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Theoretical study on the mechanism of stable phosphorus ylides derived from 5-aminoindazole in the presence of different dialkyl acetyelenedicarboxylates

Mohammad Zakarianezhad*, Motahare Shool

Department of Chemistry, Payame Noor University, P.O. BOX 7815753613, Tehran, Iran

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Abstract

In the recent work, the reaction mechanism between triphenylphosphine **1**, dialkyl acetylenedicarboxylates **2** in the presence of NH-acid, such as 5-aminoindazole **3** were investigated theoretically. Quantum mechanical studies were performed for evaluation of potential energy surfaces of all structures participated in the reaction mechanism both in the gas phase and in dichloromethane. The first step of all reactions was recognized as a rate-determining step in the reaction mechanism. All the possible structures participated on the reaction coordinate were well predicted. Quantum mechanical calculations were clarified how the ylides exist in solution as a mixture of two geometrical isomers (*Z*- and *E*-) as a minor or major form.

Keywords: NH-acid; theoretical study; *Z*- and *E*-rotamers; 5-aminoindazole; triphenylphosphine.

Introduction

Organophosphorus compounds can be considered as significant reagents and intermediates in organic synthesis [1]. In this class, phosphorus ylides is an important group, that has been applied in many reactions and synthesis of organic compounds [2-11]. The dominant function of these compounds is to change the carbonyl groups into carbon-carbon double bonds [12]. The most important method used for the synthesis of phosphorus ylides, is the reaction of phosphonium salt with a base [13, 14]. Recently, a method has been organized for the preparation of this family by applying a new way using vinyl phosphonium salts [15, 16]. The phosphonium salts are most often changed into the ylides by treatment with a strong base, though weaker bases can be used if the salt is acidic enough. Michael addition of phosphorus (III) compounds such as triphenylphosphine to acetylenic esters leads to reactive 1, 3-dipolar intermediate betains that are not discovered even at low temperature [17]. A protic reagent, NH, such as methanol, amide, imide, etc. can trap these unstable species to produce various compounds such as ylides [5,11]. These ylides are a combination of the two geometrical isomers, although some ylides exhibit one geometrical isomer. It is impossible to assign the stability of

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*Corresponding author: Mohammad Zakarianezhad
Tel: +98 (34) 42306870, Fax: +98 (34) 42306870
E-mail: mzakarianejad@yahoo.com

the two *Z*- and *E*-isomers in phosphorus ylides by experimental methods such as ^{1}H and ^{13}C NMR and IR spectroscopies, mass spectrometry and elemental analysis data. So, quantum mechanical calculation has been done in order to obtain a better understanding of the most important geometrical parameters and realize how these isomers can exist in two different *E*- and *Z*-forms. A facile synthesis of the reaction between triphenylphosphine **1**, dialkyl acetylendicarboxylates **2** and 5-aminoindazole **3** (as a NH- heterocyclic compound) for generation of phosphorus ylides **4** involving the two geometrical isomers such as *Z*- and *E*-isomers have been earlier reported [18]. The reaction is shown in Figure 1.

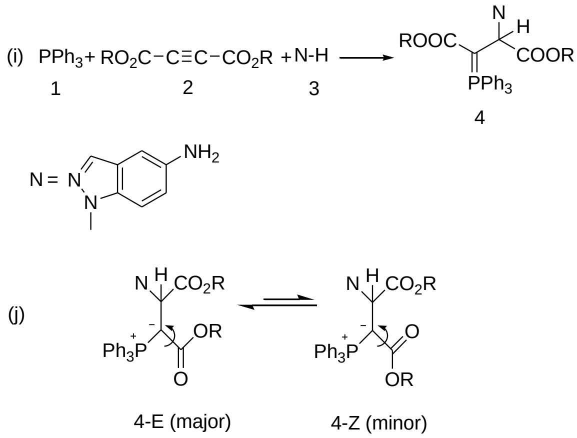

Figure 1. (i) The reaction between triphenylphosphine **1**, dialkyl acetylenedicarboxylate **2** and 5-aminoindazole **3** for generation of stable phosphorus ylides **4** (**j**) The two rotamers **4-*E*** and **4-*Z*** of ylide **4**

Materials and Methods

All Geometrical structures were optimized at oniom(B3LYP/6-311++g(d,p):HF/6-31g) level of theory by using Gaussian 09 [19]. The corresponding frequencies of the structures were estimated at the same level of theory to check the stationary points without imaginary frequencies and the transition states with only one imaginary frequency. Also, the intrinsic reaction coordinate (IRC) approach [20 and 21] was performed to ensure that the given transition state connects with the corresponding reactants and products.

