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Theoretical Calculations on the Wittig Reaction Revisited

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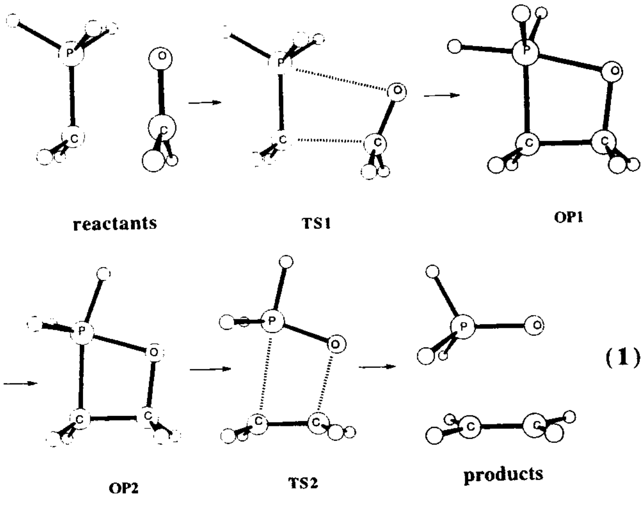
Abstract: A series of Wittig reactions was calculated at the HF/3-21G* and B3LYP/6-31G* levels to understand the origin of the different product selectivities for different classes of ylides. Both alkylidenetriphenylphosphorane (nonstabilized ylide) and benzylidenetriphenylphosphorane (semistabilized ylide) yielded two types of transition states (TS) with a nearly planar and a puckered structure. The planar TS gave trans oxaphosphetane (OP), whereas the puckered TS led to cis OP. In contrast to previous semiempirical calculations, the present calculations showed that while a planar trans TS is more stable than a puckered cis TS for the semistabilized ylide, a puckered cis TS is more stable for the reaction of the nonstabilized ylide with benzaldehyde. These calculated selectivities agree with experiment. The carbonyl carbon kinetic isotope effects (KIEs) were computed at HF/3-21G* for the reactions of benzaldehyde with butylidenetriphenylphosphorane and with benzylidenetriphenylphosphorane. The reaction of the semistabilized ylide gave ^{13}C KIE of 1.051 at 0 °C, which is in qualitative agreement with the experimental KIE. In contrast, ^{13}C KIE for the reaction of the nonstabilized ylide with benzaldehyde was calculated to be 1.039, disagreeing with the experimental isotope effect of unity. This implies that although the product selectivity is reproduced by a pair of the planar trans TS and the puckered cis TS, the latter may not be the true rate-determining TS for the cis-OP formation process for the nonstabilized ylide reaction.

Introduction

The Wittig reaction is one of the most important classes of reactions because of its versatile utility in synthetic applications, and extensive experimental efforts have been devoted to elucidate the reaction mechanism. These studies have revealed that the reaction characteristics depend on a variety of factors such as the structures of a ylide and a carbonyl compound, solvent, additives, and the base used to generate a ylide.[1,2] In an often assumed scheme, a ylide and an aldehyde form an oxaphosphetane (OP) intermediate, which after pseudorotation gives phosphine and alkene products (eq 1).



(1)

In discussing the reaction mechanism, it is informative to compare the reactions of a nonstabilized ylide (alkylidene ylide) and a semistabilized ylide (benzylidene ylide). In both reactions with benzaldehyde the OP intermediates were detected by NMR at low temperatures.[3,4] However, the stability of OP is quite different; the OP intermediate formed in the reaction of a nonstabilized ylide is stable at −78 °C and affords products only at −20 °C or higher whereas the OP in the reaction of a semistabilized ylide easily escapes detection and can only be detected by the use of a specially designed semistabilized ylide.[4] Another point to be noted is that the reaction of a nonstabilized ylide under Li-salt free conditions gives exclusively cis alkene whereas the reaction of a semistabilized ylide gives a mixture of trans/cis alkenes.[1b,2,5−7]

The current mechanistic interest is focused on the origin of the stereochemical variation (the trans/cis selectivity) of OP and hence the product alkenes. Several models have been proposed to rationalize the intriguing high cis selectivity of a nonstabilized ylide by several authors, which include Schlosser, Bestmann, McEwen, Vedejs, and us.[8−12] According to Vedejs' model,[11] the reaction of a stabilized ylide proceeds through a late planar

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(1) Among recent reviews of the Wittig reaction, see: (a) Johnson, A. W. *Ylides and Imines of Phosphorus*; Wiley: New York, 1993. (b) Maryanoff, B.; Reitz, A. E. *Chem. Rev.* **1989**, *89*, 863.

