

## Evidence for a Continuous Transition between Thiophosphetane and Betaine-Type Structures in the Thio-Wittig Reaction

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The Wittig olefination belongs to a small group of essential reaction types in organic synthesis for building up carbon-containing frameworks. Its reaction mechanism has been a subject of intensive investigation.<sup>1</sup> The key role of oxaphosphetane intermediates was established unequivocally.<sup>2</sup> However, the involvement of betaine intermediates was controversial for a long time.<sup>3</sup> It now appears to be established experimentally that betaines are not formed in the reaction between a nonstabilized phosphorus ylide of the type  $\text{Ar}_3\text{P}=\text{CR}^1\text{R}^2$  ( $\text{R}^1, \text{R}^2 = \text{H}$  or alkyl) with ketones or aldehydes.<sup>4</sup> We have recently found that a reactive intermediate exhibiting a pronounced thiophosphetane character is formed upon treatment of  $\text{Ph}_3\text{P}=\text{C}^*\text{H}_2$  (**1a**) with  $\text{Ph}_2\text{C}^*\text{C}=\text{S}$  (**2a**) (both reagents  $^{13}\text{C}$  labeled at the marked positions when necessary).<sup>5</sup> In toluene- $d_8$  solution at  $-30^\circ\text{C}$ , the intermediate **4a** ( $\text{R} = \text{R}^3 = \text{Ph}$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ) is formed. It exhibits a  $^{31}\text{P}$  NMR signal at  $-40$  ppm, i.e., in the range expected of a thiophosphetane structure. We have now carried out the reaction between the ylide **1a** and thiobenzophenone **2a** in dichloromethane- $d_2$  and obtained a markedly different  $^{31}\text{P}$  NMR spectroscopic feature at  $\delta +1.0$  ppm (at 243 K). The chemical behavior of the thus-formed intermediate in  $\text{CD}_2\text{Cl}_2$  is not much different from the species obtained in toluene- $d_8$ . It starts to decompose at slightly elevated temperatures ( $\tau_{1/2} \approx 20$  min at 263 K) to produce  $\text{Ph}_3\text{PS} + \text{Ph}_2\text{C}=\text{CH}_2$  via a 2,2-diphenylthiirane intermediate (**5a**) and  $\text{PPh}_3$  (see Scheme 1).

In a second set of experiments, the intermediate (**4a/4'a**) was generated in toluene- $d_8$ , and dichloromethane- $d_2$  was then added to the solution. This had a marked effect on the  $^{31}\text{P}$  NMR chemical shift of the intermediate. The presence of ca. 20 vol % of the polar  $\text{CD}_2\text{Cl}_2$  solvent results in shifting the  $^{31}\text{P}$  NMR signal of **4a** from  $\delta -40$  to  $-20$  ppm (at 243 K). The consecutive addition of another four 0.185 mL portions of  $\text{CD}_2\text{Cl}_2$  to the sample resulted in a further shifting of the  $^{31}\text{P}$  NMR resonance and the observation of a continuous transition (see Figure 1)

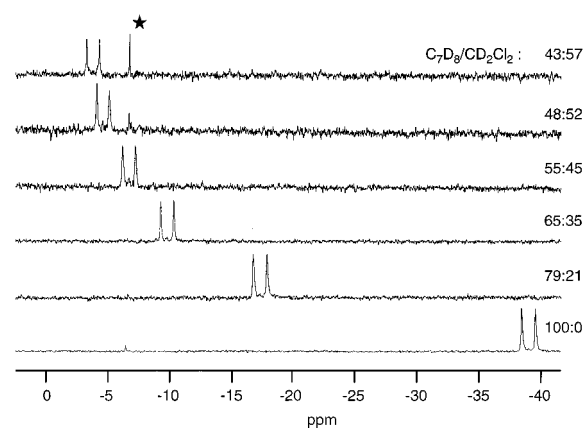
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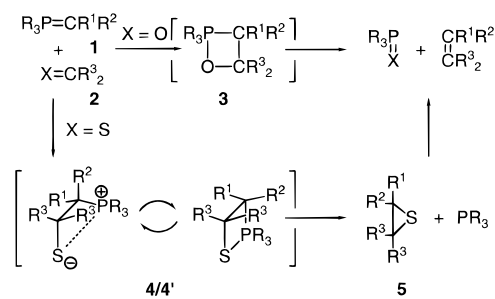
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**Figure 1.** Dependence of the  $^{31}\text{P}$  NMR chemical shift of the **4a/4'a** intermediate (prepared from  $\text{Ph}_3\text{P}=\text{C}^*\text{H}_2$  and  $\text{Ph}_2\text{C}=\text{S}$ ; an asterisk marks a small amount of the  $\text{PPh}_3$  decomposition product) with the toluene/dichloromethane (toluene- $d_8$ /dichloromethane- $d_2$  ratio in volume %) ratio (at 233 K).

