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Molecular Modeling of Debromolaurinterol Isolated from Sea hare (*Aplysia kurodai*) Using MOPAC Software

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Abstract

This study aimed to obtain a molecular model of a cytotoxic compound debromolaurinterol isolated by Tsukamoto et al. (2005) from sea hare (*Aplysia kurodai*) using Molecular Orbital Package (MOPAC) software. This semi-empirical approach was done by creating a Z-matrix of the molecule which was then converted to its MOPAC input data. Optimization of these data had provided the specific bond distance , bond angle, dihedral angle of the most stable molecular geometry. Furthermore, calculated energies like heat of formation (-6.75618 kcal/mol), ionization energy (8.80571 eV), electronic energy (-17,174.16327 eV) and core-core repulsion energy (14,651.44307 eV) were generated. The interatomic distances between atoms of the molecule were also provided that may greatly influence the physical and chemical properties. Finally, MOPAC calculations generated visual models of the most stable molecular geometry in stick, ball and stick, wireframe and space fill configuration. This study therefore provided new information which is very important for chemistry educators as well as biosynthetic chemist in designing possible chemical reactions in order to synthesize product or its derivative that are experimentally difficult to conduct.

Keywords: *Aplysia kurodai*; molecular modeling; Molecular Orbital Package (MOPAC); z-matrix; theoretical calculations

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1. Introduction

In chemistry, molecules are more appreciated and well understood by visualization in a three dimensional structure. Hence, models like ball and sticks are likely being used. However, its use is limited when molecules are as big and bulky like debromolaurinterol. Bond lengths, bond angles, dihedral angles between atoms of the molecule have to be taken into account. Conventionally, the time independent mathematical Shrodinger equation will be used to calculate bond stretching, angle bending, dihedral term and different types of electrostatic attraction. This is a very tedious and time consuming task. This is where computers will come in and do the dirty jobs in computing. The use of Molecular Orbital Package (MOPAC) will calculate, visualize, rotate, manipulate and optimize the geometry of molecules on a computer display giving us a model of the molecule. MOPAC calculations can also give information that influences its physical, chemical and biological properties. It will also serve as baseline information that can be used in the synthesis of its derivatives and how it affects the reactivity of the molecule [1].

There are number of compounds that have already been isolated. One of these is the new cytotoxic and antibacterial compound debromolaurinterol from sea hare, *Aplysia kurodai*. Its structure and biological activities were determined [2]. Structure elucidation was done using Nuclear Magnetic Resonance (NMR) and Mass spectroscopy (MS) which afforded the planar structure of the molecule and was supported by the results of [3, 4]. However, specific bond length, bond angles, dihedral angles, heat of formation and other chemical constants that best describe the molecule are still unknown. Hence, this study was aimed to obtain a molecular model of the compound debromolaurinterol via semi-empirical approach using Molecular Orbital Package (MOPAC) software. This study was limited only on obtaining some of the constants such as heat of formation, ionization energy, electrostatic energy and core-core repulsion. Further, it only emphasized on wireframe, stick, ball and stick and space fill as the visual models of debromolaurinetrol.

2. Materials and Methods

The study used MOPAC version (WinMpac7.21) written by Dr. Roman Shchepin and Dmitriy Litvinov. The semi-empirical method used in these calculations was Modified Neglect of Diatomic Overlap (MNDO). The structure of the molecule, debromolaurinterol was conveniently defined by means of a Z-matrix. This is a method of defining the molecule atom by atom in terms of bond lengths, bond angles and dihedral angles.

2.1 How the Program Worked

MOPAC worked by specifying the type of calculation which was controlled by keywords. The key words used were VECTORS, SYMMETRY and BONDS. As default, these keywords must be capitalized. VECTORS keyword stands for print final eigenvectors while SYMMETRY imposes symmetry conditions and BONDS for print final bond-order matrix. The program then read the initial molecular geometry in z-matrix form. MOPAC performed iterative computations with optimization until it finally found a more realistic and most stable geometry [5]. The calculations were done using Sony Vaio personal computer in Windows 7 with Dual-Core E-450 APU @ 1.65GHz and 2GB Random Access Memory (RAM).