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four-centered transition state (TS) that favors trans OP whereas the reaction of a nonstabilized ylide goes through an early puckered TS due to a steric effect of bulky substituents (Ph or alkyl) on the ylide phosphorus, and the reaction favors cis OP. It was claimed later, however, that although the reaction of a semistablized ylide goes through a polar cyclic TS as in the previous models, the reaction of a nonstabilized ylide that has a strong nucleophilic addition character proceeds via a single electron-transfer step.[12] The cis selectivity for the latter reaction is realized through a puckered TS for the cyclization step of the radical-ion pair that is formed by the initial electron transfer. The product-determining step (cyclization) and the rate-determining step (electron transfer) are different in this scheme. This model is primarily based on the fact that the OP formation step of nonstabilized ylides shows a very small carbonyl carbon kinetic isotope effect (KIE) as in the reactions of RLi[13] whereas the KIE is significantly larger for a semistabilized ylide.

Extensive MO calculations have been carried out on the nature of the Wittig reagents[14] and the Wittig reactions.[10,15−17] Both semiempirical (MNDO and PM3)[10,15] and ab initio (HF/4-31G)[16,17] calculations of the simplest model system, eq 2,

$$H_3P{=}CH_2 + H_2C{=}O \qquad (2)$$

indicated that the TS for the OP formation step has a planar geometry with the C−C bond formation advanced over the P−O bond formation. The same structural feature was also obtained at a higher level of calculations (MP2/ZD+d).[17] Although there is no trans/cis geometrical isomer in the simplest model system, the planar TS geometry appeared to disagree with the puckered TS model[11] proposed by Vedejs for the reaction of nonstabilized ylides. However, the argument of the Wittig mechanism based on such a simple model system as eq 2 may not be conclusive because the presence of three phenyl groups on the ylide phosphorus can play an important role in determining the conformation of the TS and the product stereochemistry.[11] More convincing argument was considered to be made possible on the basis of the results of more realistic reaction systems. The semiempirical MNDO[15c] and PM3[10] calculations were then carried out for $Ph_3P{=}CHMe + MeCHO$ (eq 7), which indicated that (1) the cis TS was higher in energy than the trans TS and (2) the TS structures were not very much puckered as suggested by Vedejs but nearly planar.

The most important reaction systems in discussing the Wittig reaction mechanism are those shown in eqs 9 and 10 because for these reactions a variety of mechanistic investigations were carried out, including trans/cis selectivities, crossover experiments, ^{31}P NMR, stereochemical drift, substituent effects, and kinetic isotope effects.[3b,d,7,18] We now report the results of a higher level of calculations for a series of OP formation reactions (eqs 3−11) with the ab initio MO (HF/3-21G*) method and the density functional (B3LYP/6-31G*) theory.

$$H_3P{=}CHMe + MeCHO \qquad (3)$$

$$H_3P{=}CHMe + PhCHO \qquad (4)$$

$$H_3P{=}CHPr + PhCHO \qquad (5)$$

$$H_3P{=}CHPh + PhCHO \qquad (6)$$

$$Ph_3P{=}CHMe + MeCHO \qquad (7)$$

$$Ph_3P{=}CHMe + PhCHO \qquad (8)$$

$$Ph_3P{=}CHPr + PhCHO \qquad (9)$$

$$Ph_3P{=}CHPh + PhCHO \qquad (10)$$

$$Ph_3P{=}CH_2 + PhCHO \qquad (11)$$

Computational Methods

Geometries were fully optimized at the Hartree−Fock (HF) level with the 3-21G* basis set[19] and verified to be either minima or transition states from their Hessian matrices for all reactions: minima for all positive eigenvalues and transition states for only one negative eigenvalue. The vibrational frequencies were also used to calculate the enthalpy of activation. To incorporate the effect of electron correlation, geometry optimization and energy calculations were carried out with nonlocal hybrid density functional theory (DFT)[20] at the B3LYP level[21] with a larger split-valence d-polarized 6-31G* basis set.[22] For reaction 3, geometry optimization and frequency analysis were carried out at the HF/3-21G, HF/3-21G*, HF/6-31G*, MP2/3-21G*, B3LYP/3-21G*, and B3LYP/6-31G* levels. Frequency calculations were, however, quite expensive and practically impossible for the TS structures located at the B3LYP/6-31G* level for eqs 4−11 (∼500 contracted basis sets with no symmetry). As is apparent from the structural similarities between HF/3-21G* and B3LYP/6-31G* the reported B3LYP structures are expected to be true TSs, which were located by using the corresponding HF/3-21G* TS structures and their Hessian matrices. All calculations were performed with the Gaussian 94 program,[23] and the optimized geometries, energies, and imaginary frequencies are given in Supporting Information. Kinetic isotope effects were calculated by using the scaled (0.89) vibrational frequencies at the HF/3-21G* level from eq 12.[24] Here, $\nu^{\ddagger}$ represents the reaction-

