

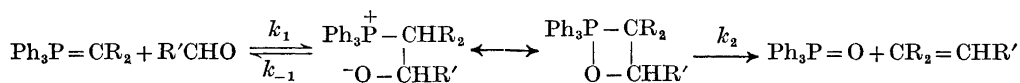
Kinetic Study of the Wittig Reaction

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The rates of reaction of a series of fluorenylidene phosphoranes with *p*-nitrobenzaldehyde have been studied in benzene. Some rate studies were also performed in acetone and in dimethylformamide. The reaction is first order in each of ylide and aldehyde. Triethylphosphine fluorenylide reacts about 2.5×10^3 times faster than triphenylphosphine fluorenylide with *p*-nitrobenzaldehyde. The reaction rate is not increased by increased polarity of the solvent. The mechanism of the reaction is discussed.

Several groups have studied the mechanism of the reaction between phosphonium ylides and carbonyl compounds, a reaction known as the Wittig reaction: ²⁻⁵



Scheme 1.

Considerable information is available regarding the effect of the structure of the ylides and of the carbonyl compound on the course and mechanism of this reaction. Although there is no direct evidence on this point, most writers agree with the proposal of Wittig *et al.*^{6,7} that the overall reaction consists of a stepwise formation of a betaine and a four-membered cyclic intermediate, followed by decomposition into olefin and phosphine oxide. It has been suggested on the basis of kinetic measurements that in the Wittig reaction of stabilized ylides, the first step consists of a slow reversible formation of the betaine followed by its rapid decomposition.^{1,2} On the other hand most studies of non-stabilized ylides indicate a rapid and reversible first step, followed by slow decomposition into products. The work of Schlosser and Christmann⁸ has shown, however, the olefin forming step to be rapid if the reaction is carried out in salt-free media. The reactivity of an ylide in the Wittig reaction is influenced both by the phosphorus substituents and by the groups attached to the carbanion portion. Most interest has focused on the reactivity

of the ylides as influenced by the carbanion substituents,¹⁻³ but there are also studies as to the effect of substitution in the phenyl groups linked to phosphorus in certain ylides.⁴ Very little is known, however, regarding the effect of phosphorus substituents, other than aryl, on the rate and course of the reaction. The main reason for this lack of information lies in difficulties associated with the isolation and handling of the ylides. As far as the present author knows, only one rate study has been performed on an alkylphosphonium ylide, and it was reported that the value of this rate constant was uncertain since the ylide, carbethoxymethylene tributylphosphorane, prepared from the parent phosphonium bromide and phenyllithium was used *in situ*.² The rate constant for the reaction with *p*-anisaldehyde was $5.6 \times 10^{-3} \text{ l mol}^{-1} \text{ s}^{-1}$, about eighty times higher than the rate constant reported for the triphenyl analogue. It was concluded that this rate increase reflected the higher nucleophilicity of the tributyl ylide. The paucity of data available regarding the relationship of substitution on phosphorus to the reactivity of the ylides, indicates that there is need for further investigations in this field.

Table 1.

Compound	Conc. of ylide (mol/l) $\times 10^4$	Conc. of aldehyde (mol/l) $\times 10^4$	Solvent	Temp.°C	<i>k</i> mol $\text{l}^{-1}\text{s}^{-1}$	E_a kcal/mol e.u.25°	ΔS^\ddagger
1 Triphenylphosphine fluorenylide	28.38	28.23	C_6H_6	25.0	1.8×10^{-2}	10.3	-34.0
	30.54	33.16		35.0	3.0×10^{-2}		
	29.83	32.23		50.0	6.9×10^{-2}		
2 Diphenylethylphosphine fluorenylide	10.01	10.24	C_6H_6	25.0	1.8	4.1	-45.6
	8.27	7.08		35.0	2.2		
	5.04	7.08		45.0	2.7		
	8.52	9.32	DMF	25.0	0.25		
	10.24	9.32	Acetone	25.0	0.84		
3 Phenyldiethylphosphine fluorenylide	0.389	0.710	C_6H_6	25.0	25	5.1	-37.0
	0.904	0.710		35.0	34		
	0.352	1.32		45.0	45		
4 Triethylphosphine fluorenylide	5.67	1.29	C_6H_6	25.0	44	4.7	-37.2
	5.58	0.570		35.0	57		
	6.46	1.29		45.0	77		
5 Tributylphosphine fluorenylide	0.648	1.22	C_6H_6	25.0	28		
6 Cyclotetramethylene phenylphosphine fluorenylide	6.749	7.762	C_6H_6	17.0	92		

The present author has undertaken a study of the reaction between a series of fluorenylides and *p*-nitrobenzaldehyde. The fluorenylides were prepared from the appropriate phosphonium bromides and sodium amide in liquid ammonia. The ylides all reacted with *p*-nitrobenzaldehyde to yield the expected *p*-nitrobenzalfluorene in excellent yield. Rate data and activation parameters for the reactions are summarized in Table 1.

