

Theoretical Study of Alkylation of 4-amino-1,2,4-Triazol in Presence of Aluminium Chloride

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ABSTRACT

The theoretical study of alkylation of 4-amino-1,2,4-triazol ($C_4N_3H_4$) in the presence of aluminum chloride ($AlCl_3$) was carried out by quantum chemical methods HF and DFT, in Lanl2Dz basis set. The results show that N-alkyl product is favorable thermodynamically. And the aluminum chloride decreases the activation energy.

Keywords: Alkylation, 4-amino-1,2,4-triazol, Aluminum chloride, HF, DFT, Lanl2DZ

INTRODUCTION

Alkyl N-amino-1,2,4-triazol are compounds which have antiviral properties [1-8]. Some 1,2,4-triazole derivatives are also known to possess pharmacological activities like antitubercular, anticonvulsant, anti-inflammatory, and analgesic activities [9-15]. These compounds are synthesized by alkylation of the triazol or directly without triazol as agent product. The triazol ring is found in several pharmaceuticals and agronomics compounds [16-18]. The triazolium salts are soluble and could strengthen the properties of triazol.

In this study, the modeling of the alkylation of triazol by ethylbromide was carried out, firstly without catalyst and secondly in the presence of aluminum chloride. Energies of the different reaction and the activation energies were calculated in aim to appreciate the effect of aluminum chloride as catalyst and to found the favorable site of the alkylation.

MATERIALS AND METHODS

The calculations were carried out by two methods, Hartree-Fock (HF) method and the Density Functional Theory (DFT). The basis set used is a double zeta basis set Lanl2dz. The calculations were made with the program Gaussian-03W [19]. The data of the program are the geometry, the multiplicity and the charge of the system. The curves were drawn with Microsoft Office Excel 2003 and the drawings of the studied chemical system were collectively realized with ChemDraw Ultra 8.0.

The modeling of the reaction was carried firstly without catalysis and secondly in presence of aluminum chloride as catalysis. Ethylbromide was used as alkylation agent.

Reaction without catalysis

4-amino-1,2,4-triazol is a symmetrical molecule. The alkylation of this molecule can be produced on N atom or C atom. To obtain the N-alkyl product we orientated the ethylbromide molecule to N^1 of the triazole (Figure 1). To obtain the C-alkyl product we orientated the ethylbromide molecule to C^5 of the triazol (Figure 2).

Reaction in presence of aluminum chloride ($AlCl_3$)

The reaction has been led in accordance with the reaction of Friedel and Crafts [20]. So the first step is the adsorption of ethylbromide on aluminum chloride. And the second step is the reaction of the adduct with the triazol.

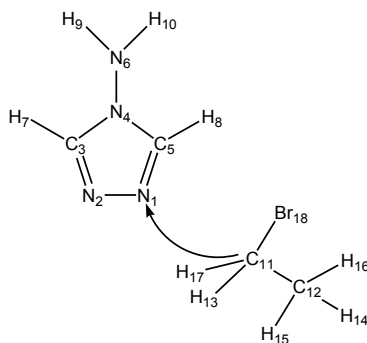


Figure 1: Number of atom in N1 attack

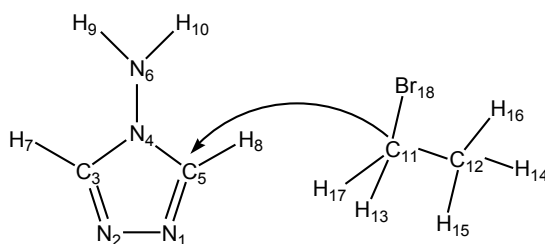


Figure 2: Number of atom in C5 attack

RESULTS AND DISCUSSION

3-1 Reaction without catalysis

The alkylation of 4-amino-1,2,4-triazol by ethylbromide without catalysis was carried out in two approach, N¹ attack and C⁵ attack.

3-1-1 N¹ attack

The reaction coordinate is the distance C¹¹N¹. The system on the start of the reaction is represented on Figure 3.

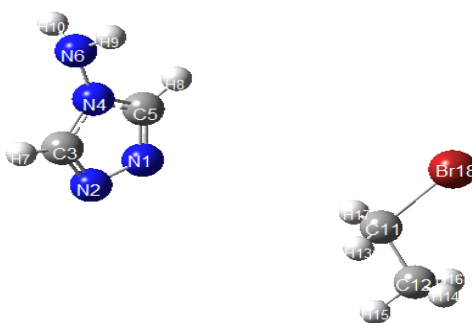


Figure 3: Initial state of N1 attack

Variation of the energy potential surface is represented on Figure 4. The curve shows that the reaction exothermic.