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Table 1. Bond Lengths and Dihedral Angles of the TS and Relative Barrier Heights for the OP-Formation Process of the Model Reaction Systems[a]

method		R_{C-C}	R_{P-O}	ϕ	$\Delta E^{\ddagger\,b}$	$\delta\Delta E^{\ddagger\,c}$	$\Delta H^{\ddagger\,b}$	$\delta\Delta H^{\ddagger\,d}$
			$H_3P{=}CHMe + MeCHO$ (eq 3)					
HF/3-21G	trans	2.262	2.783	6.7	−2.9	−0.5	−1.6	−0.5
	cis	2.251	2.742	7.0	−2.4		−1.1	
HF/3-21G*	trans	2.149	2.638	6.4	5.3	−1.0	6.5	−1.0
	cis	2.175	2.589	0.8	6.3		7.5	
HF/6-31G*	trans	2.094	2.687	13.0	9.7	−0.9	10.9	−0.9
	cis	2.092	2.661	20.3	10.6		11.8	
B3LYP/3-21G*	trans	2.253	2.882	46.5	−4.4	−0.8	−3.4	−0.4
	cis	2.284	2.846	35.0	−3.6		−3.0	
MP2/3-21G*	trans	2.157	2.858	45.0	−2.0	−1.4	−1.2	−1.2
	cis	2.181	2.824	34.7	−0.6		0.0	
B3LYP/6-31G*	trans	2.124	2.862	39.0	1.4	−0.1	2.4	0.0
	cis	2.118	2.850	37.5	1.5		2.4	
			$H_3P{=}CHMe + PhCHO$ (eq 4)					
HF/3-21G*	trans	2.160	2.660	7.8	5.7	−0.5	6.6	−0.5
	cis	2.182	2.613	3.5	6.2		7.1	
B3LYP/6-31G*	trans	2.088	2.868	43.5	1.9	−0.4		
	cis	2.094	2.824	39.2	2.3			
			$H_3P{=}CHPr + PhCHO$ (eq 5)					
HF/3-21G*	trans	2.154	2.651	9.7	6.1	−0.6	6.9	−0.7
	cis	2.171	2.598	4.8	6.7		7.6	
B3LYP/6-31G*	trans	2.089	2.847	40.6	2.7	0.0		
	cis	2.100	2.810	36.2	2.7			
			$H_3P{=}CHPh + PhCHO$ (eq 6)					
HF/3-21G*	trans	2.116	2.540	13.5	7.4	−0.7	8.5	−0.8
	cis	2.155	2.504	30.4	8.1		9.3	
B3LYP/6-31G*	trans	2.168	2.468	38.5	6.5	−0.4		
	cis	2.134	2.479	34.8	6.9			

[a] Bond lengths, dihedral angles, and barrier heights are shown in Å, deg, and kcal/mol, respectively. ϕ denotes the dihedral angle at the C−C bond (in P−C−C−O) as shown in Chart 1. [b] These values can be negative because van der Waals complexes exist prior to the TSs. See text. [c] Energy difference between the trans/cis TSs ($\Delta E^{\ddagger}_{trans} - \Delta E^{\ddagger}_{cis}$). [d] Enthalpy difference between the trans/cis TSs ($\Delta H^{\ddagger}_{trans} - \Delta H^{\ddagger}_{cis}$).

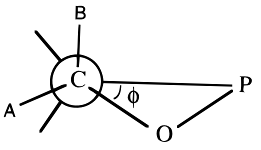
coordinate frequency and u denotes $h\nu/kT$, in which h and k are the Planck constant and the Bolzmann constant, respectively.

$$\frac{k_1}{k_2} = \left[\frac{\nu^{\neq}_{L1}}{\nu^{\neq}_{L2}}\right] \frac{\prod^{3n-6}\frac{u_{2i}}{u_{1i}}\prod^{3n-6}\left(\frac{1-e^{-u_{1i}}}{1-e^{-u_{2i}}}\right)\exp[\sum^{3n-6}(u_{1i}-u_{2i})/2]}{\prod^{3n-7}\frac{u^{\neq}_{2i}}{u^{\neq}_{1i}}\prod^{3n-7}\left(\frac{1-e^{-u^{\neq}_{1i}}}{1-e^{-u^{\neq}_{2i}}}\right)\exp[\sum^{3n-7}(u^{\neq}_{1i}-u^{\neq}_{2i})/2]} \quad (12)$$

