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Theoretical study on the substituent effect of a Wittig reaction

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Abstract. The substituent effects of F, H and methyl (Me) in replacement of phenyl (Ph) groups bonding with the ylide phosphorus in Wittig reactions have been examined theoretically by performing ab intio calculations. It is shown that the energy barrier for the Wittig reaction with F as the substituent is much higher than that with H, Me and Ph. The Wittig reaction is found to be more favorable with the substituent in the order $F < H < Ph < Me$. The reactions are found to proceed through two transition states: the formation and the decomposition of oxaphosphetane. We conclude that only the model of the Wittig reaction in which Ph is simplified to Me can reasonably describe the real Wittig reaction.

Key words: Wittig reaction – Substituent effect

1 Introduction

The Wittig reaction, the reaction of a phosphorus ylide with a carbonyl compound, plays a significant role in organic synthesis. Extensive experimental effort has been made to elucidate the reaction mechanism [1–3]. Usually, the reaction pathway is assumed to start from the formation of an oxaphosphetane (OP) intermediate, go through a pseudorotational rotation and at last decompose into the products. The OP intermediates involved were detected experimentally by NMR [4–8]. Correspondingly, several theoretical investigations on the Wittig reagents [9–14] have also been performed. A simplified model system, $H_3P=CH_2 + H_2C=O$, has been adopted to study the Wittig reaction mechanisms by semiempirical [15–18] and ab initio [19–22] calculations. The ab intio calculations indicated that for such a simple model system, the Wittig reaction proceeds mainly through two transition states (TS). The first TS corresponds to the formation of OP and has a smaller energy barrier than the second TS for the decomposition of OP, which is thus more rate-determining. As is well known, the reaction characteristics may depend on a variety of factors, for example, the structure of an ylide and the structure of a carbonyl compound. Thus, such a simple model of the Wittig reaction may not provide conclusive results because it ignores the important role played by the common phenyl (Ph) groups bonding with the ylide phosphorus. Recently, by considering three Ph substituents, Yamataka and Nagase [23] made a thorough study at the HF/3-21G* and B3LYP/6-31G* levels of theory on the origin of the different product selectivities for different classes of ylides. They showed that both alkylidenetriphenylphosphorane (nonstabilized ylide) and benzylidenetriphenylphosphorane (semistablilized ylide) yielded two types of TS for OP formation with a nearly planar and a puckered structure; the planar TS gave *trans*-OP, whereas the puckered TS led to *cis*-OP. However, they laid particular emphasis only on the OP formation step in the Wittig reactions. Therefore, a detailed study on the substituent effect on the whole Wittig reaction still needs to be performed.

In the present study, the substituent effect of the Wittig reaction $X_3P=CH_2 + H_2C=O \rightarrow X_3P=O + H_2C=CH_2$ for $X=$ F, H, methyl (Me) and Ph is investigated. We aim to provide answers to various related issues, such as

1. How the activation barriers changes when using a H or a Me group to replace the Ph group of the phosphorus ylide.
2. How the Wittig reaction surface would alternate if a distinct halogen substituent, such as F, to connect with phosphorus is used.
3. The differences of the reaction pathways of the Wittig reaction with respect to various substituents.

2 Computational approaches

Ab initio molecular orbital calculations were carried out using the GAUSSIAN 98 package [24]. The structures of all the complexes,

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intermediates and TSs were fully optimized at the Hartree–Fock level using the basis set of 6-31G*. The optimized geometries were used to calculate the vibrational harmonic frequencies and zero-point energies. The minima are characterized with all real frequencies, while each TS structure is characterized with one imaginary frequency. To verify that the TS structure is the right saddle point connecting the corresponding reactants and products of interest, intrinsic reaction coordinate [25] calculations were performed to examine the reaction path. In order to include electron correlations, MP2/6-31G* single-point energy calculations (using the second-order Møller–Plesset perturbation theory with the 6-31G* basis set) were performed using optimized structures with HF/6-31G*, which is designated by MP2/6-31G*//HF/6-31G*. Since Hartree–Fock theory is reasonably good at computing molecular structures [26], the use of Hartree–Fock geometries and MP2 single-point energies could be expected to provide reliable energetics. The single-point energy at such a high-level calculation is found to be considerably accurate for the present reaction system. For instance, for the rate-determining step of the Wittig reaction $H_3P = CH_2 + H_2C = O \rightarrow H_3P = O + H_2C = CH_2$, the barrier calculated at the MP2/6-31G*//HF/6-31G* level (24.1 kcal/mol) is very close to that (24.6 kcal/mol) calculated at the standard MP2/6-31G* level.

