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Quantum mechanical calculation for determination of more stable isomer of phosphorous ylide involving an indole

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Abstract: Stable crystalline phosphorus ylides were obtained in excellent yields from the 1:1:1 addition reactions between triphenylphosphine and dialkyl acetylenedicarboxylates, in the presence of NH-acid, such as indole. These stable ylides exist in solution as a mixture of two geometrical isomers as a result of restricted rotation around the carbon-carbon partial double bond resulting from conjugation of the ylide moiety with the adjacent carbonyl group. In the recent work, the stability of the *Z*- and the *E*- isomers were undertaken for the two rotamers of phosphorus ylides involving an indole [namely dimethyl 2-(indole-1-yl)-3-(triphenyl- phosphanylidene)- butanedioate(**4a**)] by means of atoms in molecules AIM, CHelpG and NBORead methods.

Keywords: Stable phosphorus ylides; Dialkyl acetylenedicarboxylates; *Z* and *E* rotamer; AIM method.

Introduction

Phosphorus ylides are important reagents in synthetic organic chemistry, especially in the synthesis of naturally occurring compounds with biological and pharmacological activity [1]. The synthesis of phosphorus ylides is an important reaction in organic chemistry because of the application of these compounds in the synthesis of organic products [2-36]. Phosphorus ylides most often are prepared by treatment of a phosphonium salt with a base. Most of the phosphonium salts are usually made from the reaction of phosphine and an alkyl halide [4-8], though they can be obtained by Michael addition of phosphorus nucleophiles to activated olefins [3,4]. A facile synthesis for the reaction between triphenylphosphine **1**, dialkyl acetylendicarboxylates **2** and indole **3** (as a NH-acid) has been earlier reported [26]. The reaction is shown in Fig 1. The *Z* and *E* isomers were optimized for all ylide structures at HF/6-31G(d,p) level of theory by Gaussian 98 package program. The energy of both geometrical isomers have been calculated at B3LYP/6-311++G** level. Atoms in molecules AIM, CHelpG and NBORead methods at HF/6-31G(d,p) level of theory have been performed in order to gain a better understanding of most geometrical parameters of both the *E*-**4(a, c)** and the *Z*-**4(a, c)** of phosphorus ylides. The numbers of critical points and intramolecular hydrogen bonds as well as the charge of atoms that constructed on the *Z* and *E* isomers have been recognized. The results altogether reveal the effective factors on stability of *Z* and *E* ylide isomers.

Results and Discussion

Theoretical study

Recently, different reports have been published on the synthesis of stable phosphorus ylides from the reaction between triphenylphosphine and reactive acetylenic esters in the presence of N-H, C-H or S-H heterocyclic compounds. These ylides usually exist as a mixture of two geometrical isomers, although some ylides exhibit one geometrical isomer. It is important to remember that in medicinal chemistry sometimes only one of the two geometrical isomers shows biological and pharmacological activity. For this reason quantum mechanical calculations have been performed in order to gain a better understanding of most important geometrical parameters and also relative energies of both geometrical isomers in the case of ylides which have two geometrical isomers or have only one geometrical isomer.

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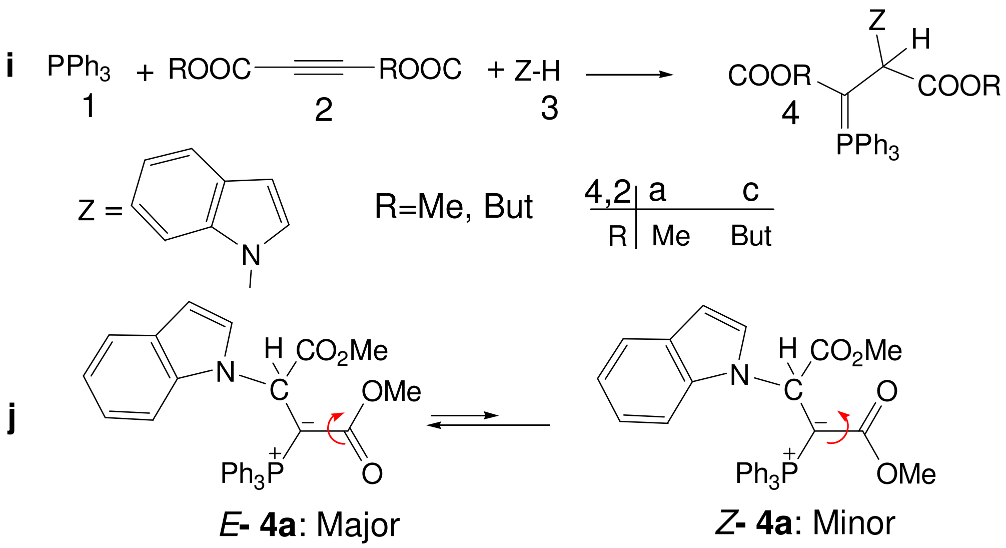
Fig. 1. (i) The reaction between triphenylphosphine **1,** dialkyl acetylenedicarboxylate **2** (**2a** or **2c)** and indole **3** for generation of stable phosphorus ylides **4** (**4a** or **4c**), **(j)** Two isomers (*Z)*-**4a** and (*E*)-**4a** (major and minor) of ylide **4a**.