Results and Discussion

Reactions of Ylides That Bear H on the Phosphorus. Reaction 3 is the simplest system in which both trans and cis TSs are possible. Both TSs were determined at the HF/3-21G, HF/3-21G*, HF/6-31G*, MP2/3-21G*, B3LYP/3-21G*, and B3LYP/6-31G* levels and the results are listed in Table 1. The calculated barrier height is negative in some cases, which is due to the presence of a loosely bound complex between ylide and aldehyde. Such an initial complex was reported previously.[17,25] The cis TS is less stable than the trans TS regardless of the calculation methods, but the energy difference becomes smaller at the B3LYP/6-31G* level. The TSs have nearly planar geometries (small P−C−C−O dihedral angle, ϕ, Chart 1) at the HF level. However, the inclusion of electron correlation makes the TSs more puckered. Electron correlation also makes the P−O bond longer in both trans and cis TSs. It should be noted that MP2 and B3LYP give similar results. It has long been believed that the presence of three phenyl groups on the ylide phosphorus has a critical influence on the geometry of a cis TS. However, even the reactions of the ylides without substituents on P give puckered TSs at B3LYP/6-31G*.

Chart 1



Reactions of Ylides That Bear Ph on the Phosphorus. The results for the reactions of ylides which bear three phenyl groups on the phosphorus are summarized in Table 2. It is apparent from the comparison of two reactions, eqs 3 and 7, that the presence of the phenyl groups on the ylide phosphorus makes the P−O bond longer, the cis TS more puckered, and the trans TS less puckered. It should be noticeable that although the trans TS is more stable than the cis TS at HF/3-21G* the cis TS is more stable than the trans TS at the B3LYP/6-31G* level. The reaction of the same nonstabilized ylide with benzaldehyde (eq

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(25) The electronic energy and the free energy of the initial complex are −6.6 and 3.8 kcal/mol at HF/3-21G, −4.8 and 4.8 kcal/mol at HF/3-21G*, and −3.3 and 5.8 kcal/mol at B3LYP/6-31G*, respectively, for the cis OP forming process of eq 3; the complex is more stable than the reactant state in terms of electronic energy, but it is less stable in terms of free energy and it most likely does not exist as a bound species. The free energy of activation is positive (20.4 kcal/mol at HF/3-21G* and 16.7 kcal/mol at B3LYP/6-31G*). The relative stabilities of the trans/cis TSs are almost the same for electronic energy, enthalpy, and free energy, and we use the $\Delta E^{\ddagger}$ values in this paper.

Table 2. Bond Lengths and Dihedral Angles of the TS and Relative Barrier Heights for the OP-Formation Process of the Real Reaction Systems[a]

method		R_{C-C}	R_{P-O}	ϕ	$\Delta E^{\ddagger}$	$\delta\Delta E^{\ddagger\,b}$	$\Delta H^{\ddagger}$	$\delta\Delta H^{\ddagger\,c}$
			$Ph_3P{=}CHMe + MeCHO$ (eq 7)					
HF/3-21G*	trans	2.139	3.488	21.4	4.1	−1.4	6.1	−1.1
	cis	1.930	3.714	97.4	5.5		7.2	
B3LYP/6-31G*	trans	2.047	3.147	23.2	3.3	1.0		
	cis	2.076	3.696	90.0	2.3			
			$Ph_3P{=}CHMe + PhCHO$ (eq 8)					
HF/3-21G*	trans	2.132	3.213	10.5	7.3	1.7	8.5	1.5
	cis	2.104	3.692	87.3	5.6		7.0	
B3LYP/6-31G*	trans	2.050	3.103	29.2	4.7	1.4		
	cis	1.977	3.660	86.5	3.3			
			$Ph_3P{=}CHPr + PhCHO$ (eq 9)					
HF/3-21G*	trans	2.106	3.151	16.3	10.0	1.5	11.3	1.4
	cis	2.072	3.556	79.9	8.5		9.9	
B3LYP/6-31G*	trans	1.985	2.994	18.4	7.7	1.8		
	cis	2.041	3.391	64.5	5.9			
			$Ph_3P{=}CHPh + PhCHO$ (eq 10)					
HF/3-21G*	trans	2.058	3.055	7.3	10.4	−2.8	11.6	−2.8
	cis	2.025	3.578	73.8	13.2		14.4	
B3LYP/6-31G*	trans	1.967	3.028	26.0	9.6	−2.1		
	cis	1.845	3.552	78.3	11.7			
			$Ph_3P{=}CH_2 + PhCHO$ (eq 11)					
HF/3-21G*	planar	2.095	3.229	13.6	7.8	2.0	9.1	1.6
	puckered	2.105	3.524	44.2	5.8		7.5	
B3LYP/6-31G*	planar	1.978	3.297	25.0	5.0	2.5		
	puckered	2.024	3.541	51.0	2.5			

[a] Bond lengths, dihedral angles, and barrier heights are shown in Å, deg, and kcal/mol, respecively. ϕ denotes the dihedral angle at the C−C bond (in P−C−C−O) as shown in Chart 1. [b] Energy difference between the trans/cis TSs ($\Delta E^{\ddagger}_{trans} - \Delta E^{\ddagger}_{cis}$). [c] Enthalpy difference between the trans/cis TSs ($\Delta H^{\ddagger}_{trans} - \Delta H^{\ddagger}_{cis}$).