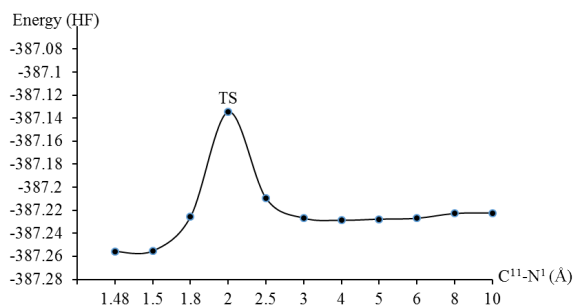


Figure 4: Variation of energies during approach N1 without catalyst

In this attack in proportion as $C^{11}N^1$ decreased, some interatomic distances of the system change. We observed the broken of the $C^{11}Br^{18}$ bond in the same time the $C^{11}N^1$ bond has been formed.

Some distances were been constant during the process. It is the cases of the bonds N^1-N^2 , $N^1=C^5$ and $N^2=C^3$. These constant values for the bond in the ring could explain that the N^1-C^{11} was established by the electron-pair on the N^1 atom.

We noticed that the transition state is close to the initial state. $C^{11}-Br^{18}$ lengthened slightly (at 0.04 Å), the lengthening of the over bonds is smaller. The transition state is represented on Figure 5.

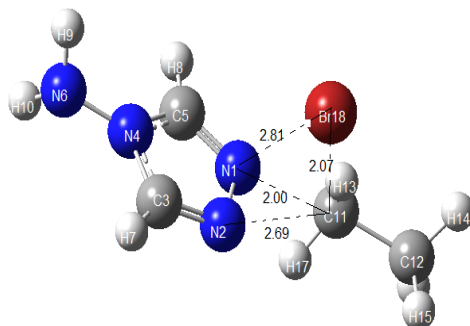


Figure 5: Transition state of N1 attack

At the end of the reaction, N^1-C^{11} bond is formed and the length is 1.48 Å according to the standard value of the simple bond N-C [21]. $C^{11}-Br^{18}$ bond was broken, in fact the length increased at 2.03 Å to 4.33 Å. Br atom was respectively at 3.71 Å and 2.98 Å to N^1 and C^5 atoms. Analysis of Mulliken population on Br atom shows high negative charge (-0.787 u.a.) and then the ring have positive charge which is localize on the C atoms. The product of the alkylation is represented on Figure 6.

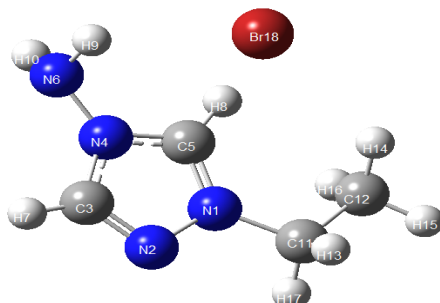


Figure 6: Product of N1 attack

3-1-2 C^5 attack

The reaction coordinate is the distance $C^{11}C^5$. The system on the start of the reaction is represented on Figure 7.

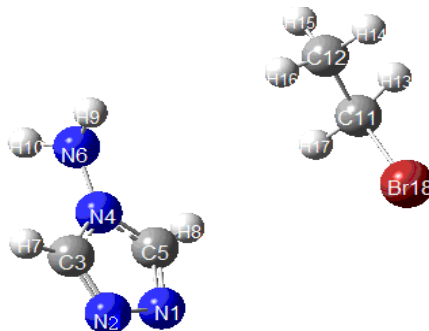


Figure 7: Initial state of C5 attack

Variation of the energy potential surface is represented on Figure 8. The curve shows that the reaction endothermic.

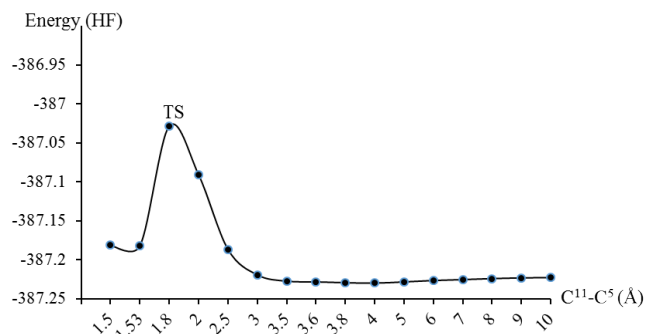


Figure 8: Variation of energies during approach C5 without catalyst

At the transition state (Figure 9), the C^{11} -Br¹⁸ bond was not broken and C^{11} -C⁵ bond was not formed, their lengths are respectively 2.08 Å and 1.80 Å. Nevertheless we observed light lengthening or shortening of the bond in the triazolic ring. The Mulliken population analysis shows that the negatives charges increased on atom N¹ (-0.1594 ua to -0.1912 ua) and C⁵ (-0.0199 ua to -0.1164 ua), that can be explain by the broken of the π bond and the partition of the electrons between atoms N¹ and C⁵.

