

# A Density-Functional Study of the Conformational Preference of Acetylcholine in the Neutral Hydrolysis

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Article

# A Density-Functional Study of the Conformational Preference of Acetylcholine in the Neutral Hydrolysis

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**Abstract:** Acetylcholine, which is associated with Alzheimer's disease, is widely known to have conformers. The preference of each conformer to undergo neutral hydrolysis is yet to be considered. In this study, we employed density-functional calculations to build the conformers and investigated their preference in one-step neutral hydrolysis. The results showed the preference in ten possible hydrolysis pathways involving seven acetylcholine conformers (reactant), four transition state structures, and two choline conformers (product). Three out of the seven acetylcholine conformers predicted from the results confirmed experimental findings on the conformers stability. We suggested that two out of ten possible pathways were observed in the experimental results based on agreement in reaction energy. Eventually, this study will emphasize the importance of considering acetylcholine conformers in its hydrolysis study.

**Keywords:** acetylcholine; conformational preference; density functional theory; neutral hydrolysis

## 1. Introduction

Acetylcholine (ACh<sup>+</sup>), the organic molecule acting as neurotransmitter in the brain, is associated with the treatment of Alzheimer's disease (AD) [1]. AD is a progressive brain disease that slowly impairs coordination among neurons and leads to loss of body function [2]. A common explanation for AD is the cholinergic hypothesis, which states the cause as ACh<sup>+</sup> depletion [3,4]. Since the role of ACh<sup>+</sup> is to transmit signals among neurons [5], its depletion can disturb the signal transmission in the brain and can lead to loss of body function.

One way to treat AD is by reducing the rate of ACh<sup>+</sup> neutral hydrolysis [1,6], which decomposes ACh<sup>+</sup> into acetic acid (AA) and choline (Ch<sup>+</sup>) [7]. The reaction is essential to return ACh<sup>+</sup> into its resting state after being activated during the signal transmission [8]. Because it is also important to preserve sufficient ACh<sup>+</sup> concentration in the brain of AD patients, reducing the rate of ACh<sup>+</sup> neutral hydrolysis becomes an option to compensate for ACh<sup>+</sup> depletion.

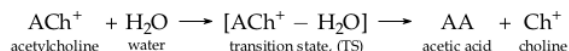
Generally, the rate of neutral hydrolysis depends on the conformers [9–12]. For example, the rate constant of bornyl acetate differs from iso-bornyl acetate acid hydrolysis up to  $2.6 \times 10^4$ /min, which has been the object of conformational study [13]. Therefore, the rate of ACh<sup>+</sup> neutral hydrolysis is also conformation dependent. The dependency is stronger when the reaction involves an enzyme as a catalyst [14,15]. In the ACh<sup>+</sup> case, at least three conformers have been investigated to understand their stability and the interconversion among the conformers and to explore the fluorination and solvent effects on each of them [16–27]. However, to the best of our knowledge, studies of ACh<sup>+</sup> conformers remain limited to its stability as an individual molecule. None have considered ACh<sup>+</sup> conformers when they interact with water in a neutral hydrolysis.

In this study, we report the preference of ACh<sup>+</sup> conformers in a neutral hydrolysis. We consider two important things: a one-step mechanism for the reaction model and the conformation of ACh<sup>+</sup> backbone dihedral angles. Despite its simplicity, the former worked well in revealing the conformational effects in the ethyl acetate neutral hydrolysis [28]. Therefore, we can focus on the conformation in one particular transition state (TS). We use the same model for ACh<sup>+</sup> neutral hydrolysis to obtain the standard enthalpy of reaction and standard Gibbs energy of activation.

## 2. Computational Methods

### 2.1. Reaction and Molecular Model

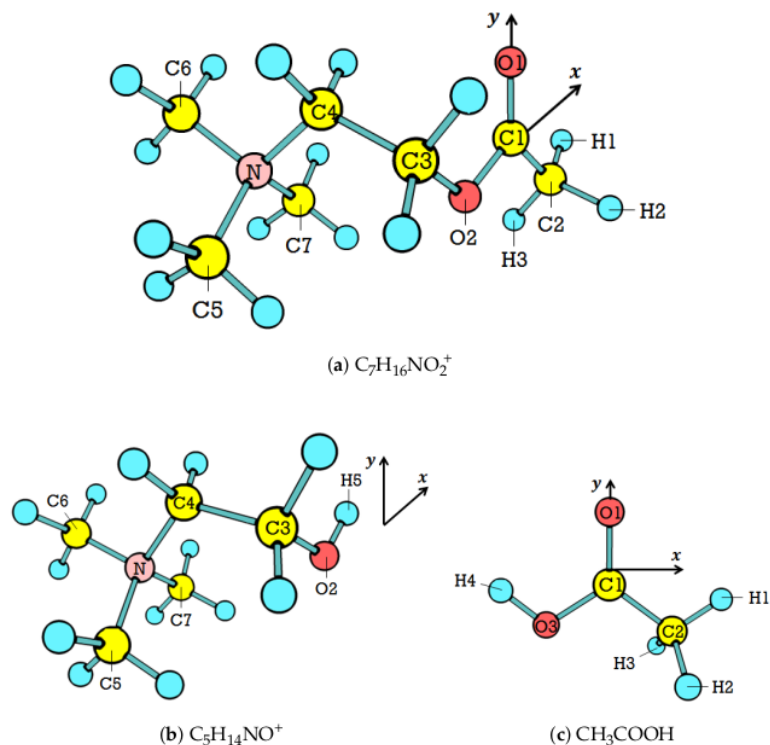
Scheme 1 represents the one-step mechanism of ACh<sup>+</sup> neutral hydrolysis. Our interest is the ACh<sup>+</sup> conformers because they potentially affect the activated complex in the TS and the final state (fs; products). In the TS, the activated complex is in the form of [ACh<sup>+</sup> – H<sub>2</sub>O]. Consequently, they can affect the reaction energy and energy barrier. We assume that the initial state (is) and the fs of the reaction are infinitely separated molecules. Figure 1 shows the generic molecular models of ACh<sup>+</sup>, Ch<sup>+</sup>, and AA. Table 1 lists the geometrical parameters of interest for this study.