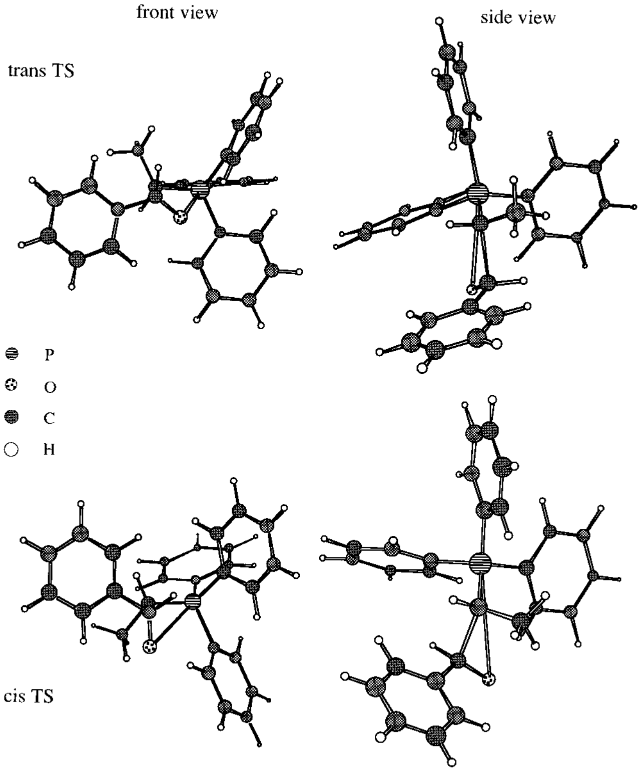


Figure 1. The trans and cis TS structures for reaction 8 calculated at B3LYP/6-31G*.

8) gave more clear-cut results. As shown in Figure 1, the cis TS has a highly puckered conformation with $\phi = 86.5°$ whereas the trans TS is planar. The cis TS is now more stable than the trans TS for reaction 8 at both HF and DFT levels. This is the first example in which the cis OP-formation TS was calculated to be more stable than the trans OP-formation TS.

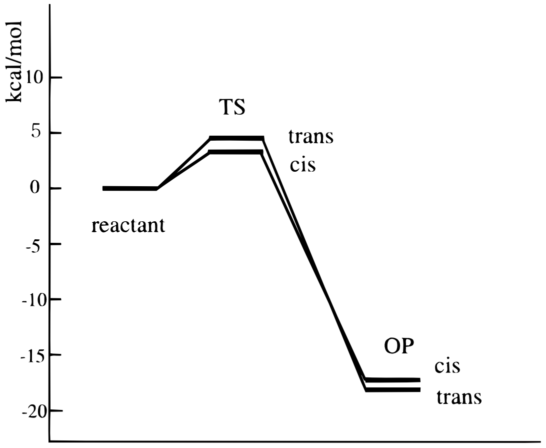


Figure 2. Reaction energy profile of reaction 8 calculated at B3LYP/6-31G*.

The barrier heights of the cis OP- and the trans OP-forming step for reaction 8 were calculated to be 3.3 and 4.7 kcal/mol at the B3LYP/6-31G* level, and the reactions were 17.4 and 17.9 kcal/mol exothermic, respectively (Figure 2). The calculated general reaction profiles are in qualitative agreement with the experimental observation for the reaction of $Ph_3P{=}CHPr + PhCHO$:[3d] (1) the OP forms quite rapidly with the cis formation preferred to trans; (2) the OPs are considerably more stable than the separated reactants; and (3) the OP reversal (backward reaction) is faster for cis than trans. Another interesting point here is that the stability of the cis and the trans OP is nearly the same whereas the cis TS leading to the cis OP is 1.4 kcal/mol more stable at the B3LYP/6-31G* level than the trans TS. This suggests that there is a factor that stabilizes the puckered cis geometry (or destabilized the planar trans geometry) at the OP formation TS.

Very similar results were obtained for the reactions of propylidenetriphenylphosphorane (nonstabilized ylide) with benzaldehyde (eq 9). Here again the cis TS is highly puckered, and a planar trans TS is less stable than a more puckered cis TS. Thus, the experimentally observed high cis preference for reaction 9 was reproduced in the present calculations.

