International Journal of Innovation and Applied Studies
ISSN 2028-9324 Vol. 25 No. 1 Dec. 2018, pp. 516-527

http://www.ijias.issr-journals.org/

DETERMINATION OF PROTONATION AND METHYLATION SITES OF NEUTRAL MAKALUVAMINES, RELATIVE STABILITY AND REACTIVITY POTENTIAL OF THE CHARGED FORMS

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ABSTRACT: Real public health problem, cancer is one of the pathologies that mobilize the entire scientific community. The conception of effective drugs against this pathology has become a challenge for all actors in research.
Some molecules such as makaluvamines have shown important anticancer properties. These molecules belong to the family of alkaloids generally active in charged forms. The purpose of our work is to determine the protonation or methylation sites, relative stability and reactivity potential of some makaluvamines by a quantum chemistry method.
B3LYP/6-311++G(d,p) theory level is used for all the calculations done. Firstly, we have estimated the gas phase basicity (GB) and proton affinity (PA) for the different heteroatoms of the molecules. Secondly, electronic energies, enthalpies of formation and free enthalpies of formation calculation permitted us to deduce the relative stability of the different forms of studied makaluvamines. Thirdly, Fukui functions, chemical softness and hardness, chemical potential and electrophilia index calculation lead us to the analysis of the reactivity.
The results obtained permit us to identify the preferred site of protonation / methylation, to show that the charged forms are more stable and more reactive than the neutral forms.

KEYWORDS: Makaluvamine, gas phase basicity (GB), proton affinity (PA), reactivity and quantum chemistry.

1 INTRODUCTION

Cancer is a growing pathology. This fact can be explained by the various types of pollution associated with new technologies and various risk factors such as alcohol or tobacco [1,2]. This pathology has become a challenge for both the physician and the chemist. Research to develop molecules to treat cancer has increased. The implementation of syntheses of new active molecules opened the way to the realization of screening. It sometimes happens to discover an equally active molecule that has lesser side effects [3]. Several molecules such as carbazoles and pyrroloiminoquinones, all of the large alkaloid family, have shown anticancer activities [4,5]. Makaluvamines belong to the family of pyrroloiminoquinone alkaloids. They have been the subject of several studies for their anti-cancer properties. That gives them an important class of marine metabolites isolated in most sponges of the genus zyzzya [6-9].Experimental work has shown significant anti-cancer activity and strong inhibition of topoisomerase II [10,11].

The research work already carried out on these molecules has mainly focused on synthetic routes and the search for biological activities. To our knowledge, these molecules have not been the subject of any structural or biological theoretical study. Alkaloids are generally more active in their charged form(s). In this work, our purpose is:

- to determine the protonation or methylation sites of some makaluvamines,
- to study the stability of the charged shapes with respect to the neutral form,
- to study the reactivity potential of the different forms.

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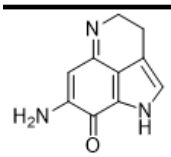
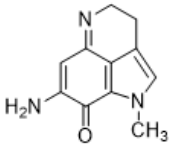
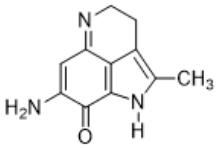
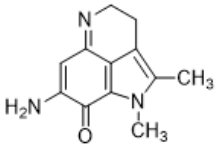
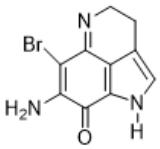
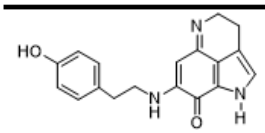
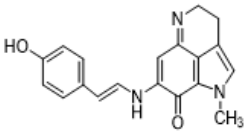
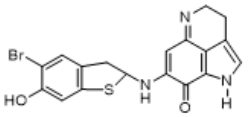
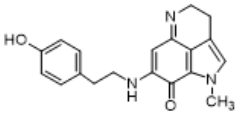
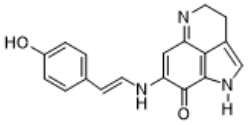
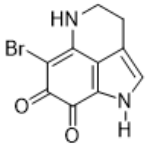
Theoretical calculations are performed in the gas phase at the B3LYP / 6-311 ++ G (d, p) theory level. An analysis of the quantities of basicity and proton affinities is carried out on sites of some selected makaluvamines. We have calculated the electronic energies, the enthalpies of formation, the free enthalpies of formation and deduced the relative stabilities. Reactivity parameters are calculated. These include the ε_{HOMO} and ε_{LUMO} energies to apply the theory of molecular boundary orbitals, Fukui functions [12], softness, hardness, chemical potential and electrophilia index.

