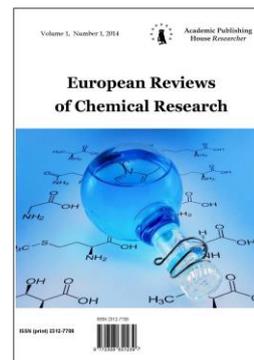


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## Articles and Statements

### Theoretical Study of the Regioselectivity of the Reaction Between Diethyl(Trichloromethyl)Phosphonate and Triethylphosphite Using the DFT Method

A. Barhoumi <sup>a</sup>, M.El idrissi <sup>b,\*</sup>, A. Zeroual <sup>a</sup>, S. Bakkas <sup>a</sup>, A. El Hajbi <sup>a</sup>, A. Tounsi <sup>b</sup>

<sup>a</sup> Chouaïb Doukkali University, El Jadida, Morocco

<sup>b</sup> Moulay Slimane University, Beni Mellal, Morocco

#### Abstract

In this study we used the DFT/B3LYP/6-311G(d,p) quantum mechanical method to propose a theoretical explanation of the regioselectivity observed experimentally in the reaction between diethyl(trichloromethyl)phosphonate and triethylphosphite using a variety of approaches, notably frontier molecular orbital theory and calculation of activity energies and reactivity indices. Our results show that triethylphosphite functions as a nucleophile while diethyl(trichloromethyl)phosphonate behaves as an electrophile. The nucleophilic attack takes place preferentially at the chlorine atom of diethyl (trichloromethyl)phosphonate rather than at the carbon, and the reaction is polar and regioselective.

**Keywords:** triethylphosphite, diethyl(trichloromethyl)phosphonate, DFT/B3LYP/6-311G(d,p), reactivity indices, activation energy.

#### 1. Introduction

Organophosphorus compounds are increasingly used in modern organic chemistry because of their potential in such varied domains as biology (Akbaş et al., 2013; Mudryk et al., 2015), medicine (Cupistiet al., 2013; Dabrzalska et al., 2015), agriculture (as plant growth regulators) and biochemistry (Engel et al., 2003). They are also of great interest as precursors in organic synthesis (Kann et al., 2003; Bricklebank et al., 2003). This versatility arises from the variable valency of phosphorus (Ellis et al., 2006; Gilheany et al., 1992).

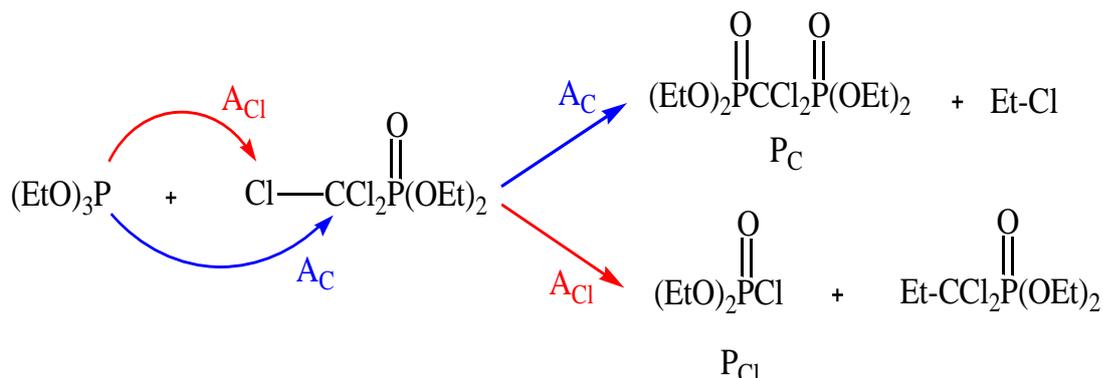
Bibliographic research shows that the reaction of the trivalent phosphorus derivatives  $[(RO)_3P, (RO)_2PR', \dots]$  with certain polyhalogenoalkanes ( $CCl_4, BrCCl_3, \dots$ ) leads to the formation of a number of products (Waschbüsch et al., 1996; Nai et al., 1997) some of which have numerous applications in industry and biology (Halazy et al., 1996). The reactivity of trivalent phosphorus with regard to polyhalogenomethanes has already been the subject of several studies (Barhoumi et al., 2018; Bakkas et al., 2000). This reactivity varies according to the nature of the substituents carried by the phosphorus atom and increases as its electropositivity increases.

