Theoretical Study of the Stability of Acetylcholine Based on Molecular Orbital Theory using Density Functional Theory

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Abstract. Some molecules in nature have a positive or negative charge. One such molecule is acetylcholine. Acetylcholine is a positively charged molecule that is responsible for Alzheimer's disease. This study evaluated acetylcholine through six simple molecules based on the ionization potential and the HOMO-LUMO gap obtained from the density functional theory calculation. The calculation results showed that the ionization potential and the HOMO-LUMO gap could explain the stability of acetylcholine and the six other molecules. As a result, acetylcholine has the same properties as five other simple molecules. Meanwhile, one other molecule has the opposite properties to acetylcholine.

Keywords: Acetylcholine, Alzheimer's disease, density functional theory, ionization potential, HOMO-LUMO gap.

INTRODUCTION

Some molecules in nature have a positive or negative charge. Positively charged molecules are formed due to the process of losing electrons, called ionization. Ionization requires a certain amount of energy to release electrons. This energy is called the ionization potential (IP). Meanwhile, negatively charged molecules are formed due to the process of receiving electrons, called gaining electrons. This process requires a certain amount of energy to release when an electron attaches to a neutral molecule. This energy is called electron affinity (EA). Both of these processes cause the molecule to reach a stable state.

One example of such a molecule is acetylcholine (ACh^+). The ACh^+ are positively charged molecules present in the brain. ACh^+ acts as a neurotransmitter, i.e. transmit impulses between the ends of two adjacent nerves. If ACh^+ in the brain reduces, it causes Alzheimer's disease.[1] One of the causes of the decrease of ACh^+ is the acetylcholinesterase enzyme catalyst's high hydrolysis activity of ACh^+. Research related to ACh^+ hydrolysis has been studied by our research group previously. [2], [3]

The ACh^+ reaches a stable state through ionization. Ionization can be studied using the density functional theory (DFT) calculation. DFT successfully predicts the ionization potential of a molecule. [4] Paper [4] revealed that the IP and EA could be predicted through the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). The importance of studying the properties of HOMO and LUMO resulting from this DFT calculation has been studied by [5].

In this study, we evaluated acetylcholine through six simple molecules based on two physical quantities, namely the IP and the HOMO-LUMO gap obtained from DFT calculations. These two physical quantities were obtained from the results of DFT calculations. In this study, DFT provided two physical quantities, namely the total electronic energy and molecular orbitals. The total electronic energy was used to calculate the ionization potential. Meanwhile, the molecular orbitals would be constructed on the energy level diagram (ELD) to calculate the HOMO-LUMO gap.

COMPUTATIONAL MODEL

Reaction Model

Scheme 1 shows the reaction model of ionization. A and A^+ were neutral and ion molecules, respectively. A consists of ACh and six simple molecules. We used the six molecules to evaluate the stability of ACh since they have similar properties to ACh. They are neutral molecules that have unpaired electrons in the HOMO.
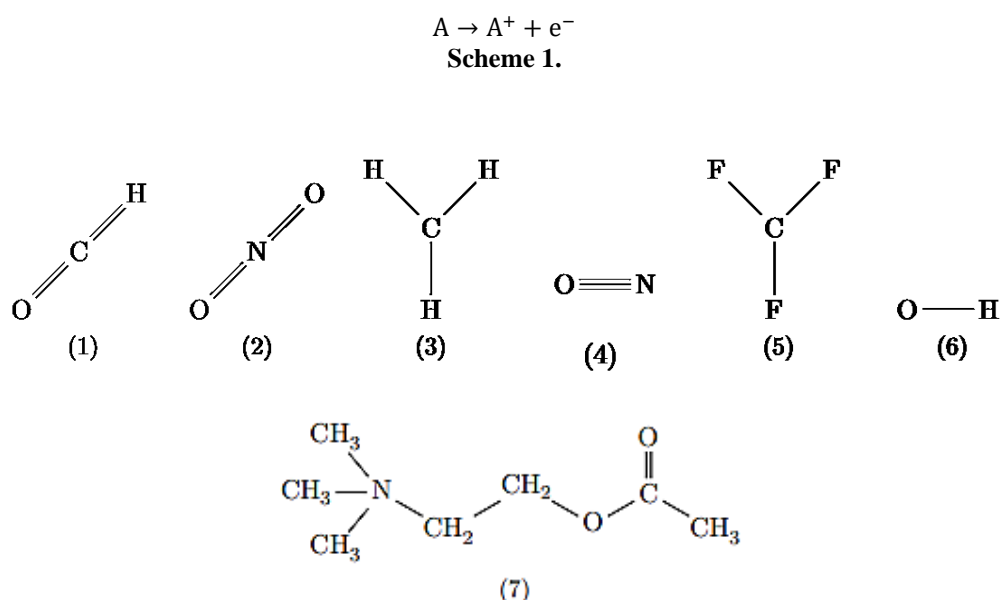
$$A \rightarrow A^+ + e^-$$
Scheme 1.

