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DFT STUDIES ON THE MECHANISM OF THE MICHAEL REACTION: THIOLATES WITH ACRILONITRILE LIKE ACCEPTOR

K. Arafet C., A. G. García L.*, R. Carrasco V.***

**** Natural Sciences Faculty, Oriente University, Santiago de Cuba, ** Informatics Sciences University, Havana, Cuba***

● Resumen

El potencial de energía de superficie (PSA) de la adición del thiolacids y aniones aminothiolacids de acrilonitrilo como aceptor de Michael en el B3LYP/6-31G (d, p) Nivel de la teoría se estudia, la reacción se analiza a través de las densidades de carga NBO. El PSE se caracteriza en primer lugar por la formación de un complejo prereactive (PC), este se forma para la estabilización en un mínimo local de energía de los reactivos; esta asociación molecular está determinada por la formación de dos enlaces de hidrógeno (HB), el sistema evoluciona de un estado de transición (TS) hasta la formación del intermediario tetraédrico (TI) con carga negativa en el carbono 2, la energía de activación determinada es baja y muy similares. La muestra NBO análisis de una manera general para todos los nucleófilos altas densidades de carga en los átomos electronegativos de S y S que favorecen la interacción con el acrilonitrilo átomos de H, que son culpables de los electrones por el efecto electroatractor del Grupo de los CN-.

Palabras clave: grupos sulfhidrilo, las adiciones de Michael, la energía de activación, la carga NBO y complejo prereactive.

● Abstract

The Potential Energy Surface (PES) of the addition the thiolacids and aminothiolacids anions to acrilonitrile like Michael acceptor at the B3LYP/6-31G(d,p) theory level is studied, the reaction is analyzed through the NBO charge densities. The PES it is characterized firstly by the formation of a prereactive complex (PC), this is formed for the stabilization in a minimum energy local of the reactants; this molecular association is determined by the formation of two hydrogen bond (HB), the system evolves for a transition state (TS) until the formation of the tetrahedral intermediary (TI) charged negatively in the carbon 2, the determined activation energy is low and very similar. The analysis NBO sample in a general way for all the nucleophiles high charge densities on the electronegative atoms of S and O that they favour the interaction with the acrilonitrile H atoms, which are faulty of electrons by the electroatractor effect of the –CN group.

Keywords: sulfhydryl groups, Michael's additions, activation energy, NBO charge and prereactive complex.

● Introduction

The interaction between sulfhydryl groups and compounds with double bond C=C it conjugated with an electroacceptor group is an example of chemical reaction in the biological means /1-5/, this is know that Michael reaction. Among the macromolecules that contain groups sulfhydryl they are the cysteine protease, proteolytic enzymes involved in different biological processes, which constitute therapeutic target of a varied spectrum of pathologies, among which are the cancer and the parasitic illnesses /6,7/.

The power nucleophilic of the groups sulfhydryl in Michael's additions has been demonstrated by diverse

authors /1-5, 8-10/, for example Friedman /9/ in a study kinetic classic of the reaction of some compound α,β-unsaturated with the groups amino and sulfhydryl of several aminoacids, aminothiolacids and thiolacids demonstrates that it take place an almost complete substitution of the groups sulfhydryl before the groups amino react in some extension.

The theoretical studies /11-14/ of reactions of Michael show energy barriers easy to overcome, in correspondence with the experimental reports / 8,9/. Kunakbaeva and collaborators /12/ in the 2003 studied at semiempiric PM3 level the Potential Energy Surfaces (PES) of seven typical reactions of sulphurs addition to acceptors of Michael whose activation energy were correlated with experimental kinetic studies carried out by Friedman /9/, which oscillate between 8,7 and 12,2 kcal.mol^{-1}. In this work with study the PES of the rate-determining step of mechanism of Michael reaction that some reactions reported by Kunakbaeva /12/, addition the thiolacids and aminothiolacids anions to acrilonitrile like Michael acceptor using the Density Functional Theory method /15/.

Computational Details

In the report of Friedman /9/ is demonstrated experimentally that the biggest nucleophilicitie in the thiol is to lightly basic pH. Under these conditions, the group thiol is in its form anionic and besides the negative charge on the atom of sulphur; the nucleophilic species have another additional charge of the carboxylic group, with the result that in the calculations they are considered the structures dianionics of the nucleophile.