3 Results and discussion

For the Wittig reaction with F, H or Me as the substituent, the whole reaction surfaces were carefully searched and three TSs were found, respectively, on the reaction pathway. These TSs are characterized as the formation of OP, as the pseudorotation of OP and as the dissociation of OP which leads to the production of phosphine and ethylene, respectively. As a representative for the three cases, Fig. 1 shows the geometric structures in the reaction pathways for H as the substituent and Fig. 2 illustrates the corresponding potential-energy profiles along with those of all the other cases considered in this work. It is noted that the energy barriers at the pseudorotational TSs (F_{TSr}, H_{TSr} or Me_{TSr}) are quite small, showing that the potential-energy surface between the two intermediates is smooth. It is noted that these energy barrier at the pseudorotational TSs are noticeable at the HF/6-31G* level of calculation, while they are generally reduced at the higher MP2/6-31G*//HF/6-31G* level of calculation, with H_{TSr} and Me_{TSr} being even lower in energy than the respective second intermediate (H_{IM2}/Me_{IM2}). Further calculations at the MP2/6-311G** level of theory for these the pseudorotational TSs show that these TSs for H and Me do not exist anymore and the respective IM1 and IM2 are actually the same stable structure (Fig. 3), similar to the IM1 structure of HF/6-31G*. This indicates that there actually exists only one intermediate in the Wittig reaction. Furthermore, the pesudorotational TS (F_{TSr}) for F is quite small (0.3 kcal/mol). Similar to the cases of H and Me, we optimized F_{TSr}, F_{IM1} and F_{IM2} again at the MP2/6-311G** level. It was found that, at this higher level of calculation, F_{TSr} is absent, and the corresponding intermediate (Fig. 3) is similar to F_{IM2} from the HF/6-31G* calculation. The reaction pathway for the Wittig reaction with Ph as the "bulky substituent" is shown in Fig. 4. In the reaction surface for Ph, there exist only two TSs and one intermediate at the MP2/6-31G*//HF/6-31G* level. The two TSs correspond to the formation and the decomposition of OP, respectively.

The related bond lengths of the extrema in these reactions are listed in Table 1. For the respective first TSs, the data show the trends of C–C bond and P–O bond formations. At F_{TS1}, the $P_{(1)}$–$O_{(4)}$ bond length (2.061 Å) is smaller than $C_{(2)}$–$C_{(3)}$ (2.291 Å), indicating that the P–O bond formation is slightly advanced compared to that of C–C formation. Conversely, for the cases of H, Me and Ph, the longer P–O bond at the first TS shows the formation of OP with a leading C–C bond formation followed by a P–O bond formation. In addition, our calculations show that the $O_{(4)}C_{(3)}C_{(2)}P_{(1)}$ dihedral angles for F, H, Me and Ph are –38°, 3°, 0° and 26°, respectively, suggesting that the first TSs for H and Me are nearly planar, while those for F and Ph are not. The relative energy to the reactants is positive for F_{TS1} (12.2 kcal/mol) and H_{TS1} (2.2 kcal/mol), but is negative for Me (–5.7 kcal/mol) and Ph (–0.5 kcal/mol). The formation of OP is found to be more favorable in the order F (16.8 kcal/mol) < H (6.2 kcal/mol) < Ph (4.7 kcal/mol) < Me (1.2 kcal/mol), according to their corresponding energy barriers with respect to the reactant-like complex. In general, the structure of the corresponding TS is more reactant-like in this order. In