Results and discussion

Energetics and geometries in gas phase

Two different reaction paths were predicted from a nucleophilic attack of triphenylphosphine **1** to dimethyl acetylenedicarboxylate **2** in different directions. The potential energy profiles for two pathways **I** and **II** are presented in Figure 2. Also, the optimized geometries of all structures are included in Figures 3. As seen, the first step is initiated by the nucleophilic attack of atom P, in the structure of triphenylphosphine **1**, to atom C6 of dimethyl acethylenedicarboxylate **2**, so as to form **I1**, passing through **TS1**. The second step includes the conformational evolution of **I1** into **I1**'. Then, **I1**' can be formed as **I2**, via hydrogen bonding, to **3**. The third step is the intermolecular proton transfer from atom N46 to atom C5 in structure **TS2**. The formation of the N46-C5 bond was expected to pass through a transition state; however, due to the high affinity of N^- towards connecting to C5, the process was not observed. Comparison of the potential energy surfaces shows that, except the product, all structures (including intermediates and transition states) in the path **I** are more stable than those of the path **II**. Thus, the overall reaction was proceeded *via* two barrier heights, 51.84 (67.74) and 31.96 (29.27) kJ/mol respectively (numbers in parentheses refer to the path **I**). The first step of the reaction with 19.88 (38.47) kJ/mol more energy barrier than the third step was recognized as rate determining step. The overall reaction with relative enthalpy and relative free energy of -99.29 (-93.82) and 23.06 (24.68) kJ/mol respectively is exothermic and non-spontaneous. In the synthesis of stable phosphorous ylide in the presence of 5-aminoindazole, **P-*E*** was recognized as major isomer [18], but, from the theoretical result, the **P-*E*** is less stable than **P-*Z*** isomer by 5.1 kJ/mole.

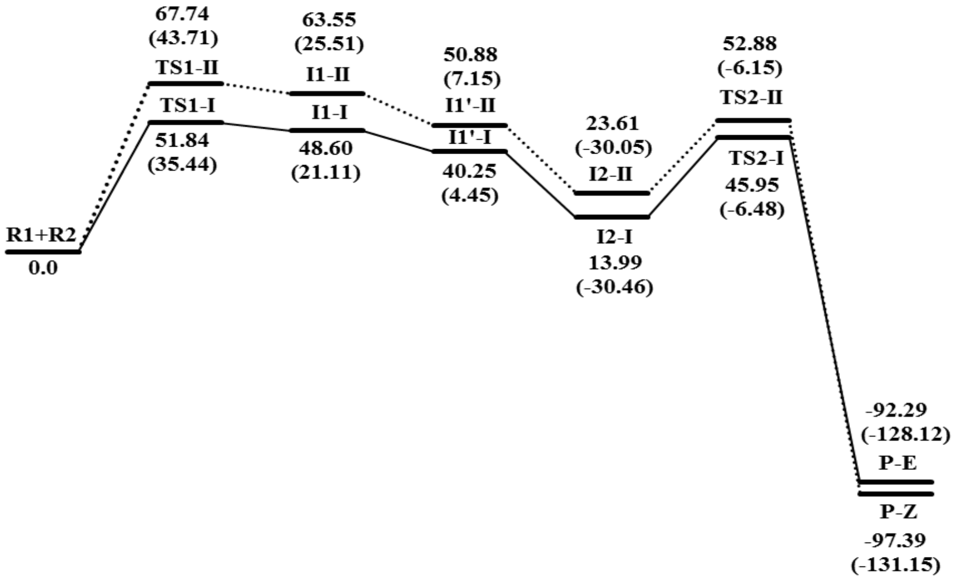

Figure 2. The potential energy profile of the reaction in two paths **I** and **II** both in gas phase and in dichloromethane (data in parentheses)

Because of this result the reaction mechanism should be investigated in more detail. The energy barrier of the first step in the path **I** is less than the path **II** and kinetic stability was created in the path **I** by 15.91 kJ/mol. It's obvious that the reaction proceeds on the path **I** with less barrier energy lead to the production of the major product (**P-*E***) which is less stable than **P-*Z*** and is plausible to convert to **P-*Z***. Results indicate that this process has the energy barrier of 72.76 or 76.48 kJ/mol which is relatively high and is not plausible (Figure 4) (It should be noted that two different energy barrier is related to orientation of COOMe group in two different orientations).

