THE EFFECT OF THE PHOSPHORYL SUBSTITUENTS ON THE STEREOCHEMISTRY OF THE HORNER REACTION

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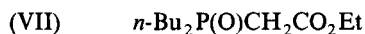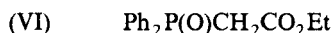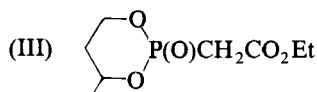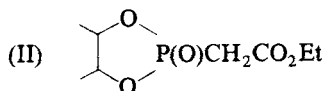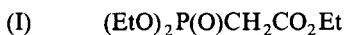*Department of Chemistry, University of Bergen, N-5014 Bergen University, Norway*

The stereochemistry of the olefin forming reaction of various phosphoryl stabilized carbanions and aldehydes in ethanol is reported. The aromatic aldehydes react with acyclic phosphoryl stabilized carbanions yielding the *trans* isomers stereoselectively, whereas the 5- and 6-membered cyclic phosphonates (II and III) resulted in high yields of *cis* isomeric olefins. The aliphatic aldehydes give rise to considerable amounts of *cis* olefins also, decreasing in the series phosphonates, phosphinates and phosphine oxides, respectively. The stereochemical results are discussed in terms of pentacoordinated reaction intermediates.

INTRODUCTION

The stereochemistry of the Horner reaction has been extensively studied since Horner and coworkers[1] first described the synthesis of olefins from phosphoryl stabilized carbanions and carbonyl compounds. However, few attempts have been made to compare the reactivity and stereochemical selectivity of phosphonates, phosphinates and phosphine oxides in the reaction with carbonyl compounds under similar conditions.[2,3] Nearly all the comparisons have been drawn using reagents with identical phosphoryl containing group (usually $(EtO)_2P(O)$-), but differing in the nature of the carbanionic group. Previously we have reported the kinetic of the Horner reaction of various phosphoryl stabilized carbanions and substituted benzaldehydes in ethanolic sodium ethoxide solution.[4] The reaction rate was found to be greatly influenced by the substituents in the phosphoryl group, and it was therefore natural also to investigate the stereochemistry of the same Horner reactions under similar reaction conditions. The following phosphoryl compounds were chosen:

(I) $\quad (EtO)_2P(O)CH_2CO_2Et$

(II) $P(O)CH_2CO_2Et$

(III) $P(O)CH_2CO_2Et$

(IV) $\quad Ph(EtO)P(O)CH_2CO_2Et$

(V) $\quad n\text{-}Bu(EtO)P(O)CH_2CO_2Et$

(VI) $\quad Ph_2P(O)CH_2CO_2Et$

(VII) $\quad n\text{-}Bu_2P(O)CH_2CO_2Et$

RESULTS AND DISCUSSION

From our previously kinetic studies of the Horner reaction it was concluded that the rate data suggested a pentacoordinated intermediate during the reaction. Stereochemical[5,10] and ^{31}P-NMR-studies[11] of the Horner reaction using 5-membered cyclic phosphonates have also given strong support for the presence of pentacoordinated intermediates. The following reaction scheme can be used to explain the formation of *cis* and *trans* olefins:
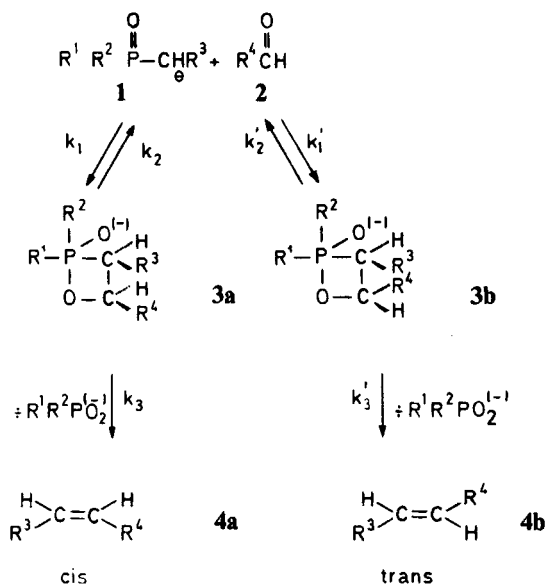
SCHEME 1

The stereochemistry of the olefins depends according to Scheme I on the relative decomposition rate constants k_2 and k_3, k'_2 and k'_3 of the stereoisomeric intermediates **3a** and **3b** to products and reactants, as well as the rate of the first step of reaction, k_1, respectively k'_1.[2] The reversible character of the intermediate will be more predominant when $k_2 \gg k_3$, resp. $k'_2 \gg k'_3$. Towards aromatic aldehydes it has been shown that k_2 is usually large in the Horner reaction.[12-14] Further it is generally accepted that the most stable *trans* olefins are formed as a result of thermodynamic control. Inspection of Table I where the yields of *cis* and *trans* products are recorded for the various phosphoryl compounds and aldehydes studied, show that benzaldehyde gives predominantly *trans* products with acylic phosphoryl compounds in accordance with the thermodynamic control postulate.