### Scheme 1



$\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R} = \text{R}^3 = \text{Ph}$  (**a**);  
 $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{Me}$ ,  $\text{R} = \text{H}$  (**b**),  $\text{R} = \text{CF}_3$  (**d**);  
 $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Me}$ ,  $\text{R} = \text{Et}$ ,  $\text{R}^3 = \text{p-C}_6\text{H}_4\text{NMe}_2$  (**e**),  $\text{p-C}_6\text{H}_4\text{OMe}$  (**f**).

toward a limiting value that is probably marked by the  $^{31}\text{P}$  NMR chemical shift in pure  $\text{CD}_2\text{Cl}_2$  solvent (see above). Addition of other polar solvents (e.g., chloroform, propylene carbonate) furnished qualitatively similar effects. By using  $^{13}\text{C}$ -labeled starting materials, we monitored a gradual shift of the  $^{13}\text{C}$ -NMR resonance adjacent to phosphorus from  $\delta 65.1$  (in toluene- $d_8$ ) to 51.7 ppm (in  $\text{CD}_2\text{Cl}_2$ ) and a continuous decrease of the respective  $^1J_{\text{PC}}$  coupling constant from 94 to 82 Hz. Both features are as expected for an increased phosphonium character, although the still large  $^1J_{\text{PC}}$  coupling constant indicates some remaining distorted pentavalent geometry at phosphorus.<sup>6</sup> The  $^{13}\text{CPh}_2$  resonance ( $\delta 50.7$ ), the  $^1J_{\text{CC}}$  (38 Hz) and  $^2J_{\text{PC}}$  (1.6 Hz) coupling constants were not affected by the change of solvent.

The  $^{31}\text{P}$  NMR chemical shift of the thio-Wittig intermediate (**4a/4'a**) shows only a very small temperature dependence in either of the solvents (toluene- $d_8$   $\delta -38.6$  (223 K),  $-40.1$  (243 K);  $\text{CD}_2\text{Cl}_2$   $\delta +4.6$  (223 K),  $+1.0$  (243 K)). The  $^{31}\text{P}$  NMR spectra of the intermediate were found to be static in both solvents down to the lowest temperature monitored (203 K in  $\text{CD}_2\text{Cl}_2$ ).<sup>7</sup> We carried out a number of control experiments. These showed, e.g.,

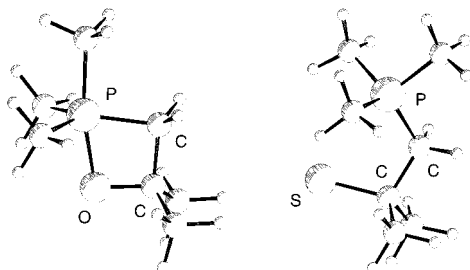
(6) Treatment of **4a** with  $[\text{Et}_3\text{O}^+][\text{BF}_4^-]$  gave the phosphonium salt  $[\text{Ph}_3\text{P}^+\text{CH}_2\text{CPh}_2\text{SEt}][\text{BF}_4^-]$  which exhibits a  $^{31}\text{P}$  NMR signal at  $\delta +19.1$  and  $^{13}\text{C}$  NMR features  $\delta 35.6$  ( $^{13}\text{CH}_2$ ) and 56.1 ( $^{13}\text{CPh}_2$ ), and  $^1J_{\text{PC}} = 62$  Hz.