2.2. The Z- Matrix

The z – matrix is a geometrical means of defining the positions of each atom relative to other atoms in the molecule of debromolaurinterol (Figure 1). A complete z-matrix mathematically describes the three dimensional shape using internal coordinates like bond length, bond angles, dihedral angles and its connectivity. For this calculation, dummy atoms were used. Dummy atoms were simply an imaginary point in space treated for geometry definition which was then removed after calculations so that only the real molecule remained. The structure of debromolaurinterol determined experimentally by Tsukamoto, et.al. [2] (Figure 1) was converted to Figure 2. The first step in writing the z-matrix was to assigned numerical values for each atom in the molecule. This was followed by choosing the atom to be the origin or reference point, in this case, the dummy atom XX_1 which was placed at the origin of the coordinate system and on top of the Z – matrix. Its position and connectivity could not be defined yet since there was no atom that precedes it. The second atom (XX_2) was defined by its distance from atom 1 only because the second atom was always placed on a predetermined axis. The third atom, C_3 was defined using the distance from XX_2 dummy atom and the XX_1- XX_2 -C_3 angle. The fourth atom (C_4) was defined exactly as the third except that an extra parameter was needed to specify its position uniquely. The exact position was defined using a dihedral angle to (C_3). Debromolaurinterol has a chemical formula of $C_{15}H_{20}O$. The exact positions of the remaining atoms were distinctly defined by the bond lengths, bond angles and dihedral angles in similar fashion described above.

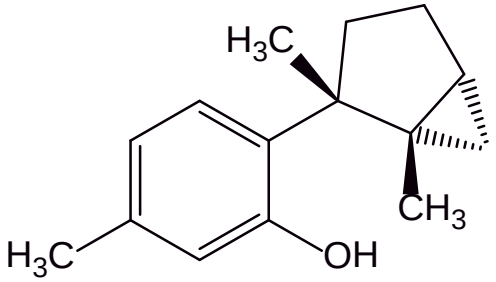

Fig. 1. Planar structure of debromolaurinterol

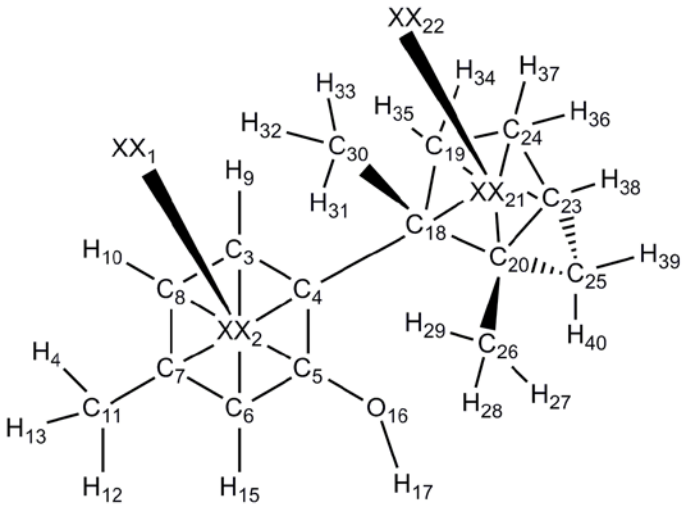

Figure 2: Atom assignment of dembromolaurinterol

2.3. MOPAC Input File

The z-matrix was then converted to its corresponding MOPAC input format for the program to read the specification of the molecule. The MOPAC input or data sets (Table 1) consisted of one line keywords, two lines of user-defined text followed by the z-matrix. First column of the z- matrix was for the atoms found in the molecule followed by the bond length values, bond angle and dihedral angles. The columns of 1's were entries that command the program to optimize the parameters. Optimization meant that estimated values are being changed into a more reasonable bond length and bond angle. The connections were written on the last three columns to the right. The zero in the last line indicated the end, an indication that there were no more atoms to consider. This MOPAC input had undergone iterative calculations to give the most stable, reasonable geometric molecular structure.

