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NMR RATE STUDY ON THE WITTIG REACTION OF 2,2-DIMETHYLPROPANAL AND TRIBUTYLBUTYLIDENEPHOSPHORANE

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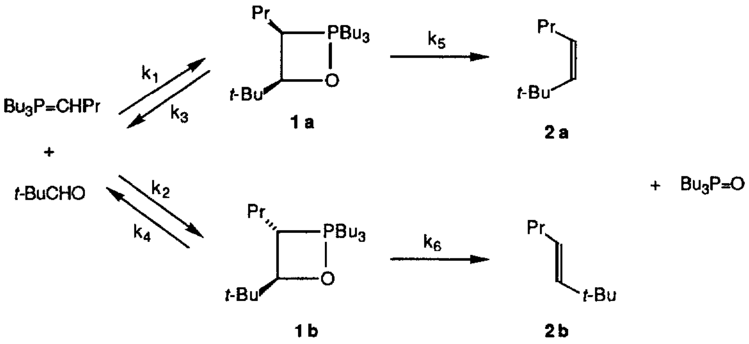
Summary: The fate of intermediate oxaphosphetanes in the reaction of *t*-BuCHO and $Bu_3P{=}CHPr$ was monitored with time. Cis oxaphosphetane **1a** was converted to trans oxaphosphetane **1b** at -55 °C with $k_3 = 1.5 \times 10^{-4}$ s^{-1}, and **1b** was converted to $Bu_3P{=}O$ and alkene **2b** at -15 °C with $k_6 = 2.7 \times 10^{-5}$ s^{-1} ($t_{1/2} = 7.0$ h).

In certain Wittig reactions of nonstabilized phosphorus ylides and aldehydes, the initial ratio of cis and trans oxaphosphetanes changes with concomitant enrichment of the trans oxaphosphetane prior to complete generation of alkenes and phosphine oxide.[1-3] To the extent that such "stereochemical drift" from cis to trans oxaphosphetane occurs, some degree of thermodynamic control is reflected in the final alkene *Z/E* ratio. In various studies from 1981 to 1986,[1,2] we have described the existence of this phenomenon for the following reaction types: {1} $Ph_3P{=}CHR$ (R = Me or Pr) + PhCHO in THF with LiBr present, {2} $Ph_3P{=}CHR$ (R = alkyl with a proximal COO^-M^+ substituent; M = Li or Na) + PhCHO, {3} $Ph_3P{=}CHR$ (R = alkyl with a proximal O^-Li^+ substituent) + R'CHO (R' = Ph or pentyl), and {4} $Bu_3P{=}CHPr$ + R'CHO (R' = Ph or *t*-Bu). However, there are many Wittig reactions of nonstabilized ylides that do not exhibit significant (>5%) stereochemical drift.[1-3]

We have been especially intrigued by the dramatic oxaphosphetane stereomutation in Wittig reactions involving $Bu_3P{=}CHPr$, since this takes place in the strict absence of salts (lithium or otherwise) and with an aliphatic aldehyde partner.[1a,2b] Recently, Vedejs and co-workers determined that this behavior, for a Wittig reaction of an aliphatic aldehyde, is confined to the pairing of a trialkylalkylidenephosphorane ($R_3P{=}CHR$, R = alkyl) with a tertiary aldehyde.[3] Given the special status of this reaction class, we decided to perform a rate study on the system by NMR at low temperature, in a similar manner to those that we have already reported.[1a,2,4]

In a representative experiment, freshly prepared and distilled ylide[5] (146 mg, 0.566 mmol) was combined with dry, deoxygenated tetrahydrofuran-d_8 (THF-d_8, 2.5 mL) in a 10-mm NMR tube equipped with a vortex suppressor and a glass capillary containing trimethylphosphite (external reference), under argon.[1a] The solution was cooled to -78 °C and distilled *t*-BuCHO (115 μL of a 5.0-M solution in THF-d_8, 0.575 mmol) was deposited via a long needle onto the side of the tube just above the liquid surface. After cooling at -78 °C for ca. 1 min, the tube was agitated briefly on a vortex stirrer. The sample was placed in the probe of a Bruker AM-360 NMR spectrometer at -55 °C and the ^{31}P signals were monitored at 145.8 MHz.[1a] The conversion of **1a** to **1b** was followed for two half-lives with a data point being collected every 10 min. The sample was returned to the dry ice bath, the probe was set to -15 °C, and the tube was replaced in the spectrometer. Now, the decomposition of **1b** to alkenes and phosphine oxide was followed for two half-lives, collecting a data point every 15 min.