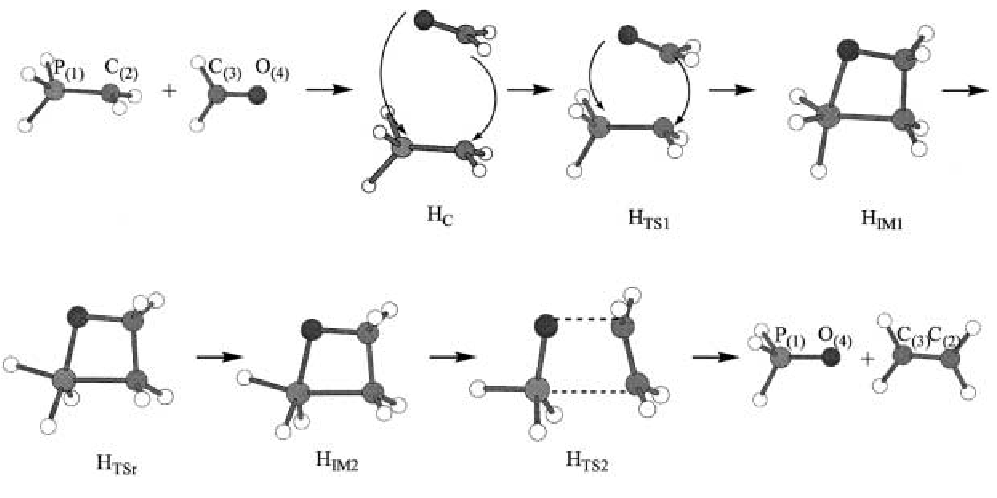


Fig. 1. Reaction route of $H_3PCH_2 + H_2CO \rightarrow H_3PO + C_2H_4$

order to observe the charge transfer in this process, we list the charges on the reactive fragments ($X_3P_{(1)}$, $C_{(2)}H_2$, $C_{(3)}H_2$ and $O_{(4)}$) in Table 2. It can be seen that in the process of the formation of OP a large charge transfer between P and O occurs. Moreover, the increased positive charge on the PX_3 fragment at the first TS is obviously increased in the order F ($0.51e$) < H ($0.72e$) < Ph ($0.76e$) < Me ($0.77e$), indicating that the increased positive charges on PX_3 may lead to a decreased energy barrier for the formation of OP when the charge variations on the O atom are relatively small. Thus, at the first TS for H, Me and Ph, the interaction between P and O is mainly electrostatic attraction, which can be expected to be the driving force for the formation of OP.

At the rate-determining step, the decomposition of OP proceeds in the way of the advanced P–C bond breaking followed by the C–O bond breaking. The corresponding TS is planar, with the $O_{(4)}C_{(3)}C_{(2)}P_{(1)}$ dihedral angle being almost zero. The energy barriers of the second TSs relative to the most stable intermediates are very close to each other for H (24.9 kcal/mol), Me (24.2 kcal/mol) and Ph (24.1 kcal/mol). They are, however, very different from that of F (37.0 kcal/mol). Here, it can be seen that the simplified model of the Wittig reagent used in the literature can predict the activation energy quite reliably for the rate-determining step. Similar to the first TS, there are also the obvious charge variations at the rate-determining TS, and the charges on PX_3 attain the maximum values. Obviously, when a simple model is used for the Wittig reagent in calculations, the main differences with the real reaction may exist at the first TS. It is worthy mentioning that the OP intermediates have indeed been detected by NMR at low temperatures [4–8]. Moreover, it has been shown experimentally that the OP derived from a nonstabilized phosphorus ylide with benzaldehyde undergoes OP reversal under typical reaction conditions [2, 3, 27]. The first TS for OP formation is suggested to be not

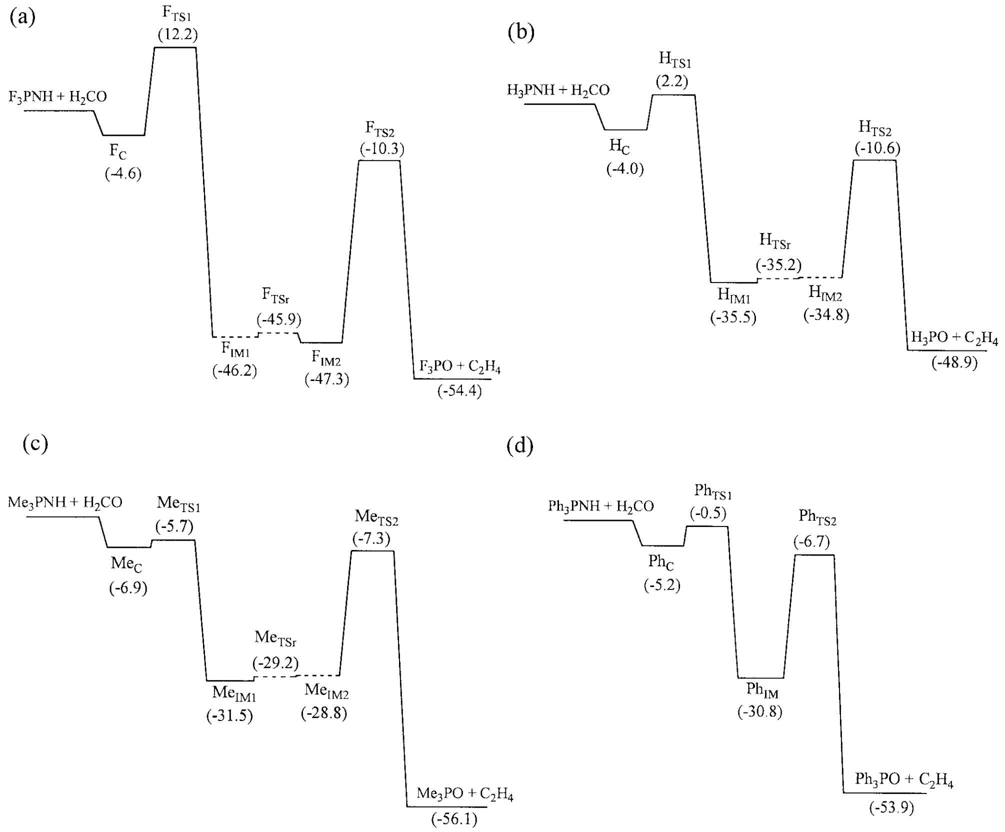
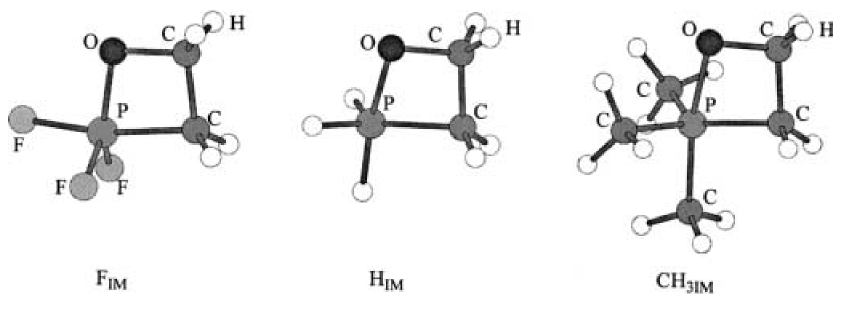