**Scheme 1.** A one-step mechanism for acetylcholine neutral hydrolysis.

**Table 1.** The geometrical parameters of interest from Figure 1 and the corresponding notations used throughout the manuscript.

Parameter	Definition	Unit
(a) ACh <sup>+</sup>		
D1	dihedral angle of C2–C1–O2–C3 (backbone)	deg.
D2	dihedral angle of C1–O2–C3–C4 (backbone)	deg.
D3	dihedral angle of O2–C3–C4–N (backbone)	deg.
D4	dihedral angle of O1–C1–C2–H1 (head)	deg.
D5	dihedral angle of C3–C4–N–C5 (tail)	deg.
(b) Ch <sup>+</sup>		
D6	dihedral angle of H5–O2–C3–C4 (backbone)	deg.
D7	dihedral angle of O2–C3–C4–N (backbone)	deg.
D8	dihedral angle of C3–C4–N–C5 (tail)	deg.



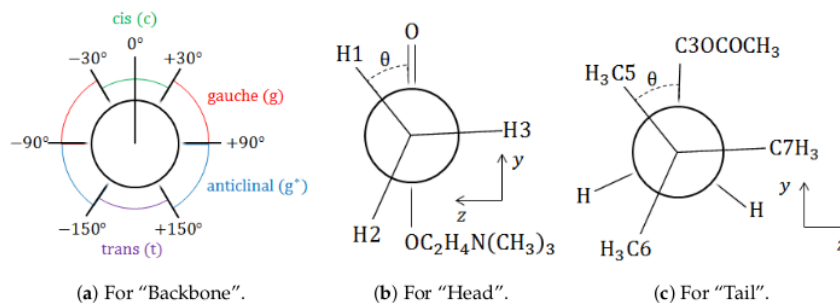
**Figure 1.** The molecular models of (a)  $ACh^+$ , (b)  $Ch^+$ , and (c) AA.

## 2.2. Conformer Formation

We built our initial  $ACh^+$  conformer based on the acetylcholine bromide ( $ACh^+Br^-$ ) crystal structure [29]. We removed the acetyl group ( $CH_3CO$ ) from the  $ACh^+$  initial conformer (Figure 1a) to build our  $Ch^+$  initial conformer. We divided  $ACh^+$  into three parts, backbone (represented by  $D1$ ,  $D2$ , and  $D3$ ), head (represented by  $D4$ ), and tail (represented by  $D5$ ), and  $Ch^+$  into two parts, backbone (represented by  $D6$  and  $D7$ ) and tail (represented by  $D8$ ), as listed in Table 1.

We varied the dihedral angles of the backbone, the head, and the tail of the initial conformer to build the potential conformers. For the  $ACh^+$  backbone, we varied the dihedral angles ( $D1$ ,  $D2$ , and  $D3$ ) with the values of  $0^\circ$ ,  $-90^\circ$ ,  $+90^\circ$ , and  $180^\circ$  that yielded  $4^3$  (four values for each of the three dihedral angles) permutations. We applied the same procedure for the  $Ch^+$  backbone ( $D6$  and  $D7$ ) that yielded  $4^2$  (four values for each of two dihedral angles) permutations. For the head and the tail, we varied the dihedral angles ( $D4$ ,  $D5$ , and  $D8$ ) between  $0^\circ$  and  $180^\circ$ , with increments of  $20^\circ$ .

Figure 2 depicts the criteria for the nomenclature of stable conformers. Figure 2a shows the criteria for each of the dihedral angles constructing the backbone. For the  $ACh^+$  backbone, three letters representing  $D1$ ,  $D2$ , and  $D3$  describe the conformation type. The letters are written in a bracket following the corresponding conformer. For example,  $ACh^+(ctg)$  that indicates an  $ACh^+$  conformer with  $D1$ ,  $D2$ , and  $D3$  are “c” (*cis*), “t” (*trans*), and “g” (*gauche*), respectively, and “g\*” is for the *anticlinal* conformation. Figure 2b,c shows the criteria to define the head and the tail conformations, which can be eclipsed or staggered. We used the same nomenclature for  $Ch^+$  conformers.



**Figure 2.** (a) The criteria to define the conformation of each dihedral angle. A line lying on  $0^\circ$  represents the bond of the first two atoms describing the dihedral angle. Newman projections (b) along C2–C1 and (c) along N–C4. For Figure 2b,c,  $\theta \cong 0^\circ$  means eclipsed conformation and  $\theta \cong 60^\circ$  means staggered conformation.

### 2.3. Energy and Structure Calculations

We employed routines of calculations based on density functional theory (DFT) [30,31] to determine the energy and the structure of molecules in the ground state and in the TS. We used B3LYP functionals and the 6-311++G(d,p) basis set integrated in Gaussian 09 software [32]. The use of B3LYP functionals follows its success in our previous similar study on chemical reactions [28,33,34] and other similar cases [35,36]. The optimization–routine calculations are to obtain the stable structures and the total electronic energy of  $\text{ACh}^+\text{Br}^-$ , water, and AA and, more importantly, to find the stable conformers of  $\text{ACh}^+$  and  $\text{Ch}^+$ . For the TS, we followed the same procedure used in our previous study [28], where we applied the TS optimization and the intrinsic reaction coordinate routines of calculation. Besides the energy and the structure, we also calculated the charge population using the Natural Bond Orbital (NBO) program [37].