Calculations

Structure and stabilities

In order to determine more stable form of both geometrical isomers [*Z*-**4(a, c)** or *E*-**4(a, c)**] of ylides **(4a** or **4c)**, first their structures were optimized at HF/6-31G(d,p) level of theory [37] by Gaussian 98 program package [38]. Also relative energy of the two rotamers has been calculated at HF/6-31G(d,p) and B3LYP/6-311++G(d,p) levels (See Figs 2 and 3). The relative stabilization energies for both [*Z*-**4(a, c)** and *E*-**4(a, c)**] isomers are reported in Table 1, as can be seen, *E*-**4a** and *Z*-**4c** isomers are more stable than *Z*-**4a** and *E*-**4c** forms (0.52 and 1.04 kcal/mol, respectively) at B3LYP level.

Table 1: The relative energy (kcal/mol) for both *Z*- and the *E*- isomers of ylides **4a** and **4c**, obtained at HF/6-31G(d,P) and B3LYP/6-311++G(d,p) levels**.**

Conformer	HF	B3LYP
Z-**4a**	0.58	0.52
E-**4a**	0.00	0.00
Z-**4c**	0.00	0.00
E-**4c**	1.95	1.04

Fig. 2. Intramolecular hydrogen bonds (dotted lines) in the two *E*-**4a** and *Z*-**4a** geometrical isomers of stable ylide **4a**.

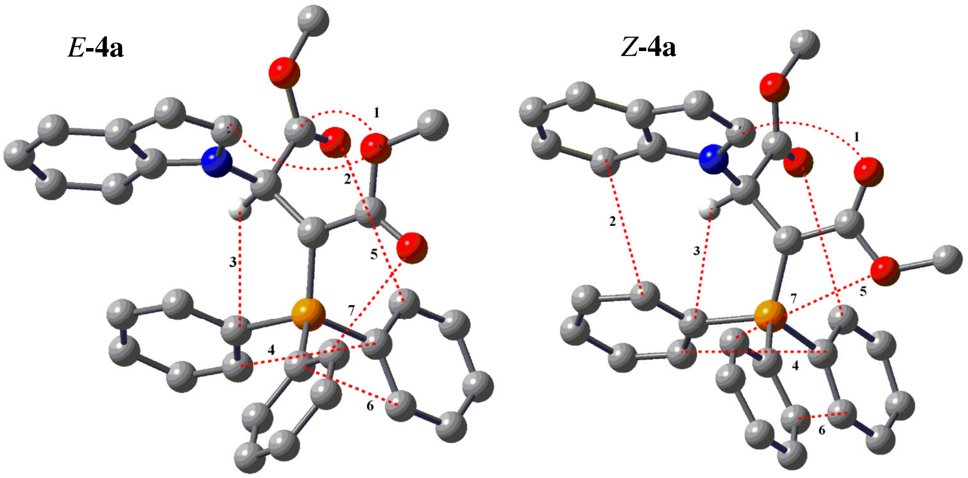
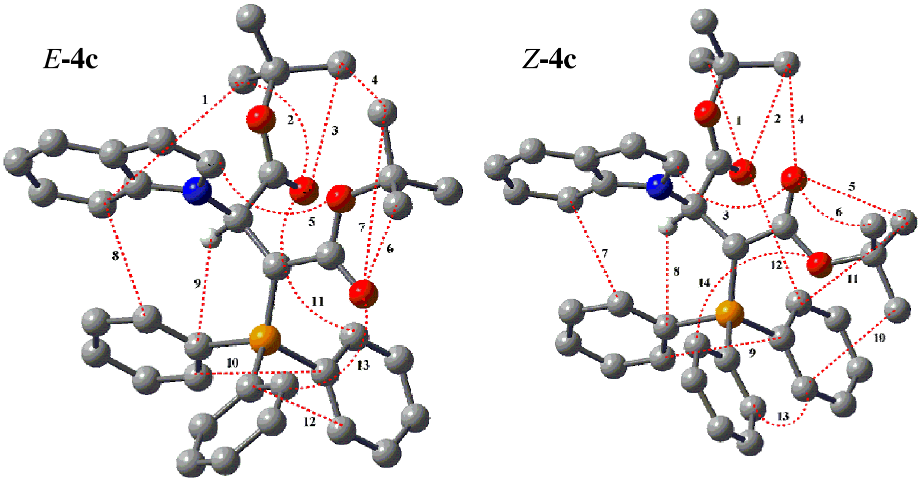