Table 1: MOPAC Input for Debromolaurinterol

Atom	Bond Length	Optimi Zation	Bond Angle	Optimi Zation	Dihedral Angle	Optimi Zation	Connectivity		
XX_1	0	1	0	1	0	1	0	0	0
XX_2	1.00	1	0	1	0	1	1	0	0
C_3	1.00	1	90	1	0	1	2	1	0
C_4	1.00	1	90	1	60	1	2	1	3
C_5	1.00	1	90	1	60	1	2	1	4
C_6	1.00	1	90	1	60	1	2	1	5
C_7	1.00	1	90	1	60	1	2	1	6
C_8	1.00	1	90	1	60	1	2	1	7
H_9	1.40	1	90	1	180	1	3	8	2
H_{10}	1.20	1	90	1	180	1	8	3	7
C_{11}	1.40	1	120	1	180	1	7	6	8
H_{12}	1.10	1	130	1	180	1	11	7	8
H_{13}	1.10	1	110	1	110	1	11	12	7
H_{14}	1.10	1	110	1	110	1	11	12	13
H_{15}	1.50	1	130	1	180	1	6	5	7
O_{16}	1.50	1	105	1	190	1	5	6	7
H_{17}	1.50	1	110	1	180	1	16	5	4
C_{18}	1.50	1	110	1	180	1	4	5	3
C_{19}	1.50	1	110	1	180	1	18	4	5
C_{20}	1.40	1	120	1	180	1	18	4	3
XX_{21}	1.40	1	40	1	180	1	18	19	20
XX_{22}	1.00	1	90	1	70	1	21	18	20
C_{23}	1.50	1	90	1	180	1	20	21	18
C_{24}	1.40	1	70	1	180	1	23	21	20
C_{25}	1.50	1	160	1	160	1	20	23	24
C_{26}	1.50	1	120	1	80	1	20	23	25

H_{27}	1.50	1	110	1	180	1	26	20	18
H_{28}	1.50	1	110	1	150	1	26	27	20
H_{29}	1.50	1	110	1	110	1	26	28	20
C_{30}	1.60	1	95	1	40	1	18	20	26
H_{31}	1.50	1	140	1	140	1	30	18	19
H_{32}	1.50	1	110	1	150	1	30	31	18
H_{33}	1.50	1	70	1	180	1	30	32	18
H_{34}	1.50	1	170	1	90	1	19	18	30
H_{35}	1.50	1	110	1	180	1	19	18	30
H_{36}	1.50	1	110	1	180	1	24	23	25
H_{37}	1.50	1	110	1	360	1	24	23	25
H_{38}	1.50	1	110	1	270	1	23	24	36
H_{39}	1.50	1	110	1	360	1	25	23	38
H_{40}	1.50	1	150	1	180	1	25	23	38
0									

3. Results and Discussion

3.1 Calculated energies

The MOPAC calculation provided energies on the enthalpy of formation (kcal/mol), electronic energy, core-core repulsion (eV) and its ionization potential (eV) for debromolaurinetrol (Table 2.)

The heat of formation of organic compounds is very important physical properties. It is the energy required for the formation by direct union of elements in the compound and can be used to predict the stability of molecules. The MOPAC calculated value of -6.75618 kcal/mol was an indication that this compound was more stable than its component elements at standard conditions [6]. There was no available literature value for the heat of formation of debromolaurinterol, hence its disparity cannot be calculated. However, studies showed that result of MOPAC calculations for other common molecules are accurate and comparable with the literature values [7,8,9,10].

Structurally, debromolaurinterol can be considered as a substituted benzene molecule. Accordingly[11], the ionization potential of benzene (9.52 eV) decreases with the introduction of substituent. Its decrease depends on the substituent and the degree of electron migration and the magnitude of overlapping between the substituent and the neighboring carbon atom in the ring. The MOPAC generated ionization potential is 8.80571 eV which was lower than that of the unsubstituted benzene. Lower ionization energy is an implication of greater stability [7].

Electronic energy is the potential energy of the electrons at the equilibrium geometry of the molecule. The contributors of potential energy are the forces between bounded vibrating atoms, nucleus and electrons, proton and neutrons and nuclei and shared electron pair in a bond. This relates to the depth of the molecular potential energy curve, therefore negative [6]. Debromolaurinterol's electronic energy value of -17,174.16327 eV

corresponds to the minimum energy that is related to the equilibrium bond length of the molecule. It has to be noted that molecules prefer to have low potential energy resulting to repulsion of each atom which will increase the distance between them, thereby lowering the potential energy.