### 2.4. Thermochemistry Calculations

We calculated the standard enthalpy of reaction ( $\Delta_r H^\circ$ ) and the standard Gibbs energy of activation ( $\Delta^\ddagger G^\circ$ ) of  $\text{ACh}^+$  neutral hydrolysis using the following formula:

$$\Delta_r H^\circ = (H^\circ_{\text{ACh}^+} + H^\circ_{\text{H}_2\text{O}}) - (H^\circ_{\text{AA}} + H^\circ_{\text{Ch}^+}) \quad (1)$$

$$\Delta^\ddagger G^\circ = (G^\circ_{\text{TS}}) - (G^\circ_{\text{ACh}^+} + G^\circ_{\text{H}_2\text{O}}) \quad (2)$$

Both  $H^\circ$  and  $G^\circ$  in Equations (1) and (2) are temperature dependent, and we assumed the reaction occurred at room temperature (298.15 K). The values were determined from the total electronic energy of the respective systems with thermal corrections.

## 3. Results and Discussion

### 3.1. The Ground-State Structure

Table 2 presents the discrepancy in geometry between the experimental value and our calculations for  $\text{ACh}^+\text{Br}^-$  in the ground state. The experimental values are from the crystal structure [29], which is comparable to our calculations in the gas phase. Overall, the values of  $\Delta_{\text{bot}}$  are within the accuracy limit, according to Young [38]. It implies that B3LYP functional and the 6-311++G(d,p) basis set are appropriate for studying  $\text{ACh}^+$ .

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**Table 2.** The optimized geometrical parameters of ACh<sup>+</sup>Br<sup>-</sup> from (a) experimental values [29] and (b) our calculations (R (in Å); A (in deg.)). The discrepancy  $\Delta_{ba}$  is the value of (b) minus (a).

Parameter	(a)	(b)	$\Delta_{ba}$
R(C1,O1)	1.192	1.202	0.010
R(C1,C2)	1.487	1.496	0.009
R(C1,O2)	1.358	1.381	0.023
R(O2,C3)	1.452	1.431	-0.021
R(C3,C4)	1.500	1.521	0.021
R(C4,N)	1.513	1.532	0.019
A(O1,C1,C2)	125.9	126.9	1.0
A(O1,C1,O2)	122.8	122.3	-0.5
A(C2,C1,O2)	111.3	110.8	-0.5
A(C1,O2,C3)	115.7	116.5	0.8
A(O2,C3,C4)	111.6	111.1	-0.5
A(C3,C4,N)	116.4	116.4	0.0

The optimization routine calculations predict the stable conformer for both ACh<sup>+</sup> and Ch<sup>+</sup>. The cartesian coordinates of the stable conformers are given in the Supplementary Materials. Only seven out of 64 potential ACh<sup>+</sup> conformers are stable in the ground state, as shown in Figure 3. For Ch<sup>+</sup>, there are only two possible out of 16 potential conformers. Tables 3 and 4 resume the results for ACh<sup>+</sup> and Ch<sup>+</sup>, respectively. In both ACh<sup>+</sup> and Ch<sup>+</sup>, the spans of the dihedral angle are more significant than those of bond lengths and bond angles, which is as expected. That is to say that the backbone determines the conformation, whereas the head (for ACh<sup>+</sup> only) is always eclipsed and the tail is always staggered.

**Table 3.** The optimized conformation type and geometrical parameters of the stable ACh<sup>+</sup> conformers (R (in Å); A and D (in deg.)).

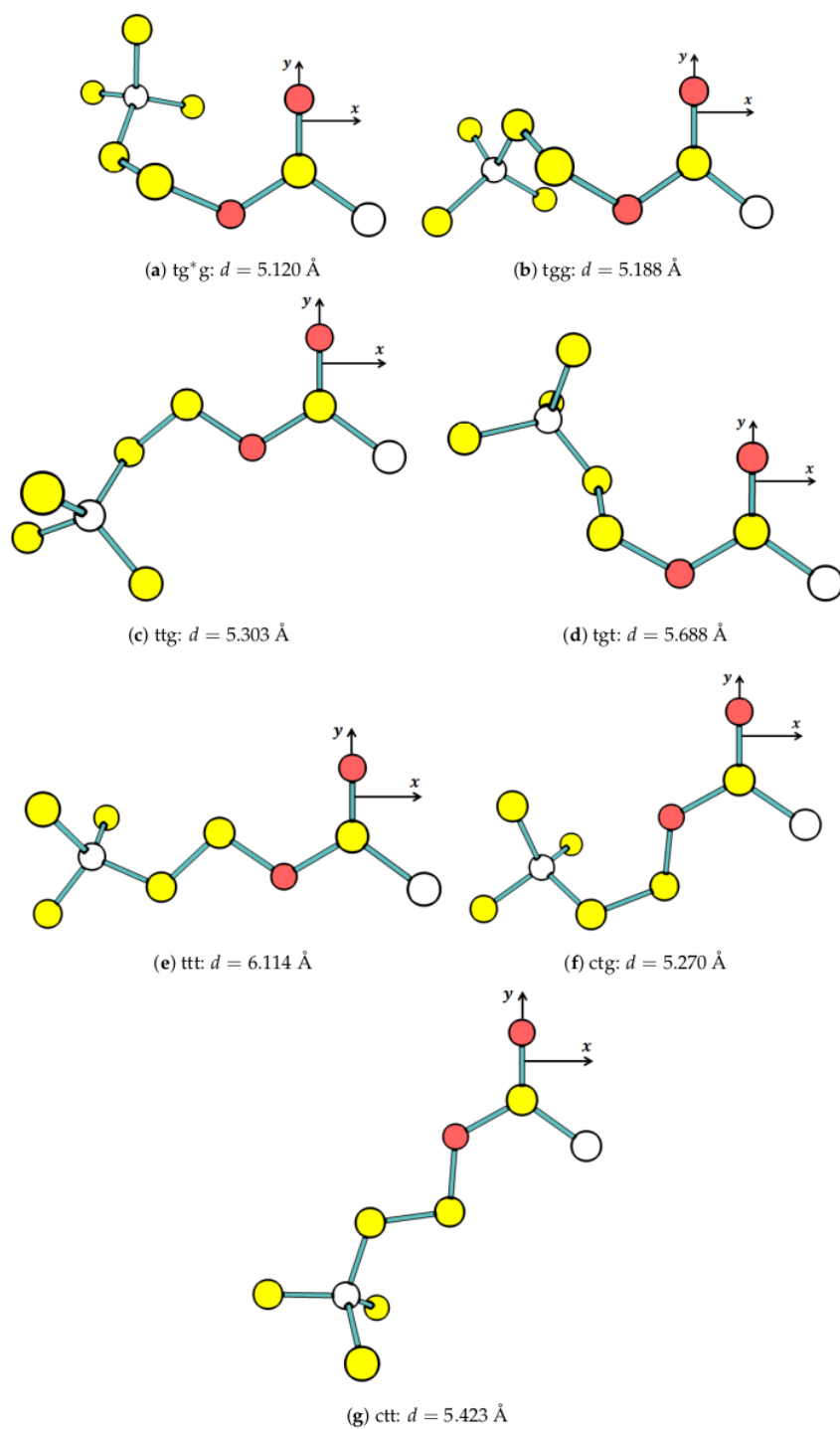
Backbone Conformation	Parameters							
	R1	R2	R3	A1	A2	D1	D2	D3
tg <sup>+</sup> g	1.497	1.369	1.532	111.5	121.8	166.6	110.4	-79.7
tgg	1.498	1.383	1.531	111.4	121.4	170.6	81.7	67.0
ttg	1.499	1.389	1.533	111.2	121.1	-178.4	166.0	65.9
tgt	1.497	1.374	1.525	111.5	121.3	174.9	80.7	-157.2
ttt	1.498	1.384	1.525	111.1	121.1	180.0	180.0	180.0
ctg	1.505	1.400	1.533	117.4	116.4	-7.4	166.7	56.7
ctt	1.507	1.397	1.523	117.3	116.8	0.0	180.0	180.0
span	0.011	0.031	0.010	6.3	5.5	180.0	99.3	124.3