The cyclic phosphoryl compounds (II and III) gave however, rise to considerable amounts of the *cis* isomers in the reactions with benzaldehyde. The results are in agreement with earlier studies of cyclic phosphonates,[6,10] and can be explained by a decrease in the reversible character of the pentacoordinated intermediate. The effect is largest for the five-membered cyclic phosphonate (II), reflecting the greatest release in ring strain upon passing from the tetrahedral phosphoryl compound to the

pentacoordinated intermediate,[15] resulting in a corresponding increase in the rate ratio k_1/k_2.

Due to the insignificant amounts of *cis* isomers obtained in the reactions between the acyclic phosphoryl compounds and benzaldehyde it was not possible to evaluate the stereoselectivity of the reactions between various phosphoryl carbanions and benzaldehyde.
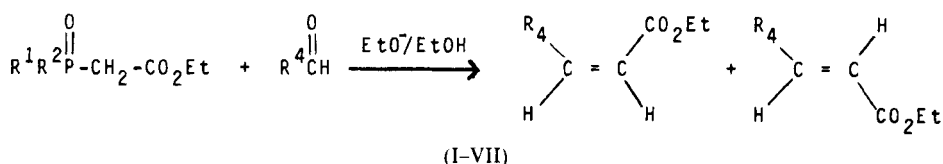
From Table I it is however, seen that the Horner reaction with aliphatic aldehydes give measurable amounts of *cis* isomers for most of the compounds studied. These results are also in accordance with earlier studies of phosphonate carbanions and aliphatic aldehydes.[16] Branched substituents at the carbonyl carbon have also been shown to increase the amount of *cis* isomers in the products.[17,18]

The increased amounts of *cis* olefins on passing from aromatic to aliphatic aldehydes are compatible with the proposed two step mechanism. An aliphatic aldehyde will retard the first step of the reaction because of the lower reactivity of the carbonyl group towards nucleophilic attack. However, the olefin forming step will be enhanced and thus resulting in less equilibration of the intermediates (**3a**) and (**3b**).

The results in Table I show that there is a decrease in the amounts of *cis* isomers in the reaction of aliphatic aldehydes upon passing from phosphonates to phosphine oxides. We have previously detected a decrease in the reaction rate of the aromatic aldehydes within the same series, reflecting that phosphine oxides have the lowest ability to stabilize a pentacoordinated intermediate.[4]

TABLE I

Isomer distribution in reactions of aldehydes with
(I–VII) in ethanolic sodium ethoxide solution

(I–VII)

| Substituents R			R⁴ = Ph		R⁴ = Pr		R⁴ = i-Pr	
R^3 = const. = -CO$_2$Et	R^1	R^2	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
(I)	EtO	EtO	~ 2	98[1]	5	95	16	84
(II)		O / O	65	35	62	38	70	30
(III)		O / O	30	70	52	48	65	35
(IV)	Ph	EtO	1	99[a]	2	98	5	95
(V)	Bu	EtO	< 1	> 99[a]	1	99	3	97
(VI)	Ph	Ph	< 1	> 99[a]	1	99	2	98
(VII)	Bu	Bu	< 1	> 99[a]	< 1	> 99	< 1	> 99

[1]Similar results were obtained when the phenyl ring was substituted with a *p*-Cl- or a *p*-MeO-group.

As the alkoxy groups in the phosphonate (I) are successively replaced by phenyl or alkyl groups (Table I), the stability of the corresponding pentacoordinated intermediates decreases (the ratio k_2/k_1 increases). The reaction will therefore proceed in the directions towards thermodynamic control of the intermediates (3a) and (3b), resulting in increased formation of *trans* isomers also from aliphatic aldehydes.

Recently Bestmann[19] has postulated a new mechanism for the Wittig reaction, a mechanism which he has also proposed for the Horner reaction. The phosphoryl stabilized carbanion (1) is assumed to react with the carbonyl compound (2) via the conformational transition state (5), (Scheme 2). As the negative charge on the carbonyl oxygen is being developed in the transition state, the oxygen is oriented towards the electrophilic phosphorus atom. Rotation around the C—C bond takes place in such a manner that the P—O bond is formed almost simultaneously, giving the intermediate (3a) in a *cis*-conformational state.