The reaction of the benzylidene (semistabilized) ylide with benzaldehyde (eq 10) gave similar structural features as for reaction 9, where the puckered cis TS has a longer P−O bond than the planar trans TS. The planar trans TS is 2.1 kcal/mol more stable than the puckered cis TS at B3LYP/6-31G*, more trans selective than what was observed experimentally for reaction 9, where nearly equal amounts of trans/cis products were obtained.[6,7] The barrier height for the trans OP formation of reaction 10 was calculated to be 9.6 kcal/mol at B3LYP/6-31G*, which is ca. 4 kcal/mol larger than that (5.9 kcal/mol) for the cis TS of reaction 9. The high barrier for the reaction of the semistabilized ylide compared to that of the nonstabilized ylide is consistent with the experimental trend.[2,7,11]

In summary, the present calculations indicate that both reactions of nonstabilized and semistabilized ylides have a pair of TSs and that the relative stability of the two TSs is reversed for the two classes of ylides. The reaction of nonstabilized ylide proceeds through a puckered cis TS, which is lower in energy than a planar trans TS, while the reaction of semistabilized ylide goes through a more stable planar trans TS than a puckered cis TS. Thus, experimental results of high preference for the cis OP formation in the reaction of nonstabilized ylides were reproduced for the first time by the B3LYP/6-31G* (as well as HF/3-21G*) calculations. The use of a ylide with three phenyl groups on P and high-level calculations are essential for this success.

Origin of the Selectivity. Although the experimentally observed selectivities were reproduced by the calculations, the origin of the selectivity difference for the two classes of ylides (nonstabilized vs semistabilized) is not apparent because the pair of TS structures are quite similar for both ylides while relative stabilities are different. To clarify why the calculated relative trans/cis energies are different for reactions 9 and 10, calculations on reaction 11 were carried out. This reaction does not give isomeric TSs, yet it would be informative to see whether the TS has a planar or a puckered structure. It is conceivable that the planar structure is more favorable than the puckered one in terms of the more effective π-orbital overlap at the cyclization TS. If, on the other hand, the reaction has a strong nucleophilic addition character the puckered TS becomes energetically advantageous in its staggered conformation with less torsional strain. This staggered conformation becomes possible only when the P−O bond formation lags much behind the C−C bond formation in the TS with nucleophilic addition character. Since steric repulsion between the ylide hydrogens and the aldehyde moiety is expected to be small in this reaction system, it would become clear which TS structure is inherently more stable in reactions of nonstabilized ylides with benzaldehyde. If the TS of reaction 11 were nearly planar, this would mean that the puckered cis TSs of nonstabilized ylides (eq 8, 9), which are more stable than the planar trans TSs, should have gained stabilization. If, on the other hand, the TS of reaction 11 had a puckered structure, this would mean that the planar trans TS for the reaction of semistabilized ylide (eq 10) is more stabilized (or less destabilized) than the puckered cis TS.

The calculations on reaction 11 gave unexpected results, in which two TSs, nearly planar and highly puckered, were obtained; the planar TS is less stable than the puckered TS by 2.5 kcal/mol at B3LYP/6-31G*. Inspection of the two TS structures for reaction 11 (Figure 3) reveals that the ylide fragment, which lies on the backside, has similar conformations and approaches benzaldehyde in different manners in the *si* face in the puckered TS and in the *re* face in the planar TS. The fact that the two TSs exist by itself indicates that the puckered conformation is inherently favorable in the reaction of $Ph_3P{=}CHR$ with benzaldehyde because for a planar conformation only one isomer is possible provided that the conformation of the phenyl groups on P is flexible (vide infra). This puckered geometry is very likely due to the high nucleophilicity of the negatively charged carbon of the nonstabilized ylide and thus the nucleophilic attack of the ylide to the carbonyl carbon of benzaldehyde is a major driving force of the reaction. This in turn suggests that the reaction of the semistabilized ylide (benzylidene ylide) with benzaldehyde may be viewed as cycloaddition rather than nucleophilic addition due to a weak nucleophilic character of the ylide carbon. This explains why the planar TS is more stable for the reaction of the semistablized ylide with benzaldehyde (eq 10), whereas the puckered TS is preferred in the reactions of the nonstabilized ylides (eqs 8, 9, and 11) in the calculations. In conclusion, the present results suggest the notion that the reaction of the semistabilized ylide with benzaldehyde proceeds through the TS of cycloaddition character whereas the reaction of the nonstabilized ylides goes through the TS of strong nucleophilic addition character.