2 STUDIED MAKALUVAMINES AND CALCULATIONS METHODS

2.1 STUDIED MAKALUVAMINES

The makaluvamines listed in the literature and those who have been purpose of this study are in Figure 1.

Makaluvamines	Nature / denomination
	Neutral / **I** Methylated / **A1**
	Neutral / **A**
	Neutral / **C**
	Neutral / **H**
	Neutral/ **N**

Makaluvamines	Nature / denomination
	Protonated / **D** Methylated / **J**
	Protonated / **E** Methylated / **G**
	Protonated / **F**
	Protonated / **K** Methylated / **P**
	Methylated / **L** Protonated / **M**
	Neutral / **O**

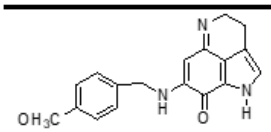
Makaluvamines	Nature / denomination
	Methylated / **V**

Fig. 1. Structures of makaluvamines listed in the literature and studied

From the molecules of this figure, it appears that the makaluvamines can be in neutral, protonated or methylated form (charged forms) on the pyridine nitrogen. We have therefore considered these three forms. Thus, a makaluvamine X in the literature, is named:

X: neutral form;

XH^+: protonated form;

X^Y : methylated form.

In Figure 2 below, is shown makaluvamine I or 7-amino-2a1, 3, 4, 8a-tetrahydropyrrolo [4,3,2-de] quinoline 8 (1H) -one. It is chosen as the basic molecule.

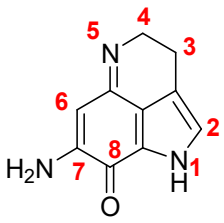


Fig. 2. Makaluvamine I, basic molecule with official numbering

Groups of compounds are formed and based on the skeleton of this compound, so:

Group 1: formed by molecules A, C and H having a methyl substituent on one of the atoms 1 or 2 of the pyrrolic ring (A and C), or both (H).

Group 2 : constituted by makaluvamines D (J), F, M (L) and V. In these compounds, a hydrogen on the amino nitrogen (N_7) is replaced by a substituent with strong electronic conjugation.

Group 3 : it is the makaluvamines E (G) and K (P) which are distinguished by the presence of two substituents. A high electronic conjugation substituent is attached to the amino nitrogen and a methyl to the pyrrolic nitrogen. Each compound in this group contains the characteristics of a group 2 compound and compound A of group 1.

Group 4 : contains the N and O makaluvamines. These compounds are obtained as a result of substitutions on the pyridine ring of the basic structure.

NB: All these groups are defined without taking into account the neutral, protonated or methylated nature of pyridine nitrogen (N_5).

2.2 CALCULATION METHOD : LEVEL OF THEORY

Calculations are made with the software Gaussian 09 [13]. The density functional theory (DFT) [14] is the method used. Earlier theoretical work on the computation of molecular properties has shown that functional hybrids such as B3LYP and others, associated with an extensive base of functions lead to values in good agreement with the experimental results [15]. The level of theory retained for this study is B3LYP / 6-311 ++ G (d, p). For each makaluvamine, the geometry optimization calculation molecular is followed by the calculation of frequencies. Energy, thermodynamic and stability parameters were determined.

2.3 QUANTITIES OF BASICITIES AND PROTON AFFINITIES OF THE STUDIED MAKALUVAMINES

The basic structural skeleton of makaluvamines contains three nitrogens. These are pyridine nitrogen (Nsp^2), pyrolic nitrogen (Nsp^3) and amino nitrogen (Nsp^3). It seemed to us necessary to evaluate their proton affinities. The determination of proton affinities requires the calculation of enthalpies of formation of the protonated species [16]. The protonation reaction of makaluvamines (B) is shown schematically by equilibrium (1) below:

$$B + H^+ \underset{2}{\overset{1}{\rightleftharpoons}} BH^+ \qquad (1)$$

The variation of any energy parameter X is obtained from the following equation (2);

$$\Delta X = \sum X(product) - \sum X(reagent) \qquad (2)$$

The proton affinity (PA) is the opposite of the enthalpy variation of the protonation reaction in the direct way (1). It was calculated from equation (3) below :

$$PA = -\Delta_r H_1 = \Delta_f H(B) + \Delta_f H(H^+) - \Delta_f H(BH^+) \qquad (3)$$

The value of the enthalpy of proton formation is a given in the literature [17]. His value is $\Delta_f H(H^+) = +367.2$ Kcal.mol^{-1}.

