THE S_N2 REACTION: A THEORETICAL-COMPUTATIONAL ANALYSIS OF A SIMPLE AND VERY INTERESTING MECHANISM

Matías Capurso[#], Rodrigo Gette[#], Gabriel Radivoy and Viviana Dorn

Instituto de Química del Sur (INQUISUR-CONICET), Depto. de Química, Universidad Nacional del Sur, Av. Alem 1253, B8000CPB Bahía Blanca, Argentina, e-mail: vdorn@uns.edu.ar

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[#] Both authors contributed equally to this manuscript

ABSTRACT

Bimolecular nucleophilic substitution (S_N2) reaction is one of the most frequently process choose as mechanism model to introduce undergraduate chemistry students in the computational chemistry methodology.

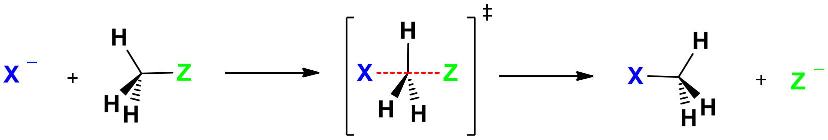
In this work, we performed a computational analysis for the ionic S_N2 reaction, where the nucleophile charged (X^-; X=F, Cl, Br, I) attacks the carbon atom of the substrate (CH_3Cl) through a backside pathway and simultaneously the leaving group is displaced (Cl^-). The calculations were performed applying DFT methods with the Gaussian09 program, the B3LYP functional, the 6-31+G* basis set for all atom except iodine (6-311G*) and the solvents effect (acetonitrile and cyclohexane) were evaluated with the PCM model. We evaluated the potential energy surface (PES) for the mentioned reaction considering the reactants, the formation of an initial complex between the nucleophile and the substrate, the transition state, a final complex where the leaving group is still bound to the substrate and the products. We analyzed the atomic charge (ESP) and the bond distance throughout the process. Gas phase and solvent studies were performed in order to analyze the solvation effects on the reactivity of the different nucleophiles. We observed that increasing solvent polarity, decreases reaction rates.

On the other hand, we thought it would be enriching, to carry out a reactivity analysis from the point of view of molecular orbitals. So, we analyzed the MOs HOMO and the MOs LUMO of the different stationary states on PES, both in a vacuum (gas phase) and in acetonitrile as the solvent.

INTRODUCTION

Computational chemistry has become a very useful technique in organic chemistry. Since it is not part of the contents of the degree subjects in our institution, students approach the research groups, to acquire basic knowledge about computational chemistry. In this way, they learn to look for reaction intermediates, transition states, evaluate bond distances and atomic charges, graph and analyze molecular orbitals, the energy calculations help them to conceptualize thermodynamic and kinetic factors in a reaction coordinate, thus integrating computational theoretical chemistry with the concepts acquired during the undergraduate degree.

Bimolecular nucleophilic substitution (S_N2) reaction is one of the most frequently process choose as mechanism model to introduce undergraduate chemistry students in the computational chemistry methodology.[1] Initially, simple computational calculations are proposed, to then increase its complexity. In Scheme 1 can be seen the general mechanism of the S_N2 reaction, where X is the nucleophile and Z, is the leaving group.



Scheme 1. General S_N2 mechanism

This reaction is continuously being reviewed and analysed by different research groups through computational theoretical studies.[2] The nucleophiles, the leaving groups, the electrophilic centre, the effect of the solvent on the reactivity, the shape of the potential energy surfaces have been evaluated. In this work, we performed a computational analysis for the ionic S_N2 reaction, applying DFT[3] methods with the Gaussian09 program.[4] In this mechanism, the nucleophile charged (X^-; X=F, Cl, Br, I) attacks the carbon atom of the substrate (CH_3Cl) through a backside pathway and simultaneously the leaving group is displaced (Cl^-). The calculations were performed using the B3LYP functional,[5] applying the 6-31+G* basis set for all atom except iodine (6-311G*) and the solvents effect (acetonitrile and cyclohexane) were evaluated with the polarizable continuum model (PCM)[6] as implemented in Gaussian09. We evaluated the potential energy surface (PES) for the mentioned reaction starting from the reactants, the formation of an initial complex between the nucleophile and the CH_3Cl, a transition state, a final complex where the leaving group is still bound to the substrate and the products. We analyzed the atomic charge (ESP)[7] and the bond distance throughout the process. Vacuum and solvent study were performed in order to analyze the solvation effects on the reactivity of the different nucleophiles. On the other hand, we thought it would be enriching, to carry out a reactivity analysis from the point of view of molecular orbitals. So, we analyzed the MOs HOMO and the MOs LUMO of the different stationary states of the PES, for the S_N2 reaction between methyl chloride and fluoride and bromide as nucleophiles, both in a gas phase and in acetonitrile as the solvent.