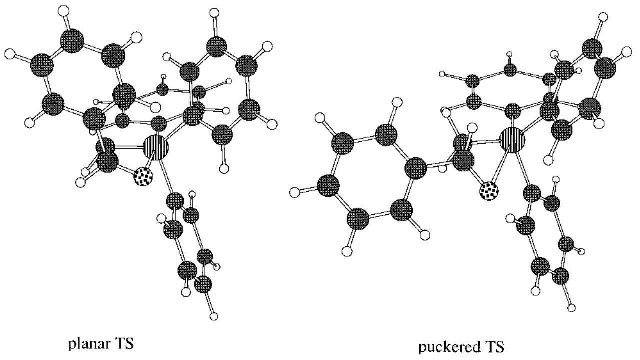


Figure 3. The planar and puckered TS structures for reaction 11 at B3LYP/6-31G*.

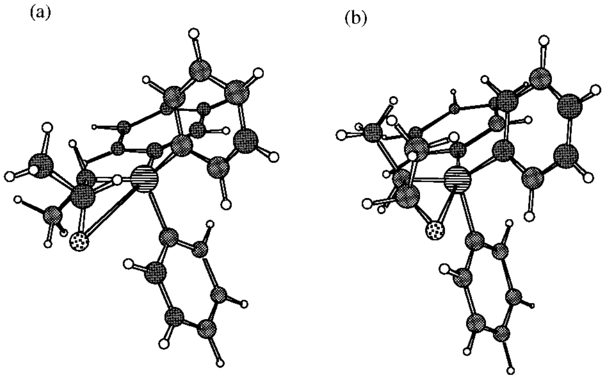
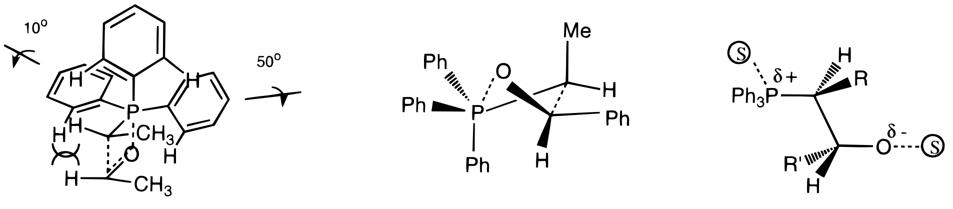


Figure 4. (a) A-form and (b) B-form of the cis TS for reaction 7 calculated at B3LYP/6-31G*.

Possible Conformational Isomers in the TSs. It is conceivable that each cis and trans TS takes several different conformations due to the five substituents, three on P, one on aldehyde, and one on the ylide carbon. This possibility was extensively examined and the results are summarized as follows.

First, due to the puckered geometry two isomers are possible in each of the cis and trans TS; in one case the substituent of

Chart 2



1 **2** **3**

aldehyde locates in the A-position in Chart 1 (designated A-form) and in the other case the substituent lies in the B-position (B-form). In the A-form, the aldehyde substituent locates away from the ylide phosphorus while it is closer to the phosphorus atom in the B-form. As easily expected, the steric interaction between the aldehyde substituent and the Ph groups on P makes the A-form more stable than the B-form for the real ylide systems. For one example, the two conformers for the cis TS of reaction 7 are illustrated in Figure 4; the A-form is 1.9 kcal/mol more stable than the B-form at B3LYP/6-31G*. In the cases of model reaction systems, on the other hand, the steric repulsion between the aldehyde substituent and the hydrogens on P is small, and therefore the energy differences between the two forms are much smaller.

The conformation of the phenyl groups on the phosphorus atom looks complicated. However, extensive search resulted in conformations as shown in Figure 1, where a pair of cis and trans TS structures for reaction 8 at B3LYP/6-31G* are illustrated; the structures of other reactions look alike. It can be seen from the side view that both cis and trans TSs have basically the same conformation at Ph_3P, in which one of the three phenyl groups lies in an apical position and the other two take equatorial positions. The equatorial phenyls tend to be perpendicular to the incipient apical oxygen−phosphorus bond to have maximal overlap between the P−O bond and the π-orbitals of the phenyl ring. Due to the steric repulsion, however, the phenyl group that is in the same side of the ylide substituent is considerably twisted. The apical Ph ring tends to be parallel to the P═C bond in cis and trans TSs and here again the P−Ph bond is slightly twisted to avoid interaction between the apical Ph and the twisted equatorial Ph.