Our aim in this work was to carry out a theoretical study, using DFT/B3LYP/6-311G(d, p), of the reactivity of  $CCl_3PO(OEt)_2$  with triethylphosphite in order to determine whether the

\* Corresponding author

E-mail addresses: [idrissi\\_82@hotmail.fr](mailto:idrissi_82@hotmail.fr) (M. El idrissi)

phosphorus attacks the carbon or the chlorine of the diethyl(trichloromethyl)phosphonate (Figure 1).



**Fig. 1.** Reaction between diethyl(trichloromethyl)phosphonate  $\text{CCl}_3\text{PO}(\text{OEt})_2$  and triethylphosphite  $(\text{EtO})_3\text{P}$

## 2. Method of calculation

The mechanism and the equilibrium geometries of the reaction between diethyl(trichloromethyl)phosphonate and triethylphosphite, as well as the transition states corresponding to the two approaches at  $A_C$  and  $A_{Cl}$ , were studied using density functional theory DFT (Parr et al., 1989; Deng et al., 1995) with base B3LYP/6-311G (d, p) (Becke et al., 1993; Lee et al., 1988). Transition states were localized and their existence confirmed by the presence of a single imaginary frequency in the Hessian matrix. The Intrinsic Reaction Coordinate (IRC) was calculated (Fukui et al., 1981a; Fukui et al., 1981b) and plotted in order to show that the transition state is indeed linked to the two minima (reactants and products). Values of enthalpy, entropy and free energy were calculated using standard statistical thermodynamics (Hehre et al., 1986). The reactivity indices were calculated from the HOMO and LUMO energies in the base state of the molecules using DFT/B3LYP/6-311G (d,p). All calculations were carried out with Gaussian 09 software (Frischet al., 2009).

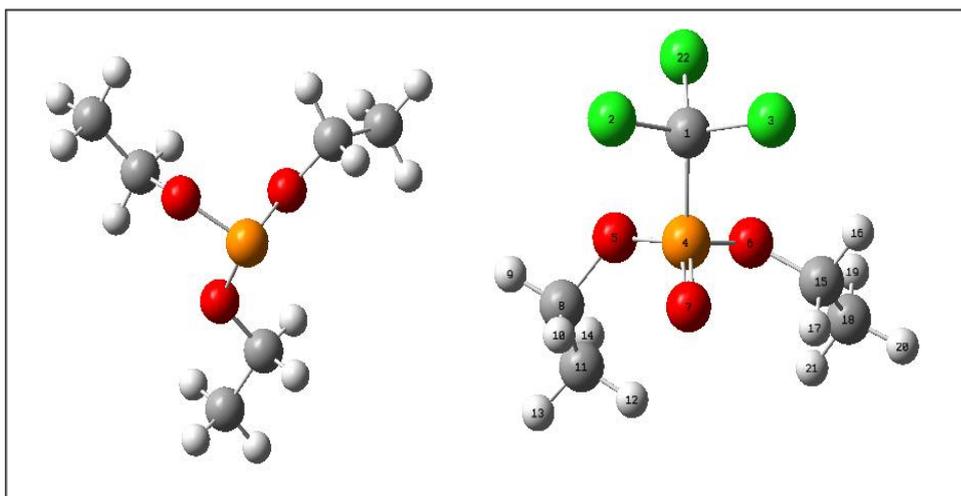
## 3. Results and discussion

### 3.1. Structural optimisation of the reactants

Table 1 shows atomic distances and bond energies of the reactant atoms of diethyl(trichloromethyl)phosphonate in its most stable form, showing that all the chlorine atoms don't have the same reactivity with regard to the most nucleophilic site of triethylphosphite. These parameters were optimised using Gaussian 09 software. Energy analysis shows that the fundamental state of triethylphosphite stabilises at  $-804.8978 \text{ a.u}$  and that of diethyl(trichloromethyl)phosphonate at  $-2144.4342 \text{ u.a}$ , in other words that triethylphosphite is more reactive.