At the outset (experimental t = 0 at -55 °C), the oxaphosphetane cis/trans ratio was 40:60 ($\delta^{31}P$: -69.6 for **1a**; -73.7 for **1b**),[1a,6] and the ylide was completely consumed (Figure 1). The signal for **1a** diminished while that for **1b** increased, with the total phosphorus for **1a** and **1b** decreasing by ca. 5% over the first two half-lives. Correspondingly, the signal for $Bu_3P{=}O$ increased by ca. 5% during this segment of the study.

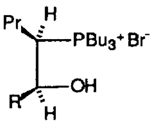


At -15 °C, the initial level of $Bu_3P{=}O$ was nearly the same as the final one in the -55 °C study. Since cis oxaphosphetane **1a** was essentially unobservable (<2%), we could only monitor the disappearance of trans oxaphosphetane **1b** and the appearance of the phosphine oxide (Figure 1). The total phosphorus for the two species was virtually constant throughout the period. After warming the sample to room temperature, capillary GLC and GLC/MS analysis (Chrompak CPSil-5CB column, 25 m x 0.22 mm x 0.12 μm) of the product mixture indicated a *Z*/*E* alkene ratio (**2a**/**2b**) of 4:96.[1a]

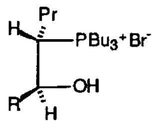
The rate data (every data point), normalized to a scale of 100 for total phosphorus, are plotted in Figure 2. The two data sets were subjected to iterative computational analysis, which afforded the following rate constants (10^{-5} s^{-1}): k_3 = 15.3 ± 0.8 (-55 °C), k_4 = 1.0 ± 0.3 (-55 °C), and k_6 = 2.7 ± 0.1 (-15 °C; $t_{1/2}$ = 7.0 h).[1a,7] Assuming a change in rate of 2.0 for every 10 °C, the k_3 value here is ca. 3 times greater than that for the reaction of $Bu_3P{=}CHPr$ and PhCHO, while the k_6 values are nearly the same.[1a,2b,8]

We also conducted a rate study via ^1H-decoupled ^{13}C NMR by using ylide enriched in ^{13}C at the α carbon.[1a] In this material, generated from $Bu_3P^{13}CH_2Pr^+Br^-$ (98 atom %) with butyllithium and then distilled, the ^{13}C label was statistically distributed among four sites. Basically, the results verified the above-mentioned rate profile, but the data at -15 °C and -55 °C were unfortunately not suitable for computational analysis because of integration problems from overlapping resonances. The ^{13}C NMR data (THF-d_8) for the labeled oxaphosphetane ring carbons are: 64.5 ppm, $^1J(PC)$ = 81.3 Hz, for **1a**; 62.8 ppm, $^1J(PC)$ = 84.6 Hz, for **1b**.[9]

From the present ^{31}P NMR rate study, it is apparent that **1a** converts to **1b** almost completely before decomposition to products transpires, presumably by a retro-Wittig process.[7b] This stereochemical drift accounts for the failure of the final *Z*/*E* alkene ratio to represent the stereochemical preference of the carbon-carbon bond-forming step (addition of ylide to aldehyde), which is captured by the initial ratio of oxaphosphetane isomers. The integrity of this original cis/trans ratio, previously confirmed by analysis of erythro and threo β-hydroxyphosphonium salts **3a** and **3b** formed in an HBr quench experiment at -60 °C,[1a] is reconfirmed by the -55 °C rate data. Thus, a temperature of about -60 °C is clearly effective for capturing the original ratio of cis and trans oxaphosphetanes, even when a bulky group is present on C-4 of the oxaphosphetane ring.