FIGURE 1. Molecular model for A. (1) formyl (OCH), (2) nitronium (NO_2), (3) methyl (CH_3), (4) nitrosonium (NO), (5) trifluoro methyl (CF_3), (6) hydroxyl (OH), (7) acetylcholine {$CH_3COOCH_2CH_2N(CH_3)_3$}.

Structure Physical Quantities

We evaluate the ionization of molecules using two physical quantities. The first quantity is IP. We determine the IP by subtraction of total electronic energy for A^+ {$E(A^+)$} and A {$E(A)$} (Equation 1).

$$IP = E(A^+) - E(A) \qquad \text{i)}$$

The second quantity is gap energy. The gap energy is the difference between the energy of the molecular orbitals in the HOMO (E_{HOMO}) and LUMO (E_{LUMO}) (Equation 2).

$$\Delta E_{HOMO-LUMO} = E_{HOMO} - E_{LUMO} \qquad \text{ii)}$$

Computational Parameters

We obtain total electronic and molecular orbital energy using DFT calculations. [6], [7] All calculations were done in the gas phase using Gaussian 16 software package. [8] The basis set and exchange-correlation functionals were 6-311+ G(d,p) and B3LYP, respectively. DFT calculations routine were as follows. [9] First, we performed geometry optimization to obtain the most stable spin-state. We considered the singlet and triplet spin states for the A^+ and the doublet and quartet spin states for the A. Second, we used the most stable spin-state to obtain the optimized geometry, the total electronic energy, and molecular orbital energy in the ground state.

RESULT AND DISCUSSION

Geometry Optimization

The geometry optimization calculation produces the ground spin state and optimized geometric structure for each molecule in Figure 2. Figure 2 shows the spin state energy diagrams for molecules A and A^+. Figure 2a shows that all molecules A have a spin-doublet state as the lowest spin state in the energy level. The results of this calculation are in agreement with the NO and OH molecules that have spin-doublet states. [10] Meanwhile, Figure 2b shows that the lowest spin-state for molecule A^+ is the spin-singlet state, except for molecule (6). The ground spin state for molecule (6) is the spin-triplet state. Therefore, we use the spin-state with the lowest energy for each molecule in subsequent calculations.
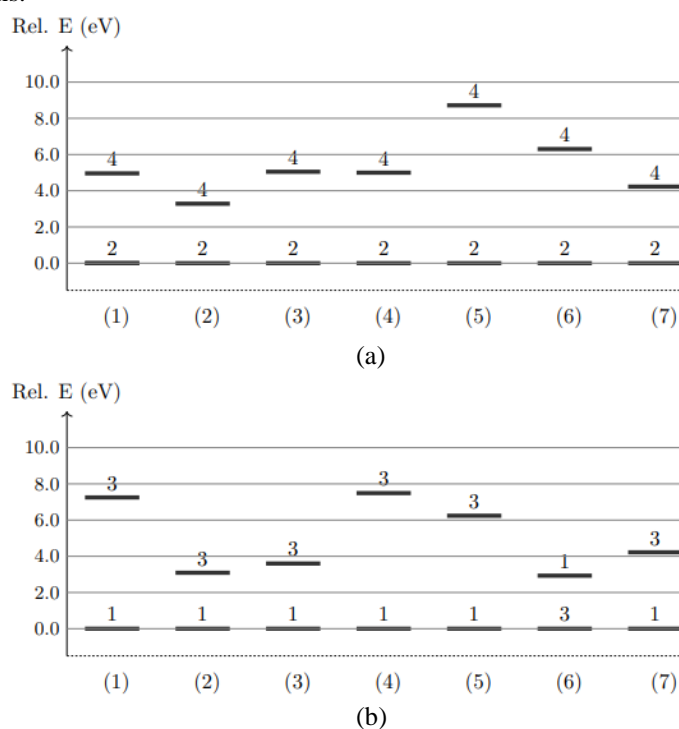