**Table 1.** Bond energy and interatomic distance of the reactant atoms in diethyl (trichloromethyl)phosphonate

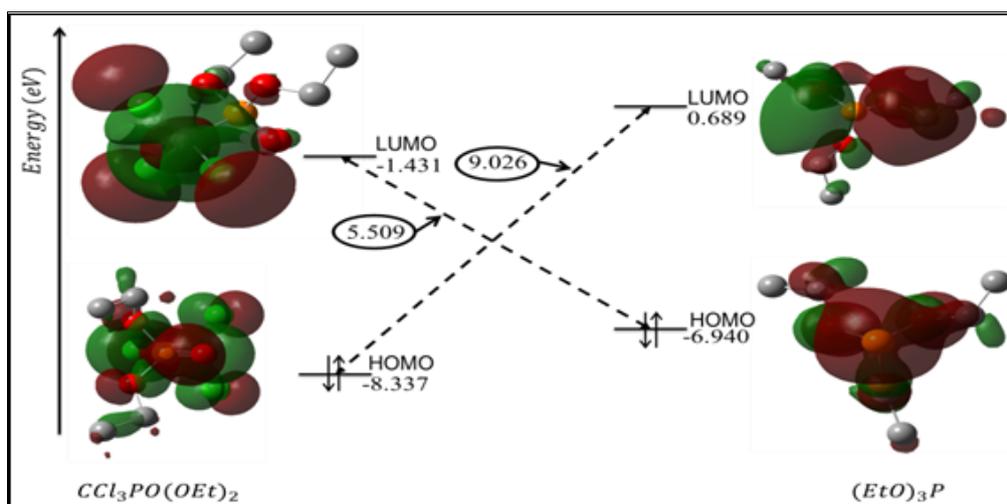
$X - Y$	$d(X - Y)$	$E(X - Y) \text{ Kcal/mol}$
$C_1 - Cl_2$	1.795	474.899
$C_1 - Cl_3$	1.803	471.937
$C_1 - Cl_{22}$	1.793	476.467



**Fig. 2.** The most stable structure of the two reactants  $(\text{EtO})_3\text{P}$  and  $\text{CCl}_3\text{PO}(\text{OEt})_2$ .

### 3.2. Study of the frontier orbitals

We calculated the HOMO/LUMO energy gap for the two possible combinations of the two reactants



**Fig.3.** Energy gap (eV) between the HOMO of triethylphosphite  $(\text{EtO})_3\text{P}$  and the LUMO of diethyl(trichloromethyl)phosphonate  $\text{CCl}_3\text{PO}(\text{OEt})_2$ .

Frontier molecular orbital theory (FMO) makes it possible to analyse the reactivity of molecules in terms of the interactions between the molecular orbitals of the reactants by taking account of only the most important interactions (Rauk et al., 1994). The orbitals considered in studying the interaction between two reactants are the HOMO (highest occupied molecular orbital) of the one and the LUMO (lowest unoccupied molecular orbital) of the other, chosen in such a way that the  $E_{\text{LUMO}} - E_{\text{HOMO}}$  energy gap is as small as possible (Mebi et al., 2011). As a general rule, the smaller the difference between the orbitals of the two reactants, the stronger the interaction between these orbitals, and the greater the stabilising effect. As Figure 4 shows, the orbital diagramme gives a good idea of the reactivity of the system. We can see that the main interaction takes place between the LUMO of diethyl(trichloromethyl)phosphonate and the HOMO of triethylphosphite.