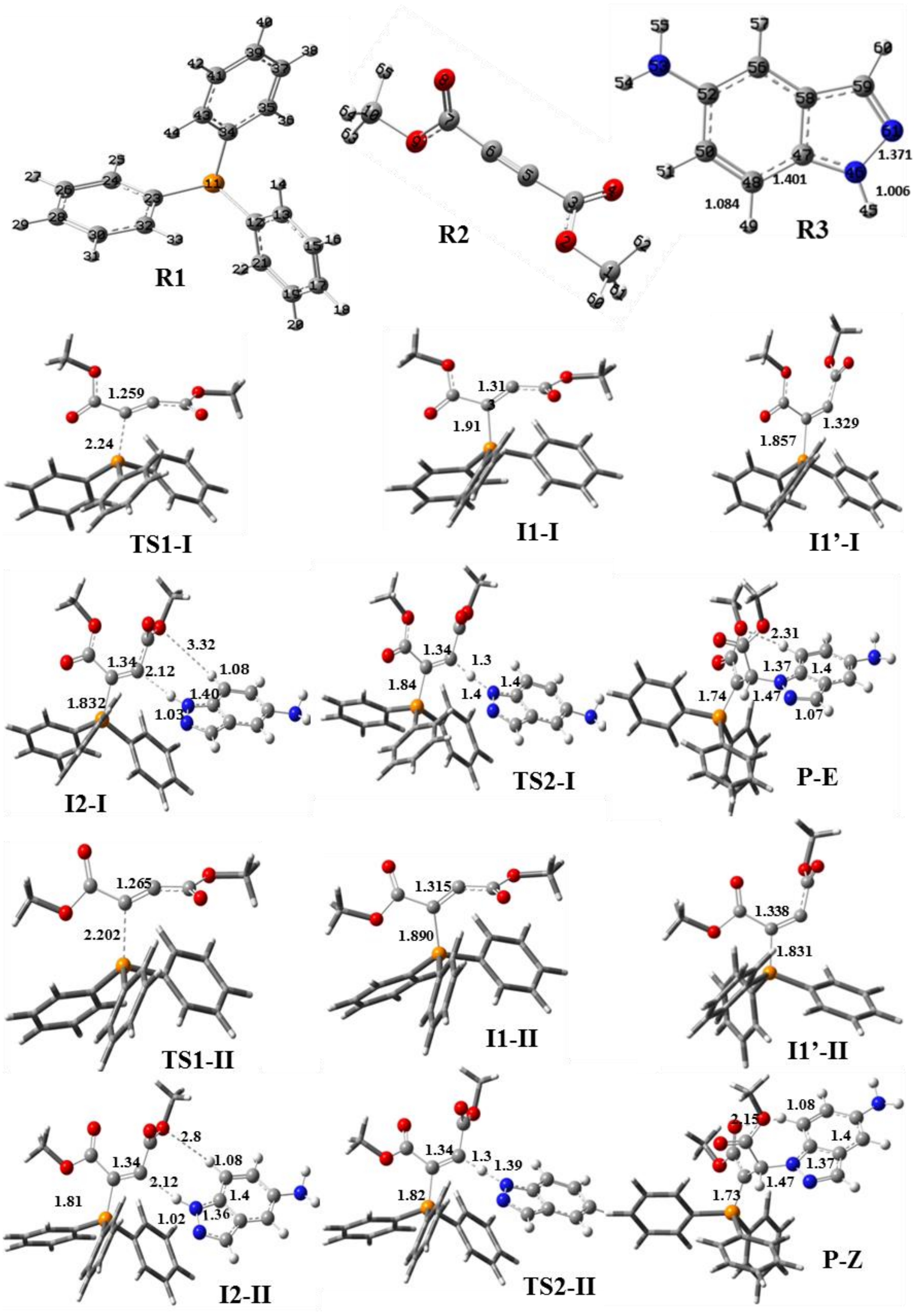

Figure 3. Optimized geometries of all structures (including reactants, transition states, intermediates and products) along the reaction paths **I** and **II**

Also, if we assume that each products convert into each other, then the **P-*Z*** should be the major isomer which is contrary with the experimental. So, from the theoretical results, the majority of product **P-*E*** is because of the kinetic priority of the path **I** compared with path **II**. Additionally, it is plausible that **I1-II** convert to **I1-I**, as a more stable isomer, with passing from 14.31kJ/mol barrier height to produce **P-*E*** as a major product (Figure 4). Moreover, the value of energy released from the formation of the products is the amount of which can easily supply the barrier height of the products interconversion. Anyway, besides the specific point in which both isomers can interconvert, it is clear that the observed ***Z*/*E*** ratio is thermodynamically controlled. However, the kinetic stability determines the preferred path for proceeding of the reaction, but the ratio of ***Z*/*E*** will control thermodynamically.

