department of Chemistry, Tekirdag / Turkey

Received June 26, 2016, Revised September 10, 2016

Amoxicillin is used to treat infections caused by bacteria, including infections of the ears, lungs, sinus, skin and urinary tract. Antibiotics those taken by living beings are disposed of from living metabolism as unchanged or little transformed. Antibiotic traces disposed of can not be treated in conventional wastewater treatment plants and enter directly to the receiving environment. In receiving environments, low concentrations of antibiotic traces can cause microorganism resistance increase and high concentrations of antibiotic traces can cause toxic effects. Therefore wastewaters those includes antibiotic traces have to be treated. In this study is discussed theoretically possible reaction pathways of amoxicillin, which has a high toxic effects and is able to dissolve in the water. For this purpose, possible reactions was examined numerically using Gaussian 09 package software. DFT method was used in theoretical study.

Keywords: Amoxicillin, DFT, OH radical, Antibiotic

INTRODUCTION

Antibiotics are currently regularly used in veterinary and human medicine, and these released into the aquatic environment pose a potential risk for aquatic and terrestrial organisms [1]. Recent studies have focused on the application of advanced oxidation processes (AOPs) to degrade pharmaceuticals in water, and this approach is based on highly reactive species such as hydroxyl radicals to destroy the target pollutant [2]. In industries, amoxicillin is presently produced through a chemical coupling process by using a β-lactam nucleus and appropriate acyl donors. Chemical coupling of amoxicillin involves the reaction of an amino β-lactam such as 6-aminopenicillanic acid (6-APA) usually having its carboxyl group protected with an activated side-chain derivative, where the protecting group is removed through hydrolysis [3]. Waste of pharmaceutical products is one of the most important basic risk factors that threaten human health and ecological balance [4].

In its reactions with organic molecules, OH behaves as an electrophile whereas O is a nucleophile. Thus, OH readily adds to unsaturated bonds while O does not. Both forms of the radical abstract H from C-H bonds and this can result in the formation of different products when the pH is raised to a range where O rather than OH is the reactant. For example, if an aromatic molecule carries an aliphatic side chain, O attacks there by H abstraction whilst OH adds preferentially to the aromatic ring [5]. Hydroxyl radical which is the most reactive type known in biological systems reacts with every biomolecule it encounters including water. Potentially, every biomolecule is a hydroxyl radical scavenger at different speeds [6]. Aromatic compounds are good detectors since they hydroxylate. In addition, the position of attack to the ring depends on the electron withdrawal and repulsion of previously present substituents. The attack of any hydroxyl radical to an aromatic compound results in the formation of a hydroxylated product [7]. In recent years, the density functional theory (Density Functional Theory, DFT) based on the methods have become very popular. Best DFT methods, requires less power from conventional correlation techniques.

This study investigated theoretically possible reaction pathways of amoxicillin and a water-soluble high toxicity. Optimized geometries draw with Gaussian calculations were made in Gaussian09 View 5 software package [8]. DFT method is used in the program. First amoxicillin molecule is drawn through Gaussview5 program on the computer. Then, Gaussian 09 program were made geometric optimization of the lowest energy state. Geometric structures have been analyzed and the bond lengths and bond angles are calculated. In this way, thanks to this program, which will be analyzed in greater costs in terms of material and experimental as more power is intended to calculate the theoretical.

* To whom all correspondence should be sent:
E-mail: yyalcin@nku.edu.tr

COMPUTATIONAL SET-UP AND METHODOLOGY

Molecular modelling

• Cartesian coordinates of the atoms of a molecule, the bond lengths, bond angles, and dihedral angles (the atomic positions);

• Depending on the molecular surface of the position of the atoms and atomic radii;

• atomic distances, atom types and the energy derived from the link arrangement

The mathematical expression is called Molecular Modelling. So theoretically the method of calculating the properties of molecules and their behaviour on the computer and is not simulated. Advances in computer technology advances in quantum chemistry and molecular modelling have played a role in use. The first theoretical calculations were made in 1927 by Walter Heitler and Fritz London. Molecular Modelling; Physics, Chemistry, Biology and supporting experimental work in the pharmaceutical industry or the results to be obtained from experimental studies are used to predict.