Fig. 3. Intramolecular hydrogen bonds (dotted lines) in the two *E*-**4c** and *Z*-**4c** geometrical isomers of stable ylide **4c**.



Further investigation was undertaken in order to determine more effective factors on stability of both isomers, on the basis of AIM calculations [39] at HF/6-31G(d,p) level of theory by the AIM2000 program package [40]. In recent years, AIM theory has often applied in the analysis of H-bonds. In this theory, the topological properties of the electron density distribution are derived from the gradient vector field of the electron density $\nabla\rho(r)$ and on the Laplacian of the electron density $\nabla^2\rho(r)$. The Laplacian of the electron density, $\nabla^2\rho(r)$, identifies regions of space wherein the electronic charge is locally depleted [$\nabla^2\rho(r) > 0$] or built up [$\nabla^2\rho(r) < 0$] [39]. Two interacting atoms in a molecule form a critical point in the electron density, where $\nabla\rho\ (r) = 0$, called the bond critical point (BCP). The values of the charge density and its Laplacian at these critical points give useful information regarding the strength of the H-bonds [40]. The ranges of $\rho(r)$ and $\nabla^2\rho(r)$ are 0.002 – 0.035 e/a_0^3 and 0.024 – 0.139 e/a_0^5, respectively, if H-bonds exist [41]. The AIM calculation indicates intramolecular hydrogen bond critical points (H-BCP) for the two *Z*-**4**(**a**, **c**) and *E*-**4**(**a**, **c**) isomers. Intramolecular H-BCPs are shown in Figs 2 and 3 (dotted line) .The electron densities $(\rho)\times10^3$, Laplacian of electron density $\nabla^2\rho(r)\times10^3$, and energy density $-H(r)\times10^4$ are also reported in (Tables 2 and 3). A negative total energy density at the BCP reflects a dominance of potential energy density, which is the consequence of accumulated stabilizing electronic charge [42]. Herein, the number of hydrogen bonds in both categories (*E*-**4a** and *Z*-**4a**) and (*E*-**4c** and *Z*-**4c**) are (7 and 7) and also (13 and 14), respectively. The values of ρ and $\nabla^2\rho\times10^3$ for those are in the ranges (0.006 – 0.014 and 0.002 – 0.011 e/a_0^3), (0.002 – 0.014 and 0.001 – 0.013 e/a_0^3), (26.35– 59.80 and 8.64 – 43.36 e/a_0^5), (7.64 – 55.49 and 6.22 – 49.68 e/a_0^5), respectively. In addition, the Hamiltonian [-H(r) $\times10^4$] are in the ranges (4.77 – 18.47 and 3.96 – 17.54 au) and (3.70 – 18.02 and 3.77 – 17.53 au), respectively (See Tables 2 and 3). These HBs show $\nabla^2\rho(r) > 0$ and $H(r) < 0$, which according to classification of Rozas et al. [43] are medium-strength hydrogen bonds. In both ylides dipole moment for the two *E*-**4a** and *E*-**4c** isomers (4.21 and 3.98 D) are smaller than the two *Z*-**4a** and *Z*-**4c** isomers (7.64 and 7.46 D, respectively) and the value of $-H_{tot}$ (=∑-H(r) $\times10^4$) for the two *Z*-**4a** and *E*-**4c** isomers (82.62 and 143.77 au) are smaller than the two *E*-**4a** *and* *Z*-**4c** isomers (92.74 and 149.14 au, respectively). The dipole moment in *E*-**4a** (4.21 D) is less than *Z*-**4a** (7.64 D) and also the value of $-H_{tot}$ in *E*-**4a** (92.74 au) is larger than in *Z*-**4a** (82.62 au) as two important fact on stability of *E*-**4a**. It seems that, stability of *E*-**4a** has been emerged from a result of the two factors, taken altogether, during those are just influenced the *E*-**4a**, as a result, this cause a slight relative stability in *E*-**4a** (0.52 kcal/mol in comparison with the *Z*-**4a** isomers) in which this is in good agreement with the experimental results [37] based upon the ^{1}H, ^{13}C, ^{31}P NMR data with slightly more experimental abundance percentage of (52%) for *E*-**4a**. Although, dipole moment in *E*-**4c** (3.98 D) is less than *Z*-**4c** (7.46 D) and appear as a effective factor an stability of *E*-**4c,** but the value of $-H_{tot}$ in *Z*-**4c** (149.14 au) is larger than in *E*-**4c** (143.77 au) and also the number of hydrogen bounds in *Z*-**4c** (14) is more than in *E*-**4c** (13), these emphasize as two important fact on stability of *Z*-**4c.** It seems that effect of later parameters ($-H_{tot}$ and H-BCP) should be overcome on effect of former parameter (dipole moment), for this reason *Z*-**4c** is more stable isomer in the category of *Z*-**4c** and *E*-**4c.** Moreover, the total number of hydrogen bonds in the two *Z*-**4c** and *E*-**4c** (14, 13) are more than two the *Z*-**4a** and *E*-**4a** (7, 7), this leads to a large rigidity in these geometrical isomers in comparison with the two *Z*-**4a** and *E*-**4a** forms. The rigidity of the two molecular structures by the very large intramolecular hydrogen bond critical points accompanied by more steric factor of the bulky tert-buthyl groups (compare with dimethy groups in both the *E*-**4a** and *Z*-**4a**, Figs 2 and 3) within the structures (*E*-**4c** and *Z*-**4c** forms) make a good opportunity for enhancement of energy barrier and also explanation of abundance percentage of the these two isomers. Hence, interconversion process between the two *E*-**4c** and *Z*-**4c** isomers needs to pass through a very high restricted barrier energy (See Fig 4, A), particular in solution media, for this reason it is possible to see only a single isomer as a lone isomer of **4c** (*Z*-**4c**). On the contrary, interconversion process for both the *E*-**4a** and *Z*-**4a** geometrical isomers pass through a considerably low energy barrier (See Fig 4, B), this leads to a plausible observation of the two *E*-**4a** and *Z*-**4a** (See Fig 1, j).