Localisation of the molecular orbitals of triethylphosphite and diethyl(trichloromethyl)phosphonate shows that the HOMO is very concentrated around the phosphorus atom, while the LUMO is concentrated around the chlorine atom (Figure 4). This indicates that the nucleophilic attack by the phosphorus atom takes place essentially at the chlorine atom.

### 3.3. Chemical concepts and reactivity indices derived using DFT

In order to determine which reactant behaves as a nucleophile (electron donor) and which as an electrophile (electron acceptor), we calculated the HOMO/LUMO energy gaps between them (Table 2).

**Table 2.** Difference between the two possible HOMO/LUMO combinations for diethyl(trichloromethyl)phosphonate  $\text{CCl}_3\text{PO}(\text{OEt})_2$  and triethylphosphite  $(\text{EtO})_3\text{P}$  (eV).

Reactants	$E_{\text{LUMO}}$	$E_{\text{HOMO}}$	$ E_{\text{HOMO}((\text{EtO})_3\text{P})} - E_{\text{LUMO}} $	$ E_{\text{HOMO}} - E_{\text{LUMO}(\text{CCl}_3\text{PO}(\text{OEt})_2)} $
$(\text{EtO})_3\text{P}$	0.689	-6.940	5.509	9.026
$\text{CCl}_3\text{PO}(\text{OEt})_2$	-1.431	-8.337		

Our results show that the  $|E_{\text{HOMO}((\text{EtO})_3\text{P})} - E_{\text{LUMO}}|$  gap is smaller than the  $|E_{\text{HOMO}} - E_{\text{LUMO}(\text{CCl}_3\text{PO}(\text{OEt})_2)}|$  gap, showing that triethylphosphite behaves as a nucleophile while diethyl(trichloromethyl)phosphonate behaves as an electrophile.

The global indices defined using conceptual DFT/B<sub>3</sub>LYP (Geerlings et al., 2003) are valuable tools for studying the reactivity of polar interactions. The static global properties electronic chemical potential  $\mu$ , chemical hardness  $\eta$ , global electrophilicity index  $\omega$  and global nucleophilicity index  $N$  are chemical properties which enable us to analyse reactivity.

We calculated the electronic chemical potential  $\mu$  and global hardness  $\eta$  from the energies of the HOMO and LUMO frontier molecular orbitals, as  $\mu = \frac{E_{\text{HOMO}} + E_{\text{LUMO}}}{2}$  and  $\eta = E_{\text{LUMO}} - E_{\text{HOMO}}$  respectively (Parr et al., 1989). The global electrophilicity index ( $\omega = \mu^2/2\eta$ ) (Parr et al., 1983) is defined as the energy stabilisation due to charge transfer. It has been shown that the nucleophile character of a molecule can be calculated without taking account of its electron density. The nucleophilicity index  $N$  is expressed in terms of the HOMO energy of tetracyanoethylene (TCE) as  $N = E_{\text{HOMO}(\text{NU})} - E_{\text{HOMO}(\text{TCE})}$  (Pérez et al., 2009). These values, together with maximum charge transfer  $\Delta N_{\text{max}}$  (Domingo et al., 1994) and the global electrophilicity gap  $\Delta\omega$  are shown in Table 3.

**Table 3.** HOMO and LUMO energy, electronic chemical potential  $\mu$ , hardness  $\eta$ , electrophilicity  $\omega$ , global nucleophilicity  $N$ , maximum charge transfer  $\Delta N_{\text{max}}$  and global electrophilicity gap  $\Delta\omega$  between  $(\text{EtO})_3\text{P}$  and  $\text{CCl}_3\text{PO}(\text{OEt})_2$  (eV)

