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Spectroscopic and DFT investigations on dialkyl or diphenyl (1,1-dichloro-2-isocyanato-2-oxoethyl) phosphonate derivatives with the potential of biological and pharmaceutical activities

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Abstract: A two-component reaction between trialkyl phosphite derivatives or triphenyl phosphite and trichloroacetyl isocyanate occurs at room temperature and dialkyl or diphenyl (1,1-dichloro-2-isocyanato-2-oxoethyl) phosphonate derivatives produce in high yields. The reaction proceeds smoothly and cleanly under mild conditions. This approach is an efficient method because the products have a wide range of biological and pharmaceutical activities including antibacterial, anti-inflammatory, antitumor, exhibit enzyme inhibitory, antiviral, antibiotic, antifungal, several applications in the agricultural industry, as well as effective ligands and extractants, and herbicidal activities. The structures of the products were deduced from their ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR and IR spectra, and elemental analysis. The synthesized molecules were optimized the B3LYP/6-311++G(d,p) level of theory and IR and NMR parameters were compared with experimental values. Also, the structural parameters and electronic properties of these molecules were calculated. The calculated spectroscopic parameters (IR and NMR) at the B3LYP/6-311++G(d,p) level of theory show good compatible with experimental values.

Keywords: Two-component reaction, Trialkyl phosphate, Trichloroacetyl isocyanate, Phosphonate, DFT calculations.

Introduction

Phosphorus compounds including the P-C bond are not specially infinite in nature. They have various biological activities [1], and a broad range of application in the fields of agricultural, industrial, and medicinal chemistry such as antibacterial [2], anti-inflammatory [3, 4], antitumor[5, 6] , exhibit enzyme inhibitory [7-11], antiviral [12], antibiotic [13], antifungal [14], several applications in the agricultural industry [14,15], as well as effective ligands and extractants [16,17] and herbicidal activities [18] .

A number of other procedures are available for the synthesis of alkyl/aryl phosphonates [19-23], but none of these methods has the generality of the Michaelis-Arbuzov reaction [24]. The Arbuzov reaction, is very useful way to form P-C bond from the reaction of an alkyl / aryl halide and trialkyl phosphite by simple S_N2 reaction [22, 23]. In general, the alkyl group of the halide connects to the phosphorus, and one alkyl from phosphorus incorporates with halogen to form the new alkyl halide. However, various procedures were expanded using different Lewis acid catalysts such as, $InCl_3$, $InBr_3$, $ZnBr_2$, $NiCl_2$, $CeCl_3$ - $7H_2O$, $CeCl_3$ - SiO_2 [24-28], that stimulate the Michaelis-Arbuzov reaction efficiently and minimize the difficulty, however they

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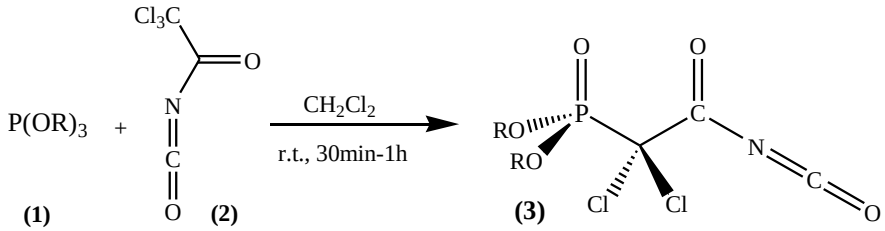
have one or more shortages such as long reaction time, low yield of the product, toxic catalyst, use of high amount of catalyst, hardness reaction conditions, and big amount of waste. Also the reaction of trichloromethyl and tribromomethyl isocyanates with phosphites or halophosphites proceeds *via* an Arbuzov rearrangement at 80- 120 ^{o}C in the presence of catalytic amount of iron (ш) chloride [29].