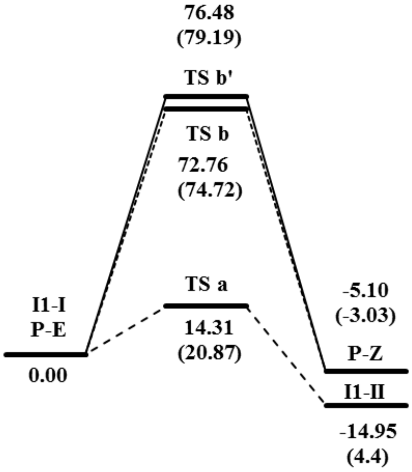

Figure 4. Potential energy diagram (kJ.mol^{-1}) (including zero point energy) for conversion pathways (**P-*E*→P-*Z*** and **I1-I→I1-II**)

Energetics in solution

In order to check the effect of solvent on the potential energy surfaces, Condensed phase calculations for dichloromethane (ε=9.00) were carried out with the polarizable continuum model (PCM). From the results in Figure 2, energy barriers of the first and third steps in the path **I** was decreased by 18.14 and 8.39 kJ/mol respectively compared with the gas phase. Also the energy barrier of the first and third steps In the path **II**, decreased by 32.3 and 4.96 kJ/mol respectively compared with the gas phase. the energy barrier of the first step is considerably more than that of the third step in paths **I** and **II**, thus, the first step of the reaction is also the rate determining step. The energy barrier of **P-*E*** to **P-*Z*** conversion increased to 79.19 and 74.72 kJ/mol (Figure 4). Also, the barrier height of the conversion of **I1-I** To **I1-II** increased to 20.87 kJ/mol compared with the gas phase. In addition to the kinetically preference of the path **E** to produce **P-*E***, conversion of **P-*E*** to **P-*Z*** needs a relatively high energy barrier.

Reaction Rate

According to the conventional transition state theory (CTST), the values of the rate constant *k*(T) for elementary bimolecular reactions in the gas phase is expressed by [22]:

$$k = \kappa\sigma \frac{k_B T}{h} \frac{Q_{TS}}{Q_R} \exp[{}^{-(E_{TS}-E_R)}\!/_{RT}]$$

Where the Q_{TS} and Q_R are the partition functions of the transition states and the reactants ($Q_{TS}= 1.59\times10^{28}$, $Q_{R1}= 1.06\times10^{21}$ and $Q_{R2}= 4.56\times10^{17}$), k_B is the Boltzmann constant ($=1.38067\times10^{-23}$), κ is the transmission coefficient (=1), and $\boldsymbol{\sigma}$ is the symmetry factor (=1). The E_{TS} and E_R are energies of the transition state and the reactants with zero point energy correction involved (E_{TS}-$E_{R)}$ =51.84kJ.mol^{-1}). The tunneling corrections were expressed as the ratio of the quantum–mechanical to classical barrier crossing rate, assuming an unsymmetrical, one-dimensional Eckart function barrier [22]. The rate constant of the first step of the reaction as overall rate constant of the reaction at 298.15 K in gas phase is 2.8×10^{-28} cm^3.molecule^{-1}.s^{-1}. By repeating the calculations in dichloromethane (as a solvent with a higher dielectric constant), the reaction rate increased to 2.11×10^{-25} by reducing the activation energy.

Conclusion

Mechanistic investigation of the reaction between triphenylphosphine **1**, dialkyl acetylenedicarboxylates **2**, in the presence of NH-acid, such as 5-aminoindazole **3** was undertaken theoretically. The results can be summarized as follows: (**1**) With respect to the theoretical data, the first step of the proposed mechanism (k_1) was recognized as rate-determining step. (**2**) Theoretical results could explain how the product, **P-*E***, can exist in solution as a major isomer. (**3**) Despite the determination of the kinetic preferred route of the reaction, the observed ***Z*/*E*** ratio is thermodynamically controlled.

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