Reactants	$E_{\text{LUMO}}$	$E_{\text{HOMO}}$	$\mu$	$\eta$	$\omega$	$N$	$\Delta\omega$	$\Delta N_{\text{max}}$
$(\text{EtO})_3\text{P}$	0.689	-6.940	-3.125	7.629	0.640	2.428	....	0.409
$\text{CCl}_3\text{PO}(\text{OEt})_2$	-1.431	-8.337	-4.884	6.906	1.727	1.031	1.087	0.707

$$\begin{cases} E_{\text{HOMO}(\text{TCE})} = -9.368 \text{ eV} \\ \Delta N_{\text{max}} = -\mu/\eta \end{cases}$$

Our results show that diethyl(trichloromethyl)phosphonate  $\text{CCl}_3\text{PO}(\text{OEt})_2$  behaves as an electrophile while triethylphosphite  $(\text{EtO})_3\text{P}$  behaves as a nucleophile. Diethyl(trichloromethyl)phosphonate has the highest electrophilicity index ( $\omega = 1.727 \text{ eV}$ ) and the lowest nucleophilicity index ( $N = 1.031 \text{ eV}$ ). Additionally, the electronic chemical potential of  $(\text{EtO})_3\text{P}$  ( $\mu = -3.125 \text{ eV}$ ) is situated at a higher energy level than that of ( $\mu = -4.884 \text{ eV}$ ),  $(\text{EtO})_3\text{P} > \mu(\text{CCl}_3\text{PO}(\text{OEt})_2)$ , in other words a stream of electrons circulating

from  $(\text{EtO})_3\text{P}$  to  $\text{CCl}_3\text{PO}(\text{OEt})_2$  stabilises the system. These results confirm that triethylphosphite behaves as a nucleophile and diethyl(trichloromethyl)phosphonate as an electrophile in this reaction.

The maximum charge transfer of ( $\Delta N_{\text{max}} = 0.707 \text{ eV}$ ) is greater than that of triethyl phosphite ( $\Delta N_{\text{max}} = 0.409 \text{ eV}$ ) and the electrophilicity gap ( $\Delta\omega = 1.087 \text{ eV}$ ) between diethyl(trichloromethyl)phosphonate and triethylphosphite is high, showing that the reaction is polar.

### 3.4. Kinetic and thermodynamic study of the nucleophilic modes of attack of $(\text{EtO})_3\text{P}$ on $\text{CCl}_3\text{PO}(\text{OEt})_2$ ( $A_{\text{Cl}}$ and $A_{\text{C}}$ )

#### 3.4.1. Thermodynamic study

We studied the feasibility and the regioselectivity of the reaction between diethyl(trichloromethyl)phosphonate  $\text{CCl}_3\text{PO}(\text{OEt})_2$  and triethylphosphite  $(\text{EtO})_3\text{P}$  from a thermodynamic point of view. In order to compare the reactivity of the two modes of attack ( $A_{\text{C}}$  and  $A_{\text{Cl}}$ ), we calculated the differences in reaction energy  $\Delta E_{\text{r}}$ , reaction enthalpy  $\Delta H_{\text{r}}$  and free enthalpy  $\Delta G_{\text{r}}$  corresponding to the formation of compounds  $\text{P}_{\text{C}}$  and  $\text{P}_{\text{Cl}}$  (Table 4).

