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COMPUTATIONAL STUDIES OF SOME TETRACYCLINE DERIVATIVES

BY

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Abstract. The aim of this paper is to analyze, from the molecular modeling point of view, tetracycline and two of its derivatives used to treat certain types of infections which may appear in human body.

The main parameters of these molecules, like polarizabilities, HOMO/LUMO energies, total energies, binding energies were computed after geometrical optimization, using HYPERCHEM.

Keywords: tetracycline derivatives; HOMO/LUMO energies; polarizability.

1. Introduction

Tetracyclines are broad-spectrum antibiotics, considered safe and with many favorable properties such as: low toxicity, low cost, which made it among the most used antibiotic groups produced and consumed worldwide. The name of these compounds derives from the four (“tetra-”) hydrocarbon rings (“-cycl-”) as it is shown in Fig 1.

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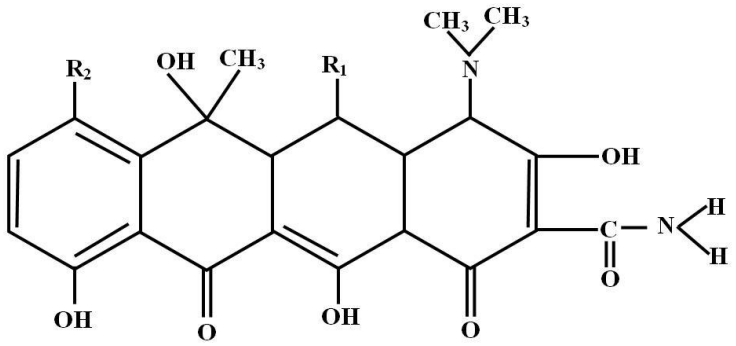

R_1, R_2 – H; Tetracycline
R_1: -H, R_2 – Cl; Chlortetracycline
R_1: -OH, R_2 – H; Oxytetracycline

Fig. 1 − Molecular structures of the studied Tetracycline derivatives.

All tetracyclines have the same mechanism of action and side effects: nausea, vomiting and diarrhea, induced photosensitivity, urticaria, headache, abdominal pain, hypertension, fever, mild leukopenia, anemia and thrombocytopenia. Patients with diabetes must be watching closely blood glucose levels (Zhanel *et al*., 2004).

The first member of the tetracycline family, chlortetracycline was discovered in 1945 by Benjamin Duggar, and received the name of aureomycin – a product of natural fermentation of the bacteria Streptomyces aureofaciens, which is present in the soil.

A second member of the teracycline group, oxytetracycline was isolated in 1947 from the bacteria Streptomyces rimosus, and received the name terramycin. Oxytetracycline was patented in 1949 and entered into commercial use in 1950 (Tripathi, 2015).

In 1953, the tetracycline molecule was discovered. It has the simplest structure from this antibiotic family and the same qualities as the other members of the class of antibiotics (Mehta Akul, 2011). There are also synthetic tetracycline derivatives, with low molecular weight, less toxic and with good therapeutic use, oral absorption and efficient hepatic excretion.

In this article the authors analyzed the above mentioned molecules using HyperChem (www.hyper.com).

2. Computational Method

Tetracycline molecules were geometrically optimized using the Polak – Ribière algorithm. PM3 method from computational chemistry, used in this paper, is a semi-empirical method for the quantum calculation of molecular

structure using the results from solving Hamiltonian of the molecular system and combine these results with the experimental data from the program database. The method was developed by J.J.P. Stewart and first published in 1989 (Stewart, 1989).

3. Results and Discussions

The structural formula for Tetracycline ($C_{22}H_{24}N_2O_8$), Chlortetracycline ($C_{22}H_{23}ClN_2O_8$) and Oxytetracycline ($C_{22}H_{24}N_2O_9$) are presented in Fig. 2.

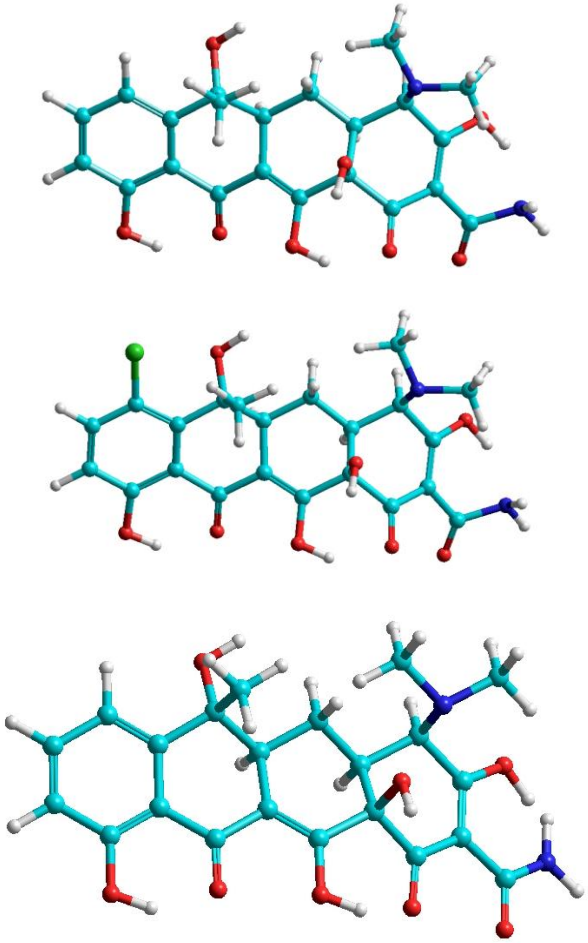

Fig. 2 – The structural formulas of studied Tetracyclines (green-carbon, white-hydrogen, blue-nitrogen, red-oxygen and dark green-chlorine).