(7) This experiment cannot distinguish between a double-minimum situation ( $\text{4} \rightleftharpoons \text{4}'$ ) that is rapid on the NMR time scale and a one-minimum situation characterized by a system-dependent continuous  $\text{4/4}'$  transition (which is graphically indicated by the new symbol of two curved arrows in Scheme 1). The additional evidence presented (see below) lead us to favor the latter explanation.

**Table 1.** Ab Initio Calculated P...X Separations and PCCX Torsional Angles of  $R_3P=CH_2 + X=C(CH_3)_2$  Reaction Intermediates (X = O, S)<sup>a</sup>

compd	4b	4c	4d	3b
X	S	S	S	O
R <sub>3</sub> P	(CH <sub>3</sub> ) <sub>3</sub> P	H <sub>3</sub> P	(CF <sub>3</sub> ) <sub>3</sub> P	(CH <sub>3</sub> ) <sub>3</sub> P
<i>d</i> P...X [Å]	3.140 <sup>+b</sup> (3.449*)	2.535 <sup>+</sup> (2.932 <sup>+</sup> )	2.243* (2.467)	1.826 <sup>+</sup> (1.830*)
θPCCX [deg]	39.1 <sup>+b</sup> (51.4*)	26.1 <sup>+</sup> (-36.1 <sup>+</sup> )	0* (-0.5)	0 <sup>+</sup> (0*)

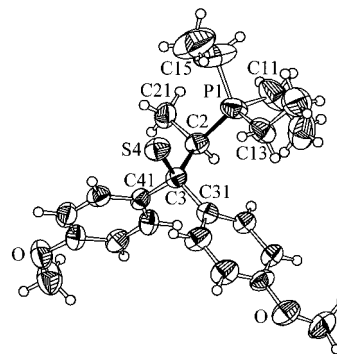
<sup>a</sup> RHF/6-31+G\*\*/6-31+G\* calculations are marked with a +; RHF/6-31G\*\*/6-31G\* are marked with an asterisk; no specific mark indicates a RHF/3-21G//3-21G calculation. Values in parentheses refer to calculations including two H<sub>2</sub>O molecules. <sup>b</sup> Values decreased to 2.615 Å (22°) at the B3LYP/6-31+G\*\*/B3LYP/6-31G\* level.

**Figure 2.** A comparison between the calculated structures of the reactive intermediate formed in the Wittig and thio-Wittig reaction between  $Me_3P=CH_2$  and  $X=CMe_2$  (X = S, O).

that the oxaphosphetane (**3a**, with same substituent pattern) does not show such a solvent response (<sup>31</sup>P NMR  $\delta$  -68.3 in toluene-*d*<sub>8</sub>,  $\delta$  -67.2 in CD<sub>2</sub>Cl<sub>2</sub> at 243 K; <sup>1</sup>J<sub>PC</sub> = 87 Hz, <sup>2</sup>J<sub>PC</sub> = 14 Hz).

We have performed a computational study on a series of model compounds (**4b–d**, **3b**, see Table 1). The ab initio calculation on the  $(CH_3)_3P=CH_2 + X=C(CH_3)_2$  reaction system (X = O and S) reveals the formation of a conventional oxaphosphetane intermediate (**3b**, R = CH<sub>3</sub>, R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = CH<sub>3</sub>) that contains a planar four-membered ring (*d* P–O 1.826 Å) even in the presence of two H<sub>2</sub>O molecules.<sup>8</sup> In contrast, the intermediate of the corresponding thio-Wittig reaction (**4b**, R = CH<sub>3</sub>, R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = CH<sub>3</sub>) is characterized by a large P...S separation (3.14 Å) that is increased to almost 3.5 Å when water is introduced into the calculation (apparently stabilizing the sulfur end of the dipolar structure by weak hydrogen bonding). The system **4b** is no longer planar (dihedral angle  $\theta$ (PCCS)  $\approx$  39°; increased to ca. 51° in **4b**·2H<sub>2</sub>O). The occurrence of the betaine-type structure (here **4b**) is strongly influenced by electronic effects. In the calculation, the P...S separation and the  $\theta$ (PCCS) angle are decreased upon reducing the phosphonium stabilization electronically by substituting the (CH<sub>3</sub>)<sub>3</sub>P moiety consecutively by H<sub>3</sub>P (**4c**) and (CF<sub>3</sub>)<sub>3</sub>P (**4d**). This results in a continuous decrease of the betaine character of the intermediate (**4b** → **4d**, see Table 1) toward a calculated thiophosphetane structure.