R1 C2-C1; R2 C1-O2; R3 C4-N; A1 C2-C1-O2; A2 O1-C1-O2.

**Table 4.** The optimized conformation type and geometrical parameters of the stable Ch<sup>+</sup> conformers (R (in Å); A and D (in deg.)).

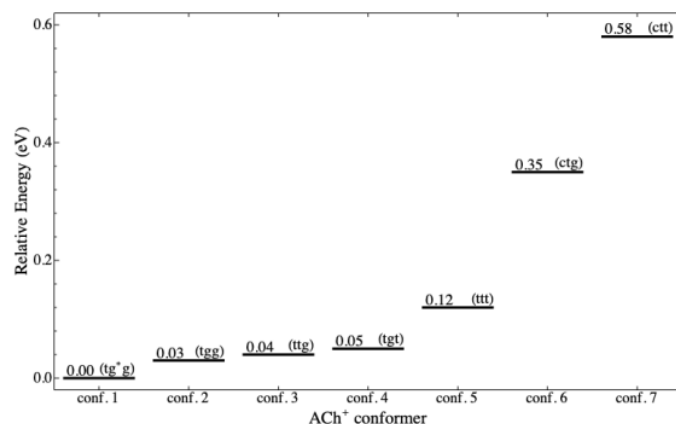
Backbone Conformation	Parameters						
	R4	R5	R6	A3	A4	D6	D7
tg	1.419	1.521	1.533	110.2	109.6	167.7	58.3
tt	1.414	1.530	1.522	110.3	102.6	179.5	178.4
span	0.004	0.009	0.011	0.1	7.0	11.8	121.2

R4 O2-C3; R5 C3-C4; R6 C4-N; A3 H5-O2-C3; A4 C3-C4-N.



**Figure 3.** The optimized structure of  $ACh^+$  conformers: For clarity, all H atoms are not displayed. The distance,  $d$ , is between C2 and N atom (white).

Figure 4 shows the energy level diagram (ELD) for the seven stable ACh<sup>+</sup> conformers in eV (1 eV  $\approx$  23.06 kcal/mol). It is clear from the energy level that there are two groups of conformers, which are low and high level. The low-level group is more stable than the high-level group. The five ACh<sup>+</sup> conformers (tg<sup>\*</sup>g, tgg, ttg, tgt, and ttt) are in the low-level group (Figure 3a–e), and the other two conformers (ctg and ctt) are in the high-level group (Figure 3f,g). Other computational studies [20,23,39,40] also conclude the stability of the five low-level conformers. It is important to note that our results support the experiments that observed ACh<sup>+</sup>(tg<sup>\*</sup>g), (tgg), and (ttg) in their stable states [29,41,42].



**Figure 4.** The energy level diagram (ELD) of the seven stable ACh<sup>+</sup> conformers. The energy is relative to ACh<sup>+</sup>(tg<sup>\*</sup>g).

The ELD displays three noticeable patterns of the conformation related to ACh<sup>+</sup> stability as individual molecules. The first is that *gauche* conformation at D1 cannot achieve stability, whereas *trans* and *cis* can. The second is that *cis* at D2 and D3 cannot achieve the stability, whereas *trans* and *gauche* (and *anticlinal*) can. The second pattern is as expected because the *cis* conformation causes two bulky groups (acetyl and trimethylamine) to be eclipsed, leading to a repulsive interaction among atoms of the two groups. The third is that *gauche* conformation at D2 and D3 makes ACh<sup>+</sup> more stable than when they are *trans*; therefore, at the same D1, it is possible to arrange the order of ACh<sup>+</sup> stability (based on D2 and D3), from the most to the least stable, as gg, tg, gt, and tt. In addition to the third pattern, it appears that the ACh<sup>+</sup> stability is more dependent on D3 than D2.