The basicity (GB), in the gas phase, is the opposite of the variation of free enthalpy in the direct way (1) of the protonation reaction. It is estimated using following equation (4) :

$$GB = -\Delta_r G°_1 = \Delta_f G(B) + \Delta_f G(H^+) - \Delta_f G°(BH^+) \quad (4)$$

The experimental value $\Delta_f G(H^+) = -6.29$ kcal.mol^{-1} was used for the calculations [18].

2.4 REACTIVITY PARAMETERS

2.4.1 MOLECULAR DESCRIPTORS

The chemical potential μ_{pot} reflects the tendency of the electron cloud to escape from the molecule. This is a global property of the molecular system. This molecular descriptor represents the slope of the total electron energy E function of the number of electrons N. external potential V (r) is kept constant. The chemical potential is also equal to the opposite of the electronegativity χ as defined by Pauling and Mulliken [19-25].

$$\mu_{pot} = \left(\frac{\partial E}{\partial N}\right)_{V(r)} = -\chi$$

It can be expressed as a function of the ionization potential PI and the electronic affinity AE

$$\mu_{pot} = -\frac{PI+AE}{2} = -\chi$$

The first derivative of the chemical potential regarding the number of electrons N leads to the hardness η and its inverse the softness S [26-28].

$$\eta = \left(\frac{\partial \mu}{\partial N}\right)_{V(r)} = \left(\frac{\partial^2 E}{\partial N^2}\right)_{V(r)} = \frac{1}{S}$$

According to the theory of acids and bases, developed by Pearson [29], these quantities can be expressed as a function of ionization potentials (PI) and electronic affinity (AE).

$$\eta = \frac{1}{S} = (PI-AE)/2$$

The ionization potential (PI) and the electronic affinity (AE) are simply obtained in the Koopmans approximation [30] according to which:

$$PI = -\varepsilon_{HOMO} \text{ et } AE = -\varepsilon_{LUMO}$$

ε_{HOMO} and ε_{LUMO} are respectively the energies of the highest occupied orbital (HOMO) and the lowest vacant orbital (LUMO). This is the theory of molecular orbitals boundaries [31].

The electrophilia index ω [32] is a descriptor developed to evaluate the ability of a molecule to promote electron transfer. It is calculated from the following relation:

$$\omega = \frac{\mu^2}{2\eta}$$

2.4.2 DUAL DESCRIPTOR

In 2004, Morell et al. [33,34] proposed a new descriptor for chemical reactivity, named "dual descriptor". It is defined as the difference between the functions of Fukui (f_k^+ et f_k^-) for a nucleophilic and electrophilic attack respectively. The calculation of the dual descriptor is done according to the following equation (5):

$$\Delta f(r) = f_k^+ - f_k^- \quad (5)$$

This new index is called "dual descriptor". It allows to simultaneously detect the electrophilic and nucleophilic regions in the molecule. So, for a particular region of the molecule:

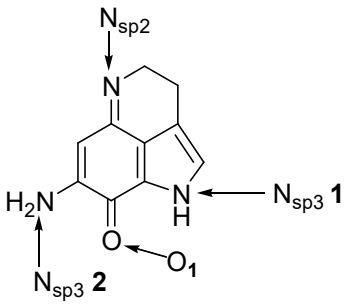
$\Delta f(r) > 0$: indicates an electrophilic region, thus favorable to a nucleophilic attack.

$\Delta f(r) < 0$: indicates a nucleophilic region, thus favorable to an electrophilic attack.

3 RESULTS AND DISCUSSIONS

3.1 QUANTITIES OF BASICITIES AND PROTON AFFINITIES

These two quantities are calculated at the chosen theory level by applying the relations described in 2.2. The denominations of the atoms selected to calculate these parameters are shown in Figure 3 below:



In the structure of makaluvamine O:

-Nsp^2 becomes Nsp^3

-$Nsp^3{}_2$ becomes O_2

In table 1, these values are in bracket.