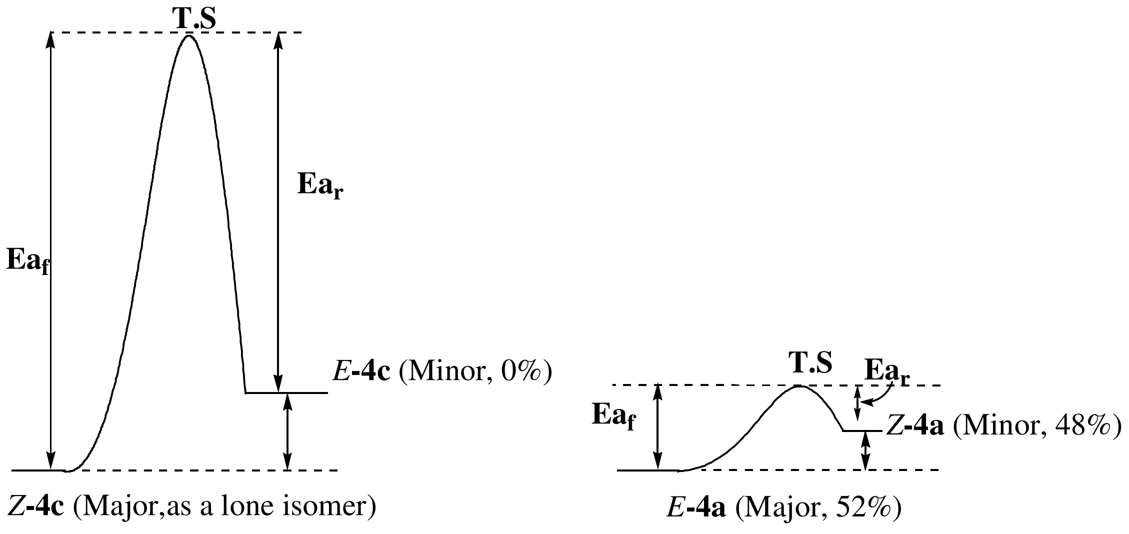
Table 2: The values of $\rho(r)\times10^3$, $\nabla^2\rho\times10^3$ and $-H(r)\times10^4$ for both the *Z*-**4a** and *E*-**4a** isomers of ylide **4a** calculated at the hydrogen bond critical points. All quantities are in atomic units.