FIGURE 2. (a) and (b) are spin-states for A dan A^+, respectively. The y-axis is the relative energy (eV) with the lowest total electronic energy. Spin singlet, doublet, triplet, and quartet state are denoted as 1, 2, 3, and 4, respectively.

Table 1 shows the optimized geometric structure for six simple molecules. Table 1 shows that all molecules' lengths and bond angles meet the accuracy criteria. The Δ_1 has a value of less than 0.017 for bond length and 1.4 degrees for bond angle. [11] This result implies that we can use 6-311+ G(d,p) basis sets and B3LYP are valid for potential ionization calculation.

The change in molecular geometry after ionization is given by Δ_2 (Table 1). In general, the molecular bond length shortens after ionization except for the O-H bond in the molecule (6). The significant change also occurs in the bond angle of the molecule (1) and (2), resulting in a shift from bent shape to linear shape. The planarity of the molecule (5) is also changed as it is observed in experiments.

TABLE 1. The selected geometric parameters for the six simple molecules in the ground state. Bond length (R, in A), bond angle (A, in degrees), and dihedral angle (D, in degrees). Δ_1 is the difference between the calculated and experimental results. Δ_2 is the difference (R, A, and D) between neutral and ion. molecules.

Id. Molecule	Parameter	Experiment	Calculation	Δ_1	A	A$^+$	Δ_2
1	R(C-H)	1.110	1.124	0.014	1.124	1.095	0.029
	R(C-O)	1.171	1.174	0.003	1.174	1.103	0.071
	A(O-C-H)	124.8	127.4	-2.7	124.7	180.0	-55.3
2	R(N-O)	1.193	1.193	0.000	1.193	1.118	0.075
	A(O-N-O)	134.1	134.5	0.4	134.5	180.0	-45.5
3	R(C-H)	1.076	1.080	0.004	1.080	1.094	-0.013
	D(H-H-C-H)	n/a	n/a	n/a	179.0	180.0	-0.1
4	R(N-O)	1.151	1.148	0.003	1.148	1.060	0.088
5	R(C-F)	1.324	1.318	0.006	1.324	1.060	0.088
	D(F-F-C-F)	n/a	n/a	n/a	124.8	180.0	-55.2
6	R(O-H)	0.967	0.976	0.009	0.976	11.037	-0.061

Ionization Potential

Figure 3 plots the IP of the calculated versus experimental results [12] for molecules (1) to (6). The plot shows that the IP calculated results had good accuracy, indicated by the R^2 value of 0.93. It implies we can use the IP for further analysis.

Figure 3 shows the existence of two groupings. The first group was molecules close to the perfect y=x line, shown in Figure 3a. The second group was molecules that were far from the perfect y=x line, as shown in Figure 3b.

Figure 3a consists of molecules (1), (3), and (6) sorted by lowest IP value. Meanwhile, Figure 4 shows the HOMO visualization for all neutral molecules. Figure 3a and Figure 4 show that molecules (1) and (6) have HOMO π^*, and π, respectively. HOMO π^* is a less stable type of bond than HOMO π. It causes more easily for molecule (1) to lose electrons than molecule (6). It means molecule (1) requires a more minor IP to lose electrons than molecule (6).