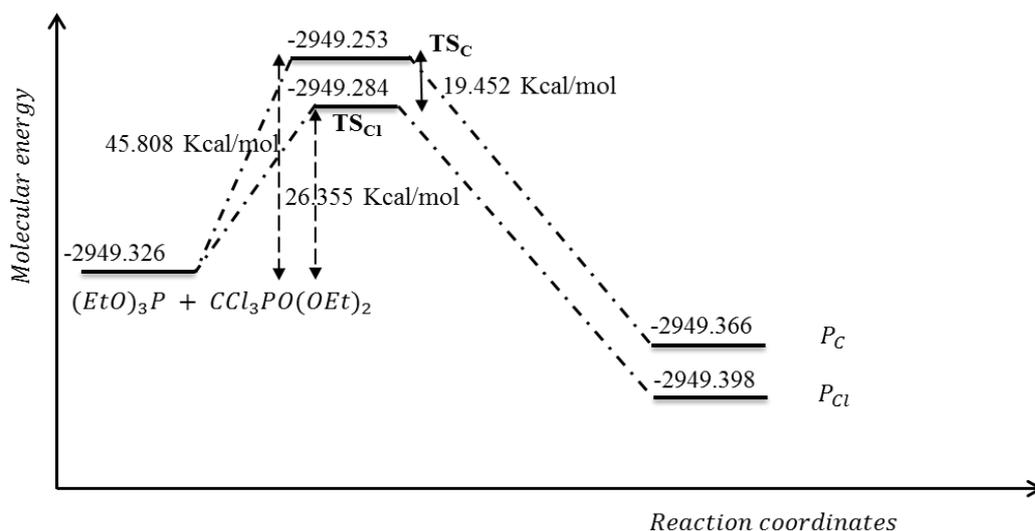
**Table 4.** Calculated values (Kcal/mole) of the differences in reaction energy  $\Delta E_{\text{r}}$ , reaction enthalpy  $\Delta H_{\text{r}}$  and free enthalpy  $\Delta G_{\text{r}}$ .

Reactants	Product	$\Delta H_{\text{r}}$	$\Delta E_{\text{r}}$	$\Delta G_{\text{r}}$
$(\text{EtO})_3\text{P} + \text{CCl}_3\text{PO}(\text{OEt})_2$	$\text{P}_{\text{C}}$	-24.606	-25.400	-21.283
	$\text{P}_{\text{Cl}}$	-44.501	-45.637	-42.630

As Table 4 shows, variations in free enthalpy  $\Delta G_{\text{r}}$  are negative whatever the mode of attack. It follows that these reactions are possible and are thermodynamically favoured. We also found that the variation in free enthalpy  $\Delta G_{\text{r}}$  corresponding to the formation of compound  $\text{P}_{\text{Cl}}$  is greater in absolute terms than that corresponding to the formation of compound  $\text{P}_{\text{C}}$ . The formation of compound  $\text{P}_{\text{C}}$  resulting from an attack on the carbon atom  $A_{\text{C}}$  is thermodynamically less favoured than the formation of compound  $\text{P}_{\text{Cl}}$ . Free enthalpy of formation of the latter is greater in absolute terms than that of compound  $\text{P}_{\text{C}}$ . The value of  $\Delta E_{\text{r}}$  corresponding to the formation of compound  $\text{P}_{\text{Cl}}$  is greater in absolute terms than that corresponding to the formation of compound  $\text{P}_{\text{C}}$ . This shows that the most favourable site for an attack is the halogen  $\text{Cl}$  rather than the carbon  $\text{C}$ .

#### 3.4.2. Structure and energy of the transition states

In order to determine the more favoured mode of attack ( $A_{\text{C}}$  or  $A_{\text{Cl}}$ ), and thus the most favoured product of the reaction between triethylphosphite and diethyl(trichloromethyl)phosphonate, we localised the transition states and calculated the activation barriers for the two possible reaction pathways. The transition states  $\text{TS}_{\text{C}}$  and  $\text{TS}_{\text{Cl}}$ , corresponding to the two modes of attack, were localised. These two transition states were confirmed by the presence of one and only one negative eigenvalue in the force constant matrix: in other words there is a single imaginary frequency in the Hessian matrix, corresponding to the vibration mode of the formation of the bonds  $\text{P} - \text{CCl}_2$  and  $\text{P} - \text{Cl}$  respectively and the splitting of bonds  $\text{C} - \text{Cl}$  and  $\text{C} - \text{CCl}_2$  respectively. The two transition states  $\text{TS}_{\text{C}}$  and  $\text{TS}_{\text{Cl}}$  are shown in Figure 5.