The rules governing the nucleophilic attack on phosphorus are based on apical attack of the nucleophile and apical departure of the leaving group.[15] The breaking of the P—C bond which must take place in the course of the reaction, can thus be achieved only if a structural reorganisation (pseudorotation) takes place so that the C—P bond becomes axial, as shown in (6).

According to Bestmann,[19] in the course of this pseudorotation, or after the trigonal bipyramidal structure (6) has been formed, the C—P bond collapses without a simultaneous opening of the P—O bond, and the carbanion (7) is formed, which on elimination of the dialkyl phosphonate anion gives the *cis* olefin (4a).
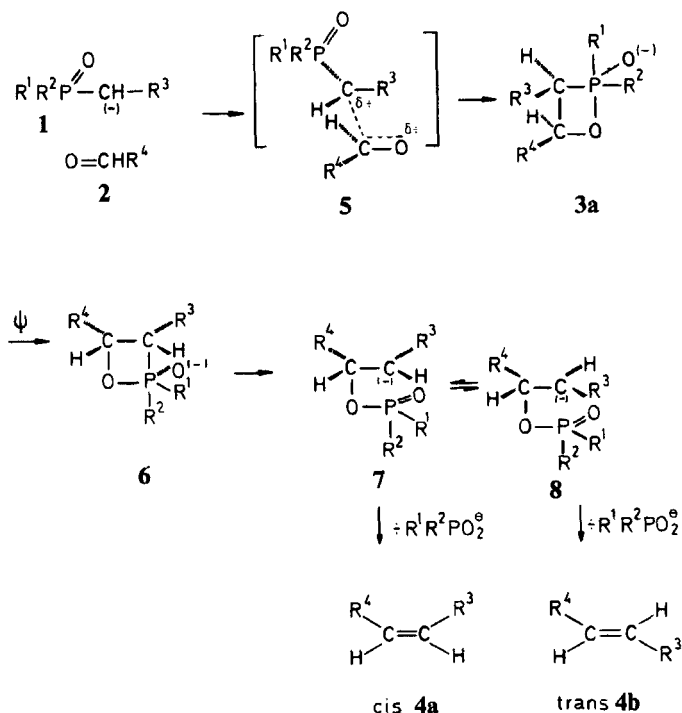
SCHEME 2

With electron withdrawing groups (e.g R^3 = CO_2Et), the carbanion is thought to be stable enough for rotation about the C—C bond to compete with the elimination rate, and the thermodynamically more stable *trans* olefin (**4b**) results, via carbanion (**8**).

There is a distinct difference in the isomer content of olefins prepared from phosphonate as compared to those formed from Wittig reagents. The former usually give a much higher percentage of the *trans* isomer.[2,3]

Bestmann[19] explains these results by the lesser leaving group ability of a dialkyl phosphate anion as compared to the triphenyl phosphine oxide. The elimination rate therefore decreases, and rotation around the C—C bond in (**7**) to the more stable conformation intermediate (**8**) takes place, which on elimination yields *trans* olefins.

Some of our stereochemical results for acyclic phosphoryl compounds seem to support this view. As the leaving group in (**7**) is changed in the series phosphate (R^1 = R^2 = EtO), phosphonate, phosphinate (R^1 = R^2 = Bu or Ph), keeping the carbanion moiety constant (R_3 = CO_2Et), the rate of elimination decreases since the base strength of the anions increases in the same series.[20] The time interval in which rotation to (**8**) can take place is increased, and a lower *cis/trans* ratio in the products is obtained.

However, the very large amounts of *cis* isomers obtained in the reactions of aldehydes with the cyclic phosphonates (II) and (III) cannot be explained by this mechanism. The first reaction step seems here to be more important in determining the stereochemistry of the olefins produced.

In the reactions with aromatic aldehydes it also seems to be the first step which determines the stereochemistry of the products, whereas with aliphatic aldehydes, the last step seems to become more important. Clearly a delicate balance of steric and electronic effects in the carbonyl compounds as well as the phosphoryl stabilized carbanions is operative in the course of the Horner reaction.

EXPERIMENTAL

Materials. The preparation of the phosphoryl compounds has previously been described.[4]

2-Carbethoxymethyl-diethylphosphonate, (I). Bp. 129°C (5 mm), n_D^{22} 1.4306, Reported[5] Bp. 109–109.5°C (0.8 mm), n_D^{18} 1.4316.