EXPERIMENTAL

Materials. Benzene was freed from thiophene by extraction with sulfuric acid. The product was then neutralized with sodium carbonate and washed with water. After drying over calcium chloride the product was fractionated from sodium. *p*-Nitrobenzaldehyde (Fluka *puriss.*) was recrystallized from ethanol, m.p. 106°, lit.⁹ 106°.

p-Nitrobenzalfluorene was synthesized in a Wittig reaction between *p*-nitrobenzaldehyde and phenyldiethylphosphine fluorenylide. The product was recrystallized from ethanol, m.p. 165°, lit.¹⁰ 167°.

The phosphines required for the syntheses of the ylides were prepared according to descriptions in the literature.¹¹⁻¹³ Triphenylphosphine fluorenylide was prepared according to the descriptions of Pinck and Hilbert.¹⁴ The ylide was recrystallized two times from benzene, m.p. 282–283°, lit.¹⁴ 253°.

The diphenylethyl, ethyldiphenyl, triethyl, and tributylfluorenyl phosphonium bromides were prepared by heating equimolar quantities of 9-bromofluorene and the appropriate phosphine.

Triethylphosphine fluorenylide. To a solution of 0.01 mol of sodium amide in dry liquid ammonia was added 0.01 mol of triethylfluorenylphosphonium bromide. The solution was vigorously stirred and the ammonia was slowly evaporated *via* a mercury valve. The apparatus was flushed with dry nitrogen during all operations. The ylide was dissolved in dry benzene and sodium bromide was filtered off. The yellow triethylphosphine fluorenylide was recrystallized three times from dry benzene, m.p. 156–158°. (Found: C 80.26; H 8.15; Calc. for C₁₉H₂₃P: C 80.82; H 8.21.)

Phenyldiethylphosphine fluorenylide was prepared from phenyldiethylfluorenylphosphonium bromide in an analogous way. The product was recrystallized two times from benzene, m.p. 204–207°. (Found: C 83.48; H 6.98. Calc. for C₂₃H₂₃P: C 83.61; H 7.02.)

Tributylphosphine fluorenylide, after an analogous preparation and two recrystallizations, had m.p. 124°, lit.¹⁵ 123–124°.

Diphenylethylphosphine fluorenylide. The preparation was carried out as for the triethylphosphine derivative, m.p. 169–171°, after two recrystallizations from benzene. (Found: C 85.41; H 6.09. Calc. for C₂₇H₂₃P: C 85.68; H 6.12.)

Rate measurements. The rates of reaction of the ylides with *p*-nitrobenzaldehyde were determined by following the ultraviolet absorption of the reaction solution at the absorption maximum of *p*-nitrobenzalfluorene at 358 m μ . The concentration of *p*-nitrobenzalfluorene was calculated from the equation

$$X = \frac{Ef - (\epsilon_1 A_0 + \epsilon_2 B_0)d}{(\epsilon_3 + \epsilon_4 - \epsilon_1 - \epsilon_2)d}$$

where E = extinction of the reaction mixture, f = dilution before the measurements were done. ϵ_1 , ϵ_2 , ϵ_3 , and ϵ_4 = molar extinction coefficients of ylide, *p*-nitrobenzaldehyde, *p*-nitrobenzalfluorene, and phosphine oxide, respectively. A_0 = initial concentration of ylide, B_0 = initial concentration of aldehyde. The rate constants were calculated according to the equation

$$kt = \frac{2.303}{A_0 - B_0} \log \frac{A_0(B_0 - X)}{B_0(A_0 - X)}$$

Solutions of the more reactive ylides (3–6) are subject to a relatively rapid degradation also when the solvents used are thoroughly dried. The degradation proceeds under

formation of fluorenone. Because of this difficulty the solutions of the ylides had to be made up immediately before each run. In case of the ylides (4–6) corrections were made also for the degradation during the runs. The rate of the degradation process was estimated from ultraviolet measurements.