Methodology

The reaction model used in the computational part of this study is the reaction between the amoxicillin molecule and the photo-generated •OH radicals [9]. Therefore, all the calculations were based on hydroxyl radical chemistry. Hydroxyl radicals can react with organic compounds by (i) hydrogen abstraction from single bonds, (ii) addition to double bonds, and (iii) one-electron oxidation, which is mostly loss of water from hydroxyl radical adducts. The reaction system under consideration consists of •OH radicals, in other words open-shell species. It is well known that open-shell molecules pose severe problems in quantum mechanical calculations. Hartree–Fock (HF) methods suffer from spin contamination, because they are wave function based. In contrast to the HF methods, density functional theory (DFT) methods use the exact electron density instead of the wave function to calculate molecular properties and energies. Electron correlation, whose absence is the main drawback to HF methods, is accounted for in DFT methods. They suffer from spin contamination less than HF methods and this feature makes them suitable for calculations involving open-shell systems. Therefore, geometry optimizations of the reactants were performed with the DFT method. The DFT calculations were carried out as implemented in GAUSSIAN 09 code [8], using the exchange-correlation functional B3LYP, which combines HF and Becke exchange terms with the Lee–Yang–Parr correlation functional, in combination with the 6-31G* basis set. Vibrational frequencies were calculated for the determination of the structures as stationary points and true minima on the potential energy surfaces. All the possible stationary geometries located as minima were generated by free rotation around single bonds [10].

RESULTS AND DISCUSSION

Theoretical prediction of the degradation mechanism

In the search for a plausible mechanism for the photocatalytic degradation reaction of amoxicillin, DFT reactivity descriptors were employed to have information about the most susceptible sites for hydroxyl radical attack. The hydroxyl radical is a very active species and has a strong electrophilic character [11]. Once formed, it can readily attack the aminotoluene molecule and produce the reaction intermediates. Fig. 1 shows the optimized structure of amoxicillin molecule and the numbering system that is used throughout the calculations. The calculated local softness and Fukui functions are presented in Table 1.

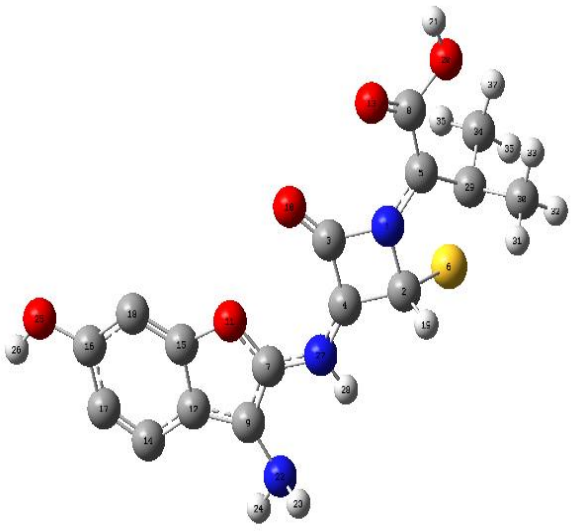

Fig. 1. Optimized structure of amoxicillin and the numbering system (gray, carbon; red, oxygen; blue, nitrogen; white, hydrogen; yellow, sulfur).

Three main competing reaction pathways shown in Fig. 2 were determined by selecting the specific sites of amoxicillin molecule, on the basis of their softness values being close to that of the •OH radical. The predicted mechanism was confirmed by comparison with the experimental results on simple structures reported in the literature, as explained below.

