

Synthesis and dynamic ^1H NMR study around C=C and C-C bonds in a particular phosphorous ylide driven from triethyl phosphite

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Abstract: Stable crystalline phosphorus ylide was obtained in excellent yield, in the presence of phthalimide as a NH-heterocyclic compound. This ylide exists in the solution as a mixture of the two isomers at ambient temperature, so dynamic ^1H NMR effects were investigated at different temperatures around the carbon-carbon single bond and carbon-carbon double bond in the two *Z*- and *E*- rotational isomers. In addition, theoretical studies were performed on the same bonds using *ab initio* methods at HF/6-31G(d,p) and B3LYP/6-31G(d,p) levels of theory. As a results, HF/6-31G(d,p) level provides better results in comparison with dynamic ^1H NMR data.

Keywords: Dynamic ^1H NMR, Triethyl phosphite, Rotational energy barrier, ab initio method, Phtalamide.

Introduction

Organophosphorus compounds are synthesis targets of interest, because of their value in a variety of industrial, biological, and chemical synthetic systems [1–5]. The physical properties and chemical reactivity of phosphate esters interlink many areas in chemistry and biology. Introduction of a phosphate monoester into a molecule such as a drug candidate enhances the water solubility, hence altering its bioavailability [6–8]. As a result, many methods have appeared describing novel syntheses of organophosphorus compounds [3]. There have been many reports of studies on the reactions between trivalent phosphorus nucleophiles and α,β -unsaturated carbonyl compounds in the presence of a proton source such as an alcohol or a phenol [9–11]. Some of the phosphorus ylides exhibited dynamic ^1H NMR effect that affords good information regarding the interchangeable process of rotational isomers that provide important kinetic data [12–16].

In continuation of our research work on preparing phosphonato-ester compounds with triphenylphosphite in the presence of NH acids [17, 18], we report here the reaction between dimethyl acetylenedicarboxylate (DMAD) and triethyl phosphite, in the presence of N-H acids (Figure 1) along with dynamic ^1H NMR effects and theoretical studies around the C-C and the C=C bonds.

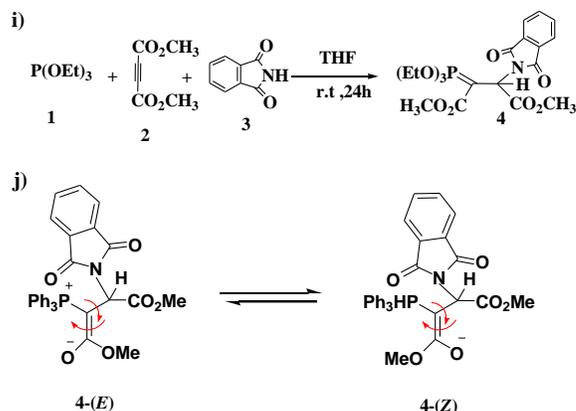


Figure 1: i) Synthesis of stable phosphorus ylide 4 j) interchangeable process between the two (*Z*)- and (*E*)- isomers of ylide 4.