METHODS

Computational Procedure: The calculations were performed applying DFT methods with the Gaussian09 program. We employed the B3LYP functional, the 6-31+G* basis set for all atom except iodine (6-311G*). Zero-point energy were computed at that level for all atoms. The characterization of all stationary points was done by Hessian matrix calculations of geometries obtained with full optimization for the minimums and for the transition state. The energies in solution were obtained within the Tomasi's polarized continuum model (PCM) as implemented in Gaussian09. The atomic charges were derived from the electrostatic potential (ESP-charges). The orbitals were built with the VMD program.

RESULTS AND DISCUSSIONS

It is known that the S_N2 reaction on a carbon center, is a process that occurs through a double-well potential energy surface (PES) in the gas phase (Figure 1, blue line). However, in the aqueous solution, this PES transforms into a unimodal one (Figure 1, green line).

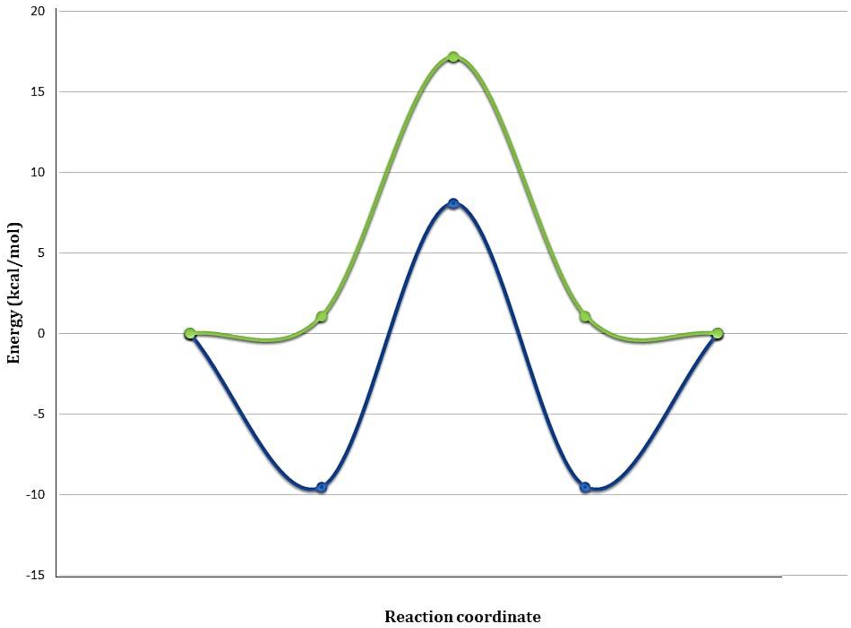


Figure 1. Solvent effect on the potential energy surfaces (PES) in a S_N2 mechanism

Based on this, we decided to study the effect of solvation on the shape of the potential energy surface (PES) for the reaction of CH_3Cl (substrate) and different nucleophiles (X^-; X=F, Cl, Br, I). As can be seen from Table 1, the studies were carried out in the gas phase, in a no polar solvent such as cyclohexane (Cy; ε=2.02) and in an aprotic polar solvent such as acetonitrile (ACN; ε=38.0).

Table 1. Energies (kcal/mol) in the gas phase, Cy and ACN to the stationary points at PES of the ionic S_N2 reaction (B3LYP/6-31+G* and 6-311G* for I, PCM=solvent)

reactives	initial complex	TS	final complex	products	medium
CH_3Cl + Cl-	$ClCH_3$---Cl	Cl---CH_3---Cl	Cl---CH_3Cl	CH_3Cl + Cl-	
-960,3862476	-960,4014362	-960,3875537	-960,4014362	-960,3862476	**gas phase**
-960,4434855	-960,4493855	-960,4299163	-960,4493855	-960,4434855	**Cy**
-960,4979295	-960,4981126	-960,4705547	-960,4981126	-960,4979295	**ACN**
CH_3Cl + F-	$ClCH_3$---F	F---CH_3---Cl	Cl---CH_3F	CH_3F + Cl-	
-599,9712194	-599,9967551	-599,9962676	-600,0393030	-600,0258111	**gas phase**
-600,0416609	-600,0489560	-600,0448631	-600,0886326	-600,0832416	**Cy**
-600,1078282	-600,1008882	-600,0916783	-600,1365553	-600,1379508	**ACN**
CH_3Cl + Br-	$ClCH_3$---Br	Br---CH_3---Cl	Cl---CH_3Br	CH_3Br + Cl-	
-3071,914705	-3071,9309271	-3071,916889	-3071,927285	-3071,907127	**gas phase**
-3071,967437	-3071,9753328	-3071,957629	-3071,973850	-3071,964306	**Cy**
-3072,017946	-3072,0194136	-3071,996614	-3072,020962	-3072,018676	**ACN**
CH_3Cl + I-	$ClCH_3$---I	I---CH_3---Cl	Cl---CH_3I	CH_3I + Cl-	
-7419,737743	-7419,747647	-7419,728013	-7419,731969	-7419,718586	**gas phase**
-7419,789004	-7419,790584	-7419,767876	-7419,776964	-7419,775654	**Cy**
-7419,837345	-7419,832233	-7419,806318	-7419,821963	-7419,829877	**ACN**

