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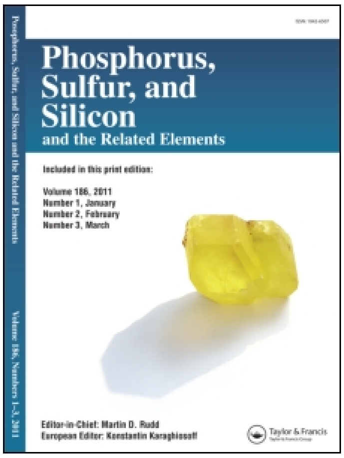

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A General Hypothesis for the Mechanism of the Wittig Reaction

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A GENERAL HYPOTHESIS FOR THE MECHANISM OF THE WITTIG REACTION

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Abstract Arguments are presented that an ionic mechanism is operative in the Wittig reaction when a metal ion is a part of the transition state leading to oxaphosphetane formation but that formation of a spin paired diradical precedes oxaphosphetane formation in other cases.

INTRODUCTION

In order to evaluate better our previous findings that $N_{2\underline{p}}$-P(IV)[1] and $O_{2\underline{p}}$-P(IV)[2] through space interactions in lithium ion-catalyzed Wittig reactions lead to greater cis-trans ratios of alkenes than in the cases of analogous reactions in which no such through space interactions are operative, we have now made a thorough study of metal ion effects in the latter types of reaction.

RESULTS

In the reactions of benzylidenediphenylmethylphosphorane with various aldehydes (0.005 mole scale) in 30 mL of anhydrous THF at -78°C in the presence of lithium chloride, the yields and cis-trans ratios of the expected alkenes are: 94%, 66:34 with benzaldehyde; 97%, 67:33 with p-methylbenzaldehyde; 90%, 54:46 with p-chlorobenzaldehyde; 81%, 68:32 with p-methoxybenzaldehyde; 88%, 48:52 with furfural; 88%, 74:26 with 1-methylpyrrole-2-carboxaldehyde; 88%, 50:50 with pivalaldehyde; 86%, 30:70 with p-nitrobenzaldehyde; 92%, 42:58 with p-(trifluoromethyl)benzaldehyde. When the ratio of LiCl to p-nitrobenzaldehyde (and ylide) is raised from 1:1 to 2:1, the cis:trans ratio of p-nitrostilbenes is raised to 36:64; when the ratio of LiCl to aldehyde is raised to 3:1, the limit for maintenance of a homogeneous solution, the cis:trans ratio of alkenes rises to 42:58. These data indicate that increasing sequestration of Li^+ by solvent occurs as the basicity of the aldehyde decreases.

When sodium chloride is present rather than lithium chloride, the reaction with benzaldehyde gives a 98% yield of stilbenes, the cis-trans ratio being 19:81; with p-methylbenzaldehyde, 84%, 17:83; with p-chlorobenzaldehyde, 86%, 25:75; with p-methoxybenzaldehyde, 87%, 18:82; with furfural, 82%, 30:70; with 1-methylpyrrole-2-carboxaldehyde, 93%, 16:84; with pivalaldehyde, 81%, 23:77; with p-nitrobenzaldehyde, 80%, 27:73; with p-(trifluoromethyl)benzaldehyde, 85%, 25:75.

When potassium chloride is present, the data are: with benzaldehyde, 96%, 18:82; with p-methylbenzaldehyde, 96%, 17:83; with p-chlorobenzaldehyde, 88%, 22:78; with p-methoxybenzaldehyde, 92%, 17:83; with furfural, 95%, 25:75; with 1-methylpyrrole-2-carboxaldehyde, 99%, 9:91; with pivalaldehyde, 92%, 21:79; with p-nitrobenzaldehyde, 89%, 34:66; with p-(trifluoromethyl)benzaldehyde, 95%, 24:76.

Unlike data presented by Maryanoff et al.[3] for fundamentally different systems, the concentration effects in the reactions described above are very small. For example, the ratio of cis:trans stilbene changes only from 66:34 to 69:31 when the volume for a 0.005 mole scale reaction of benzaldehyde with ylide, with LiCl present, is changed from 30 mL to 80 mL. Even smaller changes are noted for the reactions of the other aldehydes. Also, no crossover products in any significant amounts are found when extraneous aldehydes are added to the reaction mixtures shortly after the original reagents are mixed.[4,5] Thus, no compelling evidence for reversal of oxaphosphetane formation is noted.