Figure 3b consists of molecules (5), (4), and (2), sorted from the lowest IP. Figure 3b and Figure 4 show that molecule (5) had HOMO σ^*, while molecules (4) and (2) had HOMO π^*. It indicated that HOMO σ is easier to lose electrons than π. Molecules (4) and (2) had the same HOMO π^*. However, they had different IP values. Apart from differences in IP values, molecules (4) and (2) differed in the number of bonds. Molecule (4) has a triple bond, while molecule (2) has a double bond. It indicated that the number of bonds affected the IP value.
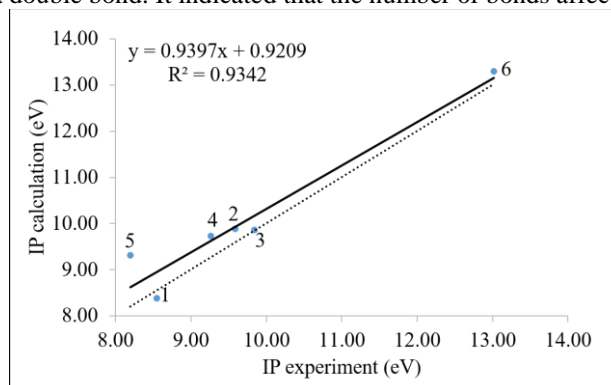

FIGURE 3. Ionization potentials for six simple molecules. The y-axis is the calculated ionization in (eV). The x-axis is experimental data as validation. The dotted line is a perfect y=x line.
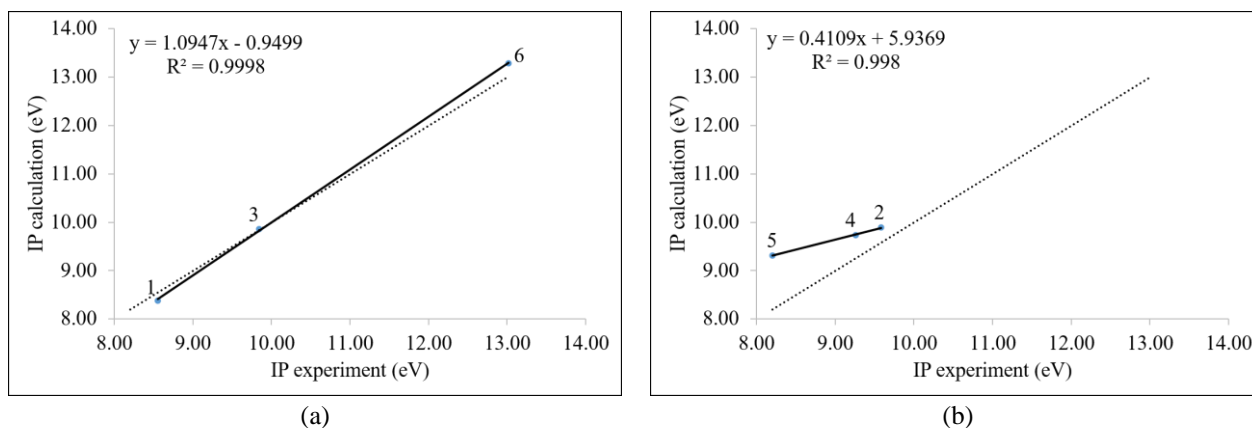
(a)   (b)

FIGURE 4. Plot the calculated ionization potential versus experimental results for (a) first group (b) the second group. The dotted line is a perfect y=x line.
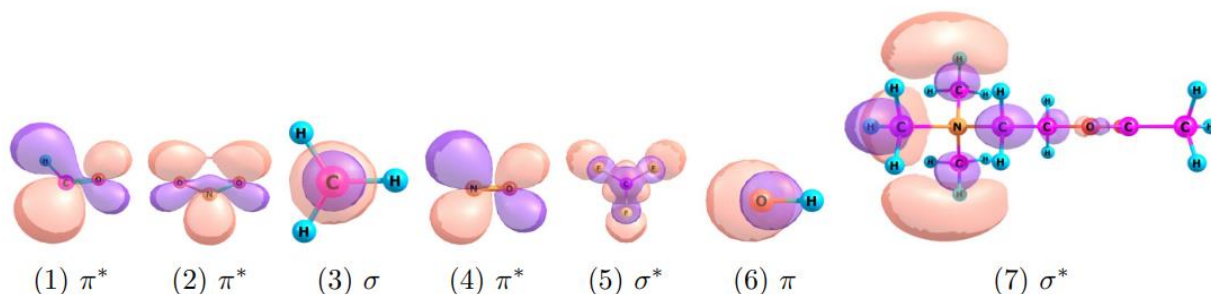