It thinks about the following reaction mechanism, where the second step is the one that limits the rate of the reaction; experimental kinetic studies /16-20/ for reactions of addition of Michael confirm that the rate-determining step of mechanism is the addition of the anion to double bond C=C:

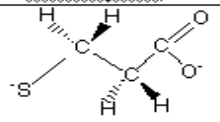
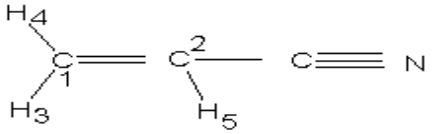
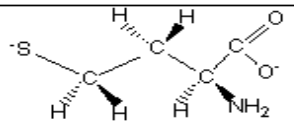
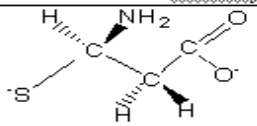
$$RSH + H_2O \leftrightarrow RS^- + H_3O^+$$

$$RS^- + CH_2{=}CH\text{-}X \leftrightarrow RSCH_2C^-HX, \text{ rate-determining step}$$

$$RSCH_2C^-HX + H_3O^+ \leftrightarrow RSCH_2CH_2X + H_2O$$

The critical points of the PES of the rate-determining step of the mechanism proposed by Friedman were optimized, the reactions have the acrilonitrile like acceptor of Michael in common: anion of the β-mercaptopropionic acid (reaction 1), anion of the homocystein (reaction 2) and the anion of the cystein (reaction 3) /see table 1/ using the functional of hybrid density B3LYP /21/, is the particularity of selecting this functional one among other functional of density due to the knowledge of the diverse applications in that this method has been used to describe systems with weak interactions /22-25/ and the base of functions 6-31G(d,p) /26/, recommended to study systems anionic /27/. The transition state was using the calculation options TS, QST2 and QST3. In all the cases the stationary points were characterized by means of the calculation of the vibrational frequencies.

TABLE 1. SPECIES THAT INTERVENE IN THE STUDIED REACTIONS

Nucleophile	Michael Acceptor
 anion of the β-mercaptopropionic acid	 acrilonitrile
 anion of the homocystein	
 anion of the cystein	

The charge densities NBO on the atoms that participate in the interaction in the different critical points are calculated according to the code NBO /28-31/.

The vibrational frequency computations have been carried out at 298,15 K and 1 atm. All calculations were performed with the Gaussian 98 program /32/. The program Molden version 4,2 /33/ for Linux was utilized to display the molecular structure, monitor the geometrical parameters and observe the molecular geometry convergence via Gaussian output file.

Analysis of the geometric parameters

In the figure 1 the different critical points of the PES are shown, firstly the formation of a prereactive complex (PC), this is formed for the stabilization in a minimum energy local of the reactants; this molecular association is determined by the formation of two hydrogen bond (HB), the system evolves for a transition state (TS) until the formation of the tetrahedral intermediary (TI) charged negatively in the carbon 2. Kunakbaeva and collaborators /12/ has intended that the TI would be later protonated to give place to the final product; this protonation was found that it occurred spontaneously without passing through any TS.