Fig. 3. Designation of the atoms for which the quantities GB and PA are calculated

In Table 1 are grouped the values of the basicity (GB) and proton affinity (PA) quantities.

Table 1. Proton affinities (PA) and gas phase basicities (GB) in kcal.mol^{-1} calculated for the atoms selected at B3LYP / 6-311 ++ G (d, p)

Molecules	**Nsp^2(Nsp^3)**		**Nsp^3 1**		**Nsp^3 2(O_2)**		O_1	
	PA	GB	PA	GB	PA	GB	PA	GB
I	612.66	239.31	556.54	183.63	579.33	205.70	582.4	209.26
A	615.64	241.92	561.53	187.69	581.26	207.71	584.81	211.56
C	615.16	241.40	560.34	187.00	581.69	207.90	581.98	209.83
H	617.52	243.88	564.91	191.4	583.47	209.87	587.92	215.03
N	610.37	233.3	553.22	179.86	577.37	203.46	579.38	205.77
O	(560.06)	(192.71)	545.82	172.85	(587.78)	(213.98)	592.88	219.28

The PA and GB quantities both explain the basicity strength of a site in the molecule. For makaluvamines I, A, C, H and N, these two quantities agree on the basicity forces of the sites examined. The decreasing order of basicity in these five makaluvamines is Nsp^2, O_1, $Nsp^3 2$ and $Nsp^3{}_1$. These results confirm that pyridine nitrogen (Nsp^2) is the priority site for the protonation or methylation of makaluvamines, the basic structure of which is molecule I. In makaluvamine O, calculated PA and GB values show that the order of protonation is O_1, O_2, Nsp^3, and $Nsp^3{}_1$.

3.2 ENERGY QUANTITIES: STABILITIES OF DIFFERENT FORMS OF MAKALUVAMINES

The electronic energies, the formation of enthalpies and the formation of free enthalpies of the neutral and either protonated or methylated forms are reported in Table 2. These values are obtained at the B3LYP / 6-311 ++ G (d, p) gas phase theory at 298.15 K. The relative stability between the neutral form and the protonated form on the one hand, and between the neutral form and the methylated form, on the other hand, is also estimated from these energies.

Table 2. Electronic energies, formation enthalpies ($\Delta_f H$), formation free enthalpies ($\Delta_f G$) and relative stabilities calculated for the selected makaluvamines. These quantities are all expressed in kcal.mol^{-1}