(1) π^* (2) π^* (3) σ (4) π^* (5) σ^* (6) π (7) σ^*

FIGURE 5. Visualization of neutral molecular HOMO for all molecules. The red orbitals are positive, while the blue orbitals are negative.

Energy Level Diagram

Figure 6 shows an energy level diagram constructed from the molecular orbital of a neutral molecule that ionized into an ion-molecule, as shown in Scheme 1. Figure 6 shows that all neutral molecules have a smaller value of HOMO-LUMO gap than their ion molecules, except for molecule (6). The small value of the HOMO-LUMO gap in neutral molecules made it easy for molecules to lose electrons. On the contrary, the significant value of the HOMO-LUMO gap in the ion molecules indicated that the molecules were difficult to release electrons. It caused the ion molecule to tend to be stable.

Figure 6f shows the opposite property for the other five molecules. Molecule (6) has a more significant HOMO-LUMO gap than its ion molecules. It caused the molecule to be challenging to release electrons from HOMO. This implies that molecule (6) in nature is impossible to ionize. However, molecule (6) will interact with other atoms or molecules to reach a stable state.
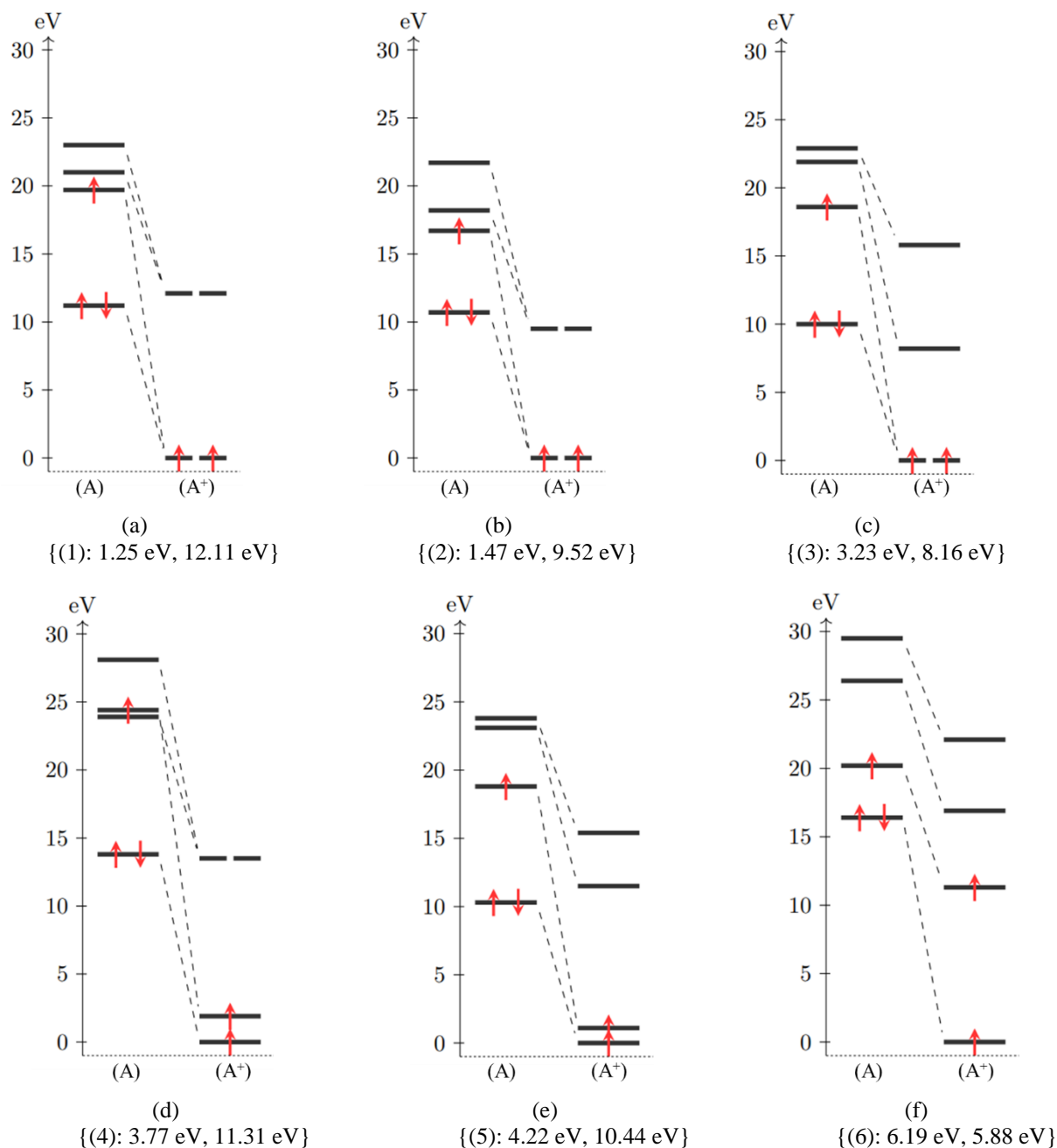
FIGURE 6. Ionization in the energy level diagram for molecules (1) through (6). The y-axis is the orbital energy relative to the molecular HOMO-1 of its ion in eV. (A) and (A⁺) are neutral molecules and ionic molecules, respectively. The numbers in curly braces are the molecular identities: the HOMO-LUMO gap for the neutral molecule, and the ionic molecule, respectively.