Charge distributions align with this pattern. The overall NBO calculations determine that more electrons are distributed in the head, resulting in the tail being positively charged (see Table 5). It agrees with the typical ACh<sup>+</sup> structure [43]. The shorter the head–tail distance, the stronger the coulombic interaction and, consequently, the more stable the conformer. Therefore, the backbone and the tail must curl up in order to shorten the head–tail distance. Such curling behavior does not only exist in gas phase but also in solvent [18,20,23,27]. The *gauche* conformation at D2 and D3 meets the condition, particularly at D3, where the head–tail distance is the shortest. Figure 3 depicts the circumstance, in which the distance gradually increases from the shortest in the g<sup>\*</sup>g conformation to the longest in the tt conformation for the low-level group and from the shortest tg to the longest tt for the high-level group.

Additionally, the charge distribution shown in Table 5 indicates an electrophilic site of all ACh<sup>+</sup> stable conformers. It is in the backbone, where C1 is located. This site is typical for the ester family. According to our study on ethyl acetate neutral hydrolysis [28], the activated complex (ACh<sup>+</sup>–water) forms between C1 and O3, the nucleophilic site of water.



**Table 5.** The atomic charge populations (in unit e) of ACh<sup>+</sup> and water: Not available values are indicated by “n.a.”.

Molecules	Head		Backbone				Tail		
	O1	C2H <sub>3</sub>	C1	O2	C3	C4	N	3(CH <sub>3</sub> )	O3
(a) ACh <sup>+</sup>									
tg <sup>+</sup> g	−0.61	0.06	0.82	−0.57	−0.07	−0.18	−0.36	1.00	n.a.
tgg	−0.58	0.05	0.81	−0.59	−0.07	−0.19	−0.35	1.00	n.a.
ttg	−0.55	0.04	0.82	−0.61	−0.07	−0.17	−0.34	1.00	n.a.
tgt	−0.55	0.06	0.82	−0.61	−0.07	−0.17	−0.35	1.00	n.a.
ttt	−0.56	0.05	0.82	−0.58	−0.06	−0.17	−0.35	1.00	n.a.
ctg	−0.52	0.02	0.82	−0.62	−0.05	−0.17	−0.35	1.01	n.a.
ctt	−0.51	0.01	0.81	−0.59	−0.05	−0.17	−0.35	1.00	n.a.
(b) Water	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	−0.91

The electrophilic site of the ACh<sup>+</sup> conformers gives a hint to the cleaving location during the hydrolysis. The cleaving location shall be the C1–O2 bond. Therefore, we extracted the C1–O2 bonding atomic orbital from the NBO calculations as listed in Table 6. All conformers have an average bonding orbital of 0.5464 C(*sp*<sup>2.90</sup>) + 0.8375 O(*sp*<sup>2.19</sup>). This bonding is relatively weaker than the C1–O2 bond of ethyl acetate, which is 0.5898 C(*sp*<sup>1.91</sup>) + 0.8076 O(*sp*<sup>1.42</sup>) [28]. It suggests that the neutral hydrolysis of ACh<sup>+</sup> is easier than that of ethyl acetate.

**Table 6.** The Natural Bond Orbital (NBO) calculation for the C1–O2 bonding based on the linear combination of atomic orbitals  $a C1(sp^n) + b O2(sp^m)$ .

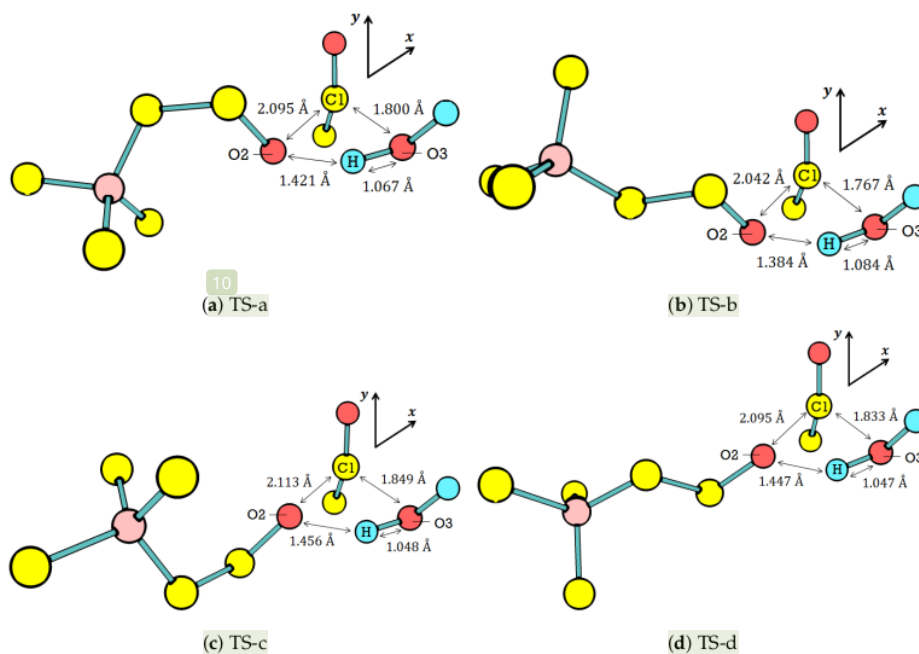
Molecules	C1		O2	
	<i>a</i>	<i>sp<sup>n</sup></i>	<i>b</i>	<i>sp<sup>m</sup></i>
(1) ACh <sup>+</sup>				
tg <sup>+</sup> g	0.5507	2.82	0.8347	2.11
tgg	0.5481	2.87	0.8364	2.20
ttg	0.5444	2.91	0.8388	2.24
tgt	0.5503	2.84	0.8350	2.19
ttt	0.5455	2.90	0.8381	2.24
ctg	0.5419	3.01	0.8404	2.17
ctt	0.5436	2.98	0.8393	2.21
average	0.5464	2.90	0.8375	2.19
(2) Ethyl acetate				
trans	0.5901	1.91	0.8073	1.42
gauche	0.5895	1.91	0.8078	1.41
average	0.5898	1.91	0.8076	1.42