Molecules	$E_{élec}$	ΔE_{elec}	$\Delta_f H$	$\Delta(\Delta_f H)$	$\Delta_f G$	$\Delta(\Delta_f G)$
I	-392907.50		-392787.54		-392817.52	
IH$^+$	-393162.49	-254.99	-393033.35	-245.81	-393063.12	-245.60
I^Y	-417836.83	-24929.33	-417689.32	-24901.78	-417721.64	-24904.12
Group 1						
A	-417581.09		-417442.76		-417475.54	
AH$^+$	-417838.68	-257.59	-417693.52	-250.76	-417723.75	-248.21
A^Y	-442512.84	-24931.75	-442347.00	-24904.24	-442382.11	-24906.57
C	-417588.81		-417450.58		-417483.56	
CH$^+$	-417845.92	-257.11	-417698.54	-247.96	-417731.24	-247.68
C^Y	-442520.18	-24931.37	-442354.41	-24903.83	-442389.66	-24906.10
H	-442262.02		-442105.37		-442140.21	
HH$^+$	-442521.49	-259.47	-442355.69	-250.32	-442390.38	-250.17
H^Y	-467195.53	-24933.51	-467011.38	-24906.01	-467048.71	-24908.50
Group 2						
D (J)	-634505.12	-259.79	-634290.98	-250.56	-634335.74	-249.68
DH$^+$ (JH$^+$)	-634764.91		-634541.54		-634585.42	
D^Y (J^Y)	-659445.32	-24940.20	-659197.29	-24906.31	-659243.48	-24907.74
F	-2498602.54		-2498407.50		-2498451.14	
FH$^+$	-2498867.19	-264.65	-2498661.90	-254.40	-2498708.21	-257.07
F^Y	-2523542.60	-24940.06	-2523318.97	-24911.47	-2523367.78	-24916.64
M (L)	-633731.71	-269.52	-633534.26	-258.68	-633573.65	-261.79
MH$^+$ (LH$^+$)	-634001.23		-633792.94		-633835.44	
M^Y (L^Y)	-658675.03	-24943.32	-658448.40	-24914.14	-658493.45	-24919.80
V	-634489.31	-266.51	-634280.95	-251.68	-634325.58	-251.20
VH$^+$	-634755.82		-634532.63		-634576.78	
V^Y	-659429.87	-24940.56	-659188.30	-24907.35	-659234.94	-24909.36
Group 3						
E (G)	-658412.08	-264.70	-658194.33	-255.80	-658240.18	-255.04
EH$^+$ (GH$^+$)	-658676.78		-658450.13		-658495.22	
E^Y (G^Y)	-683348.24	-24936.16	-683103.13	-24908.80	-683150.61	-24910.43
K (P)	-659178.66	-261.85	-658946.12	-252.38	-658993.44	-251.85
KH$^+$ (PH$^+$)	-659440.51		-659198.50		-659245.29	
K^Y (P^Y)	-684114.79	-24936.13	-683854.65	-24908.53	-683903.53	-24910.09
Group 4						
N	-2007882.86	-252.27	-2007768.23	-243.18	-2007801.46	-242.59
NH$^+$	-2008135.13		-2008011.41		-2008044.05	
N^Y	-2032801.54	-24918.68	-2032659.48	-24891.25	-2032694.15	-24892.69
O	-2020354.59	-228.72	-2020247.38	-220.59	-2020280.12	-220.27
OH$^+$	-2020583.31		-2020467.97		-2020500.39	
O^Y	-2045247.43	-24892.84	-2045113.66	-24866.28	-2045148.79	-24868.67

Enthalpies of formation ($\Delta_f H$) and free enthalpies of formation ($\Delta_f G$) of makaluvamines are all negative. The formation of these molecules is done according to a spontaneous exothermic process. For each structure, our calculations give the electronic energy E_{elec} lower than the free enthalpy of formation $\Delta_f G$ which is also lower than the enthalpy of formation $\Delta_f H$.

Whatever the type of energy considered, makaluvamines are stabilized by protonation. Such a reaction lowers the energy of the makaluvamine molecule globally between 220 and 270 kcal.mol^{-1}. These molecules are even more stable when they are methylated. The methyl radical (CH_3^+) has a donor inductive effect (+ I). The stability of the methylated structure compared to the neutral makaluvamine is estimated between 24866 and 24944 kcal.mol^{-1}. The lowest decreases in energy are observed at the level of makaluvamine O protoned or methylated on oxygen O_2. The energy decreases from 220.3 kcal.mol^{-1} to 228.7 kcal.mol^{-1} for protonation and from 24866.3 kcal.mol^{-1} to 24892.8 kcal.mol^{-1} for methylation. Also, when this makaluvamine is

protonated or methylated on pyridine nitrogen, the structures are less stable from about 21.2 kcal.mol^{-1} to 21.7 kcal.mol^{-1} and 16.0 kcal.mol^{-1}, 6 kcal.mol^{-1} respectively.

The comparison of the energies of the neutral (X), protonated (XH^+) and methylated (X^γ) structures of the makaluvamines of each group with those of I, IH^+ and I^γ respectively shows that:

- The energies of the molecules A/C, AH^+/CH^+ and A^γ/C^γ are lower from 24658 kcal.mol-1 to 24684 kcal.mol^{-1} compared to those I, IH^+ and I^γ respectively. All the energy parameters agree on this result. As for makaluvamine H having two methyl substituents, the energy gap between H, HH^+ and H^γ then their respective analogues I, IH^+ and I^γ is estimated from 49072.0 kcal.mol^{-1} to 49359.0 kcal.mol^{-1}. This gap corresponds to twice the differences observed for makaluvamines A and C. The presence of methyl substituent (s) on the pyrrolic ring stabilizes the group 1 makaluvamines. These results show that the two methyls jointly contribute to stabilize the different structures of makaluvamine H.
- Except for the F molecule, the X, XH^+ and X^γ structures of makaluvamines D (J), M (L) and V of group 2, compared with I, IH^+ and I^γ, respectively, have lower energies of 241493.41 kcal.mol^{-1} to 240838.74 kcal.mol^{-1}. The three energy parameters agree on this result. For the structures F, FH + and F^γ, the energies are much lower, between 2105619.96 kcal.mol^{-1} and 2105705.76 kcal.mol^{-1}. The bicyclo substituent containing three heteroatoms undoubtedly confers a great stability on makaluvamine F. Indeed, for this compound, there are more mesomeric forms.
- The X, XH^+ and X^γ structures of makaluvamines E (G) and K (P) of group 3 are also more stable than I, IH^+ and I^γ respectively by 265406.79 kcal.mol^{-1} at 266278.02 kcal.mol^{-1}. This stability results from the contribution of the two substituents that specify this group. It also appears that these structures of group 3 makaluvamines are more stable than their groups 1 and 2 analogs. The difference between the energies of two similar structures of groups 3 and 1 corresponds on average to the stabilization energy of the substituent on the amino nitrogen. It is worth at least 240 000 kcal.mol^{-1}.
- The bromine on the C_6 carbon of the pyridine ring of the N, NH^+ and N^γ structures of the N molecule of group 4 stabilizes them very strongly compared to their analogs I, IH^+ and I^γ respectively. The three energy quantities estimate these more stable structures from 1614964.70 kcal.mol^{-1} to 1614983.94 kcal.mol^{-1}. As for makaluvamine O, it is the molecule N whose amino substituent is replaced by a carbonyl oxygen on the C_7 carbon. This oxygen contributes to lowering the energies of the structures O, OH^+ and O^γ compared with those of N, NH^+ and N^γ between 12445.90 kcal.mol^{-1} and 12479.15 kcal.mol^{-1}. In the end, the O, OH^+ and O^γ structures have lower energies of 1627410.60 kcal.mol^{-1} at 1627462.60 kcal.mol^{-1} compared to those of I, IH^+ and I^γ. All energy calculations agree on these results.

Group 4 compounds are the more stable among the studied makaluvamines. These results reveal that the heteroatoms on pyridine ring increase exceptionally the stability of the molecules.

3.3 REACTIVITY PARAMETERS

The reactivity parameters examined in this series of compounds are: the energies of the HOMO (ε_{HOMO}), the LUMO (ε_{LUMO}), the chemical potential (μ_{pot}), the electrophilia index (ω), the hardness (η), the softness (S), the energy gap of the boundary orbitals ($\Delta\varepsilon$) and the dipole moment (μ_D). The calculated values of said parameters are reported in table 3.

Table 3. Energies of the HOMO and LUMO frontier orbitals, chemical potential, hardness, electrophilia, softness $(eV)^{-1}$, energy gap and dipole moment (Debye). The other parameters are expressed in eV