In connection with our interest in the use or synthesis of phosphorus compounds [30-33], the synthesis of dialkyl or diphenyl (1,1-dichloro-2-isocyanato-2-oxoethyl) phosphonate derivatives **(3)** by a two-component reaction of trialkyl phosphite derivatives or triphenyl phosphite **(1)** and trichloroacetyl isocyanate **(2)**, *via* a method suitable not requiring toxic catalysts and reagents, in high yields and fairly mild reaction condition, is reported herein (Scheme **1**). Also, theoretical studied at the B3LYP/6-311++G(d,p) level were used to illustration of electronic, structural and spectroscopic properties of these synthesized molecules.



(1) **(2)** **(3)**

R= Me, Et, *iso* -Pr, Ph

Scheme 1: Two-component reactions of trialkyl phosphite or triphenyl phosphite derivatives and trichloroacetyl isocyanate

Table 1: Synthesis of dialkyl or diphenyl (1,1-dichloro-2-isocyanato-2-oxoethyl) phosphonate derivatives.

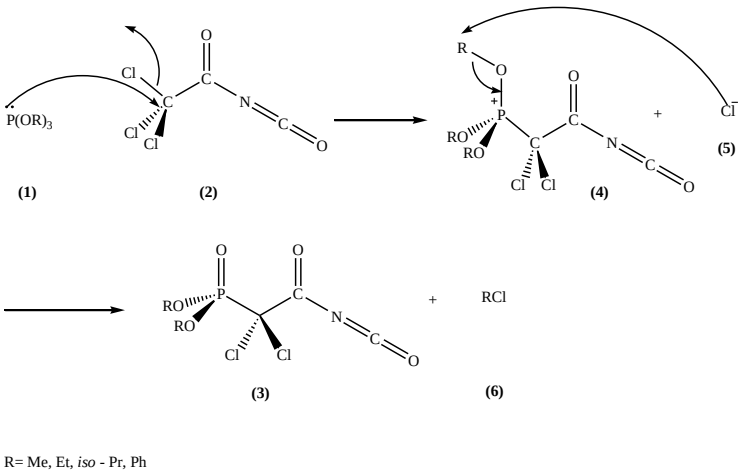
Entry	R	Products	Yield
1	Me	3a	85
2	Et	3b	89
3	*iso*-Pr	3c	80
4	Ph	3d	85

Result and Discussion

Trialkyl phosphite derivatives or triaryl phosphite **(1)** and trichloroacetyl isocyanate **(2)** react *via* a two-component reaction to give dialkyl or diphenyl (1,1-dichloro-2- isocyanato-2-oxoethyl)phosphonate derivatives **(3)** (Scheme **1**). The reaction proceeds smoothly and cleanly, and affords the products in high yields. A mechanistic rationalization for this reaction is provided in Scheme **2**. The structures of the products were deduced from their ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR and IR spectra, and elemental analysis. For example the ^{1}H-NMR spectrum of **3a** exhibited distinct signals at δ_H 3.74 ppm (6H, *d*) arising from two OMe groups. The ^{13}C-NMR spectrum of **3a** showed 4 distinct resonances arising from two OMe groups (δc 54.10 ppm), CCl_2 group (δc 91.83 ppm), 2C=O (δc 164.28 and 167.22 ppm). ^{31}P-NMR spectrum of **3a** exhibited distinct one signal at (δ_P 1.97 ppm).

these reactions, *N*-formylmorpholine is nucleophile and the reactions weren't carried out between only **1** and **2**. Also, these reactions weren't performed between **1** and **2** in the presence of *N*-formylmorpholine as a nucleophile.

Mechanistically, the reaction starts with formation of alkanoyl or aroyl isothiocyanate **4**, followed by addition of *N*-formylmorpholine to generate the intermediate **5**. Intermediate **5** would be attacked by negative charge in **6** and loss of *N*-formylmorpholine and NCSH to produce **3** (Scheme **2**).