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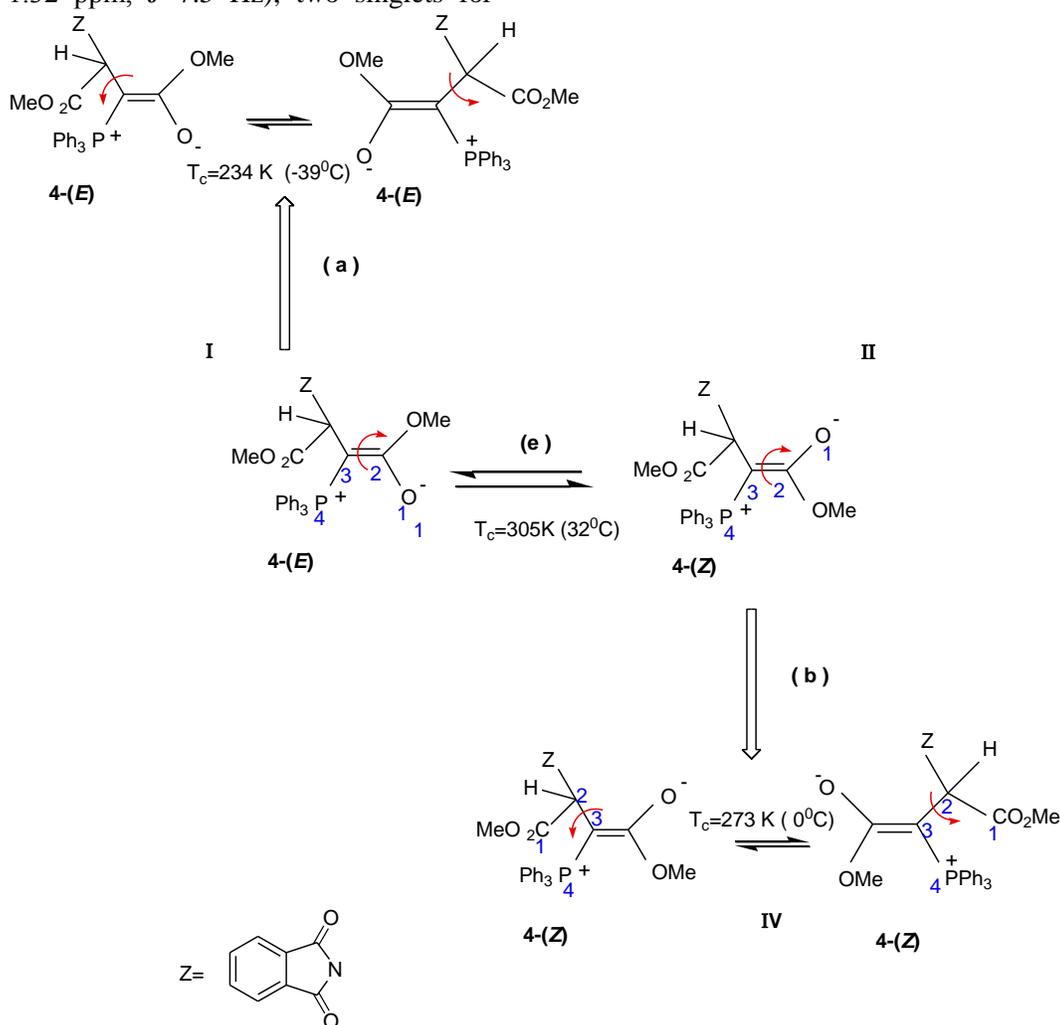
Results and discussion

Synthesis:

We now describe a mild and efficient protocol for the synthesis of stable phosphorus ylide from the reaction between triethyl phosphate **1**, electron-deficient dimethyl acetylenedicarboxylates **2**, and phthalimide **3** as a N-H heterocyclic compound shown in Figure 1. The molecular structure of compound **4** was deduced from IR, ^1H NMR, ^{13}C NMR, ^{31}P NMR spectroscopy, and mass spectra. The ^1H NMR data for compound **4** are accumulated in the experimental section. The ^1H NMR spectrum of compound **4** exhibited three triplet for methyl protons of ethoxy groups ($\delta = 1.32$ ppm, $J=7.5$ Hz), two singlets for

methoxy groups ($\delta = 4.23$ and 4.27 ppm), a broadening doublet for H ylide ($\delta = 6.14$ and 6.20 ppm). The ^{13}C NMR spectrum of **4** showed 14 distinct resonances in agreement with the proposed structure. The ^{31}P NMR shift was recorded for **4** at 51.49 ppm. The IR spectrum of **4** displayed characteristic carbonyl absorption at 1749 and 1684cm^{-1} . Although the mechanism of this reaction has not been experimentally established. A possible mechanism has been proposed on the basis of literature reported [19-23] (see Figure 1).

In ylide **4**, $\text{C}_2\text{-C}_3$ bond, has a partial double bond character due to the conjugation with adjacent carbonyl group, shown in Scheme 1.



