The Stereochemistry of Wittig Olefin Synthesis

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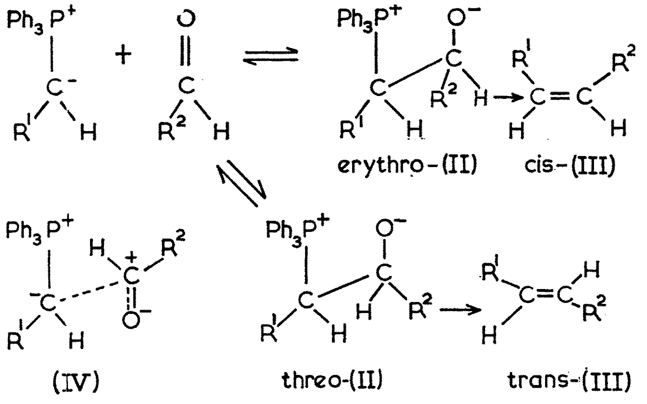
Summary A trigonal-bipyramidal co-ordination complex of ylide and aldehyde is suggested to explain the stereochemistry of the Wittig olefin synthesis.

UNTIL recently it was thought that the Wittig olefin synthesis produced largely *trans*-disubstituted olefins,[1] but that the *cis* : *trans*-ratio could be increased in some cases by the use of special polar solvents and added salts.[2] Supposedly this was due to solvation and ion-pair complex formation with various polarized transition states or intermediates, *e.g.* the betaines (II). The electronic effect of substituents on the nucleophilic and electrophilic character of ylide and carbonyl components of the reaction was also shown to affect the *cis* : *trans*-ratio of the resulting olefins.[3]

While resonance-stabilized ylides such as (I; $R = CO_2Et$) react with aldehydes to give almost exclusively *trans*-olefins, it has become apparent[4,5] that nonstabilized ylides (I; R = alkyl) give predominantly the thermodynamically less stable *cis*-olefins. This is particularly true in salt-free nonpolar solvents at low temperatures, where the ratio of *cis*- to *trans*-olefins is sometimes greater than 95 : 5.[4]

The Wittig olefin synthesis is usually pictured as below, where *erythro*-betaine (II) is the precursor of *cis*-olefin (III) and *threo*-betaine (II) leads to *trans*-product. It has been shown in a number of cases that betaine formation is reversible and where conversion of betaine into olefin is slow, the less sterically hindered *threo*-betaine is the more thermodynamically favoured form (see discussions by Johnson[1a] and Schlosser[4]). Schlosser[4] also showed that deprotonation of *erythro*-(II), and then re-protonation, results in nearly complete epimerization to *threo*-(II).

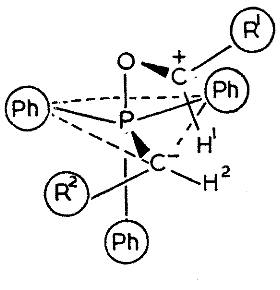


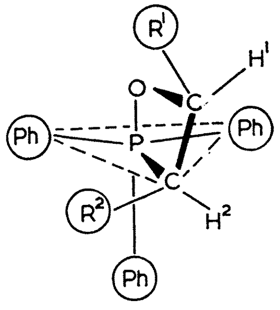
No convincing explanation has yet been given for the preferred formation of the less stable *erythro*-betaines and *cis*-olefins in the reaction of nonstabilized ylides with aldehydes in nonpolar media. Bergelson[6] has recently attributed the preferred formation of *erythro*-betaine to attraction of carbonyl oxygen to one of the phenyl groups attached to phosphorus in the ylide.

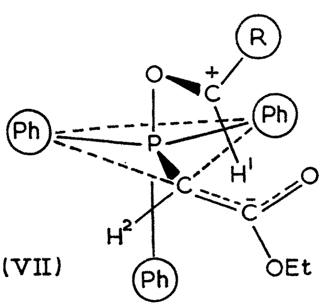
If one considers, as is usually done, that C–C bond formation between ylide and aldehyde is the first step of the reaction, the only sterically likely conformation for the transition state leading to *erythro*-betaine is that depicted in (IV), with greatest separation of opposite charges on phosphorus and oxygen. While this may represent the reaction path in polar solvents or in the presence of salts,[2] it hardly seems likely in nonpolar media. Attempts to bring ylide carbon and aldehyde carbon together in any other conformation would favour *threo*-betaine formation on steric grounds.

There are two factors which could conceivably have a steric effect on betaine formation which have not been adequately discussed. One is the steric configuration of substituents on phosphorus (generally written noncommittally as above),† and the other, whether the carbonyl oxygen co-ordinates with phosphorus before C–C bond formation takes place. This latter point has been considered briefly by Bergelson[2] but soon dismissed because he thought from steric considerations that prior co-ordination of oxygen on phosphorus would invariably give *threo*-betaines and *trans*-olefins.‡

If one considers models of such co-ordination complexes


(V)


(VI)


(VII)

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† Johnson (ref. 1a) pictured the cyclic transition state for elimination of triphenylphosphine oxide from a betaine with trigonal-bipyramidal phosphorus, but did not consider the stereochemical consequences.