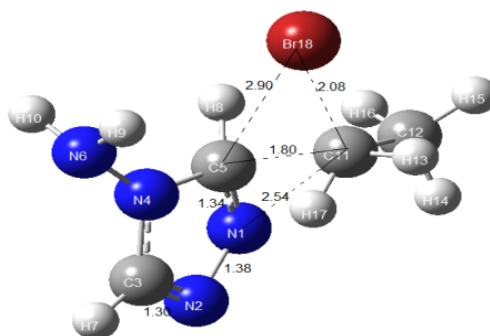


Figure 9: Transition state of C5 attack

At the end of the process, we notice the formation of the bond C^5 - C^{11} at 1.54 Å (Figure 10). We observe that the aromaticity was disappeared, in fact the double bonds $C^5=N^1$ and $C^3=N^2$ of the ring became simple bonds; the lengths in the product are respectively 1.45 Å and 1.42 Å.

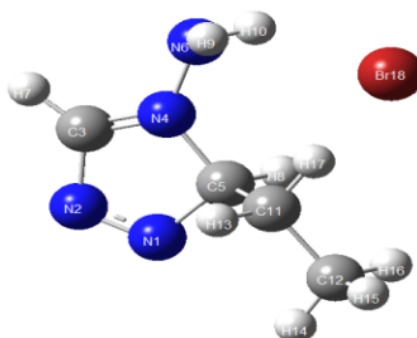


Figure 10: Product of C5 attack

The energetic result of the alkylation of 4-amino-1,2,4-triazol without catalysis is give in the Table 1.

Table 1: Summary of energy values of attacks without catalyst

	Ea (kcal/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)
N1 attack	55.12	-16.26	-15.57
C5 attack	121.96	26.54	34.99

We notice that the activation energy for the N¹ attack is smaller than C⁵ attack one so the attack on N¹ could be fast than the attack on C⁵. And the reaction on N¹ is exothermic but endothermic on C⁵, that can explain by the aromaticity

of the product formed for N¹ attack and the loss of aromaticity for C⁵ one. Concerning free Gibbs energies, the result shows that attack on C⁵ atom have positive value so the reaction is not spontaneous in this attack, but it is spontaneous on atom N¹ regarding the negative value. It is probably the reason that the C-alkylation of triazol is due by radical process [22].

3-2 Alkylation in presence of AlCl₃

The alkylation of 4-amino-1,2,4-triazol by ethane bromide on AlCl₃ is carried out. In a accordance with the reaction of Friedel and Crafts, the first step consisted to the adsorption of ethyl bromide on the catalyst (AlCl₃). The system in the minimum of the adsorption was represented on Figure 11.

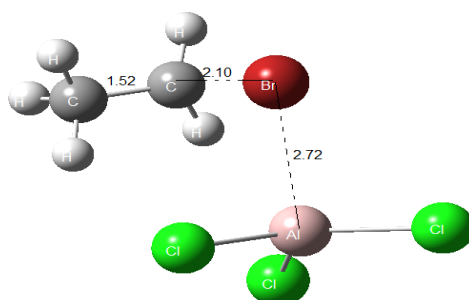


Figure 11: Adduct formed between CH₃CH₂Br and AlCl₃

The system formed in the adsorption process reacts with the triazol; the initial state was represented by Figure 12.

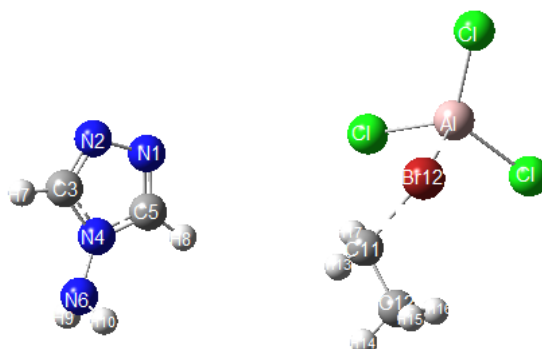


Figure 12: Initial state

The variation of the of potential energy surface according to the coordinate of reaction C⁵-C¹¹ is represented on Figure 13. This graph shows a maximum around 3.5 Å. The reaction is exothermic because the initial state has higher energy than the final state.