R= Me, Et, *iso* - Pr, Ph

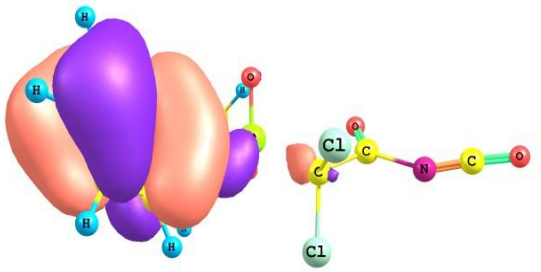
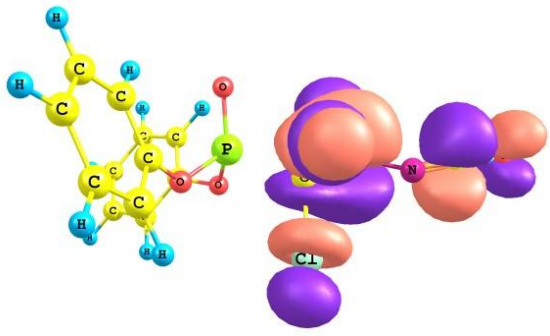
Scheme 2: A proposed Mechanism for the Formation of **(3).**

Absolute energy, zero point vibration energy, absolute thermodynamics parameters, molar capacity at constant volume, dipole moment of synthesized molecules are gathered in Table **2**. The calculated of bond distances of P-O and C=O at the B3LYP/6-311++G(d,p) level of theory are listed in Table **3**.

Also, the total density of states (DOS) of the prepared molecules are presented in Figure **2**. The varieties of the HOMOs, LUMOs, and energy gaps can be observed more easily and vividly.

Table 2: Zero-point correction (a.u), absolute thermodynamics parameters (G and H in a.u, S in cal/mol.K), molar capacity at constant volume (in cal/mol.K), isotropic and anisotropic polarizability values of the synthesized molecules.

R	Zero-point correction	G	H	S	Cv	α_{iso}	α_{aniso}
OPh	0.2266	-2270.4639	-2270.3831	170.25	81.46	239.78	45.31
OMe	0.1225	-1886.9881	-1886.9235	135.95	54.42	129.63	42.75
OEt	0.1789	-1965.5976	-1965.5254	151.92	64.28	154.93	47.03
OiPr	0.2343	-2044.2031	-2044.1258	162.68	75.48	178.94	48.68