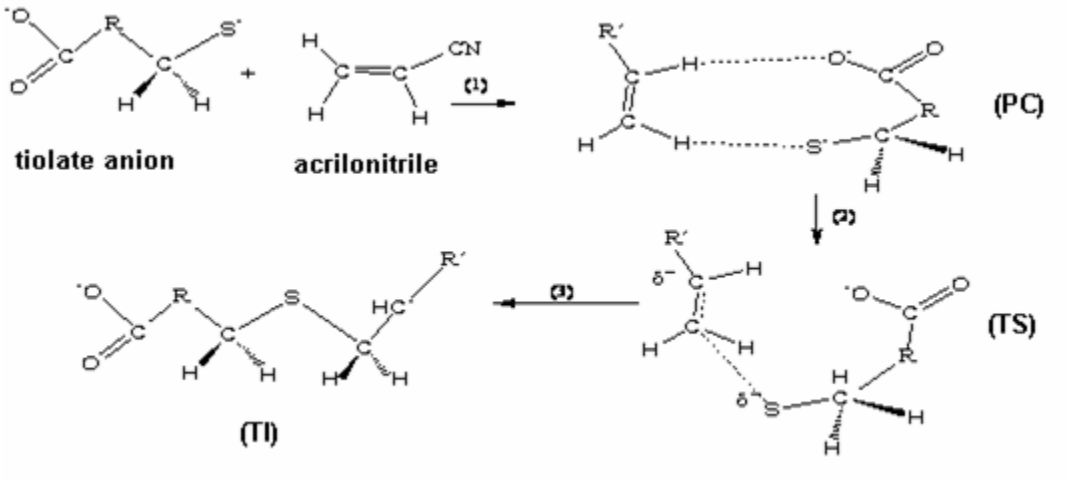


Fig. 1 Critical points for the reaction studied at the B3LYP/6-31G(dp) level of theory.

TABLE 2. DISTANCES (IN Å), BOND AND DIHEDRAL ANGLES MORE IMPORTANT OF THE DIFFERENT CRITICAL POINTS AT THE B3LYP/6-31G(DP) LEVEL OF THEORY

Reactions	Critical points	Geometric parameters				
		d(S-H3)	d(O-H5)	d(S-C1)	α(S-C1-C2)	τ(S-C1-C2-H5)
Reaction 1	PC1	**1,83**	**1,76**	3,02	116,50	1,96
	TS1	2,58	7,80	2,80	130,40	71,60
	TI1	2,44	7,42	2,02	117,00	68,70
Reaction 2	PC2	**2,52**	**1,97**	3,62	123,60	3,40
	TS2	2,37	8,29	3,40	120,70	27,60
	TI2	2,41	----	1,89	114,90	69,40
Reaction 3	PC3	**2,62**	**1,94**	3,71	119,44	-6,94
	TS3	2,57	7,26	2,81	130,95	71,85
	TI3	2,43	7,10	1,89	114,60	63,28

In all the PCs they are formed two HB: between the atom of sulfur of the nucleophile and one of the atoms of hydrogen binding to the C1 (H3) (see Table II) and between an atom of oxygen of the carboxylic group and the hydrogen together to the C2 (H5). These are classified /34-36/ like weak HB because it involves interactions of type donor weak-acceptor weak for the case: C-H···S; and of type donor weak-strong acceptor for: C-H···O. The first of these interactions presents distances that go from the 1,83 Å, for the PC1 until the 2,62 Å for the PC3, while the distance H···O is calculated to smaller values with 1,76 Å for the PC1 and 1,97 Å in the PC2, given the biggest electronegative in the oxygen atom. The interaction C-H···S in the PC has been reported by other authors /11,12,37/ for similar reactions, the interaction C-H···O that alone it is reported /12/ for the reaction that involves the anion of mercaptoacetic acid and the acrilonitrile with the PM3 semiempiric method. It is necessary to point out that Thomas /11/ in a study at different levels of theory of the reaction among HS - and CH_3S - with the acrolein they establish the formation of two prereactive complexes, characterized by the interaction S···H, in a case with the H in position cis to the C-C single bond, and in the other case with the H in position trans, being the first one more stable than the second, although the difference in stability is very little: non superior to 1,50 kcal, this result is similar to that reported by Wong /37/ on the Michael addition of cyanide to acrolein, in our case the formed interaction is with the H in position trans what favors the additional interaction C-H···O that stabilizes even more the system like it will be seen later on.

In the figure 2 where it is shown the optimized geometries of the critical points for the reaction between the cystein anion and the acrilonitrile, it is evidenced the rupture of the interaction between the oxygen atom and the H5 in the TS, where it has not still been formed the bond S-C, the distances S-C have diminished in the TS with regard to the PC; this rupture favors the approach from the sulfur atom to that of C1, until finally the formation of the bond in the TI at distances that oscillate between 1,89 and 2,02 Å (see table 2), all the reactions in a general way have the same behavior.