Scheme 1: Interchangeable processes in ylide **4** containing different rotational isomers

Dynamic effect for the E and Z rotational isomers as a result of restricted rotational process around the partial carbon-carbon double bond (Scheme 1, process e):

The ^1H NMR spectrum of the 4-(E) and 4-(Z) isomers at 10°C showed a broad resonance for the methine proton (H-C-C-P , $^3J_{\text{PH}}$) in comparison with a corresponding two doublets that was measured at 0°C . The methine proton coalesces near 32°C (305K) and appears as a broad doublet at 42°C , which is relevant

to restricted rotational process around the carbon-carbon double bond. Investigation of such behavior in the phosphorus ylide **4** at variable temperatures allowed us to calculate the rotational energy barrier (ΔG^\ddagger) on the basis of ^1H NMR study for the restricted rotational process around the carbon-carbon double bond (Table 1). Using the expression $k_c = \pi\Delta\nu/\sqrt{2}$, first-order rate constant was calculated for bond rotational process. Application of the absolute rate theory with a transmission coefficient (k) of one, gave Gibbs free rotational energy barrier. These values are

	ΔS^\ddagger (kJ/mol)	ΔH^\ddagger (kJ/mol)	k_c (s $^{-1}$)	ΔG^\ddagger (kJ/mol)	$\Delta\nu$ (Hz)	δ (ppm)	T_c (K)
Experimental ^a	-0.06	47.11	22.42	65.71	20	3.7-3.72	305
Theoretical ^b	-0.007	61.67	-	64.01	-	-	305
Theoretical ^c	0.002	46.36	-	45.74	-	-	305

^a Experimental data obtained from the ^1H NMR study

$$k_c = \frac{\pi\Delta\delta}{\sqrt{2}}, \quad \Delta G^\ddagger = 1.91T_c \left(9.97 + \log \frac{T_c}{\Delta\delta} \right), \quad \Delta H^\ddagger = -R \times 2.303 \times \frac{\Delta \log k_c / T_c}{\Delta 1/T_c}$$

$$\Delta S^\ddagger = \frac{\Delta H^\ddagger - \Delta G^\ddagger}{T}$$

^b Theoretic data obtained using *ab initio* method at HF/6-31G(d,p) level of theory for synthesized ylide **4** at 305 K.

$$\Delta H^\ddagger = H_{TS} - H_E, \quad \Delta G^\ddagger = G_{TS} - G_E, \quad \Delta S^\ddagger = \frac{\Delta H^\ddagger - \Delta G^\ddagger}{T}$$

^c Theoretical data obtained using *ab initio* method at B3LYP/6-31G(d,p) level of theory for synthesized ylide **4** (305 K)

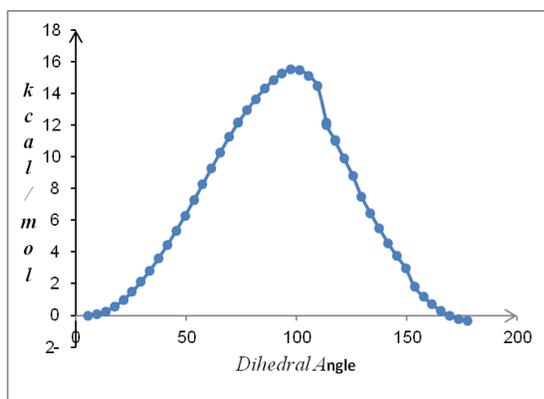


Figure 2: Relative energy versus dihedral angle $\text{O}_1\text{C}_2\text{C}_3\text{P}_4$ in phosphorus ylide **4**.

In order to determine the rotational energy barrier (ΔG^\ddagger) around the $\text{C}=\text{C}$ bond using the quantum mechanical calculations in the rotational interchangeable processes of the two *Z*- and *E*-isomers in ylide **4** (Scheme 1), first their structures were optimized at HF/6-31G level of theory by Gaussian 03 program package [24] Then, relative energy was plotted versus dihedral angle $\text{O}_1\text{C}_2\text{C}_3\text{P}_4$ (Scheme 1) as shown in Figure 3. The corresponding structures, with respect to all points (*E*, TS and *Z*) in Figure 2 were drawn in Figure 3.

reported in Table 1. Effect of temperature on the rate constant was investigated on the basis of measurement of different chemical shifts in a series of other separate experiments. The results were too small so that the changes in the first-order rate constant and Gibbs free energy barrier are negligible in comparison with the results obtained at 32 °C (305 K).