	HOMO	**LUMO**
OPh		

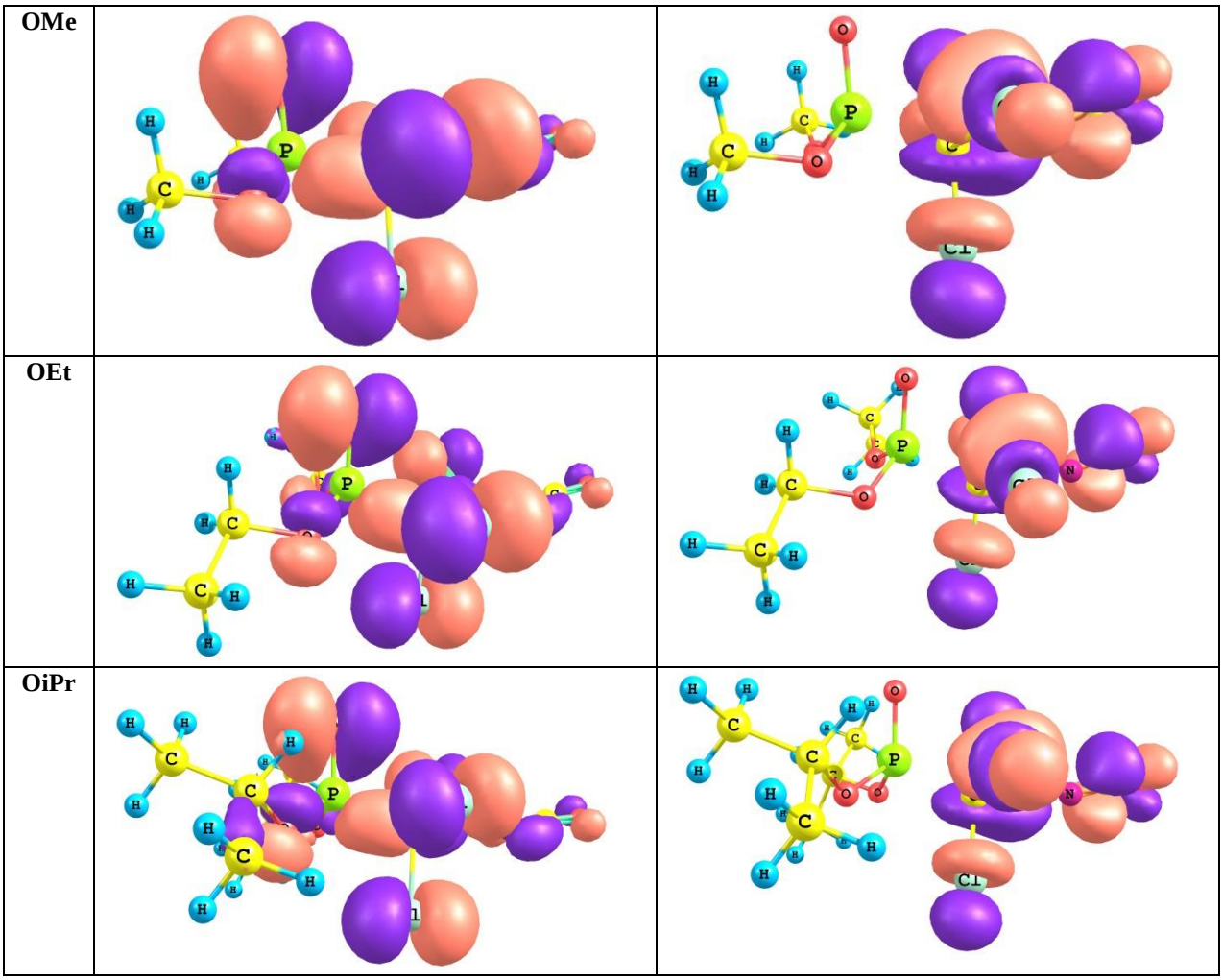


Figure 1: Plots of frontier orbitals of the synthesized molecules in this investigation.

Table 3: Absolute energy (a.u), dipole moment (Debye), frontier orbital energies (a,u), hardness (eV), chemical potential (eV) electrophilicity (eV) and bond distances (in Å) of C=O and P-O bonds in the molecules.

R	E	μ	E(HOMO)	E(LUMO)	η	μ	ω	r(C=O)	r(PO)
OPh	-2270.6332	2.70	-0.2579	-0.0949	2.22	-4.80	5.19	1.199	1.473
OMe	-1887.0637	2.61	-0.3044	-0.0970	2.82	-5.46	5.28	1.202	1.478
OEt	-1965.7245	2.92	-0.3010	-0.0950	2.80	-5.39	5.18	1.202	1.478
OiPr	-2044.3829	3.36	-0.2973	-0.0893	2.83	-5.26	4.89	1.198	1.479

Figure **1** presents the plots of frontier orbitals of the synthesized molecules in this investigation. Frontier orbital energies, hardness, chemical potential and electrophilicity of these molecules are gathered in Table **3**.