Core-core repulsion energy is the electrostatic interaction between positively charged particles. The MOPAC calculation for core-core repulsion (14, 651 eV) was positive. A positive value means that a positive charge particle will be repelled in this particular region of space [12].

MOPAC also provided the most stable molecular geometry of debromolaurinterol with an optimized bond length that ranged from 1.0 to 1.6 A^o. Specifically, the average computed C-H bond length was 1.06 compared to the literature value of 1.09 for most molecules containing C-H bonds. The C-C bond distance of 1.54 was the same with the literature value while C=C had a disparity of 0.08. Moreover, the O –H separation using MOPAC was 0.95 while the literature was 0.96. C-O bond on the other hand was 1.36. These results as summarized in Table 3 below shows negative difference for some which implied that calculated values were lesser than the already established literature values.

Table 2: Calculated values of the final heat of formation, ionization potential and core-core repulsion of debromolaurinterol

Properties	MOPAC Computed Values
Final heat of formation	-6.75618 kcal/mol
Electronic energy	-17174.16327 eV
Core-core repulsion	14651.44307 eV
Ionization potential	8.80571 eV

Table 3: The disparity between MOPAC calculated value from literature value on bond length.

Bond Between Atoms	Average MOPAC Calculated Value, Angstrom (MCV)	Literature Value, Angstrom (LV)	Disparity (MCV-LV)
C-H	1.06	1.09	-0.03
C-C	1.54	1.54	0.00
C=C	1.42	1.34	0.08
O-H	0.95	0.96	-0.01
C-O	1.36	1.43	-0.07

Martin S. Silberberg. *Chemistry: The Molecular Nature of Matter and Change*. 2nd ed Mc Graw-Hill Companies,Inc. USA., 2000, pp. 244.

3.2 The Interatomic Distances of Atoms in Debromolaurinterol

MOPAC calculated interatomic distances can give insights to synthetic chemist to determine if introduction of reagents targeting specific reactive site will proceed to the desired reaction products. These will save time, money and other resources. Take for an instance the calculated interatomic distance between C_{30} and C_{26} which were both located above the plane. Theoretically, it must be expected that this distance will be greater than C_{30} and C_{25} which were on opposite side of the plane. True to its result, C_{30}-C_{26} had a distance of 2.97 A^o compared to C_{30} - C_{25} of 4.01 A^o. Another important application of the result of MOPAC calculation is determining the feasibility of a particular reaction. Take into consideration the aromatic OH, phenol can easily be alkylated via Williamson synthesis **[**13] to produce an ether compound. However, debromolaurinterol is a disubstituted phenol compound which may not favor alkylation reaction to proceed. The bulky substituents at the ortho position especially the CH_3's and cyclopropyl moieties (Figure 3) may have some steric effect with –OH. The interatomic distance of O_{16} to $CH_2(C_{25})$, $CH_3(C_{26})$ and $CH_3(C_{30})$ are shown in Figure 3. The, alkylation of –OH is either slow or impossible especially for bigger alkyl groups that will be introduced to the phenol. Thus, this will provide crucial information among Chemists for possible oxidation of reactive OH. Moreover, the position of the cyclopropane in MOPAC calculated geometry corroborates with the result of Tsukamoto et al. experiment because this is the position that provides less steric effect considering that the methyl group C_{12} in Figure 1 is projected upward extending into space, away from the rest of the molecule. The lesser the steric effect for organic compounds the more stable it will be [13].

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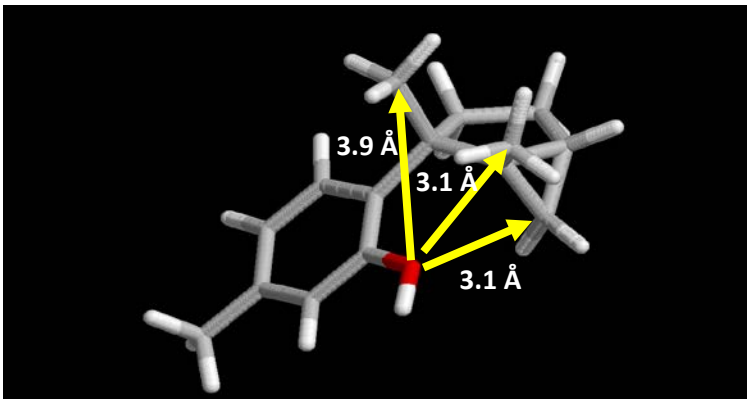

Figure 3: Selected calculated interatomic distance of debromolaurinterol.