Evaluation of Acetylcholine Stability

We evaluated the molecular stability of ACh⁺ based on the IP and the HOMO-LUMO gap. The IP of the molecule was 2.80 eV. It was the smallest value of the six other molecules studied. It implies that the molecule is most easily ionized. The statement was supported by Figure 5 that the HOMO of the molecule was σ^*. HOMO antibonding has the highest orbital energy, is less stable, and has difficulty binding electrons. It implies that HOMO ACh is the easiest to remove electrons to achieve stability.

Figure 6g shows that the HOMO-LUMO gap between ACh and their ions were 0.31 eV and 6.87 eV, respectively. It is the smallest value of the six other molecules studied. It implies that the small HOMO-LUMO gap of ACh caused HOMO to tend to lose electrons. Preferably, the large HOMO-LUMO gap of ACh^+ made it difficult for HOMO to release electrons. It implies that ACh^+ molecules tend to be stable.
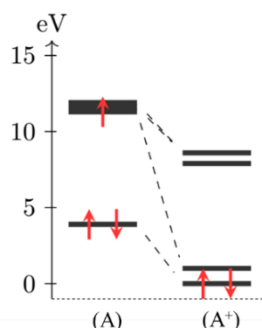

FIGURE 7. Ionization in the energy level diagram for molecules (7). The y-axis is the orbital energy relative to the molecular HOMO-1 of its ion in eV. The HOMO-LUMO gap for (A) and (A^+) are 0.31 and 6.87 eV, respectively.

CONCLUSION

We have reported the evaluation of ACh^+ based on the IP and the HOMO-LUMO gap. We found that the ACh^+ had the same property as the other molecules we studied, except for the OH molecule. The IP and the HOMO-LUMO gap of ACh were 2.80 eV and 0.31 eV, respectively. Both of them were the smallest value of other molecules. We argued that the small HOMO-LUMO gap of ACh caused the molecule to be easily ionized. On the contrary, the large HOMO LUMO gap of ACh^+ made the molecule stable.

On the other hand, we noted that the OH molecule had a different property from other molecules. OH's IP and HOMO-LUMO gap were 13.29 eV and 6.19 eV, respectively. Both of these values had greatest than other molecules. These results supported that the IP has a relationship with the HOMO-LUMO gap of the neutral molecule. Therefore, this study found the stability of the ACh based on the IP and the HOMO-LUMO gap.

ACKNOWLEDGMENTS

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