Fig. 2a–d. Potential-energy profiles (kcal/mol) for the Wittig reaction for X = F, H, Ph and Me determined at the MP2/6-31G*//HF/6-31G* level of theory



F_{IM} H_{IM} CH_{3IM}

Fig. 3. Optimized structures of the intermediates at the MP2/6-311G** level

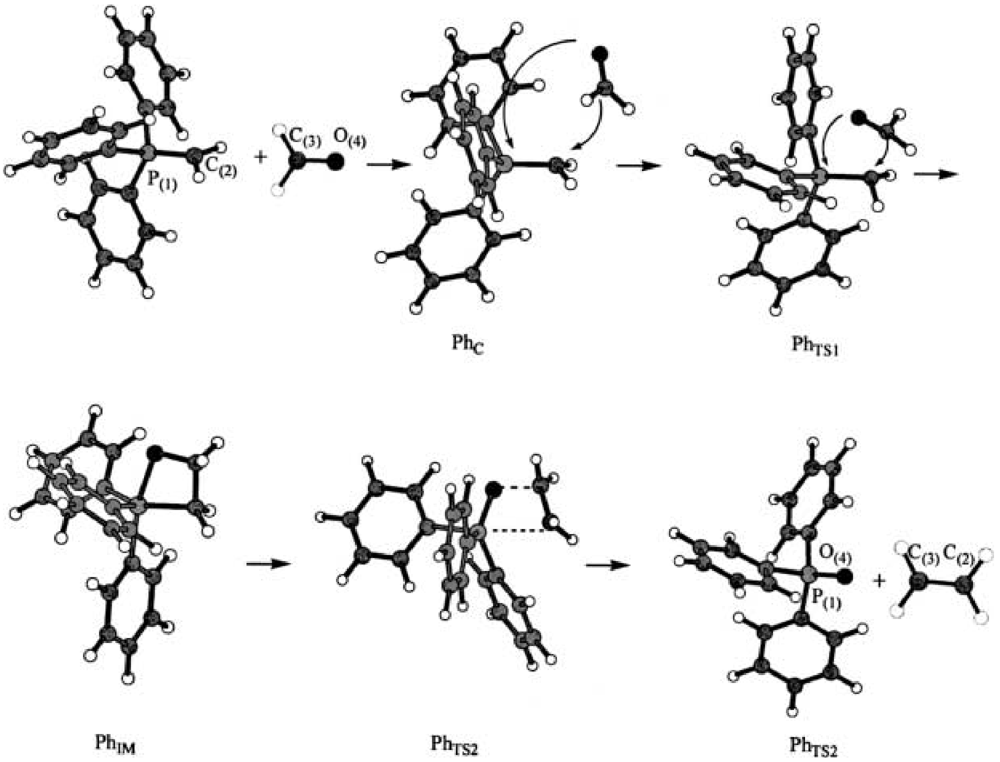


Fig. 4. Reaction route of $Ph_3PCH_2 + H_2CO \rightarrow Ph_3PO + C_2H_4$

Table 1. Bond length of extrema on Wittig reaction surfaces determined at the HF/6-31G* level of theory