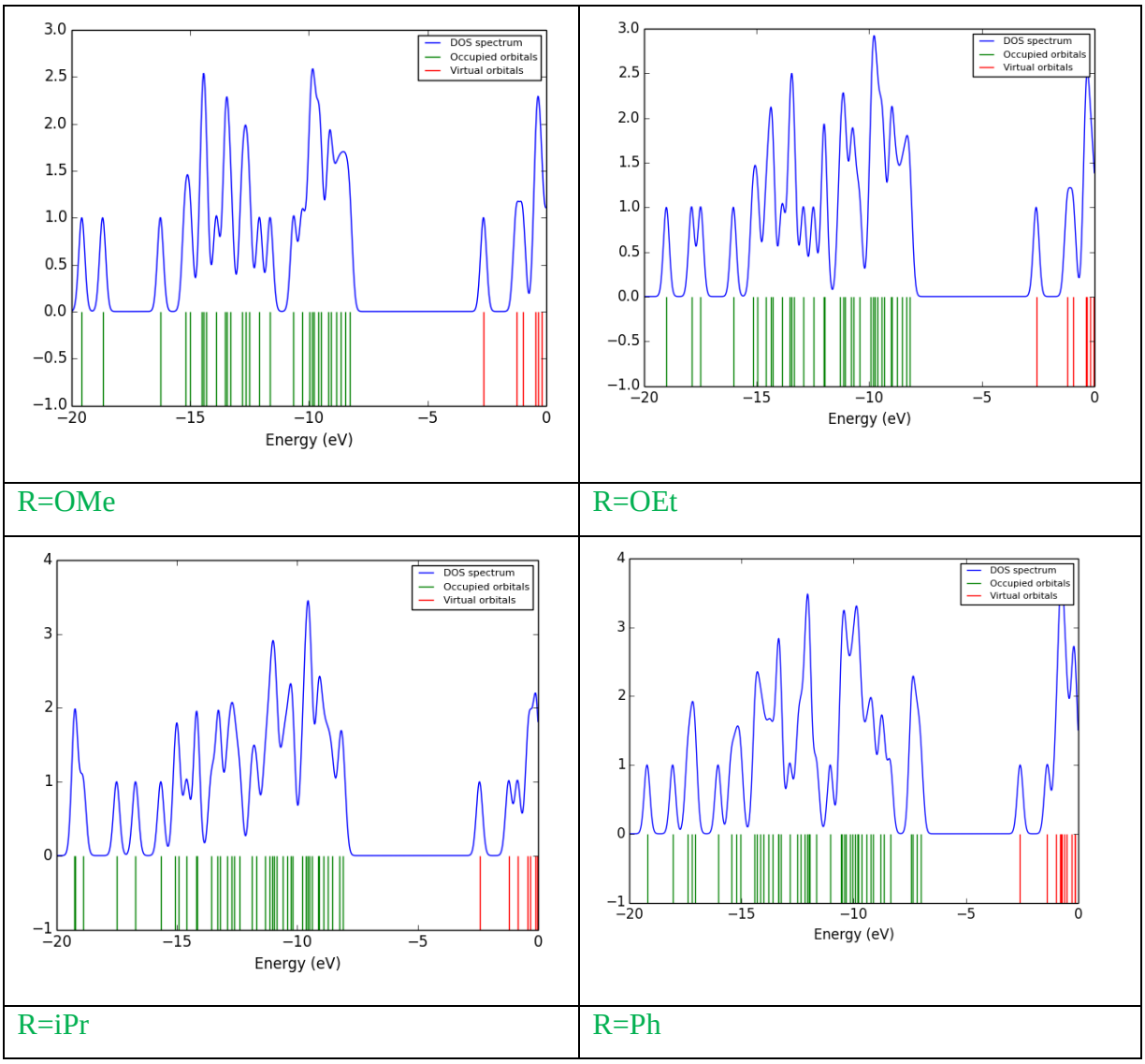


Figure 2: The total density of states (DOS) of the prepared molecules.

The hardness and chemical potential of these molecules are evaluated from the energies of frontier orbitals (HOMO and LUMO) by means of the following approximate equations:

$\mu=(\varepsilon_{HOMO}+\varepsilon_{LUMO})/2$

$\eta=(\varepsilon_{HOMO}-\varepsilon_{LUMO})/2$

Where μ and η are the chemical potential (the negative of the electronegativity) and hardness, respectively [34, 35]. On the other hand, the electrophilicity index,ω, for each molecule measured by means of Parr, Szentpaly, and Liu [36] using the formula:

$$\omega = \frac{\mu^2}{2\eta}$$

It can be seen the most hardness, electrophilicity values and lowest chemical potential value for R=OMe.