We observed that all the structures were shown to be more stable energetically under solvated conditions than ones in vacuum. Despite the notable difference in the solvation capacity between the both solvents study (acetonitrile and cyclohexane), as indicated by the Hughes-Ingold rules, an increase in polarity solvent produces a small decrease on the rates of the reaction, due to the dispersal of charges in the transition state. For example, in the case of Cl^- as nucleophile, the activation energy (Ea) was 12.2 kcal/mol in Cy as the solvent, and Ea=17.3 kcal/mol in ACN as the solvent, as can be seen from Figure 2. For the others nucleophiles, Br^- and I^-, that values were very similar: for Br^- Ea=11.1 and 14.3 kcal/mol in Cy and ACN respectively (Figure 4), and for I^- Ea=14.2 (Cy) and 16.2 kcal/mol (ACN) (Figure 5). As is known, in the gas phase, F^- was the best nucleophile, with an Ea=0.3 kcal/mol, besides the process was very exothermic ΔH=-26.7 kcal/mol (Figure 3). Between Cl^- and Br^-, the last one showed to be the best nucleophile in the aprotic polar solvent. The reaction was exothermic (-1 kcal/mol). We can to clarify that we were forced to use a different base set for iodine, so a comparison between this and the other halogens, would not be very appropriate from the energy point of view.

As can be seen from Figures 3-5, all the studied nucleophiles showed a double-well PES in the gas phase (blue line) and in cyclohexane (orange line) and a unimodal PES in acetonitrile (green line). We think that this effect is due to the changes in solvation of the different stationary points by the solvents.