‡ Initial co-ordination of oxygen on phosphorus was also considered (personal communication from Dr. P. F. Beal) to offer a possible explanation for the ready reaction of alkyltriphenylphosphonium halides with sodium salts of α-hydroxymethylene ketones, which results in a typical Wittig olefination of the potentially aldehydic hydroxymethylene group (P. F. Beal, J. C. Babcock, and F. H. Lincoln, *J. Amer. Chem. Soc.*, 1966, **88**, 3131).

using trigonal-bipyramidal phosphorus with oxygen complexed at an apical position[7] and with the ylide carbon equatorial (necessary for subsequent bond formation with the aldehyde), the least sterically hindered position for the aldehyde is as shown in (V). This model has the bulky aldehyde alkyl group (R^1)§ directed upwards, away from the equatorial substituents around phosphorus, and with the aldehyde hydrogen directed downwards into the least sterically crowded trisection of the equatorial plane, between H^2 and Ph. Now the formation of a bond between C^+ and C^- is most easily accomplished by a small anticlockwise rotation about the C^+–O bond, giving the *erythro*-intermediate, pictured now as (VI).¶ While this brings the R^1 and R^2 groups into an eclipsed conformation, the alternate mode of rotation (clockwise), about C^+–O to give the *threo*-intermediate requires greater rotation and movement of groups and serious interaction of R^1 with the closest equatorial Ph group.

This picture explains the observed stereochemical consequences of the reaction of nonstabilized ylides in nonpolar media, but need not operate exclusively in the presence of polar additives which could co-ordinate with phosphorus more strongly than does carbonyl oxygen. It might also be modified to account for the preponderance of *trans*-olefins produced from stabilized ylides (*i.e.*, with R = CO_2Et) with aldehydes. The electron-rich ylide substituent CO_2Et in this case would tend to orient the phosphorus-co-ordinated aldehyde toward the trisection which contains the CO_2Et group, in spite of steric effects, as in (VII). Now, bond formation between C^+ and C^- performed as above, forms the *threo*-intermediate, and finally *trans*-olefin.

I acknowledge helpful discussion with Drs. R. C. Kelly and J. B. Hester of these laboratories.

(*Received, April 3rd,* 1969; *Com.* 472.)

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§ It seems that the greater the steric hindrance of the aldehyde component, the greater is the proportion of *cis*-olefin formed. While a 6-*exo*-formylbicyclo[3,1,0]hexane reacted with hexylidenetriphenylphosphorane to give 80:20 ratio of *cis*- to *trans*-olefins, only *cis*-olefin could be detected from the corresponding *endo*-aldehyde (U. Axen, F. H. Lincoln, and J. L. Thompson, *Chem. Comm.*, 1969, 303).

¶ The intermediate (VI) is not pictured as the betaine, but as the oxaphosphetane, the immediate precursor of olefin and triphenylphosphine oxide. There seems to be no compelling need to postulate a betaine intermediate in this case, since even at −30° no evidence for betaines could be found (ref. 4) and the rate of formation of olefin from intermediate is faster than the initial combination of ylide and aldehyde (ref. 6). An attempt was made to detect intermediates in the reaction of ethoxycarbonylmethylenetriphenylphosphorane and n-heptanal in C_6D_6 at 35° by n.m.r. spectroscopy. No proton resonances were detected which could not be ascribed either to starting materials or the expected products. It seems that only when the reaction takes place in the presence of salts or polar solvents (co-ordination on phosphorus?) can betaines be intercepted (ref. 4). Also, one crystalline ylide–ketone adduct, albeit of a special type, was shown to possess the cyclic oxaphosphetane structure by *X*-ray crystallographic and n.m.r. spectral studies (G. H. Birum and C. H. Matthews, *J. Org. Chem.*, 1967, **32**, 3554.)

[1] (a) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, 1966; (b) S. Trippett, *Quart. Rev.*, 1963, **17**, 406.

[2] L. D. Bergelson and M. M. Shemyakin, *Pure and Appl. Chem.*, 1964, **9**, 271; *Angew. Chem. Internat. Edn.*, 1964, **1**, 250; *Tetrahedron* 1963, **19**, 149. See, however, H. O. House, V. K. Jones, and G. A. Frank, *J. Org. Chem.*, 1964, **29**, 3327.

[3] R. Ketcham, D. Jambotkar, and L. Martinelli, *J. Org. Chem.*, 1962, **27**, 4666; H. O. House and G. H. Rasmussen, *ibid.*, 1961, **26**, 4278; A. W. Johnson and V. L. Kyllingstad, *ibid.*, 1966, **31**, 334.

[4] M. Schlosser and K. F. Christmann, *Annalen*, 1967, **708**, 1, and earlier references therein.

[5] W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike and J. L. Thompson, *J. Amer. Chem. Soc.*, 1968, **90**, 5895.

[6] L. D. Bergelson, L. I. Barsukov, and M. M. Shemyakin, *Zhur. obshchei Khim.*, 1968, **38**, 846.

[7] F. H. Westheimer, *Accounts Chem. Res.*, 1968, **1**, 70 and references therein.