Mechanistic Consideration. The experimental cis selectivity in the reactions of nonstabilized ylides with aldehyde has been explained by several model transition structures. In 1982, Schlosser proposed that the interaction of the ylide substituent with the neighboring phenyl ring leads to a four-centered planar TS that has the conformation shown in **1** (Chart 2). In this model, the steric repulsion between an *o*-hydrogen atom of a phenyl group and one of the substituents of aldehyde is an important factor that makes the cis TS more stable than trans.[8] In Vedejs' model the TS for a nonstabilized ylide has a cyclic puckered structure (**2**, Chart 2). The structure was considered to be favored because the puckered TS can avoid several unfavorable steric repulsions such as the gauche interaction between the developing P−O bond and the phosphorus ligands.[11] Because of the puckered structure a cis TS is more stable than a trans TS. For the trans-selective reaction of stabilized ylides more planar TS was assumed. Bestmann claimed that cis OP is formed via a quasi-betaine TS, in which the P−O bond formation is not advanced, although the origin of the cis selectivity was not explicitly presented.[9] In a recent proposal by McEwen, a solvated erythro TS (**3**, Chart 2) was considered, which through rotation and ring closure gives cis OP without intervention of a betaine intermediate.[10] All these models assume that OP is formed via a single-step process. There is another model, an ET mechanism, where the OP formation consists of multisteps. In this mechanism the reaction is initiated by an initial slow electron transfer, followed by subsequent rapid reaction(s) of the transient radical ion-pair intermediate. The rate is determined by the electron-transfer step whereas the product selectivity is determined by the subsequent step(s); if the product OP is formed via direct cyclization of the radical ion pair, cis OP is preferred through a crisscrossed (puckered) TS structure.[12]

It appears that Vedejs' model and Bestmann's TS are consistent with the present calculations, which indicate that the cis selectivity for nonstabilized ylides arises from a puckered TS with less advanced P−O bond formation. The result that the TS leading to trans product (eq 10) is more planar than the cis TS also agrees with Vedejs' proposal. On the other hand, Schlosser's model disagrees with the calculated results because in that model a planar TS is considered whereas the calculated cis-selective TSs are puckered. To further confirm this point, we have searched for TS starting from Schlosser's geometry shown in Chart 2, **1**, and obtained the puckered TS illustrated in Figure 4a. It is not appropriate to compare the present results with McEwen's model because it considers the effect of solvation, which was not incorporated in the present calculations. The same is true for the ET model because the ET process cannot be well treated by the calculations without solvents.

Kinetic isotope effects are a well-known tool to characterize the nature of the TS at the rate-determining step of chemical reactions.[26] In particular, a carbon KIE is a useful diagnosis to see whether the bonding to the carbon changes at the rate-determining TS. The carbonyl-carbon-13 KIE (k_{12}/k_{13}) was calculated to be 1.039 for reaction 9 and 1.051 for reaction 10. These values seem reasonable for the calculated TS structures of these reactions, in which the C−C bond formation takes place at these TSs. A series of KIEs has been measured experimentally for Wittig reactions of benzaldehyde, e.g., for reaction 9 under the Li salt-free conditions gave a negligible carbonyl-carbon-14 KIE ($k_{12}/k_{14} = 0.998 \pm 0.002$) at 0 °C whereas reaction 10 under the same reaction conditions yielded a large KIE ($k_{12}/k_{14} = 1.060 \pm 0.003$).[7,12] Agreement between calculation and observation is satisfactory for the reaction of the semistabilized ylide (eq 10) in a sense that in both cases KIEs are large and normal. Thus, the reaction of the benzylidene ylide with benzaldehyde is considered to go through the planar cyclic TS as calculated. In contrast, the calculated and observed KIEs disagree for the reaction of the nonstabilized ylide (eq 9), suggesting that the calculated cis OP-formation process may not represent what actually occurs experimentally. The disagreement implies that although the product selectivity is

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(26) Melander, L.; Saunders: W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1780. Fry, A. In *Isotope Effects in Chemical Reactions*; Collins, C. J., Bowman, N. S., Eds.; Van Nostrand-Reinhold: New York, 1970; Chapter 6.

reproduced by a pair of the planar trans and the puckered cis TS, the latter is not the true rate-determining TS for the cis-OP-formation process for the nonstabilized ylide reaction.

The addition of carbon nucleophiles to benzaldehyde often goes through the electron-transfer process.[13,27] Even though the reaction is initiated by electron transfer, the product-forming radical coupling step is likely to resemble the polar OP-forming process in the TS characteristics, and therefore it is reasonable that the trans/cis selectivity was reproduced by the present calculations. Furthermore, since the TS characteristics of the electron-transfer process are different from the polar TS it is also reasonable that the calculations based on the polar mechanism fail to obtain agreement with the KIE experiment. Calculations of kinetic data such as KIEs would require a more elaborated method that can deal with the electron-transfer process. A full description of the Wittig reaction of nonstabilized ylides by means of theoretical calculations remains as a challenge in a future study.

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Supporting Information Available: Tables of HF/3-21G* and B3LYP/6-31G* optimized geometries, imaginary frequencies, and energies (14 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA974237F

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[27] Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* **1989**, *111*, 4912.