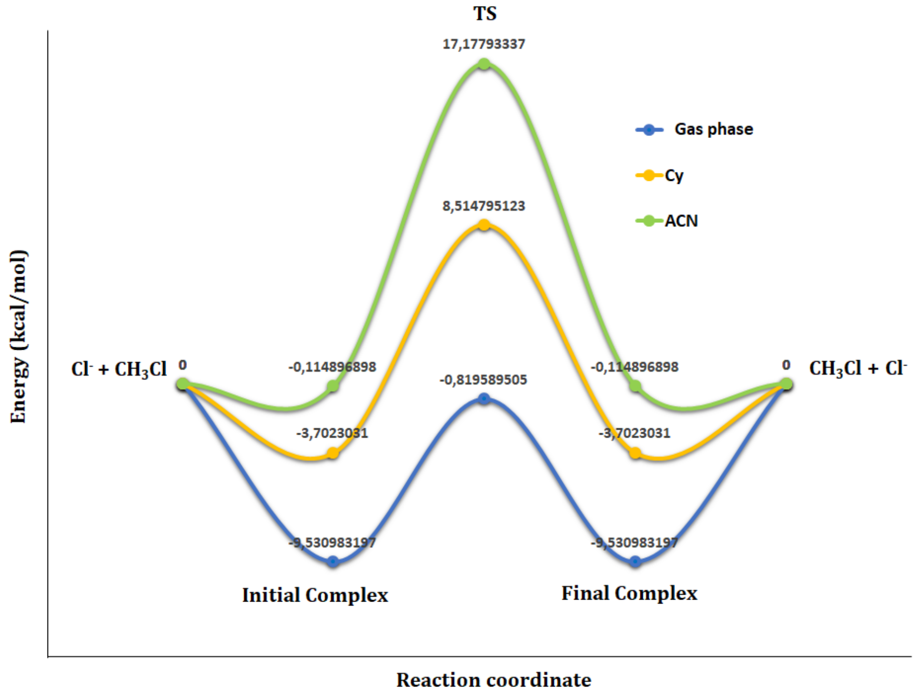


Figure 2. Solvent effect on the PES for the S_N2 reaction of Cl^- and CH_3Cl

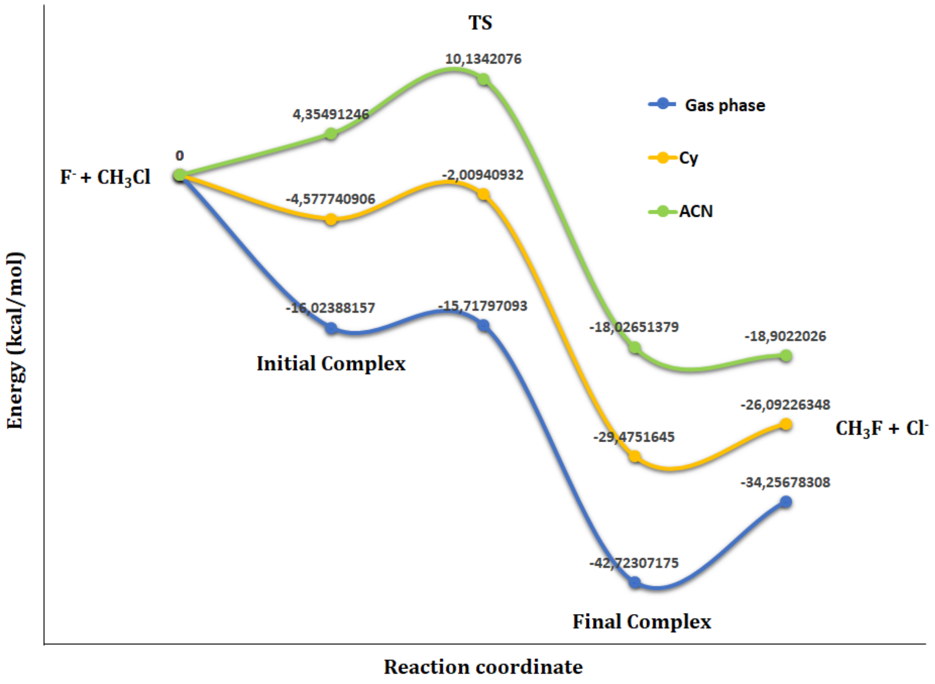


Figure 3. Solvent effect on the PES for the S_N2 reaction of F^- and CH_3Cl

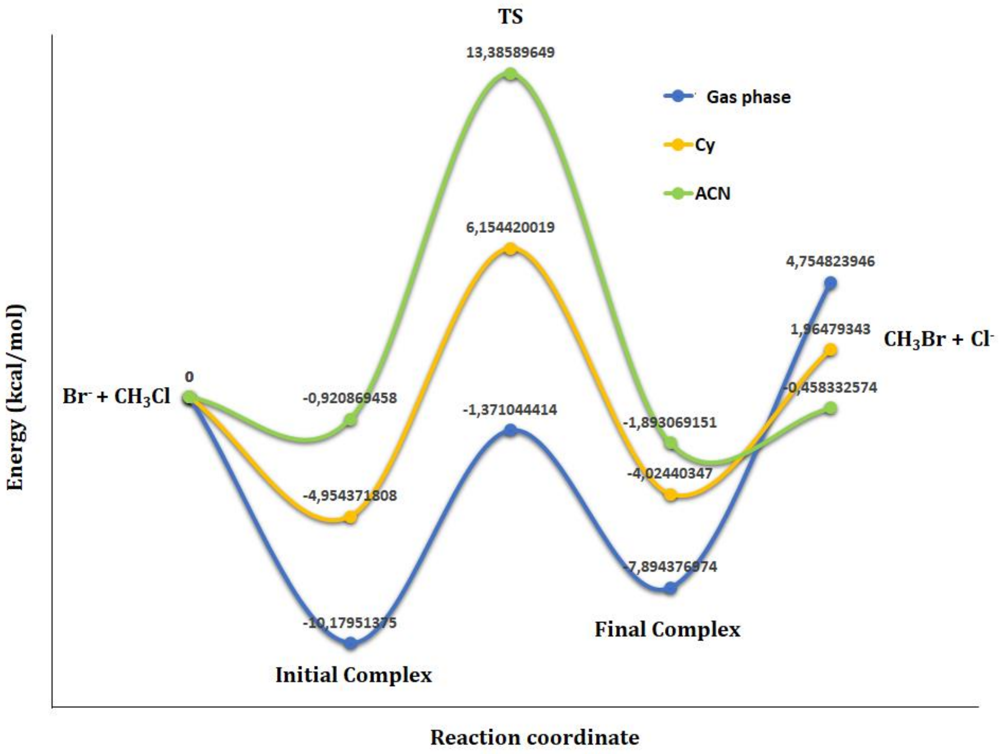


Figure 4. Solvent effect on the PES for the S_N2 reaction of Br^- and CH_3Cl

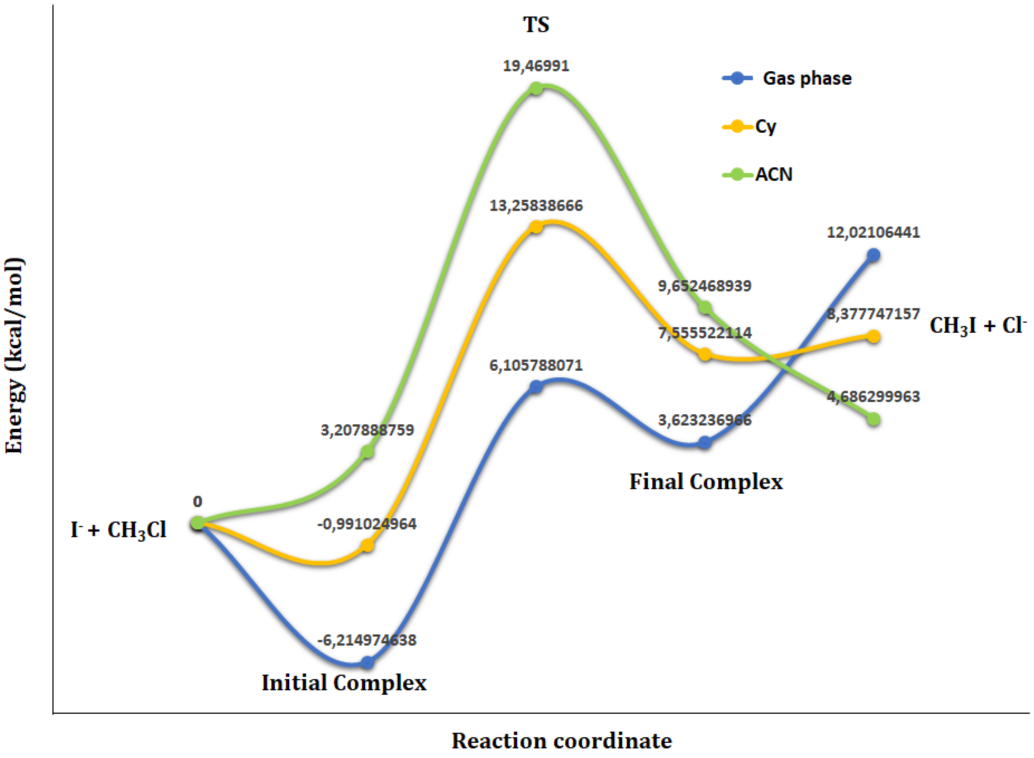
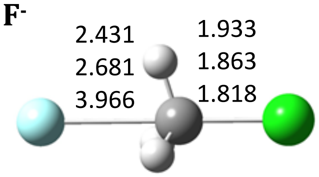
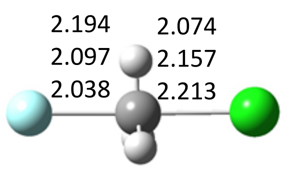
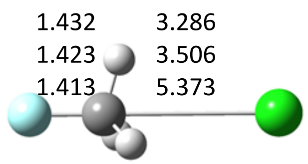