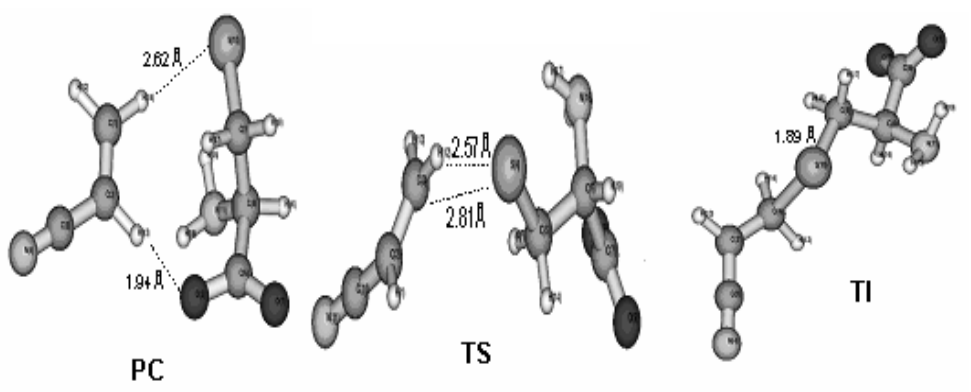


Fig. 2 Geometries optimized of the reaction between cystein anion and acrilonitrile at the B3LYP/6-31G(dp) level of theory.

Reaction and activation energy

In the table 3 and 4 are reflected the absolute energy and the enthalpy and free energy of Gibbs from the critical points at the B3LYP/6-31G(dp) level of theory. It is guaranteed that the reagents and intermediaries of reaction minimum in the PES, when calculating the vibrational frequencies and to verify that all are positive. In turn, the TS were verified checking in the vibrational frequencies calculated, the presence of an imaginary frequency.

TABLE 3 ENERGIES IN HARTREE/PARTICLE OF THE PES CRITICAL POINTS AT THE B3LYP/6-31G(DP) LEVEL OF THEORY

Reactions	E(acrilonitrile) = -170,836 242 2			
	Nucleophile	PC	TS	TI
1	-665,309 847 0	-836,195 583 7	-836,186 539 2	-836,197 591 1
2	-760,003 223 3	-930,872 909 6	-930,865 728 4	-930,881 714 6
3	-720,674 316 9	-891,554 541 2	-891,547 246 0	-891,556 164 6

TABLE 4 ENTHALPIES AND FREE ENERGY OF GIBBS IN HARTREE/PARTICLE OF THE PES CRITICAL POINTS AT THE B3LYP/6-31G(DP) LEVEL OF THEORY

Reagents and intermediaries	H	G
Acrilonitrile	-170,780 276	-170,811 260
Anion of the β-mercaptopropionic acid	-665,234 920	-665,274 491
TI1	-836,065 462	-836,118 962
Anion of the homocystein	-759,879 996	-759,924 611
TI2	-930,700 906	-930,760 521
Anion of the cystein	-720,580 405	-720,621 059
TI3	-891,405 100	-891,460 498

In spite of the weak characteristic interaction of the PC, minimum that is characterized fundamentally by the formation of two HB, a marked stabilization of the system is observed that oscillates between the 21 and 38 kcal.mol^{-1} (see table 5), bigger than those reported by Thomas and Kollman /11/ that are at the HF/6-31+G(d) level of theory for the reaction among the HS^- and the acrolein: 9.97 for the trans PC and 11.15 for the cis PC, and for the reaction CH_3S^- and the acrolein: 13.53 for the trans PC and 12.02 for the cis PC, the difference among the stabilizations due to the interaction S-H in cis and in trans it is similar and very small: 1.18 kcal.mol^{-1}, similar behavior at the MP2/6-31+G(d) level, with the result that a second interaction of H (C-H···O) stabilizes energily in more measure the system.