3a R = *t*-Bu
4a R = *c*-Hx



3b R = *t*-Bu
4b R = *c*-Hx

The special status of a tertiary aldehyde/trialkyl ylide combination derives from results with eight different reagent pairings: a primary or tertiary aldehyde with $Ph_3P{=}CHR$, $Ph_2RP{=}CHR$, $PhR_2P{=}CHR$, or $R_3P{=}CHR$ (R = alkyl).[3] One might also wonder about the pairing of a secondary aldehyde with a trialkyl ylide; thus, we examined the Wittig reaction of cyclohexanecarboxaldehyde (*c*-HxCHO) with $Bu_3P{=}CHPr$ at low temperature. At -55 °C in THF-d_8, one oxaphosphetane signal was detected by ^{31}P NMR ($\delta^{31}P$ -72.7), presumably for the trans isomer.[10] After warming, GLC and GLC/MS analysis indicated a 10:90 ratio of *Z*/*E* alkenes (*c*-HxCH=CHPr). To gain further insight, a low temperature quench experiment was performed.[1a] Addition of gaseous HBr to a reaction mixture at -70 °C yielded a 12:88 mixture of erythro/threo β-hydroxyphosphonium salts, **4a** and **4b** ($\delta^{31}P$: 38.9 and 37.2, respectively).[11] Consequently, a secondary aldehyde/trialkyl ylide combination does not show significant stereochemical drift, further underscoring the uniqueness of the title reaction.

Figure 1. Four stages of the reaction of $Bu_3P{=}CHPr$ and *t*-BuCHO in THF-d_8 (0.27 M), as monitored by ^{31}P NMR at 145.8 MHz. (a) Initial spectrum at -55 °C. The singlets are (from left to right): $(MeO)_3P$, $Bu_3P{=}O$, **1a**, and **1b**. The $Bu_3P{=}O$ derives principally from the original ylide (ca. 12%).[5] (b) Final spectrum after two half-lives at -55 °C. (c) Initial spectrum at -15 °C. (d) Final spectrum after two half-lives at -15 °C.

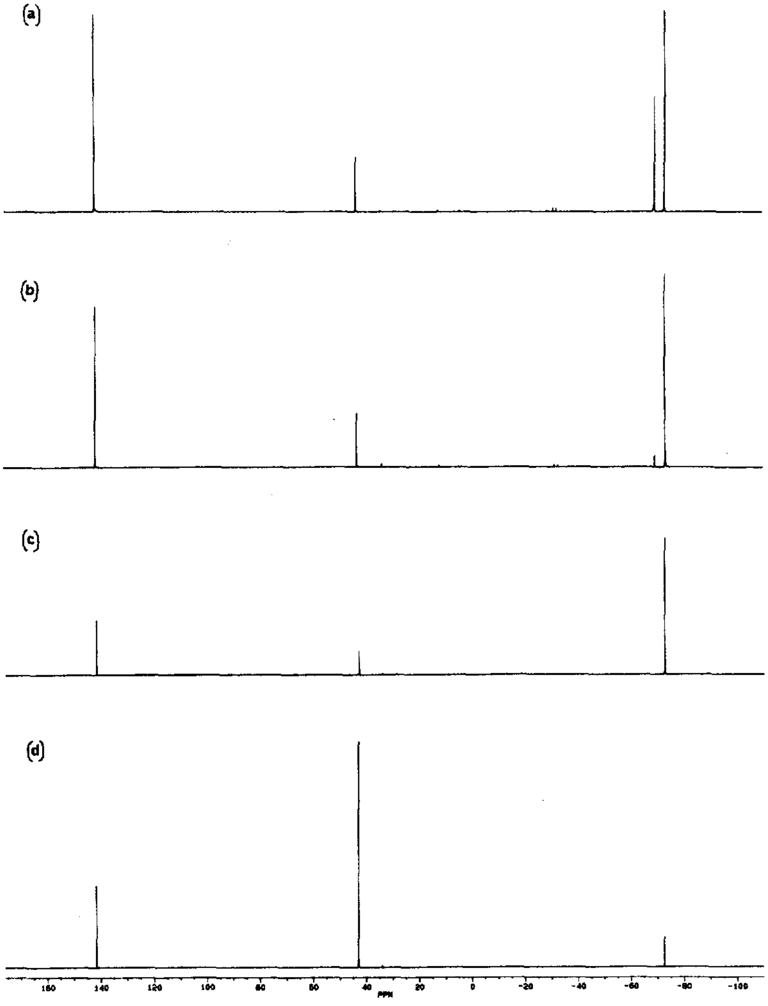
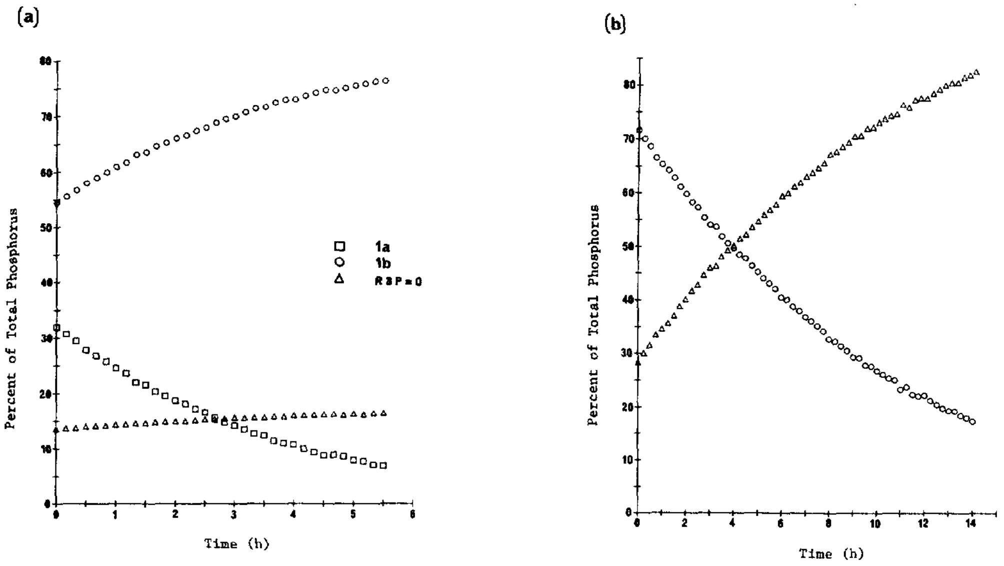