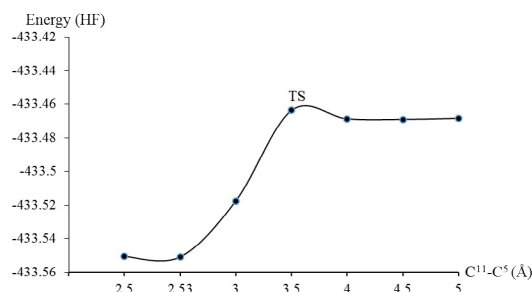


Figure 13: Variation of energies during approach C5 in presence of AlCl₃

The state of transition is reached when the distance C¹¹-C⁵ is about 3.50 Å and N¹-C¹¹ about 3.01 Å (Figure 14). In this stage, the interaction between the triazole and the ethyl bromide is weak; so the initial structure of these molecules undergoes no notorious modification. However the ethyl bromide being adsorbed on the aluminum chloride, the connection C¹¹-Br¹⁸ weakens, because we indeed noted a light stretching at the beginning of the formation of the electrophilic which is the carbonium ion. Besides we note a strengthening of the connection Al-Br¹⁸.

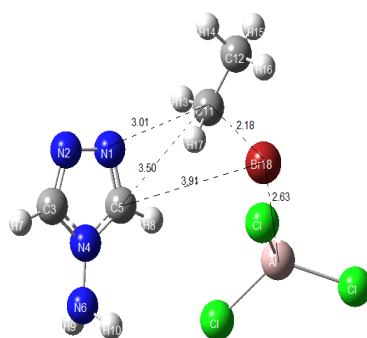
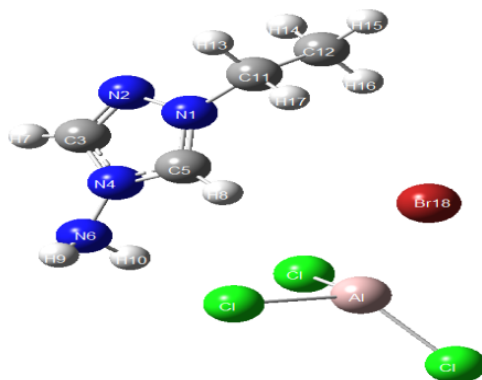


Figure 14: Transition state

The formation of the electrophilic helped the reaction. Indeed the electron pair the nitrogen atom N¹ attacks the electrophilic to establish the connection N¹-C¹¹. We obtain N-éthyl-4-amino-1,2,4-triazolium bromide (Figure 15) at the end of the process. Just like in the case of the approach N¹ without catalysis the aromaticity of the cycle is kept because electrons participating in this aromaticity do not step in this reaction.

Figure 15: Product in presence of AlCl₃

The energetic result of the process was reported Table 2. The activation energy was 2.94 kcal.mol⁻¹ for the calculation made in HF, so the catalyst allowed the reduction in the barrier of energy, what has confirmed the role of catalysts in the reaction. For the calculation DFT, the process did not pass by transition state, we could give some explanation by the fact that Lewis's acid allowed the formation of carbonium ion which is bound with nitrogen atom by electrons pair.

Table 2: Summary of energy values for alkylation in presence of AlCl₃

	Ea (kcal.mol ⁻¹)	ΔH (kcal.mol ⁻¹)	ΔG (kcal.mol ⁻¹)
HF	2,94	-58,35	-50,67
DFT	-	-57,24	-48,32

The negative value of the enthalpy shows that the reaction is exothermic; also it is thermodynamically favorable on the basis of the obtained free Gibbs energy.

The summary of the energy parameters of the reactions with or without catalyst is reported in Table 3.

Table 3: Energy recapitulative of alkylation of 4-amino-1,2,4-triazol

		Ea (kcal/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)
Without catalyst	HF	55,12	-16,26	-15,57
	DFT	58,92	-14,75	-10,20
In presence of AlCl ₃	HF	2,93	-58,35	-50,67
	DFT	-	-57,24	-48,32

We note that the presence of the aluminum chloride has reduced the energy barrier. Of more the processes is thermodynamically favorable for both case about the N¹ attack, because free Gibbs energies are negative.

CONCLUSION

The alkylation of the 4-amino-1,2,4-triazole was carried out by approaching two sites reactive. We observed that both

approach N¹ and C⁵ without catalyst has led to two products which are respectively N-ethyl-4-amino-1,2,4-triazolium bromide and 5-ethyl-4-amino-1,2,4-triazolium bromide. The energetically study of both reactions shows that the approach N¹ is more favored than the approach C⁵. The approach C⁵ would be thermodynamically unfavorable.

The presence of the aluminum chloride has reduced the energy of activation and led to the same product as that of the approach N¹. The aluminum chloride could be used as catalyst of this reaction.

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