We searched for an experimentally accessible system suited for a direct comparison with our computational results. Borisova et al. had recently reported on the possible generation of a betaine-type intermediate (**4e**, R = ethyl, R<sup>1</sup> = H, R<sup>2</sup> = CH<sub>3</sub>, R<sup>3</sup> = *p*-C<sub>6</sub>H<sub>4</sub>-NMe<sub>2</sub>; <sup>31</sup>P NMR in pyridine-*d*<sub>5</sub>  $\delta$  +25.3) in the reaction of Et<sub>3</sub>P=CHCH<sub>3</sub> with Michler's thioketone.<sup>9</sup> We have now treated the ylide triethylethylidene phosphorane with 4,4'-di-*p*-methoxythiobenzophenone in tetrahydrofuran. At 273 K, the reactive intermediate **4f** (<sup>31</sup>P NMR  $\delta$  +20.7 ppm, <sup>1</sup>J<sub>PC</sub> = 70.8

**Figure 3.** Molecular structure of the gauche-betaine-type thio-Wittig intermediate **4f** in the crystal. Selected bond lengths (Å) and angles (deg): P1–C11 1.812(9), P1–C13 1.818(7), P1–C15 1.788(9), P1–C2 1.845(7), C2–C21 1.528(9), C2–C3 1.554(8), C3–S4 1.833(6), C3–C1 1.531(9), C3–C41 1.547(9), C11–P1–C13 106.0(4), C11–P1–C15 98.7(6), C13–P1–C15 111.2(5), C2–P1–C11 104.1(4), C2–P1–C13 117.6(3), C2–P1–C15 116.4(5), P1–C2–C21 107.7(5), P1–C2–C3 113.0(4), C2–C3–S4 105.9(4), C2–C3–C31 112.4(5), C2–C3–C41 108.0(5), S4–C3–C31 111.0(4), S4–C3–C41 113.1(4), C31–C3–C41 106.6(5).

Hz, <sup>3</sup>J<sub>PC(ipso-Ar)</sub> = 0 and 14.1 Hz) is formed. Low-temperature crystallization furnished single crystals of **4f** that were suited for an X-ray crystal structure analysis.<sup>10</sup> In the crystal, the PR<sub>4</sub> geometry in **4f** is distorted toward tetrahedral (see Figure 3), and there is a very large P...S separation of 3.109(5) Å, although this is still within the sum of the van der Waals radii (3.6 Å).<sup>11</sup> The  $\theta$ (PCCS) torsional angle amounts to 47.7(5)°. Thus, the P1–C2 (1.845(7) Å) and C3–S4 (1.833(6) Å) vectors are in a gauche orientation, as are C3–S4 and C2–C21 (1.528(9) Å). The overall bonding situation of the isolated compound **4f** is very similar to the calculated structure **4b** (at the + marked level, see Table 1). It has a pronounced betaine-type character with probably a small component of a weak dipolar or internal ion pair type P...S interaction; **4f** could be termed a "gauche-betaine".<sup>12</sup>

The combined results of this chemical, computational, and structural study point to the potential involvement of betaine-type structures in the thio-Wittig reaction of these ylides. There seems to be a transition<sup>7</sup> between thiaphosphetane- and gauche-betaine-type structures of the intermediates involved depending on the reaction conditions and the electronic features. Whether this is a sulfur-specific effect in this area of the Wittig chemistry, which is related to the P–S vs P–O bond energy difference, will be investigated.

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**Supporting Information Available:** Details on the calculations and the X-ray crystal structure analysis (45 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(10) Crystal data: P2<sub>1</sub>/n (No. 14),  $\lambda$  = 0.710 73 Å, *T* = 223 K, 5631 reflections collected ( $-h$ ,  $-k$ ,  $\pm l$ ), 5270 independent and 2340 observed reflections [ $I \geq 2 \sigma(I)$ ], 281 refined parameters, *R* = 0.098, *wR*<sup>2</sup> = 0.285.

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(12) The anti-periplanar structure of **4b** ( $\theta$ (PCCS) = 180°) was calculated to be a transition state.

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