3.3 Visual Models of Debromolaurinterol

One of MOPAC general purpose is to generate a visual model of the molecule under study. Molecular geometry of the molecule can be viewed at any desired angle by simply rotating the molecule using different models namely, the wireframe (Figure 4), ball and stick (Figure 5), stick (Figure 6) and space fill configurations (Figure 7). The structure can be more appreciated in organic chemistry, biochemistry especially for large bulky molecules.

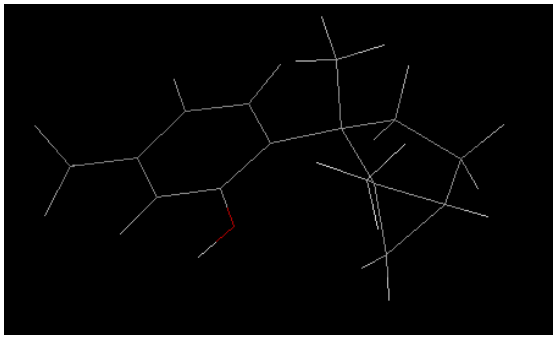

Figure 4: MOPAC wireframe model of debromolaurinterol

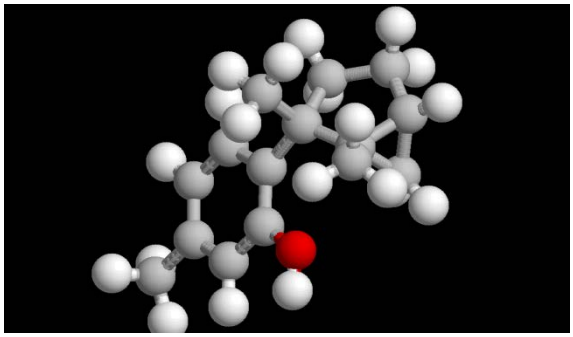

Figure 5: MOPAC ball and stick model of debromolaurinterol

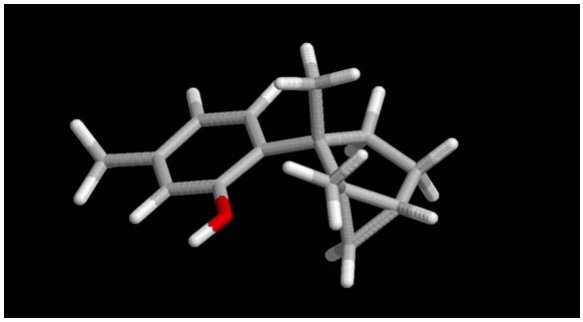

Figure 6: MOPAC stick model of debromolaurinterol

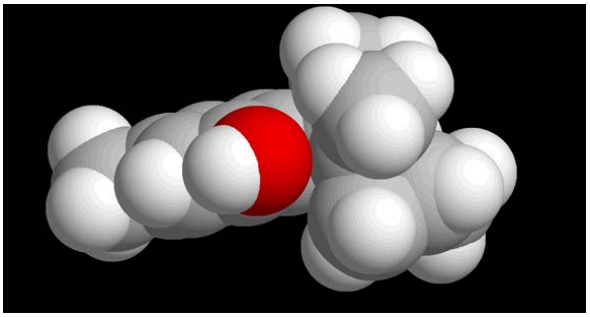

Figure 7: MOPAC space fill model of debromolaurinterol

4. Conclusion

The previously unknown parameters of debromolaurinterol like bond length, bond angle, dihedral angle, interatomic distances, heat of formation, ionization potential, electronic energy and core-core repulsion were established through MOPAC calculations. Moreover, it generated a three dimensional model of the most stable conformation of the molecule. MOPAC can also be used to perform calculations for newly discovered compounds especially if experimental data are wanting or where current experimental procedures fail.

This study recommends to perform calculations of debromolaurinterol using other molecular modeling software for comparison with MOPAC calculations result. It is further recommended to make initial guess of the coordinates within the proximity of the true orientation of the molecule to minimize computational time.

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