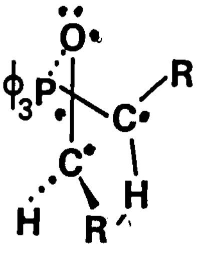
Additional evidence that these reactions, with LiCl, NaCl, or KCl present, occur under kinetic control and without any significant degree of equilibrium or Wittig reversal was obtained from ^{31}P NMR studies carried out at -78°C. For reactions carried out in an NMR tube, with the spectrum being taken within a minute of the mixing of the reagents, only signals attributable to the ylide (*ca.* +1 to -5 δ) and to the phosphine oxide (*ca.* +25 to +30 δ) could be detected. Only in the case of the reaction of the ylide with pivalaldehyde, with sodium chloride present, could a very small signal in the region expected for an oxaphosphetane ($\delta = -68.7$) be detected. Thus, as in our previous study[1] and in other similar cases,[4,5] the reactions are very fast, and the energy barriers for pseudorotation of oxaphosphetanes[6] and for their conversion to products are small compared to the energy barriers for reversal of oxaphosphetane formation.[7]

As in the case with stabilized ylides,[8] we have found that, with our semistabilized ylides, the stereochemistry of alkene formation (*cis*-*trans* ratio) is determined by the time that oxaphosphetane intermediates have been formed; in fact the stereochemistry is determined when the new carbon to carbon bond has been formed. Specifically, the reactions of *erythro*-(2-hydroxy-1,2-diphenylethyl)methyldiphenylphosphonium iodide, prepared independently by the epoxide route,[9-11] with *n*-butyllithium, sodium *bis*(trimethylsilyl)amide, or potassium *bis*(trimethylsilyl)amide in anhydrous THF at -78°C give exclusively *cis*-stilbene in 88-97% yields. Also, examination of the ^{31}P NMR spectrum of each reaction mixture at -78°C within a minute of the mixing of the reagents reveals only the presence of the phosphine oxide product.

Bergelson *et al.*[12] have reported the existence of an anion effect on alkene ratios formed in some Wittig reactions, a fact which has largely been ignored by later workers. We have found that, in the reaction of benzyldiphenylmethylphosphonium iodide with sodium *bis*(trimethylsilyl)amide under the usual conditions, the *cis*:*trans* ratio of stilbenes produced is 69:31, as against a ratio of 19:81 when potassium *bis*(trimethylsilyl)amide is used as the base.[13] The ratio of 18:82 is obtained in the salt free reaction, as when KI is present in the reaction mixture. Similar results are obtained when pivalaldehyde is used in place of benzaldehyde. Here the *cis*-*trans* ratios of alkenes are about 66:34 in the presence of LiI or NaI, and 21:79 in the presence of KI.

DISCUSSION

The results cited above and additional data from the literature[14] suggest that an ionic mechanism is operative when a metal ion is a part of the transition state leading to oxaphosphetane formation but that formation of a spin paired diradical precedes oxaphosphetane formation in other cases. The mechanism of the ionic pathway has been discussed previously,[2] but in an overly simplified manner.[15] The mechanism of the spin paired diradical mechanism is of greater interest because it can possibly explain the heretofore most puzzling feature of Wittig reactions; *viz.*, why the reaction of unstable ylides with aldehydes gives mainly *cis*-alkenes under a wide variety of conditions; why semistable ylides give variable mixtures of geometrically isomeric alkenes; and why stable ylides give mainly *trans*-alkenes. The Vedejs[4] model for the geometry of the transition state can be used to illustrate the arguments.[16] The crisscrossed approach of an aldehyde to an ylide under conditions wherein no metal ion is complexed to either reagent gives rise to mainly two spin paired diradicals, *1* and *2*, of which *1* has less steric strain and is the predominant initial unstable intermediate. It should be noted that the radicaloid centers of *1* occupy *p* orbitals that are orthogonal. Thus, substantial bond reorganization would be required for *1* to undergo ring closure to form the *cis*-oxaphosphetane. Although there would be substantial stabilization of the Linnett[17,18] radicaloid center of *1*, there would be little stabilization of the other radicaloid center if R were a simple alkyl group (arising from an unstable ylide). Thus, bond reorganization and ring closure to the _cis_-oxaphosphetane would be relatively uncomplicated. Accordingly, in the absence of any significant degree of Wittig reversal, the _cis_-alkene would predominate. On the other hand, if R is an aryl group (arising from a semistable ylide), a well stabilized benzylic radicaloid center would be present in _1_. Owing to the substantial stabilization of _1_, because of the presence of both Linnett and benzylic radicaloid centers, its half life would be sufficient to permit rotation about either or both of the P-C and O-C bonds during bond reorganization and ring closure, thereby permitting a significant degree of isomerization to the thermodynamically favored _trans_-oxaphosphetane to occur. Of course, if R is an acyl, cyano, or similar group (arising from a stable ylide), the stabilization of _1_ will be even greater, thus permitting almost complete isomerization to the _trans_ isomer in the formation of the oxaphosphetane.[19]



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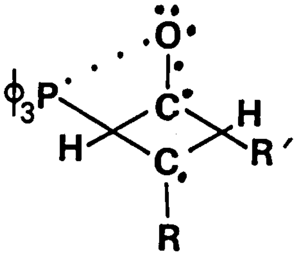

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14. W. E. McEwen, B. D. Beaver and J. V. Cooney, Phosphorus Sulfur, 25, 255 (1985).
15. Eight stereoisomeric oxaphosphetanes can be formed in the initial stage of the reactions under discussion here. Two of them (enantiomers), which would lead to cis-alkene, arise via less sterically hindered transition states than the others.
16. Theoretical chemists[7] believe that, in the Wittig reaction under salt-free conditions, C-C bond formation runs slightly ahead of P-O bond formation. However, their model bears little relationship to real Wittig reactions.
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