The main energetic parameters (like total energy of the molecule, heat of formation) were computed and listed in Table 1.

Table 1
Maine Energetic Parameters of Tetracycline, Chlortetracycline, Oxytetracycline

Studied compounds / Main energetic parameters	Tetracycline	Chlortetracycline	Oxytetracycline
Total energy (kcal/mol)	-130298.589	-137246.51	-137072.46
Heat of formation (kcal/mol)	-5981.904	-5962.589	-6083.259
Binding energy (kcal/mol)	-269.404	-273.201	-311.188
E_{HOMO} (eV)	-8.958	-8.770	-9.062
E_{LUMO} (eV)	-1.098	-1.121	-1.343
$\Delta E = \lvert E_{HOMO} - E_{LUMO} \rvert$ (eV)	7.860	7.649	7.719

Molecular orbital theory is a very important in chemistry, being used comprehensively to illustrate chemical reactivity of a compound. For example, molecules with large HOMO-LUMO gaps are usually stable and unreactive; unlike those with small gaps. The energies of the frontier molecular orbital: HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) will be used further to calculate other physical characteristics of the molecule.

The difference $E_{HOMO} - E_{LUMO}$, named HOMO/LUMO gap (Fig. 3), represents the lowest energy electronic excitation that a molecule may posses. Also, if the values of E_{HOMO} and E_{LUMO} are known, the ionization potential and the electron affinity can be estimated (Koopmans, 1934).

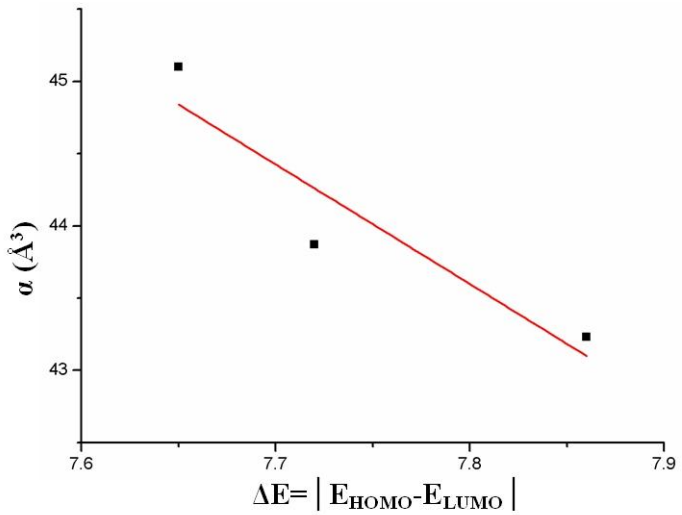

Fig. 3 – Dependence of energy gaps *vs*. polarizabilities of Tetracycline derivatives.

With the values for energies of HOMO and LUMO levels, the hardness, chemical potential and electrophilicity index can be estimated. Also, the electrophilicity index is used as a possible descriptor for the biological activity (Parthasarathi *et al*. 2004). In this context, surface, volume, hydration energy, logP and refractivity index are molecular descriptors and are playing an important role in determination of biological activity for a certain pharmaceutical compound. Taking into consideration the obtained data from Table 2, logP is negative (logP < 0) for all studied molecules, meaning that all three compounds are soluble in water.

Table 2
QSAR Parameters of Studied Tetracycline Derivatives

	Tetracycline	Chlortetracycline	Oxytetracycline
Molecule surface ($Å^2$)	597.30	609.96	599.82
Volume ($Å^3$)	1076.35	1109.43	1082.67
Hydration energy (kcal/mol)	-21.64	-20.90	-23.08
logP	-3.09	-3.31	-3.86
Refractivity ($Å^3$)	116.52	121.24	117.73
Polarizability ($Å^3$)	43.23	45.16	43.87

4. Conclusions

1. Three Tetracycline derivatives used to treat almost any kind of infections have been studied using HYPERCHEM.

2. The main parameters were computed by using the above mentioned program. The results are very important in future synthesis of new drugs as derivatives of Tetracycline.

3. The study is important in the discovery of new drugs because it provides information on the interaction of a known drug with other molecules.

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STUDII COMPUTAȚIONALE ALE UNOR DERIVAȚI DE TETRACICLINĂ

(Rezumat)

Scopul acestui articol este de a analiza, din punctul de vedere al modelării moleculare, tetraciclina şi doi dintre cei mai importanţi derivaţi ai acesteia utilizaţi în tratamentul unor infecţii ce pot apărea, la un moment dat, în corpul uman. Principalii parametrii ai acestor molecule cum ar fi polarizabilitatea, energiile orbitalilor de frontieră, energia totală, energia de legătură etc. au fost calculate după optimizarea geometriei moleculare şi efectuarea unui calcul utilizând programul HYPERCHEM.