RESULTS AND DISCUSSION

The rate data for the reaction between *p*-nitrobenzaldehyde and the various phosphonium ylides are summarized in Table 1. Energies and entropies of activation have also been calculated and recorded in the same table. As can be seen from Table 1 the most reactive ylide, triethylphosphine fluorenylide, reacts about 2.5×10^3 times faster with *p*-nitrobenzaldehyde than its triphenyl analogue. Johnson and La Count¹⁵ have proposed that fluorene ylides react with carbonyl compounds by a mechanism involving rate determining betaine formation. They made several attempts to intercept the reaction between triphenyl- resp. tributylphosphine fluorenylide and several carbonyl compounds in hope to trap any betaine as its conjugate acid. No betaine hydrobromide could be detected in the reaction mixture on treatment of the latter with excess hydrogen bromide, however. The present rate data for the ylides (1–5) is in agreement with the view of Johnson and La Count that the first step in Scheme 1 is rate determining, since the most nucleophilic ylides show the fastest reaction. But, it may, as pointed out by Rüdhardt and coworkers,⁴ also be possible that the second step is rate controlling, if the rate of decomposition of the intermediate back to reactants is high. If this is so, the higher reactivity of the alkyl substituted phosphonium fluorenylides suggests that the substituents exert greater influence on the equilibrium between reactants and intermediate than on the reactivity in the olefin forming step. The replacement of phenyl with ethyl implies higher electron density on the carbanion portion of the ylide and must be expected to increase their nucleophilicity thereby strongly affecting the first step of the reaction. The result will be an increase in $K = k_1/k_{-1}$ (Scheme 1). It seems to be generally accepted that substituents which increase the electron density on the phosphorus atom will lead to decreased reactivity in the olefin forming step. A decreased reactivity in the olefin forming step will not be reflected in the overall rate, however, if the olefin forming step is the fastest. Neither will decreased reactivity in the second step be reflected in the overall rate when the second step is rate controlling, if in the equilibrium $K = k_1/k_{-1}$, K is much increased as a result of the substitution. Thus, it is impossible to make a decision between the two abovementioned mechanistic possibilities from the present kinetic data alone. It should be remembered, however, that in the Wittig reaction of unstabilized phosphoranes $k_1 \leq k_2$.⁸ This makes it improbable that $k_1 > k_2$ in the analogous reaction of stabilized phosphoranes, since the electron withdrawing substituents present in the latter ylides strongly decrease their reactivity in the first step of the reaction, whereas the olefin forming step is enhanced. Thus the most plausible mechanism appears to be a rate determining initial step followed by a fast olefin forming step.

The activation parameters are of the same order of magnitude as those found in the Wittig reaction of β -keto stabilized phosphoranes. The high negative entropies of activation point to a highly ordered transition state.

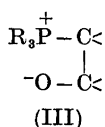
The results from the present investigation seem to indicate that both electronic and steric factors play an important role in these reactions. The relative high rate difference between triphenylphosphine fluorenylide and the diphenylethyl analogue indicates that the lower reactivity of the triphenylphosphine fluorenylide is partly due to steric reasons. The same conclusion may also be drawn from the unexpected decrease in reactivity between triethylphosphine fluorenylide and its tributyl analogue. It must be stated, however, that results from measurements of the acidities of phenacyl phosphonium salts have shown that replacement of methyl by butyl also led to a decrease in the pK_a of these compounds.¹⁷ This implies that butyl is electron withdrawing with respect to methyl. If this is so, the tributylphosphine fluorenylide ought to be less reactive than its triethyl analogue in the Wittig reaction, regardless of steric hindrance. The 6.2 kcal difference in energy of activation between diphenylethyl and triphenylphosphine fluorenylide is a reflection of the additional energy needed to overcome the steric hindrance of the third phenyl group of triphenylphosphine fluorenylide to attack on the carbonyl group of the aldehyde. The extraordinary high negative entropy of activation of the diphenylethyl derivative may be attributed to a more highly ordered transition state in this case.

A point of special interest is the evidence the kinetic results bear upon the postulated intermediacy of betaines. The evidence so far collected in favour of the formation of betaines in the Wittig reaction consists chiefly of the observation that certain betaine-lithium halide adducts can be isolated from the reaction of unstabilized ylides with aldehydes when the reaction is carried out in the presence of lithium halides. In the Wittig reaction of stabilized phosphoranes no intermediate compound has ever been isolated or detected, and in view of the influence of the solvent it appears unnecessary to postulate any intermediacy of betaines when the reaction is performed in aprotic media in the absence of additives (Lewis acids).