### 3.2. The Transition State Structure

The calculations narrow down the TS geometry from seven possible reactants to four [ACh<sup>+</sup>–water] activated complexes. The cartesian coordinates of the four activated complexes are given in the Supplementary Materials. Table 7 lists the seven possible reactants (codes Re1–Re7). Figure 5 displays the optimized activated complex of these four [ACh<sup>+</sup>–water]. The overall orientation of water with respect to ACh<sup>+</sup> is similar to our previous study on [ethyl acetate–water] activated complex [28]. This similarity suggests that ACh<sup>+</sup> neutral hydrolysis resembles base-induced ester hydrolysis.

**Table 7.** The code for reactants (initial state (is)) and products (final state (fs)) from Scheme 1.

Code	Systems	State
Re1	ACh <sup>+</sup> (tg <sup>+</sup> g) + water	is
Re2	ACh <sup>+</sup> (tgg) + water	is
Re3	ACh <sup>+</sup> (tgg) + water	is
Re4	ACh <sup>+</sup> (tgt) + water	is
Re5	ACh <sup>+</sup> (ttt) + water	is
Re6	ACh <sup>+</sup> (ctg) + water	is
Re7	ACh <sup>+</sup> (ctt) + water	is
Pr1	AA + Ch <sup>+</sup> (tg)	fs
Pr2	AA + Ch <sup>+</sup> (tt)	fs

**Figure 5.** The four possible TS geometries.

The ACh<sup>+</sup>–water interaction in all four possible TSs elongates C1–O2, which makes it an important parameter since it is the cleaving location, as we have discussed in Table 6. The elongation of C1–O2 is around 50% (from 1.40 Å (Table 3) to 2.10 Å (Figure 5)). It is significantly larger than that of the C1–O2 in ethyl acetate–water interaction, which is around 33% [28]. The large C1–O2 elongation is explainable according to the bonding orbital of C1–O2 described in Table 6. The bond in ACh<sup>+</sup> is weaker than that in ethyl acetate; therefore, the bond is easier to break in ACh<sup>+</sup> relative to ethyl acetate. Consequently, ACh<sup>+</sup> neutral hydrolysis is expected to be faster than that of ethyl acetate. This expectation agrees with the experimental data showing that, at room temperature, the rate constant of the former is 10<sup>−9</sup>/s [44], whereas that of the latter is 10<sup>−10</sup>/s [45].

In addition to the C1–O2 elongation, there are two other similarities among the four TS geometries. First, the elongation is large enough to split the acetyl group from the rest of ACh<sup>+</sup>. For comparison, the generalization of C–O bond lengths in saturated molecules, like ACh<sup>+</sup>, has been widely assumed as 1.43 Å. Meanwhile, the O3 of water is still too far from C1 to form a covalent bond. The activated complex thus consists of three groups: water, acetyl, and choline. The three groups interact with each

other through noncovalent interactions to form the activated complex, which lies on the TS. Second,  $\text{ACh}^+$  prefers the curling  $D2$  and  $D3$  in the presence of water. The curling  $D2$  and  $D3$  relates the  $\text{ACh}^+$  in the TS to the one in the ground state: (ttg), (tgt), (ctg), and (ctt). Since the curling,  $D2$  and  $D3$  also affect the C2–N distance and the seven  $\text{ACh}^+$  conformers are grouped into three curling levels. The levels are extreme ( $d < 5.20 \text{ \AA}$ ), medium ( $5.30 < d < 5.70 \text{ \AA}$ ), and low ( $d > 5.70 \text{ \AA}$ ). Accordingly, all TS geometries require the medium curling level of  $\text{ACh}^+$  conformers.

Among the four TS geometries, TS-b is the most favorable one for product formation. Generally, the product formation requires the elongation of C1–O2 and O3–H in the TS with respect to the ground state, as well as shortening the distances of C1–O3 and O2–H (distances between groups in the activated complex). The shortened C1–O3 and O2–H promote the formation of AA and  $\text{Ch}^+$ , respectively. TS-b meets most of the requirements for product formation as its O3–H is the longest, whereas its C1–O3 and O2–H are the shortest among the four TS geometries.