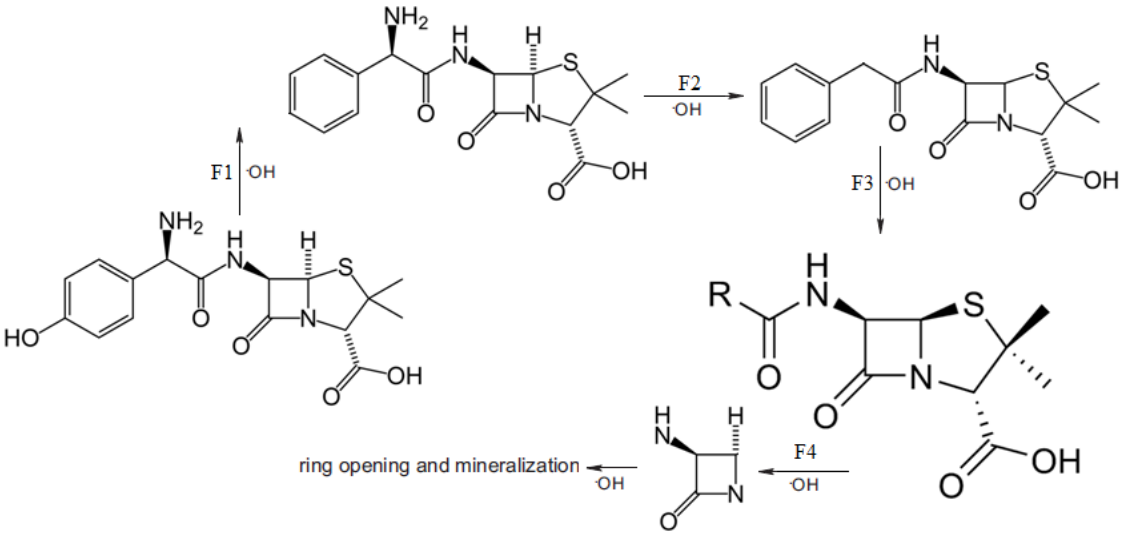

Fig. 2. Possible pathways for the photocatalytic degradation of amoxicillin.

Table 1. Chemical reactivity descriptors for amoxicillin and for the •OH radical.

	f◦	s◦	Δs◦
S6	0.1489	1.17176	1.6103
C5	0.0457	0.5698	2.6879
N22	0.0311	0.3941	2.9845
N5	0.0269	0.3267	2.8896
N27	0.0265	0.2789	2.9547
C7	0.0274	0.5336	2.5478
C9	0.0368	0.4897	2.6489
H21	0.0258	0.3126	2.9478
H26	0.0121	0.1427	3.0643
H23	0.0048	0.0568	3.1507

OH radical fragmentation reaction is carried out with the N22 had attacked. OH bond breakage of the molecular fragments resulting ampiciline 1 (F1) has been called. Geometry optimization results obtained is shown in Fig. 3.

Electronegative group NH_2 group of breakage caused by penicillin G molecule fragment 2 (F2) has been called and shown in Fig. 4.

Due to the electronegativity of the oxygen bound to a benzene ring group of benzene ring was separated from the resulting penicillin molecule fragment 3 (F3) has been called. Geometry optimization results obtained is shown in Fig.5.

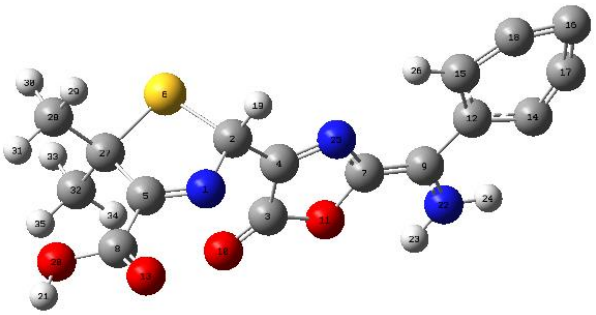

Fig. 3. Optimized structure of ampiciline.

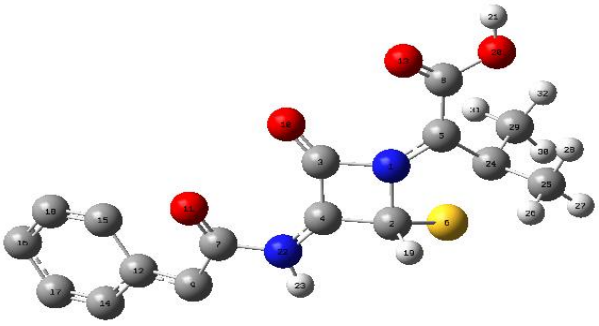

Fig. 4. Optimized structure of penicillin G.

Sulfur and oxygen electronegativity due to the degradation reactions was realized. The smallest fragment and into the water, which is harmless substances β-lactam antibiotics has become. Molecular fragment, 4 (F4) has been called. Geometry optimization results obtained is shown in Fig.6.

Degradation of amoxicillin was predicted to occur through intramolecular β- lactam, ring cleavages followed by subsequent reactions with •OH radicals transforming the fragments into smaller species such as SO_4^{2-}, NO_3^- and NH_4^+.