Solvent effects on the Wittig reaction of stable ylides have been studied by Rüchardt *et al.*⁴ In the reaction between carboethoxymethylene triphenylphosphorane and benzaldehyde a rate decrease was observed in the highly polar media dimethyl formamide (DMF) and dimethyl sulphoxide (DMSO) as compared with benzene. This finding seems inconsistent with the reversible formation of a betaine in the rate determining step of the reaction. In the course of the present study some rate measurements were performed in DMF and acetone. As can be seen from Table 1 there is a rate decrease in both media as compared with benzene. The rate decrease observed in polar media may be rationalized if it is assumed that the transition state in the rate determining step of the reaction is of a less polar character than has been hitherto usually assumed. The solvent effect may thus indicate that the reaction mechanism is better represented by a more or less completely concerted formation of the P—O bond with that of the C—C bond between ylide and aldehyde. Presumably the four-membered cyclic intermediate is formed in a reversible first step, whereafter the reaction is completed with an irreversible decomposition into phosphine oxide and olefin. Also the "phospholane effect"¹⁶ observed in the reaction of the phospholane derivative (6) is in accordance with the latter mechanism. No rate increase would be expected in the compound (6)

as compared with (3) if the rate determining step is the formation of a betaine. The situation may be different in hydrogen bonding solvents such as alcohols. The high rate increase in the Wittig reaction of stabilized phosphoranes observed in these media ^{2,4} can be ascribed to the stabilizing effect of the hydrogen bonds between solvent molecules and the activated complex.

Recent studies ¹⁸ of the Wittig reaction of β -keto-stabilized phosphoranes in benzene, DMF, and methanol have shown that the reaction in DMF is accompanied by more negative reaction entropies and higher energies of activation. These findings also argue against the formation of betaines in the rate determining step. The eclipsed conformation (III) is the only sterically likely conformation for the betaine intermediate in nonpolar media:



In more polar solvents, however, rotations about the aldehyde-ylide C-C bond ought to be less restricted in the activated state, thus leading to less negative reaction entropies.

REFERENCES

1. Fliszar, S., Hudson, R. F. and Salvadori, G. *Helv. Chim. Acta* **46** (1963) 1580.
2. Speziale, A. J. and Bissing, D. E. *J. Am. Chem. Soc.* **85** (1963) 3878.
3. Shubina, L. V., Malkes, L. Y., Zadorozhnyi, and Ishchenko, I. K. *Zh. Obshch. Khim.* **36** (1966) 1991.
4. Röchardt, C., Panse, P. and Eichler, S. *Chem. Ber.* **100** (1967) 1144.
5. Bergelson, L. D., Barsukov, L. I. and Shemyakin, M. M. *Zh. Obshch. Khim.* **38** (1968) 846.
6. Wittig, G. and Geissler, G. *Ann.* **580** (1953) 44.
7. Wittig, G. and Schöllkopf, U. *Chem. Ber.* **87** (1954) 1318.
8. Schlosser, M. and Christmann, K. F. *Ann.* **708** (1967) 1.
9. Fisher, O. *Ber.* **14** (1881) 2525.
10. Bergmann, E. D., Hirshberg, Y., Lavie, D., Sprinzak, Y. and Szmuszkovicz, J. *Bull. Soc. Chim. France* **1952** 703.
11. Horner, L. In Houben-Weyl, *Methoden der Org. Chemie* 12/1, Georg Thieme, Stuttgart 1963, p. 33.
12. Horner, L., Hoffman, H. and Wippel, H. G. *Ibid.* p. 34.
13. Grüttner, G. and Krause, E. *Ber.* **49** (1916) 437.
14. Pinck, L. A. and Hilbert, G. A. *J. Am. Chem. Soc.* **69** (1947) 723.
15. Johnson, A. W. and La Count, R. B. *Tetrahedron* **9** (1960) 130.
16. Aksnes, G. and Frøyen, P. *Acta Chem. Scand.* **24** (1970) 809.
17. Johnson, A. W. and Amel, R. T. *Can. J. Chem.* **46** (1968) 461.
18. Berg, T. *Private communication.*

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