Molecules	ε_{HOMO}	ε_{LUMO}	μ_{pot}	η	ω	S	$\Delta\varepsilon$	μ_D
I	-5.83	-2.61	-1.61	1.61	0.81	0.62	3.22	2.35
IH^+	-10.21	-7.09	-1.56	1.56	0.78	0.64	3.11	3.69
I^{γ}	-10.07	-6.96	-1.55	1.55	0.78	0.64	3.11	3.43
Groupe 1								
A	-5.75	-2.53	-1.61	1.61	0.81	0.62	3.23	2.71
AH^+	-10.05	-6.93	-1.56	1.56	0.78	0.64	3.12	3.81
A^{γ}	-9.92	-6.80	-1.56	1.56	0.78	0.64	3.12	3.53
C	-5.72	-2.51	-1.60	1.60	0.80	0.62	3.21	3.11
CH^+	-9.91	-6.94	-1.49	1.49	0.74	0.67	2.97	3.92
C^{γ}	-9.78	-6.82	-1.48	1.48	0.74	0.67	2.97	3.69
H	-5.64	-2.43	-1.60	1.60	0.80	0.62	3.21	3.36
HH^+	-9.77	-6.80	-1.49	1.49	0.74	0.67	2.97	4.01
H^{γ}	-9.65	-6.68	-1.49	1.49	0.74	0.67	2.97	3.78
Groupe 2								
D (J)	-5.51	-2.50	-1.51	1.51	0.75	0.66	3.01	2.40
DH^+ (JH^+)	-8.73	-6.67	-1.03	1.03	0.52	0.97	2.06	8.19
D^{γ} (J^{γ})	-8.38	-6.65	-0.87	0.87	0.43	1.15	1.73	10.76
F	-5.95	-2.75	-1.60	1.60	0.80	0.63	3.2	5.44
FH^+	-8.24	-6.92	-0.66	0.66	0.33	1.51	1.32	19.71
F^{γ}	-8.29	-6.76	-0.77	0.77	0.38	1.30	1.54	18.65
M (L)	-5.57	-2.47	-1.55	1.55	0.78	0.65	3.1	2.85
MH^+ (LH^+)	-8.48	-6.53	-0.97	0.97	0.49	1.03	1.94	5.51
M^{γ} (L^{γ})	-8.42	-6.46	-0.98	0.98	0.49	1.02	1.97	5.23
V	-5.56	-2.46	-1.55	1.55	0.78	0.65	3.1	2.30
VH+	-8.62	-6.68	-0.97	0.97	0.49	1.03	1.94	10.59
V^{γ}	-8.59	-6.57	-1.01	1.01	0.51	0.99	2.02	10.13
Groupe 3								
E(G)	-5.51	-2.40	-1.56	1.56	0.78	0.64	3.11	3.41
EH^+(GH^+)	-8.39	-6.42	-0.99	0.99	0.49	1.01	1.98	5.27
E^{γ}(G^{γ})	-8.44	-6.41	-1.02	1.02	0.51	0.99	2.03	6.72
K(P)	-5.52	-2.42	-1.55	1.55	0.78	0.65	3.1	2.69
KH^+(PH^+)	-8.43	-6.60	-0.91	0.91	0.46	1.09	1.83	8.77
K^{γ}(P^{γ})	-8.35	-6.35	-1.00	1.00	0.50	1.00	2.00	7.13
Groupe 4								
N	-5.89	-2.81	-1.54	1.54	0.77	0.65	3.08	3.94
NH^+	-10.15	-7.23	-1.46	1.46	0.73	0.68	2.92	4.23
N^{γ}	-9.99	-7.14	-1.43	1.43	0.71	0.70	2.85	4.47
O	-6.09	-3.02	-1.53	1.53	0.77	0.65	3.07	10.00
OH^+	-10.46	-7.22	-1.62	1.62	0.81	0.62	3.24	12.86
O^{γ}	-10.32	-7.11	-1.60	1.60	0.80	0.62	3.21	12.75

The results of our calculations reported in Table 3 show that for a given type of structure (X or XH^+ or X^{γ}), the energies ε_{HOMO} and ε_{LUMO} vary not much. For neutral molecules (X), ε_{HOMO} is between -5.51 eV and -6.09 eV. As for ε_{LUMO}, it is between -2.40 eV and -3.02 eV. For the protonated molecules (XH^+), ε_{HOMO} is between -8.24 eV and -10.46 eV then ε_{LUMO} -6.42 eV and -7.22 eV. In the methylated molecules, ε_{HOMO} is between -8.29 eV and -10.32 eV then ε_{LUMO} -6.35 eV and -7.14 eV.

For a given makaluvamine X, the ε_{HOMO} and ε_{LUMO} energies of the protonated form (XH^+) are lower and higher for the neutral form (X).

The only exception to this observation is makaluvamine F; ε_{HOMO} (F^{γ}) is lower than ε_{HOMO} (F). For the series of makaluvamines studied, our calculations indicate that protonation or methylation lowers the energy of the low vacant orbital (LUMO) from 4 eV to 4.5 eV. HOMO energy is also lowered by 4 eV to 4.4 eV for reference molecule I and those in groups 1 and 4 when they

are protonated or methylated. The HOMO energy of group 2 and group 3 makaluvamines only decrease from 2.3 eV to 3.2 eV after protonation or methylation. The "voluminous" substituents on the amino nitrogen of makaluvamines of groups 2 and 3 could be the cause of this low energy drop in the HOMO. The gap between ε_{HOMO} and ε_{LUMO} is practically constant for all the neutral structures of the studied makaluvamines. It ranges from 3.01 eV to 3.23 eV and averages 3.14 eV. Our calculations also show that protonation or methylation of a molecule reduces this energy gap. This reflects a rapprochement of the HOMO and LUMO orbitals in makaluvamine and an increase in its reactivity potential. This is the case for all the makaluvamines we study except the O molecule. In this makaluvamine, our calculations indicate a removal of the HOMO and LUMO orbitals after protonation or methylation on O_2.