	$P_{(1)}$–$C_{(2)}$	$C_{(3)}$–$O_{(4)}$	$P_{(1)}$–$O_{(4)}$	$C_{(2)}$–$C_{(3)}$
F_C	1.604	1.187	3.022	4.209
F_{TS1}	1.695	1.237	2.061	2.291
F_{IM1}	1.816	1.421	1.651	1.529
F_{TSr}	1.837	1.428	1.625	1.525
F_{IM2}	1.852	1.439	1.599	1.528
F_{TS2}	2.187	2.007	1.488	1.397
H_C	1.680	1.189	3.583	3.212
H_{TS1}	1.746	1.242	2.687	2.063
H_{IM1}	1.846	1.401	1.751	1.534
H_{TSr}	1.915	1.428	1.666	1.518
H_{IM2}	1.924	1.431	1.657	1.518
H_{TS2}	2.385	1.819	1.532	1.404
Me_C	1.691	1.191	3.863	3.097
Me_{TS1}	1.747	1.241	3.072	2.067
Me_{IM1}	1.855	1.393	1.812	1.529
Me_{TSr}	1.936	1.416	1.697	1.515
Me_{IM2}	1.964	1.424	1.670	1.514
Me_{TS2}	2.620	1.698	1.547	1.420
Ph_C	1.684	1.189	4.798	3.244
Ph_{TS1}	1.756	1.239	3.312	2.023
Ph_{IM}	1.860	1.394	1.797	1.525
Ph_{TS2}	2.610	1.687	1.547	1.422

Table 2. Charges on the reactive fragments of extrema on Wittig reaction surfaces determined at the HF/6-31G* level of theory

	$P_{(1)}X_3$	$C_{(2)}H_2$	$C_{(3)}H_2$	$O_{(4)}$	D
F_C	0.37	−0.39	0.46	−0.44	3.07
F_{TS1}	0.51	−0.43	0.56	−0.64	3.11
F_{IM1}	0.50	−0.18	0.37	−0.69	3.91
F_{TSr}	0.49	−0.19	0.36	−0.66	3.93
F_{IM2}	0.50	−0.22	0.36	−0.64	3.98
F_{TS2}	0.58	−0.30	0.45	−0.73	4.61
H_C	0.49	−0.48	0.46	−0.47	1.65
H_{TS1}	0.72	−0.46	0.44	−0.70	5.15
H_{IM1}	0.64	−0.20	0.34	−0.77	2.25
H_{TSr}	0.63	−0.28	0.34	−0.70	1.99
H_{IM2}	0.63	−0.29	0.34	−0.69	1.96
H_{TS2}	0.75	−0.38	0.38	−0.75	1.50
Me_C	0.54	−0.52	0.47	−0.49	2.66
Me_{TS1}	0.77	−0.51	0.43	−0.69	6.19
Me_{IM1}	0.74	−0.24	0.32	−0.82	2.09
Me_{TSr}	0.73	−0.32	0.32	−0.73	1.99
Me_{IM2}	0.74	−0.36	0.33	−0.71	1.94
Me_{TS2}	0.88	−0.46	0.35	−0.77	3.27
Ph_C	0.50	−0.48	0.45	−0.47	4.69
Ph_{TS1}	0.76	−0.50	0.42	−0.68	7.18
Ph_{IM}	0.71	−0.22	0.32	−0.81	1.50
Ph_{TS2}	0.85	−0.42	0.36	−0.79	3.16

energetically much less favorable than the second TS for OP decomposition; however, the calculations for H predict a very large difference (12.8 kcal/mol) between the energies of these two TSs. For the cases of Me and Ph, the corresponding predicted energy differences are 1.6 and 6.2 kcal/mol, respectively. So, we conclude that the model simplified by replacing Ph with Me may be much better than the simplest model with all the three substituents bonding with phosphorus replaced with H atoms.

4 Conclusions

The Wittig reactions with H, Me or Ph as substituents are much different from that with F. The Wittig reaction is energetically more favorable with the substituent in the order F < H < Ph < Me. The reaction mechanisms for all the substituents considered here show two TSs, one being OP formation and the other being OP decomposition. The simplest model (with the substituent being simplified with a H atom) for the Wittig reaction can predict a reliable energy barrier only for the rate-determing step, with the calculated energy difference between the two main TSs being, however, very large. The model Wittig reaction with Ph simplified with Me is very reasonable.

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