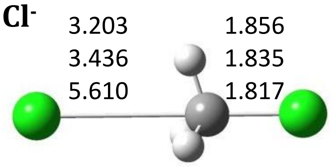
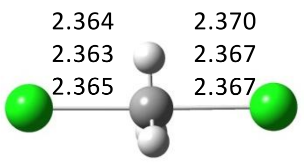
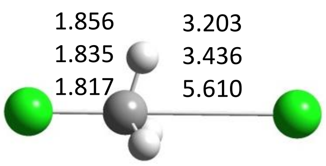
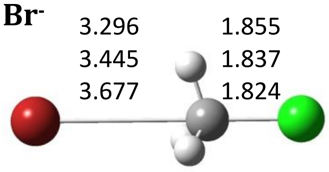
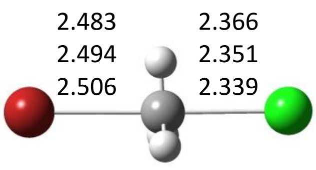
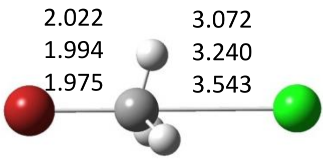


Figure 5. Solvent effect on the PES for the S_N2 reaction of I^- and CH_3Cl

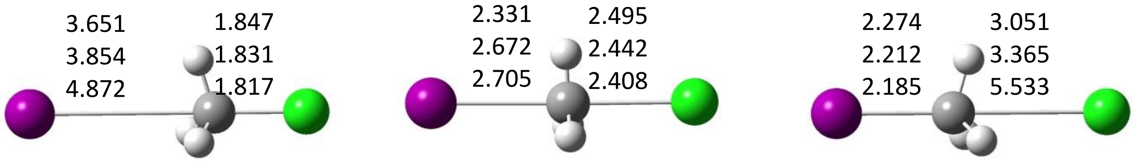
Table 2. ESP-charges for the stationary points at PES in the gas phase, Cy and ACN (B3LYP/6-31+G* and 6-311G* for I, PCM=solvent)