Table 1. Selected ^1H chemical shifts (at 500.1 MHz, in ppm, Me_4Si) along with activation parameters in CDCl_3 , for restricted rotational process around the carbon-carbon double bond (Scheme 1, process e).

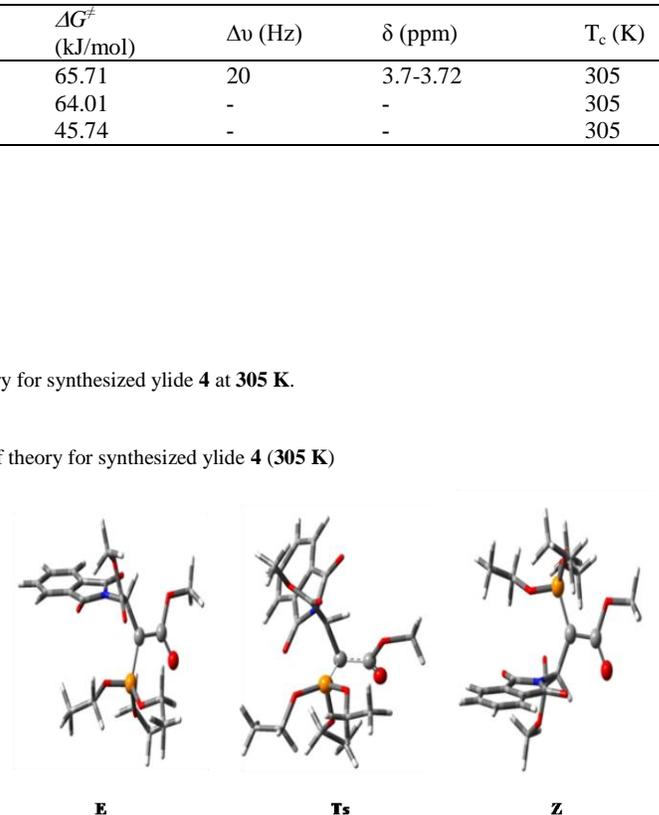


Figure 3: Structures corresponding to *E*, TS and *Z* points with respect to Figure 2.

Frequency calculations were employed for transition and stationary points (*TS*, *E-4a* and *Z-4a*) and the results are reported in Table 2. First negative frequency value could be considered as a strong proof for confirmation of *TS* structure. On the basis of theoretical calculations, for synthesized ylide **4**, and data obtained from the Figure 3, the free Gibbs rotational energy barrier (ΔG^\ddagger), ΔH^\ddagger and ΔS^\ddagger calculated around carbon-carbon double bond. As can be seen from Table 1; there is, a good agreement between the experimental and theoretical data at HF/6-31G(d,p) level of theory.

Dynamic effect for the E-4 and Z-4 rotational isomers as a result of restricted rotational process around the

partial carbon-carbon single bond (processes a and b, Scheme 1):

Further investigations through the ^1H NMR spectra of compound **4** was accompanied by another dynamic ^1H NMR effect which is attributed to the restricted rotational process around the carbon-carbon single bond (Scheme 1 processes a and b).

Herein, when temperature was decreased with respect to ambient temperature, the ^1H NMR spectrum of the **4-(E)** isomer in CDCl_3 at $+10^\circ\text{C}$ showed a resonance arising from the ylide protons which is sharpened in comparison to a corresponding doublet

that was measured at ambient temperature. When temperature was decreased more, the ylide protons coalescence near -39°C (234 K) and finally hydrogen of ylide appear as a two quadrupole doublets ($\delta=6.05$ and 6.21 ppm) at -50°C (223 K), which is related to the restricted rotational barrier around the carbon-carbon single bond in the **4-(E)** of compound **4** (see Scheme 1 process a). It must be mentioned that the ylide protons of **4-(Z)** isomer coalescence near 0.0°C (273 K) and appear as a two quadrupole doublets ($\delta=6.20$ and 6.11 ppm) at -10°C (253 K) (Scheme 1, process b). These values are collected in Table 3.