The response of a system in an applied electric field describes with polarizabilities [36]. These parameters define the molecular interactions strength of (like the long range intermolecular induction, dispersion forces, etc.), the cross sections of different scattering and collision processes, and the nonlinear optical properties of the system [37].

The isotropic polarizability <α > is calculated as the mean value as given in the following equation [38]:

$$\langle \alpha \rangle = \frac{(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})}{3}$$

And the polarizability anisotropy invariant is:

$$\Delta\alpha = \left[\frac{(\alpha_{XX} - \alpha_{YY})^2 + (\alpha_{YY} - \alpha_{ZZ})^2 + (\alpha_{ZZ} - \alpha_{XX})^2}{2}\right]^{\frac{1}{2}}$$

The calculated isotropic polarizability values indicate the most values of α_{iso} and α_{aniso} for R=Ph and OiPr, respectively (Table **2**).

The experimental and theoretical values of υ(P-O) and υ(C=O) are listed in Table **4**. It can be found good compatible between experimental and theoretical values.

Table 4. Stretching wavenumbers (cm^{-1}) of C=O and P-O bonds for the synthesized molecules.

R	υ(C=O)		υ(PO)	
	exp	theo	exp	theo
OPh	1694.00	1786.45	1225.00	1285.42
OMe	1696.00	1772.66	1226.00	1269.99
OEt	1699.00	1773.11	1224.00	1267.43
OiPr	1704.00	1788.10	1223.00	1266.27

Also, ^{1}H, ^{13}C, ^{31}P-NMR spectra of synthesized molecules are provided to characterize of them. ^{13}C NMR experimental and theoretical chemical shift values are gathered in Table **5**. There good comparison between experimental and theoretical chemical shift values.

Table 5. Stretching wavenumbers (cm^{-1}) of C=O and P-O bonds for the synthesized molecules.

R	$\underline{C}Cl_2$		$\underline{C}(O)$	
	exp	theo	exp	theo
OPh	92.74	95.3961	167.34	164.1006
OMe	92.66	93.9455	167.22	167.3065
OEt	92.51	94.2053	166.78	167.2025
OiPr	92.84	95.2136	167.08	164.1619

Molecular electrostatic potential (MEP)

The molecular electrostatic potential (MEP) is a significant parameter in determining molecular size, shape besides positive, negative and neutral electrostatic potential regions in terms of color grading. Electrostatic potential map of the prepared molecule in the presence of R=Et is presented in Figure **2**. This parameters is very valuable to illustrate the relationship between molecular structure with its physiochemical property. In case of MEP, the red color signifies the negative charges or the electrophilic regions and the green color denotes the positive charges or the nucleophilic regions. Negative regions are regularly related with the lone pair of electronegative atoms. MEP is decreasing in the order of blue > green > yellow > orange > red. According to the Figure **3**, O atom of oxo group of bonded to phosphorous has negative potential.

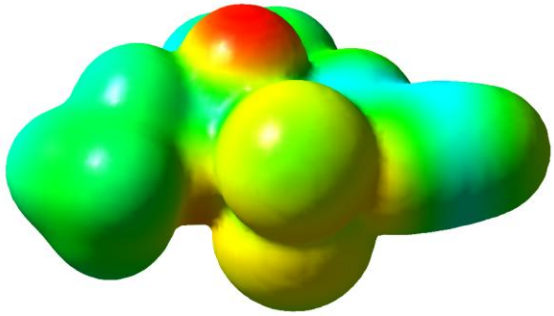


Figure 3: Electrostatic potential maps of the prepared molecule in the presence of R=Et.