medium	Initial complex			TS			final complex		
	F	C	Cl	F	C	Cl	F	C	Cl
Gas phase	-0,919226	0,350280	-0,431054	-0,855653	0,419605	-0,563953	-0,386110	0,366005	-0,979895
Cyclohexane	-0,969862	0,295338	-0,325476	-0,834176	0,457668	-0,623492	-0,359097	0,351721	-0,992624
Acetonitrile	-0,995115	0,218417	-0,223702	-0,827332	0,494112	-0,666780	-0,329067	0,324878	-0,995811
	Cl	C	Cl	Cl	C	Cl	Cl	C	Cl
Gas phase	-0,966727	0,288636	-0,321905	-0,721680	0,440154	-0,718474	-0,321905	0,288636	-0,966727
Cyclohexane	-0,989683	0,265494	-0,275810	-0,728953	0,455967	-0,727014	-0,275810	0,265494	-0,989683
Acetonitrile	-0,996887	0,221818	-0,224931	-0,742535	0,483993	-0,741457	-0,224931	0,221818	-0,996887
	Br	C	Cl	Br	C	Cl	Br	C	Cl
Gas phase	-0,977789	0,287873	-0,310084	-0,714824	0,420334	-0,705510	-0,313878	0,259218	-0,945340
Cyclohexane	-0,998460	0,269990	-0,271531	-0,718476	0,419629	-0,701153	-0,250189	0,228794	-0,978605
Acetonitrile	-1,013396	0,247397	-0,234001	-0,737449	0,447250	-0,709801	-0,191500	0,188741	-0,997241
	I	C	Cl	I	C	Cl	I	C	Cl
Gas phase	-0,940664	0,245309	-0,304644	-0,612063	0,351473	-0,739410	-0,348560	0,275338	-0,926778
Cyclohexane	-0,969899	0,245269	-0,275370	-0,642339	0,371812	-0,729473	-0,244679	0,223227	-0,978548
Acetonitrile	-0,988262	0,213118	-0,224856	-0,673620	0,405243	-0,731623	-0,149619	0,144718	-0,995099

Table 3. C-X distances (Å) for the stationary points at PES in the gas phase (top value), Cy (middle value) and ACN (bottom value), (B3LYP/6-31+G* and 6-311G* for I, PCM=solvent)

	Initial complex	TS	final complex
F^-	 2.431 1.933 2.681 1.863 3.966 1.818	 2.194 2.074 2.097 2.157 2.038 2.213	 1.432 3.286 1.423 3.506 1.413 5.373
Cl^-	 3.203 1.856 3.436 1.835 5.610 1.817	 2.364 2.370 2.363 2.367 2.365 2.367	 1.856 3.203 1.835 3.436 1.817 5.610
Br^-	 3.296 1.855 3.445 1.837 3.677 1.824	 2.483 2.366 2.494 2.351 2.506 2.339	 2.022 3.072 1.994 3.240 1.975 3.543

I$^-$



According to the Hammond postulate, when two consecutive states in a potential energy surface, have similar energies, their interconversion will involve only a small reorganization of the molecular structure, and so, most exothermic reaction should be having an early TS. This happens in the S$_N$2 with F$^-$ as nucleophile, where the C-F bond distance is relatively large at the transition state, similar to the distance C-F at initial complex, as we already mentioned, in gas phase, where the reaction is more exothermic (Table 3). The opposing happens in the S$_N$2 with Br$^-$ and I$^-$ as nucleophiles, which are endothermic in gas phase, and in agreement, have a late TS.

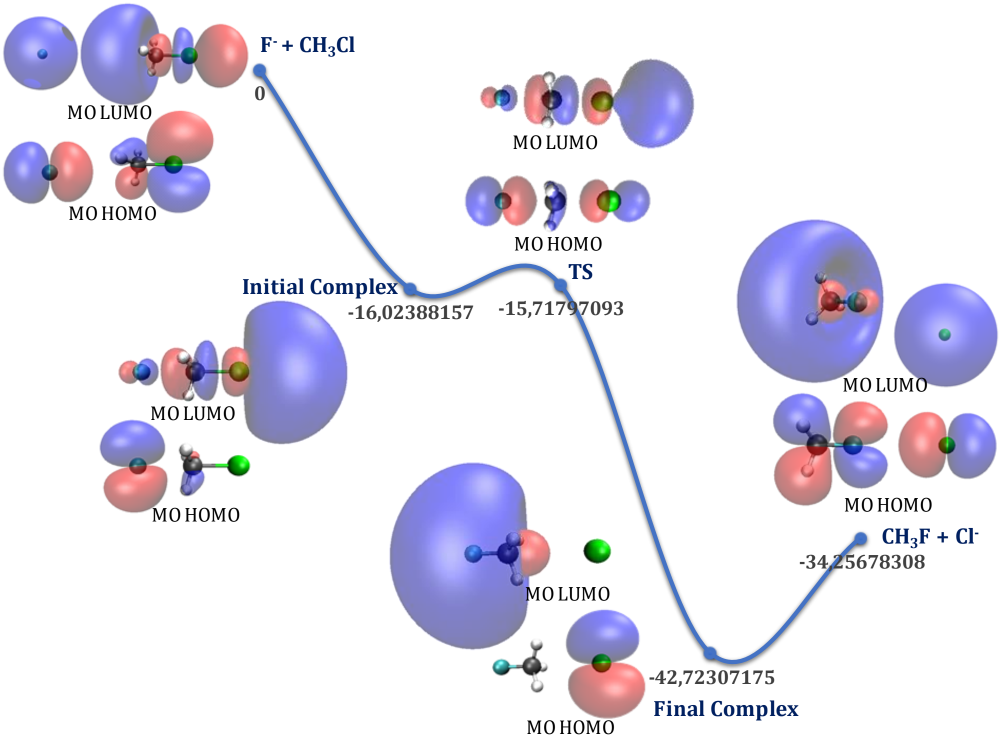


Figure 6. MOs HOMO and MOs LUMO for the stationary points at PES for the S$_N$2 reaction of F$^-$ and CH$_3$Cl in the gas phase