Table 2. Frequency data obtained for *E*, *TS* and *Z* structures respectively in the ylide **4**.

Isomer	<i>E</i>	<i>TS</i>	<i>Z</i>
First frequency	(22.35) ^a , (21.86) ^b	(-135) ^a , (-166) ^b	(18.25) ^a , (19.55) ^b

^a Obtained at HF/6-31G(d,p)

^b Obtained at B3LYP/6-31G(d,p)

Table 3: Selected ^1H chemical shifts (at 500.1 MHz, in ppm, Me_4Si) along with activation parameters in CDCl_3 , for restricted rotational process around the carbon-carbon single bond (Scheme 1 process a and b).

	ΔS^\ddagger (kJ/mol)	ΔH^\ddagger (kJ/mol)	k_c (s^{-1})	ΔG^\ddagger (kJ/mol)	$\Delta\nu$ (Hz)	δ (ppm)	T_c (K)
Experimental 4-(E) ^a			194.28	62 ± 2	80	6.21-6.05	234
Experimental 4-(Z) ^a			88.81	57 ± 2	40	6.11-6.20	273
Theoretical ^b	-0.05	28.62	-	43.34	-	-	273
Theoretical ^c	-0.02	28.88	-	33.35	-	-	273

^a Experimental data obtained from the ^1H NMR study

^b Theoretic data obtained using *ab initio* method at HF/6-31G(d,p) level of theory in the **4-(Z)** isomer at 273 K.

^c Theoretical data obtained using *ab initio* method at B3LYP/6-31G(d,p) level of theory in the **4-(Z)** isomer at 273 K

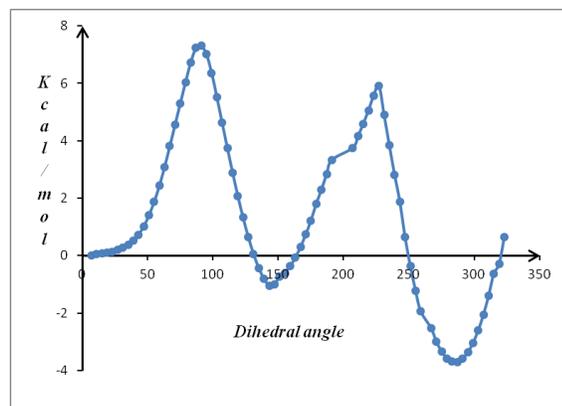


Figure 4: Relative energy versus dihedral angle $\text{C}_1\text{C}_2\text{C}_3\text{P}_4$ in the **4-(Z)** isomer.

In addition, theoretical calculations were carried out on the basis of rotation around the carbon-carbon single bond only in the **4-(Z)** isomer ($\text{PPh}_3\text{-C} \rightleftharpoons \text{CCO}_2\text{Me}$) using *ab initio* method at HF/6-

31G(d,p) and B3LYP/6-31G(d,p) levels of theory. The same procedure alike the previous section was employed for this process. Then, relative energy versus dihedral angle ($\text{C}_1\text{C}_2\text{C}_3\text{P}_4$, see Scheme 1) was plotted in Figure 4.

As can be seen, the two transition states (TS (1) and TS (2)) have appeared on this plot. Frequency calculations were employed for TS (1) and GS (1) and the results are reported in Table 4. First negative frequency values could be considered as a strong proof for the confirmation of TS (1) structures. Rotational energy barrier (ΔG^\ddagger) calculations for TS (1) and TS (2) points exhibited that TS (1) has a higher value of ΔG^\ddagger with respect to TS (2), hence TS (1) was chosen as a main rotational barrier. As a result, all theoretical data were reported in Table 3 on the basis of this pathway (TS (1)) for a interchangeable process of the **4-(Z)** isomer. As can be seen, HF/6-31G (d,p) provide better

data than B3LYP/6-31G (d,p) (see amount of ΔG^\ddagger in Table 3).