Conclusion

The reported method offers a mild, simple, and efficient route for the preparation of dialkyl or diphenyl (1,1-dichloro-2-isocyanato-2-oxoethyl) phosphonate derivatives *via* a two-component reaction of trialkyl phosphite derivatives or triphenyl phosphite and trichloroacetyl isocyanate, in high yields and fairly mild reaction conditions. The calculated spectroscopic parameters (IR and NMR) at the B3LYP/6-311++G(d,p) level of theory show good compatible with experimental values.

Experimental

The starting materials and solvent were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an electrothermal 9100 apparatus and are uncorrected. The IR spectra were recorded on a Jasco FT-IR 6300 spectrometer. The ^{1}H-NMR and ^{13}C-NMR spectra were measured ($CDCl_3$ solution) with a

Bruker DRX-250 Avance spectrometer at 250.0 and 62.5 MHz, respectively. The elemental analyses were realized using a Heraeus CHN-O-rapid analyzer.

General procedure for the synthesis of dialkyl or diphenyl phosphonates:

To a magnetically stirred solution of trichloroacetyl isocyanate (**2**, 1 mmol) in CH_2Cl_2 (5mL) was added trialkyl phosphite derivatives or triphenyl phosphite (**1**, 1mmol) at -10^{o}C. The mixture was stirred at room temperature for 30 minutes until 1 hours. Then the mixture was filtrated and washed with CH_2Cl_2, and the products **3a-d** were obtained. The characterization data of the compounds are given below:

Dimethyl (1,1-dichloro-2-isocyanato-2-oxoethyl) phosphonate (3a):

Colorless solid, mp: 127.9-129.7 ^{o}C, yield: 85%; Anal. Calcd. for $C_5H_6Cl_2NO_5P$: C, 22.92; H, 2.31; N, 5.35. Found: C, 23.05; H, 2.28; N, 5.28; IR (KBr, cm^{-1}): 2966 (CH, aliphatic), 1696 (C=O), 1617 (C=O), 1226 (P=O), 1047 (P-O-C), 831 and 824 (C-Cl, Str.); ^{1}H-NMR (250 MHz, $CDCl_3$, δ / ppm): 3.74 (6H, *d*, $^3J_{PH}$ = 11.0 Hz, $2OCH_3$); ^{13}C- NMR (62.5 MHz, $CDCl_3$, δ / ppm): 54.10 ($2OCH_3$, *d*, $^2J_{POC}$ = 5.7 Hz), 92.66 (CCl_2, *d*, $^1J_{PC}$ = 104.41 Hz), 164.28 and 167.22 (2C=O); ^{31}P-NMR (101 MHz, $CDCl_3$, δ / ppm): 1.97 (*s*).

Diethyl (1,1-dichloro-2-isocyanato-2-oxoethyl) phosphonate (3b):

Colorless solid, mp: 140.1-141.7 ^{o}C, yield: 89%; Anal. Calcd. for $C_7H_{10}Cl_2NO_5P$: C, 28.99; H, 3.48; N, 4.83. Found: C, 29.06; H, 3.43; N, 4.76; IR (KBr, cm^{-1}): 2975 (CH, aliphatic), 1699 (C=O), 1620 (C=O), 1224 (P=O), 1043 (P-O-C), 825 and 814 (C-Cl, Str.); ^{1}H-NMR (250 MHz, $CDCl_3$, δ / ppm): 1.33 (6H, *t*, $^3J_{HH}$ = 7.1 Hz, $2CH_3$), 4.10 (4H, *q*, $^3J_{HH}$ = 7.1 Hz, $2OCH_2$); ^{13}C- NMR (62.5 MHz, $CDCl_3$, δ / ppm): 16.00 (CH_3, *d*, $^3J_{POCC}$ = 6.9 Hz), 16.06 (CH_3, *d*, $^3J_{POCC}$ = 6.9 Hz), 63.55 (OCH_2, *d*, $^2J_{POC}$ = 5.7 Hz), 63.92 (OCH_2, *d*, $^2J_{POC}$ = 5.7 Hz), 92.51 (CCl_2, *d*, $^1J_{PC}$ = 175.49 Hz), 164.90 and 166.78 (2C=O). ^{31}P-NMR (101 MHz, $CDCl_3$, δ / ppm): - 1.12 (*s*).