2-Carbethoxymethyl-4,5-dimethyl-2-oxo-1,3,2-dioxaphospholane (II). Bp. 138°C (0.05 mm), n_D^{22} 1.4517, Reported[6] Bp. 135°C (0.3 mm), n_D^{20} 1.4550.

2-Carbethoxymethyl-4-methyl-2-oxo-1,3,2-dioxaphosphoriane, (III). Bp. 136°C (0.01 mm), n_D^{22} 1.4610.

o-Ethyl-phenyl-2-carbethoxymethyl phosphinate, (IV). Bp. 122–23°C (0.05 mm), n_D^{22} 1.5080, Reported[7] Bp. 142–8° < (0.9 mm), n_D^{20} 1.5078.

o-Ethyl-butyl-2-carbethoxymethyl-phosphinate, (V). Bp. 78°C (0.04 mm), n_D^{22} 1.4465.

Diphenyl-2-carbethoxymethyl-phosphineoxide, (VI). Mp. 76–77°C, Reported[8] 75.5–76.5°C.

Di-n-butyl-2-carbethoxymethyl-phosphineoxide, (VII). Bp. 109°C (0.05 mm), n_D^{22} 1.4619, Reported[9] Bp. 145–46°C (2 mm), n_D^{22} 1.4625.

The aldehydes were distilled prior to use. Sodium ethoxide solution were prepared by dissolving fresh cut sodium metal in dry ethanol under Argon atmosphere (Conc. ~ 0.1 M), and standardized against hydrochloric acid.

Method. Equimolar amounts of the reagents were mixed under an Argon atmosphere in dry ethanol, (final concentration ~ 0.05 M). After appropriate reaction times (depending on substrate reactivity, 5–150 min.), the reaction mixtures were neutralized with dilute hydrochloric acid. The isomers in the olefin mixture of the various products were then analyzed by GLC on a 10% Carbowax 20 M column (4 m). Injector and column temperature were kept as low as possible to prevent isomerizations during analysis. A check was undertaken by running pure *cis* or *trans* isomers (obtained by preparative GLC) prior to each new analysis.

REFERENCES

1. L. Horner, H. Hoffman and H. G. Wippel, *Chem. Ber.*, **91**, 61 (1958).
2. W. S. Wadsworth, Jr., *Org. React.*, **25**, 73 (1978).
3. B. J. Walker in "Organophosphorus reagents in organic synthesis," (Ed. by J I. Cadogan), (Academic Press, London, 1979), Ch. 3.
4. R. O. Larsen and G. Aksnes, *Phosphorus and Sulphur*, in press.
5. J. Wolinsky and K. L. Ericson, *J. Org. Chem.*, **30**, 2208 (1965).
6. E. Breuer and D. M. Bannett, *Tetrahedron*, **34**, 997 (1978).
7. N. N. Melnikov, Ya. A. Mandelbaum, V. I. Lomaskina and V. S. Livshits, *Zh. Obshch. Khim.*, **31**, 3949 (1961).
8. E. S. Petrov, E. N. Tsvetkov, M. I. Terekhova and R. A. Kabachnik, *Czv. Akad. Nauk SSSR, Ser. Khim.*, **3**, 534 (1976).
9. R. A. Malevannaya, E. N. Tsvetkov and M. I. Kabachnik, *Zh. Obshch. Khim.*, **41**, 2359 (1971).
10. E. Breuer and D. Bannet, *Tetr. Lett.*, 1141 (1977).
11. E. Breuer, S. Zbaida and E. Segall, *Tetra. Lett.*, 2203 (1979).
12. D. Danion and R. Carrie, *Tetrahedron*, **28**, 4223 (1972).
13. B. Dechamps, G. Lefebre and J. Seyden-Penne, *Tetrahedron*, **28**, 4209 (1972).
14. T. Bottin-Strzalko, *Tetrahedron*, **29**, 4199 (1973).
15. P. Gillespie, F. Ramirez, I. Ugi and D. Marquarding, *Angew. Chem., Internat. ed.*, **12**, 91 (1973).
16. D. E. Mcgreer and N. W. K. Chin, *Can. J. Chem.*, **46**, 2225 (1968).
17. G. Jones and R. F. Maisey, *Chem. Commun.*, 543 (1968).
18. T. H. Kinstle and B. Y. Mandanas, *Chem. Commun.*, 1699 (1968).
19. H. J. Bestmann, *Pure Appl. Chem.*, **51**, 515 (1979); **52**, 771 (1980).
20. M. I. Kabachnik, T. A. Mastrukova, A. E. Shipov and T. A. Melentyreva, *Tetrahedron*, **9**, 10 (1960).