Later on the system evolves toward the formation of a TS for that which should conquer an energy barrier of little activation energy, the 6 kcal.mol^{-1} they don't surpass at the level B3LYP/6-31G(dp), but they continue being low, that which goes in correspondence with that reported by other authors, for example: Kim and colaboradores /8/ study the kinetics of the reaction between the cystein and the cinnamaldehyde by polarographic and spectroscopic methods reporting an activation energy of 9,17 kcal.mol^{-1}; Kunakbaeva and collaborators /12/ at PM3 semiempiric method reports values of seven typical reactions of sulphurs addition to acceptors of Michael that oscillate between 9,7 and 12,2 kcal.mol^{-1}; Thomas and Kollman /11/ for the addition of HS^- and CH_3S^- to the acrolein at the HF/6-31G(d) level values of 17,70 and 12,30 kcal.mol^{-1} report and at the level MP2/6-31+G(d) of 4,50 and 0,50 kcal.mol^{-1}, respectively; Strajbl and collaborators /14/ in the thiols addition to the formamide at the B3LYP/AUG-ccpVDZ//HF/6-31G(d) with the Langevine dipoles salvation model shows energy of activation of 20 kcal.mol^{-1}. Like rule general /38/, reactions with smaller energy barriers or similar to 21 kcal.mol^{-1} proceed quickly to ambient temperature, with the result that it is of hoping the studied reactions proceed spontaneously to this temperature.

And finally with the formation of a local minimum (TI), there is still a stabilization bigger than the system (see table 4) oscillating between 26 and 32 kcal.mol^{-1} due to the formation S-C bond.

In a general way, in the studied reactions a decrease of the energy of the system also manifested in the negative values of the enthalpy and free energies of Gibbs variations

TABLE 5 RELATIVE ENERGIES OF THE PES CRITICAL POINTS WITH REGARD TO THE REAGENTS, ENTHALPIES AND FREE ENERGIES OF GIBBS VARIATIONS FOR THE REACTIONS STUDIED IN KCAL.MOL^{-1} AT THE B3LYP/6-31G(DP) LEVEL OF THEORY

Reactions	PC	TS	Ea	TI	ΔH	ΔG
1	-31,06	-25,38	5,68	-32,32	-31,54	-20,84
2	-20,99	-16,48	4,51	-26,51	-25,50	-15,47
3	-27,60	-23,02	4,58	-28,62	-27,87	-17,68

NBO charge densities

Different authors /39-41/ have been demonstrated in structure-reactivity studies the importance of the coulombic interaction in Michael's reactions. The charge density on the atoms of S, O, H5, H3 in the reagents, allows to check that electrostaticly is feasible the formation of the HB bond that characterizes the PC formation. The atoms of S and O of the anions present high charge densities, around the 0,83e (see table 6), those which interaction with the atoms H3 and H5 of the acrilonitrile, that are faulty of electrons, around 0,23e and 0,27e. Product of this interaction in the PC these hydrogen's show an increase of their electronic deficiency, while the S atom decrease of their electronic density. Independently of the nucleophile a general way the electronic densities on the atoms of interest show a behavior similar, high charge densities on the S and O electronegative atoms, that they favour the interaction with the H atoms of the acrilonitrile, which are faulty of electrons by the electroatractor effect of the –CN group.

TABLE 6 NBO CHARGE DENSITIES OF THE ATOMS THAT PARTICIPATE IN THE PC FORMATION AT THE B3LYP/6-31G(DP) LEVEL OF THEORY

Reactions	Especies	δS	δO	δH3	δH5	δC1	δC2
1	Anion of the β-mercaptopropionic acid	-0,83	-0,82	----	----	----	----
	Acrilonitrile	----	----	0,23	0,27	-0,34	-0,35
	PC	-0,76	-0,82	0,27	0,33	-0,35	-0,40
2	Anion of the homocystein	-0,79	-0,81	----	----	----	----
	Acrilonitrile	----	----	0,23	0,27	-0,34	-0,35
	PC	-0,76	-0,79	0,28	0,33	-0,34	-0,41
3	Anion of the cystein	-0,80	-0,82	----	----	----	----
	Acrilonitrile	----	----	0,23	0,27	-0,34	-0,35
	PC	-0,76	-0,83	0,27	0,33	-0,34	-0,40

Conclusions

· The PES it is characterized firstly by the formation of a prereactive complex (PC), this is formed for the stabilization in a minimum energy local of the reactants; this molecular association is determined by the formation of two hydrogen bond (HB), the system evolves for a transition state (TS) until the formation of the tetrahedral intermediary (TI) charged negatively in the carbon 2, the determined activation energy is low and very similar.

· The analysis NBO sample in a general way for all the nucleophiles high charge densities on the electronegative atoms of S and O that they

favour the interaction with the acrilonitrile H atoms, which are faulty of electrons by the electroatractor effect of the –CN group.

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