E	$\rho\times10^3$	$\nabla^2\rho\times10^3$	$-H(r)\times10^4$	*Z*	$\rho\times10^3$	$\nabla^2\rho\times10^3$	$-H(r)\times10^4$
1	13.58	59.80	17.14	1	9.35	35.87	10.56
2	6.92	29.22	11.80	2	2.92	8.64	3.96
3	12.26	44.34	17.20	3	11.84	43.36	17.41
4	9.91	38.35	18.47	4	9.60	36.38	17.54
5	7.11	26.35	7.70	5	8.07	29.01	6.73
6	8.86	32.22	15.66	6	9.15	31.49	14.28
7	14.71	51.34	4.77	7	9.32	37.41	12.16

Table 3: The values of $\rho(r) \times 10^3$, $\nabla^2\rho \times 10^3$ and $-H(r) \times 10^4$ for both the *Z*-**4b** and *E*-**4b** isomers of ylide **4b** calculated at the hydrogen bond critical points. All quantities are in atomic units.

E	$\rho \times 10^3$	$\nabla^2\rho \times 10^3$	$-H(r)\times 10^4$	*Z*	$\rho \times 10^3$	$\nabla^2\rho \times 10^3$	$-H(r)\times 10^4$
1	2.67	8.48	4.81	1	11.41	44.06	12.49
2	10.53	41.61	13.45	2	11.61	45.32	13.30
3	12.82	48.93	12.37	3	9.64	36.90	10.54
4	5.96	21.77	11.36	4	3.42	15.07	8.21
5	9.82	38.04	10.42	5	12.61	48.19	12.45
6	14.54	55.49	12.85	6	13.10	49.68	11.95
7	11.74	45.12	12.17	7	2.81	8.36	3.87
8	2.45	7.64	3.70	8	12.15	44.26	17.35
9	12.90	45.63	16.23	9	9.69	36.57	17.53
10	9.84	37.58	18.02	10	2.69	8.63	4.78
11	9.26	32.29	5.41	11	1.93	6.22	3.77
12	8.97	31.58	15.13	12	8.55	30.24	6.13
13	13.40	48.72	7.84	13	9.19	31.82	14.26
				14	9.10	36.88	12.51

Fig. 4. Interchargeable process of geometrical isomers for ylides **4a** and **4c**. **A)** A very high restricted barrier energy for interconversion process between the two *E*-**4c** and *Z*-**4c** isomers. **B)** A Low restricted barrier energy for interconversion process between the two *E*-**4a** and *Z*-**4a** isomers.



(A) **(B)**

Also, the charge on different atoms which are calculated by AIM, CHelpG and NBORead methods at HF/6-31G(d,p) level are reported in Table 4 for the two *Z*- and *E*- isomers of ylides **4a** and **4c**. There is good agreement between the results in three methods.

Table 4: The charges on different atoms for the two *Z* and *E* isomers in both ylides **4a** and **4c** calculated by AIM, NBO and CHelpG methods, respectively at HF/6-31G(d,p) theoretical level.

number of atom	*Z*-**4a**	*E*-**4a**	*Z*-**4c**	*E*-**4c**
	1.85[a]	1.84	1.86	1.86
C_1	0.95[b]	0.95	0.96	0.96
	0.95[c]	0.91	0.95	0.95
	-7.53×10^{-1}	-7.84×10^{-1}	-7.55×10^{-1}	-7.42×10^{-1}
C_2	-0.89	-0.88	-0.89	-0.87
	-0.76	-0.74	-0.83	-0.82
	7.77×10^{-1}	7.51×10^{-1}	7.92×10^{-1}	7.94×10^{-1}
C_3	-0.08	-0.09	-0.08	-0.09
	0.47	0.49	0.70	0.70
	3.24	3.23	3.25	3.23
$P_{11}(P_8)$[d]	1.87	1.88	1.87	1.88
	0.27	0.24	0.33	0.25
	-1.39	-1.41	-1.40	-1.42
$O_{45}(O_{42})$	-0.77	-0.80	-0.79	-0.81
	-0.65	-0.71	-0.65	-0.70
	-1.29	-1.28	-1.30	-1.28
$O_{46}(O_{43})$	-0.66	-0.65	-0.69	-0.67
	-0.45	-0.35	-0.58	-0.62

[a] Calculated by AIM method.
[b] Calculated by NBORead method.
[c] Calculated by CHelpG method.
[d] The numbers for **4c** structures are in parentheses.

Conclusion

The assignment of the *Z* and *E* isomers as a major or minor form in both ylides **4a** and **4c** were undertaken by AIM method. Quantum mechanical calculation was clarified how ylides **4a** and **4c** exist in solution as a mixture of two geometrical isomers.

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