Energies are shown in the Table 2 of possible reaction pathways.

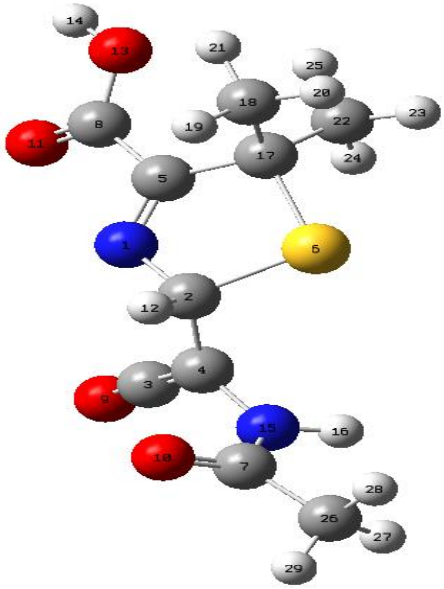

Fig. 5. Optimized structure of penicillin.

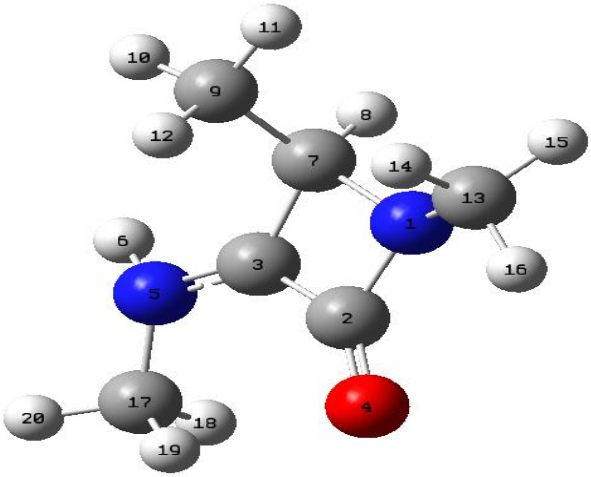

Fig.6. Optimized structure of β-lactam.

Table 2. According to the DFT method energy values.

	Energy (kcal/mol)
Ampicilin	-928.330
Penicillin G	-893.047
Penicillin	-751.029
β-lactam	-263.507

CONCLUSIONS

As a result, decomposition, requires further energy. OH radicals are used to degrade antibiotic substances in water. As seen in our Fragments harmful amoxicillin β-lactam is up fragmented and has become harmless to the environment. Our objective is that antibiotic substances involved in the water to break down to the smallest harmless and to remove the water. This fragmentation theoretically realized as shown in the results.

Acknowledgements: *The authors greatly appreciate Namik Kemal University Research Foundation for financial support. Project number: NKUBAP.00.10.AR.15.14*

REFERENCES

1. W. Xu, G. Zhang, S. Zou, X. Li, Y. Liu, *Environ. Pollut.* **145**, 672 (2007).
2. M. Klavarioti, D. Mantzavinos, D. Kassinos, *Environ. Intern.* **35** ,402 (2009).
3. I. Alemzadeh, G. Borghei, L. Vafi, R. Roostaazad, *Chem. Chem. Eng.* **17** (1), 106 (2010).
4. L. Povyakel, O. Bobyliova, S. Snoz, Y. Bardik, *Toxicology Letters*, **180**, 197 (2008).
5. V.G. Buxton, L.C. Greenstock, P.W. Helman, B.A. Ross, *Journal of Physical and Chemical Reference Data*, **17**, 513 (1988).
6. M. Anbar, P. Neta, *Int. J. Radiat Isot*, **18**, 495, (1965).
7. B. Halliwell, M. Grootveld, J.M.C. Gutteridge, (1988), *Methods of Bıochemical Analysıs*, **33**, 59-90.
8. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 09, Revision B.04, Gaussian, Inc., Pittsburgh, PA, 2009.
9. N. San, M. Kilic, Z. Cinar, *J. Adv. Oxid. Technol.* **10**(1), 51 (2007).
10. J.P. Stewart, *J. Comput. Chem*. **10**, 221 (1989).
11. V. Brezová, M. Ceppan, E. Brandsteterova, M. Breza, L. Lapcik, *J. Photochem. Photobiol. A: Chem.* **59,** 385 (1991).