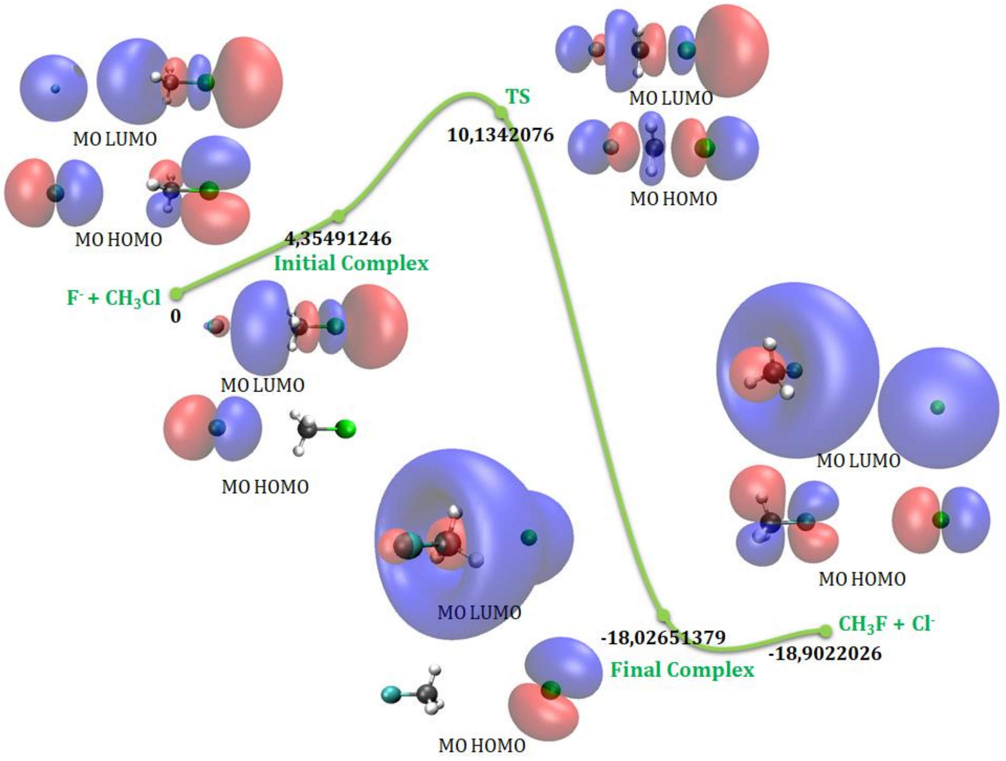


Figure 7. MOs HOMO and MOs LUMO for the stationary points at PES for the S_N2 reaction of F^- and CH_3Cl in ACN

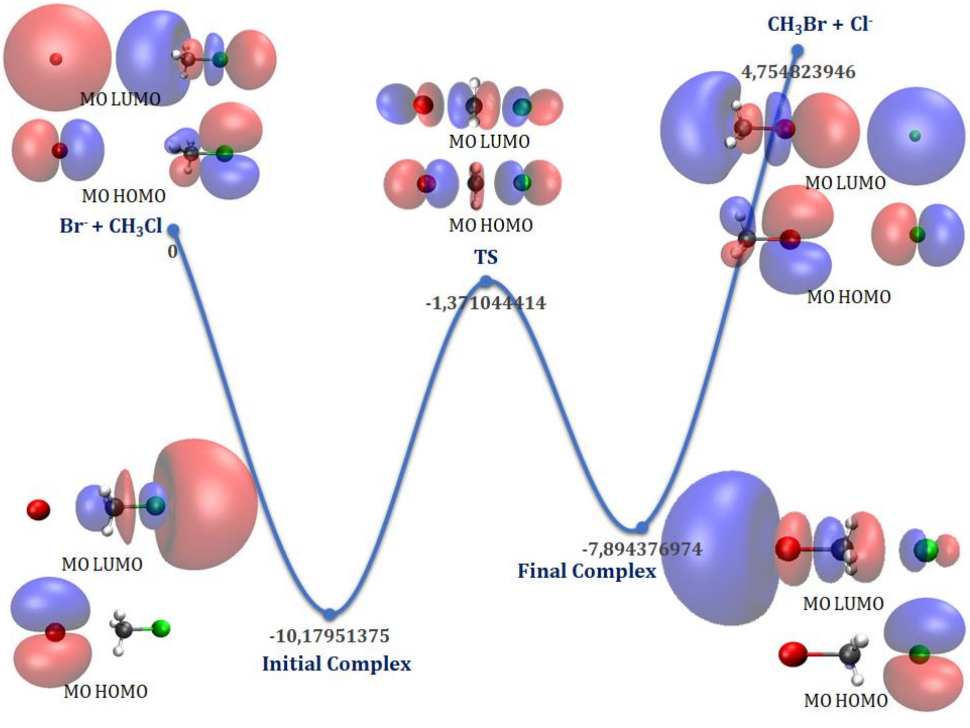


Figure 8. MOs HOMO and MOs LUMO for the stationary points at PES for the S_N2 reaction of Br^- and CH_3Cl in the gas phase