Diisopropyl (1,1-dichloro-2-isocyanato-2-oxoethyl) phosphonate (3c):

Colorless solid, mp: 133.3- 135.0 ^{o}C, yield: 80%; Anal. Calcd. for $C_9H_{14}Cl_2NO_5P$: C, 33.98; H, 4.44; N, 4.40. Found: C, 34.06; H, 4.49; N, 4.36; IR (KBr, cm^{-1}): 2980 (CH, aliphatic), 1704 (C=O), 1624 (C=O), 1223 (P=O), 1045 (P-O-C), 832 and 821 (C-Cl, Str.); ^{1}H-NMR (250 MHz, $CDCl_3$, δ / ppm): 1.34 (12H, *dd*, $^3J_{HH}$ = 6.0 Hz, $^4J_{PH}$ = 3.0 Hz, $4CH_3$), 4.62 (2H, *sept*, $^3J_{HH}$ = 5.6 Hz, 2OCH); ^{13}C- NMR (62.5 MHz, $CDCl_3$, δ / ppm): 23.53 ($2CH_3$, *d*, $^3J_{POCC}$ = 4.7 Hz), 23.61 ($2CH_3$, *d*, $^3J_{POCC}$ = 4.7 Hz), 72.47 (*d*, $^2J_{POC}$ = 5.7 Hz, OCH), 72.65 (*d*, $^2J_{POC}$ = 5.7 Hz, OCH), 92.84 (CCl_2, *d*, $^1J_{PC}$ = 134.61 Hz), 163.64 and 167.08 (2C=O). ^{31}P-NMR (101 MHz, $CDCl_3$, δ / ppm): - 2.41 (*s*).

Diphenyl (1,1-dichloro-2-isocyanato-2-oxoethyl) phosphonate (3d):

Colorless solid, mp: 145.2- 146.9 ^{o}C, yield: 85%; Anal. Calcd. for $C_{15}H_{10}Cl_2NO_5P$: C, 46.66; H, 2.61; N, 3.63. Found: C, 45.58; H, 2.63; N, 3.70; IR (KBr, cm^{-1}): 3247 (CH, aromatic), 2977 (CH, aliphatic), 1694 (C=O), 1617 (C=O), 1225 (P=O), 1060 (P-O-C), 833 and 758 (C-Cl, Str.); ^{1}H-NMR (250 MHz, $CDCl_3$, δ / ppm): 6.84- 7.00 and 7.20- 7.31 (10H, 2*m*, arom CH); ^{13}C- NMR (62.5 MHz, $CDCl_3$, δ / ppm): 92.74 (CCl_2, *d*, $^1J_{PC}$ = 139.01 Hz), 115.48, 120.88, 129.77 and 155.35 (aromatic carbons), 164.87 and 167.34 (2C=O). ^{31}P-NMR (101 MHz, $CDCl_3$, δ / ppm): 8.58 (*s*).

Computational methods:

The structures of the synthesized molecules were optimized by the B3LYP method [39], and 6-311++G(d,p) [40, 41] is chosen as basis set.

The optimization was done along with a frequency calculation for each complex to verify that the geometry was a real minimum without any imaginary frequency.^{13}C NMR Chemical shift values of the molecules were calculated using the Gauge independent atomic orbital (GIAO) [42] method at the B3LYP/6-311++G(d,p) level of theory.

An electrostatic potential map (EPM) was shown from a set of point charges in order to characterize the best possible molecular quantum potential points defined around the molecule, plotted with the program GaussView 5.0.

The GaussSum 3.0 software package was used to evaluate the of density of states (DOS) spectrum of the molecules [43] .

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