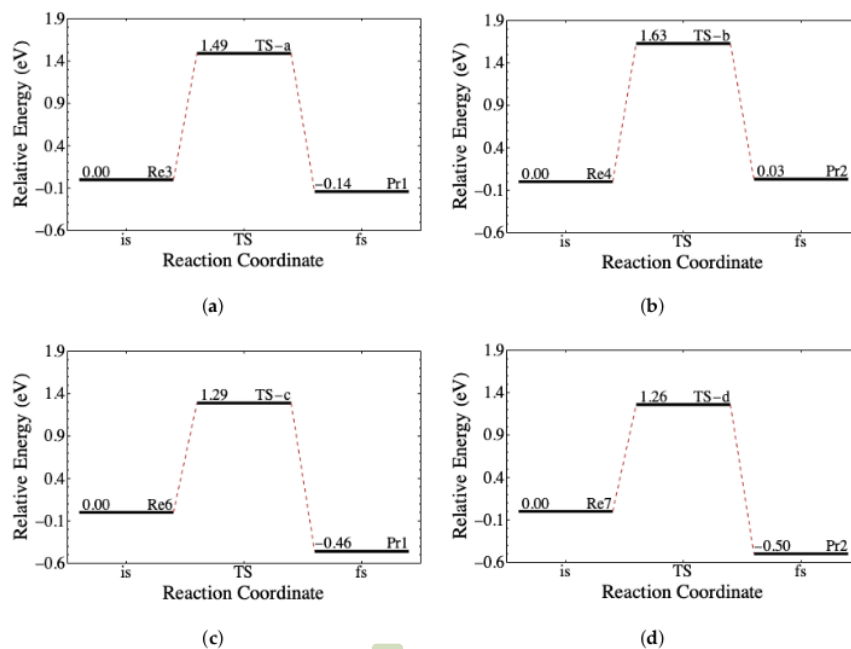
### 3.3. The Reaction Coordinate

Figure 6 shows the neutral hydrolysis reaction coordinate in the ELD. The ELD involves four out of the seven potential reactants (see Table 7) capable of forming the activated complex at the TS through a one-step mechanism. The possible reactants are Re3, Re4, Re6, and Re7, which are related to the aforementioned  $\text{ACh}^+$  curling levels. The possible products are Pr1 and Pr2, which comprise  $\text{Ch}^+(\text{tg})$  and  $\text{Ch}^+(\text{tt})$  from Table 4. Although the TS depends on the curling levels of  $D2$  and  $D3$  of the  $\text{ACh}^+$  conformers, the products depend only on  $D3$ . Since  $D3$  does not contain the electrophilic site, it does not change when  $\text{ACh}^+$  is hydrolyzed into  $\text{Ch}^+$ .

Figure 7 shows the pre-hydrolysis reaction coordinate in the ELD. There are three out of seven potential reactants that require a pre-hydrolysis process (Re1, Re2, and Re5). These reactants need to undergo conformational isomerization to form either  $\text{ACh}^+(\text{tg})$  or  $\text{ACh}^+(\text{tgt})$  with the energy barriers at no more than 0.11 eV. It implies that the conformational isomerization can occur by thermal energy. Together with Figure 6, Figure 7 suggests that all seven potential reactants can perform hydrolysis in four pathways. The reactants with the low-level group of  $\text{ACh}^+$  conformers go through Re3 or Re4 before going to either TS-a or TS-b. Both pathways are possible because the energy barrier to form Re3 and Re4 is no more than 0.11 eV. Meanwhile, the reactants with the high-level group of  $\text{ACh}^+$  conformers go directly to TS-c and TS-d.

Table 8 shows the  $\Delta_r H^\circ$  for all possible reaction coordinates in Figures 6 and 7. The calculations of  $\Delta_r H^\circ$  suggest that reactants with the high-level  $\text{ACh}^+$  conformers are always exothermic and go toward either Pr1 or Pr2. Meanwhile, reactants from the low-level group are exothermic if they go toward Pr1, but they are endothermic if they go toward Pr2. Experimentally, the reaction is endothermic, with  $\Delta_r H^\circ$  being +0.28 kcal/mol [46]. According to our results, Pr2 is mostly the product of the hydrolysis. In particular, the experiment observed mostly reactions (viii) or (ix), suggesting that the practically preferred  $\text{ACh}^+$  conformer undergoes neutral hydrolysis, which is (tgt) or (ttt). It is worthwhile to mention that our results are in line with the study of Zhorov et al. [47], which suggest that  $\text{ACh}^+$  with  $D2$  and  $D3$  being *trans* is productive for the  $\text{ACh}^+$  hydrolysis catalyzed by acetylcholinesterase (AChE), as well as the study of Chothia and Pauling [48], which suggests that the  $\text{ACh}^+$  conformation relevant for its interaction with AChE is the one with  $D1$ ,  $D2$ , and  $D3$  being *trans*.

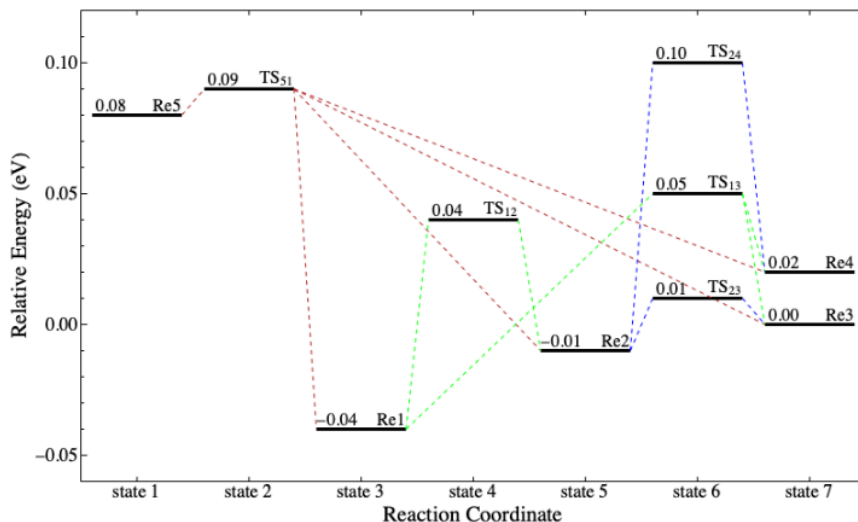
In addition to  $\Delta_r H^\circ$ , Table 8 shows  $\Delta^\ddagger G^\circ$ . As expected,  $\Delta^\ddagger G^\circ$  of reactants with the high-level  $\text{ACh}^+$  conformers are lower than that of reactants with the low-level conformers. Consequently, reactions (v) and (x) are favorable to occur due to the low activation energy and the high exothermicity. However, the energy level of both  $\text{ACh}^+(\text{ctt})$  and (ctg) are more than 0.30 eV higher than the most stable conformer. They can transform to  $\text{ACh}^+(\text{tgt})$  and (ttg) via conformational isomerization according to the reaction coordinate depicted in Figure 8. The energy barrier is no more than 0.33 eV, which is still in the order of thermal energy. It implies that, despite a low  $\Delta^\ddagger G^\circ$ , the number of  $\text{ACh}^+(\text{ctt})$  and (ctg) in nature is likely lower than that in the low-level group.