Figure 2. Plot of rate data for the reaction of $Bu_3P{=}CHPr$ and *t*-BuCHO. Panels: (a) -55 °C; (b) -15 °C.



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References and Notes

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4. Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 1068.
5. The phosphorus ylide always contained a small amount of $Bu_3P{=}O$, varying from 5-15% of the total phosphorus (^{31}P NMR integration). The amount indicated is corrected for oxide content.
6. The ^{31}P chemical shift was referenced to 85% H_3PO_4 at ambient probe temperature, rather than at -20 °C, as before.[1a] This could account for the present 0.4-ppm difference in chemical shift (downfield shift).
7. (a) Computations were performed with "PCNONLIN & NONLIN84: Software for the Statistical Analysis of Nonlinear Models", *Amer. Statistician*, Vol. 40, No. 1 (1986). (b) The reaction model used was equilibration of **1a** and **1b**, and conversion of **1b** to **2b**, since disappearance of **1a** could not be observed at -15 °C. However, since **1a** probably disappears at a rate similar to that for **1b**, the rate constants will be slightly biased.[1a] Although the reversal rate for **1b** is laden with error, the computations indicated that k_4 is not zero; the computer model with $k_4 = 0$ gave an inferior fit.[1a] Experience suggests that $k_4 << k_3$.[1a] (c) Regarding k_3, the rate constant determined at -55 °C was $k_2k_3/(k_1 + k_2) = 9.17 \pm 0.5 \times 10^{-5}\ s^{-1}$; then, by setting $k_1/k_2 = 40/60$ (initial ratio of **1a**:**1b**) we obtained $k_3 = 1.53 \pm 0.13 \times 10^{-4}\ s^{-1}$; an identical treatment was applied to k_4.[1a] (d) The value for k_6 at -55 °C was computed to be $2.4 \times 10^{-6}\ s^{-1}$.
8. The k_3 and k_4 values of 120 and 4.0 $10^{-5}\ s^{-1}$ in Table I of ref 1a are really *for -10 °C*, not -40 °C as mistakenly indicated.[2b]
9. (a) By integration of ^{13}C signals, the initial oxaphosphetane cis/trans ratio was 1:2 and the final alkene *Z*/*E* ratio (**2a**/**2b**) was 3:97. (b) The $^1J(PC)$ values are consistent with a predominance of an equatorial ring carbon (axial P-O bond): Kay, P. B.; Trippett, S. *J. Chem. Res. (S)* **1986**, 62.
10. Other spectral features: A signal for $Bu_3P{=}O$ was present ($\delta^{31}P$ 41.7), but the amount of newly formed $Bu_3P{=}O$ was minimal; no $Bu_3P{=}CHPr$ remained; there was no P(IV) resonance due to enolate formation.[1a]
11. (a) A resonance for Bu_4P^+ at 33.5 ppm, due to unreacted ylide, was also present. (b) The outcome of this ^{31}P NMR analysis was supported by ^1H and ^{13}C NMR data for the mixture of salts.

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