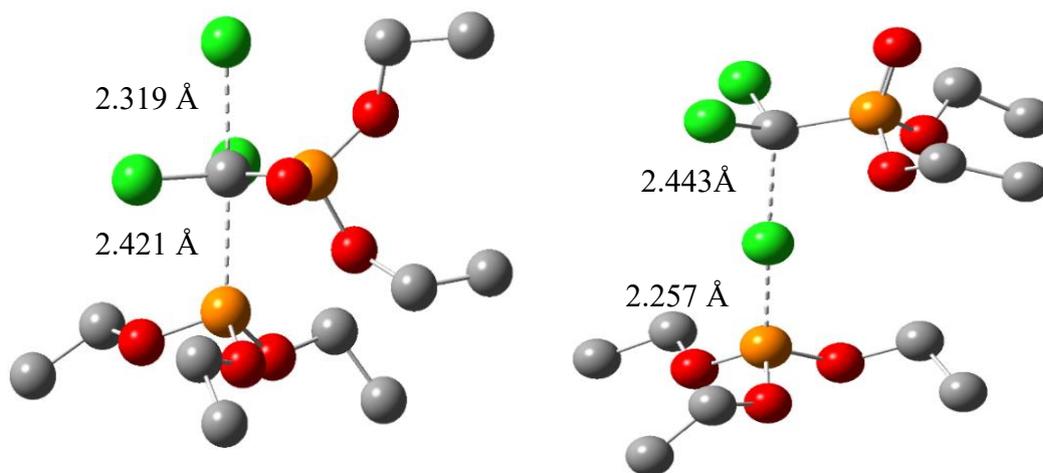


**Fig. 5.** Energy profile in (u. a) of the reaction between diethyl (trichloromethyl) phosphonate and triethylphosphite

The potential energy surface (PES) corresponding to the two modes of attack shows that the energy of the transition state corresponding to the attack on the chlorine atom  $TS_{Cl}$  is  $19.452 \text{ Kcal/mol}$  below the energy of the transition state corresponding to the attack on the carbon atom  $TS_C$ . The activation energy is  $45.808 \text{ Kcal/mol}$  for  $A_C$  and  $26.355 \text{ Kcal/mol}$  for  $A_{Cl}$ . In other words, the attack on the chlorine atom is kinetically preferred to the attack on the carbon atom.

We can conclude from this theoretical investigation that, while both modes of attack by triethylphosphite on trichloromethylphosphine oxide ( $A_{Cl}$  and  $A_C$ ) are thermodynamically possible, the products formed by the attack on the chlorine atom are kinetically and thermodynamically preferred.

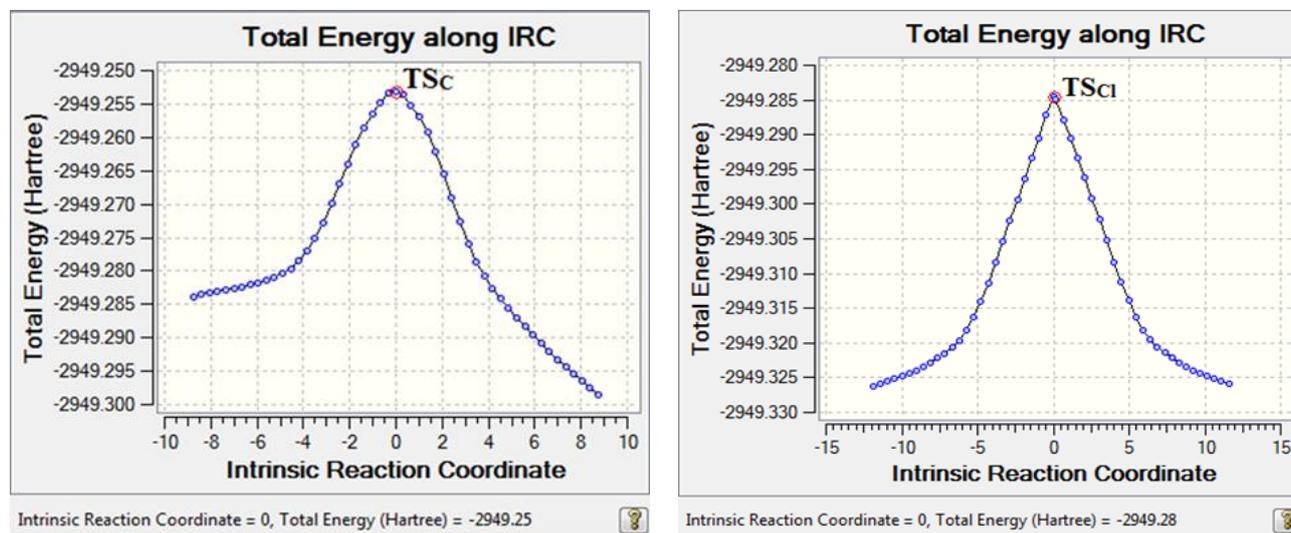
The structure of the transition state associated with reaction pathway  $A_{Cl}$  is more stable than that associated with  $A_C$ . The two structures optimised using DFT/B3LYP/6-311G(d,p) are shown in Figure 6. Phosphite tends to react more with chlorine than with carbon because of the difference in length between bonds  $P - CCl_2$  and  $P - Cl$  in the transition state ( $P - Cl < d(P - Cl_2)$ ).