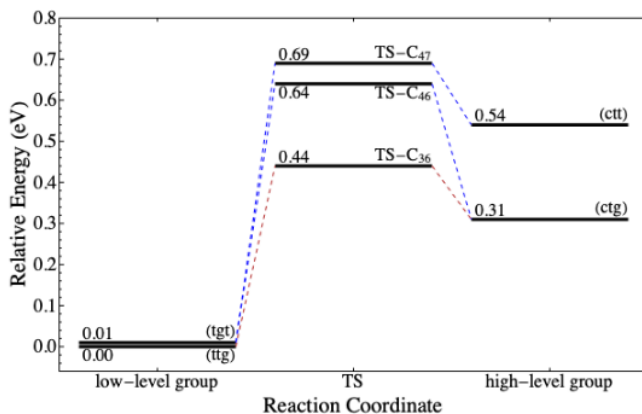
**Figure 6.** The ELDs for four possible TSs: (a) TS-a, (b) TS-b, (c) TS-c, and (d) TS-d, and their related initial (is) and final states (fs). The code of the reactants and the products follows Table 7. The relative energy of each TS corresponds to the energy barrier, whereas the relative energy of the fs corresponds to the reaction energy.

**Table 8.** The standard enthalpy of reaction ( $\Delta_r H^\circ$ ) and the standard Gibbs energy of activation ( $\Delta^\ddagger G^\circ$ ) at 298.15 K (in kcal/mol): For Re5, only the shortest pathway is listed.

Number	Reaction	$\Delta_r H^\circ$	$\Delta^\ddagger G^\circ$
a) Reactions that yield Pr1			
(i)	Re1 $\rightarrow$ Re2 $\rightarrow$ Re3 $\rightarrow$ Ts-a $\rightarrow$ Pr1	-1.67	45.28
(ii)	Re2 $\rightarrow$ Re3 $\rightarrow$ Ts-a $\rightarrow$ Pr1	-2.14	45.28
(iii)	Re3 $\rightarrow$ Ts-a $\rightarrow$ Pr1	-2.33	45.28
(iv)	Re5 $\rightarrow$ Re3 $\rightarrow$ Ts-a $\rightarrow$ Pr1	-4.17	45.28
(v)	Re6 $\rightarrow$ Ts-c $\rightarrow$ Pr1	-9.45	39.28
b) Reactions that yield Pr2			
(vi)	Re1 $\rightarrow$ Re4 $\rightarrow$ Ts-b $\rightarrow$ Pr2	+2.61	47.04
(vii)	Re2 $\rightarrow$ Re4 $\rightarrow$ Ts-b $\rightarrow$ Pr2	+2.14	47.04
(viii)	Re4 $\rightarrow$ Ts-b $\rightarrow$ Pr2	+1.38	47.04
(ix)	Re5 $\rightarrow$ Re4 $\rightarrow$ Ts-b $\rightarrow$ Pr2	+0.10	47.04
(x)	Re7 $\rightarrow$ Ts-d $\rightarrow$ Pr2	-10.33	38.95



**Figure 7.** The reaction coordinates for all potential reactants in Table 7 before forming the activated complex (TS-a, TS-b, TS-c, and TS-d): TS<sub>12</sub> means the transition state of conformational isomerization from Re1 to Re2.



**Figure 8.** The reaction coordinates from low- to high-level groups of ACh<sup>+</sup> conformers: The TS between ACh<sup>+</sup>(ttg) and (ctt) is almost 3 eV, and it is not displayed for the sake of clarity.

#### 4. Conclusion

We have reported that each ACh<sup>+</sup> conformer exhibited different conformational preferences when existing as an individual molecule and as an activated [ACh<sup>+</sup>-water] complex of a neutral hydrolysis. As an individual molecule, we obtained seven possible ACh<sup>+</sup> conformers: five low-level and two high-level conformers, each with a unique backbone conformation. Three out of the five low-level conformers were observed in the experiments. However, only four out of the seven conformers were capable of undergoing direct neutral hydrolysis via four distinct TSs, while the others had to go through some possible pre-hydrolysis pathways before forming the TS. Among the four TS structures, TS-b was the most favorable one to form the product of the neutral hydrolysis. The structure offered an insight for constructing the starting TS structure of ACh<sup>+</sup> neutral hydrolysis catalyzed by AChE.

In this study, we proposed ten possible reaction pathways of ACh<sup>+</sup> neutral hydrolysis. The most favorable reactions involved the high-level conformer with  $\Delta^\ddagger G^\circ$  being 38.95 kcal/mol and  $\Delta_r H^\circ$  being  $-10.33$  kcal/mol. Importantly, we suggested two possible reactions involving low-level conformers ((*trans, gauche, trans*) and (*trans, trans, trans*)) with  $\Delta_r H^\circ$  values of  $+1.38$  and  $+0.10$  kcal/mol, agreeing with the experimental observations. Furthermore, we argued that one had to consider ACh<sup>+</sup> conformers when studying its hydrolysis.

**Supplementary Materials:** Supplementary Materials are provided. The supplementary materials are available online.

**Author Contributions:** Conceptualization: F.R.; formal analysis: R.N.F., F.A., M.M., and I.P.; investigation: R.N.F., N.D.A., and V.K.; methodology: F.R. and R.N.F.; writing—original draft preparation: R.N.F.; writing—review and editing: F.R., H.K.D., and R.N.F. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflict of interest.

## Abbreviations

The following abbreviations are used in this manuscript:

AA	Acetic Acid
ACh <sup>+</sup>	Acetylcholine
Ch <sup>+</sup>	Choline
ELD	Energy Level Diagram
TS	Transition State

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**Sample Availability:** Samples of the compounds are not available from the authors.



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