Table 4: Frequency data obtained for Gs and TS (1) structures respectively in the ylide 4.

Conformer	GS (1)	TS (1)
First frequency	(18.28) ^a , (19.58) ^b	(-26.43) ^a , (-23.68) ^b

^a Obtained at HF/6-31G(d,p)

^b Obtained at B3LYP/6-31G(d,p)

Conclusion

The theoretical results on the basis of mechanical calculations, using ab initio method at HF/6-31G(d, p) and B3LYP/6-31G(d, p) levels of theory indicated that rotational energy barrier parameters for interchangeable process between the two isomers (**4-E** and **4-Z**) were consistent with the experimental dynamic ¹H NMR data at HF/6-31G(d,p) level. It seems that HF/6-31G(d,p) as a lower basis set provide a better results in comparison with the higher basis set such as B3LYP/6-31G(d, p) level. Perhaps large molecule alike ylide 4 along with a large number of atoms and also four atoms of vast size such as, phosphorous, nitrogen and oxygen made enough complication in relation to higher basis set.

Experimental

Melting points, IR, and UV spectra of all compounds were measured on an Electrothermal 9100 apparatus, a Shimadzu IR-460 spectrometer, and a Cary UV/Vis spectrophotometer model Bio-300 ¹H, ¹³C, and ³¹P NMR spectra were obtained from a Bruker DRX-300 Avance instrument with CDCl₃ as solvent at 300.1, 121.4, and 75.5 MHz, respectively. The mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Heraeus CHM-O-Rapid analyzer. Dialkyl methylenedicarboxylates, triethylenephosphine, and phthalimide were purchased from Fluka (Buchs, Switzerland) and used without further purification.

Preparation of Dimethyl-2-(phthalimide-N-yl)-3-(triethoxyphosphoranylidene)-butanedioate:

To a magnetically stirred solution of triethylenephosphine1 (1mmol), phthalimide3 (1 mmol), in 10 ml tetrahydro furane was added, dropwise methylenedicarboxylates 2 (1mmol) at ambient

temperature over 10 min. The extent of reaction monitored by TLC. After completion of the reaction, solvent was removed under reduced pressure and the solid residue was washed with cold diethyl ether for the extraction of final product. The product was recrystallized in diethyl ether. mp: 112-114 °C, (KBr) (ν_{\max} , cm⁻¹): 1749, 1716, 1684; ¹H NMR (400 MHz, CDCl₃), δ : 1.34 (9H, t, $J=7.2$ Hz, P-O-CH₂-CH₃), 3.72 (6H, 2s, 2OMe), 4.168-4.238 (6H, m, O-CH₂-CH₃), 6.19 (1H, d, $J_{\text{HP}}=22.8$ Hz, CHN), 7.69 (2H, s, Ar), 7.83 (2H, s, Ar); ¹³C NMR (100.6 MHz, CDCl₃) δ : 15.93 and 15.99 (d, $J_{\text{CP}}=6$ Hz, P-O-CH₂-CH₃), 44.1 (d, $J_{\text{CP}}=22.7$ Hz, C=P) 50.00 and 52.35 (2s, 2OMe) 52.89 and 53.01 (d, $J_{\text{CP}}=12$ Hz, CHN), 64.54 and 64.76 (d, $J_{\text{CP}}=22$ Hz, P-O-CH₂-CH₃) 123.06, 132.38, 133.61 (s, Ar), 167 (s, CHN) 169.2 (d, ²J_{CP}=19.5 Hz, C=O), 170.85 (s, $J_{\text{CP}}=16.4$ Hz, C=O); ³¹P NMR (162 MHz, CDCl₃) δ : 51.94; MS m/z (%): 456.3 (M+1, 25), 424 (32), 396.3 (20), 368.3 (15), 336.2 (54).

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