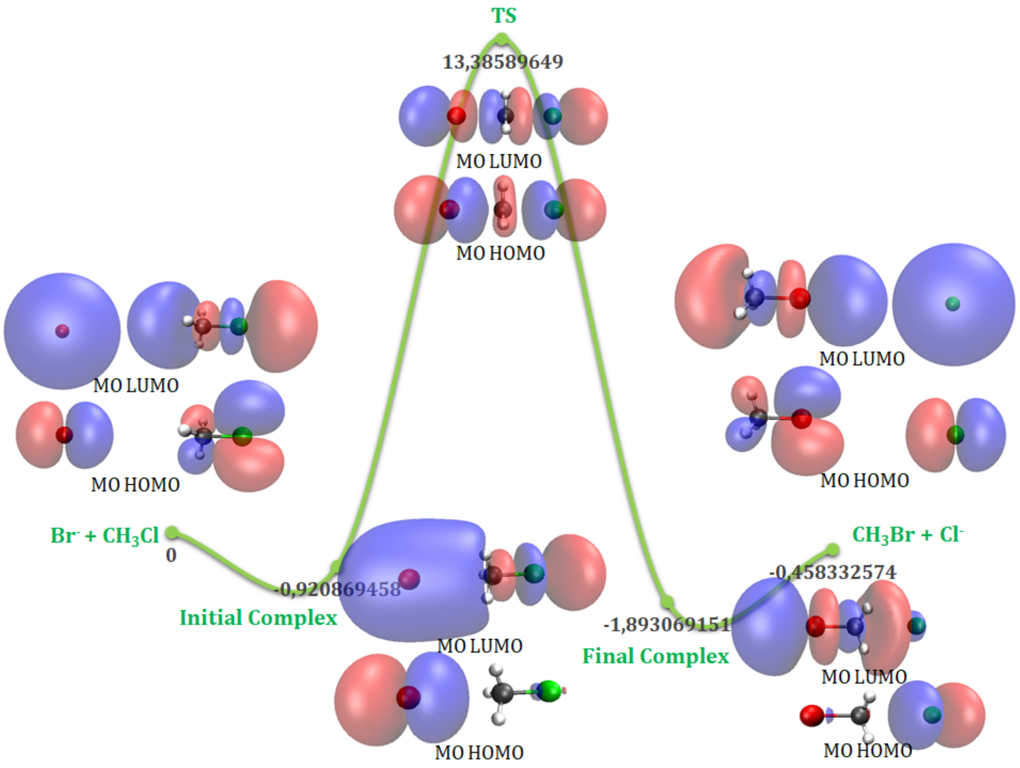


Figure 9. MOs HOMO and MOs LUMO for the stationary points at PES for the S_N2 reaction of Br^- and CH_3Cl in ACN

On the other hand, we carry out a reactivity analysis from the point of view of molecular orbitals. As can be seen from Figures 6-9, we graphed the MOs HOMO and the MOs LUMO of the different stationary points at the PES, for the S_N2 reaction between methyl chloride and fluoride and bromide as nucleophiles, both in a gas phase and in acetonitrile as the solvent. If we observe the MO LUMO of the substrate, it is an σ* orbital, antibonding between C-Cl, indicating that this bond will cleave during the attack of the nucleophile. This is also observed at the initial complex, where the orbital on the Cl is larger, indicating that the leaving group is less attached to the C. It is also observed from the shape of the MOs, that the TS is very similar to the initial complex in the case of the reaction with F^-, indicating an early TS, in the gas phase and in acetonitrile.

CONCLUSIONS

We performed a computational analysis for the ionic S_N2 reaction, where the nucleophile charged (X^-; X=F, Cl, Br, I) attacks the carbon atom of the substrate (CH_3Cl) through a backside pathway and simultaneously the leaving group is displaced (Cl^-). All the structures were shown to be more stable energetically under solvated conditions than ones in vacuum. As is known, fluoride was the best nucleophile in the gas phase, and bromide was the best in ACN as the solvent. Despite the notable difference in the solvation capacity between acetonitrile and cyclohexane, an increase in polarity solvent produces a small decrease on the rates of the reaction, due to the dispersal of charges in the transition state. The values obtained for the atomic charges (ESP) and the bond distances C-X, are in accord to the Hammond postulated for the system, that is, an early TS is observed in the reaction with fluoride, and a late TS is observed when the bromide is the nucleophile. The MOs analysis are in agreement with the concepts mentioned above.

Acknowledgements

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