**Fig. 6.** Bond lengths of the transition states in the reaction between triethylphosphite and diethyl(trichloromethyl)phosphonate

### 3.5. Determination of the intrinsic reaction coordinates (IRC).

On the basis of the optimised geometry of the transition state we calculated the IRC (Intrinsic Reaction Coordinate) (Lee et al., 1988; Fukui et al., 1981) in order to confirm that the transition state indeed links the reactants and the products. Figure 7 presents the reaction pathway corresponding to the two modes of attack and shows that the transition state is indeed linked to the two minima (reactants and products).



**Fig. 7.** IRC of the reaction between triethylphosphite and diethyl(trichloromethyl)phosphonate ( $A_{Cl}/A_C$ )

Natural population analysis of the reaction shows that the charge transfer from the nucleophile to the electrophile is 0.554(e) for transition state  $TS_C$  and 0.648(e) for transition state  $TS_{Cl}$ . This indicates that  $TS_{Cl}$  is more stable and favorable, and that the reaction is polar in character. These results confirm the findings obtained from the HOMO/LUMO energy gaps and the global indices  $\omega$ ,  $N$  and  $\mu$ .

### 4. Conclusion

Theoretical study of the reaction between diethyl(trichloromethyl)phosphonate  $CCl_3PO(OEt)_2$  and triethylphosphite  $(EtO)_3P$  using DFT/B3LYP/6-311G (d, p) shows that whatever the mode of attack of the phosphorus atom ( $A_{Cl}$  and  $A_C$ ) on diethyl(trichloromethyl)phosphonate, the corresponding variations in free enthalpy  $\Delta G_r$  are negative, indicating that these attacks are thermodynamically possible. Calculation of the global indices shows that triethyl phosphite behaves as a nucleophile and diethyl(trichloromethyl)phosphonate as an electrophile. The reaction is characterised by a relatively high charge transfer, implying a polar mechanism. The variation in reaction enthalpy  $\Delta H_r$  is highly exothermic for the reaction leading to formation of compound  $P_{Cl}$ . Consequently this reaction is favoured, since the products formed are stable and their formation releases energy. Localisation of the HOMO of triethylphosphite and the LUMO of diethyl(trichloromethyl)phosphonate shows that the phosphorus atom is the nucleophile centre of the former while the chlorine atom is the electrophile centre of the latter. The thermodynamic and kinetic study shows that the stable products of the reaction between diethyl(trichloromethyl)phosphonate and triethylphosphite are those resulting from the attack on the chlorine atom.

### 5. Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper. Also, they declare that this paper or part of it has not been published elsewhere.

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