As expected, an increase in the dipole moment of the XH^+ and X^Y structures compared to the neutral makaluvamine X is observed. This results from a modification of the positions of the barycentres of the positive and negative charges in these structures. Thus, makaluvamines acquire greater intermolecular interaction [35] in the forms XH^+ and X^Y. For some makaluvamines, the dipole moment is greater when the molecule is protonated and for others it is larger for the methylated structure. No form is absolutely more interactive than the other for all makaluvamines.

By observing hardness η and softness S, it appears that η decreases as a result of protonation or methylation while S increases. The opposite is true for makaluvamine O. A high value of hardness is synonymous with stability and a high value of softness being synonymous with high reactivity, the studied makaluvamines (except O) are more reactive in the forms XH^+ and X^Y.

All the analyzed reactivity parameters, energy gap Δε, dipole moment μ_D, hardness η and softness S, reveal that the studied makaluvamines with the exception of the molecule O have a greater reactivity potential when they are protonated or methylated. The greatest variations of these analyzed parameters are observed with the compounds of groups 2 and 3.

These are the molecules that have the greatest potential for reactivity.

3.4 FUKUI FUNCTIONS

The analysis of Fukui functions was performed using Hirschfeld populations [36]. These functions are calculated for the atoms globally involved in the conjugation of the electrons of the makaluvamine I structural skeleton. The atoms joining the different cycles are excluded from this analysis. They cannot be sites of structural modulation. The results of our calculations are summarized in Table 4.

Table 4. Fukui functions of some atoms of the makaluvamine I

Atomes	$q_K(N)$	$q_K(N+1)$	$q_K(N-1)$	f^+K	f^-K	Δf
N_5	7.200658	7.299561	7.113602	0.098903	0.087056	0.011847
N^7	7.174408	7.213311	7.046135	0.038903	0.128273	-0.08937
O^8	8.291496	8.419139	8.240793	0.127643	0.050703	0.07694
N_1	7.065986	7.102128	7.03516	0.036142	0.030826	0.005316
C_2	6.001116	6.068307	5.931534	0.067191	0.069582	-0.002391

The results in Table 4 show that for the C_2 and N^7 atoms (linked to C_7), the dual descriptor is negative. These are sites that are very incline to electrophilic attack. The nitrogen N^7, with a lower value of the descriptor, represents the privileged site of this type of attack. These results would explain why most makaluvamines have structures modulated on N^7 nitrogen. For the other atoms N_1, N_5 and O^8 (bound to C_8) the dual descriptor is positive. These atoms are therefore more favorable to nucleophilic attacks. N_5 nitrogen is the favorable site of the three. N_1 nitrogen is the least favorable.

4 CONCLUSION

The literature has revealed that makaluvamine molecules can exist in three forms; neutral, protonated and methylated. The calculation of the quantity of basicity (GB) and the proton affinity (PA) of the potential sites of the basic molecule of the compounds studied led to the identification and confirmation of pyridine nitrogen as the preferred site of protonation or methylation. In a second step, the analysis of the electronic energy and thermodynamic parameters made it possible to study the stability of a series of makaluvamines. It has become clear that protonation on the indicated nitrogen atom stabilizes these molecules by at least 200 kcal.mol^{-1}. A molecule of makaluvamine methylated on this nitrogen is even more stable than the

neutral form of at least 24860 kcal.mol^{-1}. In sum, makaluvamines in charged forms are more stable. Thirdly, the analysis of the energies of the HOMO (ε_{HOMO}), the LUMO (ε_{LUMO}), the energy gap of the frontier orbitals ($\Delta\varepsilon$), the hardness (η), the softness (S) and the moment Dipolar (μ_D) clearly showed that charged (protonated or methylated) makaluvamine molecules have a greater potential for reactivity. Calculation of Fukui functions has also shown that amino nitrogen (C_7 bonded N^7) and C_2 carbon are in this order sites incline to electrophilic attack. They lend themselves to structural modulations.

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