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On the Effect of Cyclodextrin on the Z/E-selectivity of Wittig Reactions with Semistabilized Ylides.

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Abstract: The Z/E-selectivity of Wittig reactions between semistabilized ylids and aromatic aldehydes is affected by the addition of host molecules such as cyclodextrins (CD) An increase in the Z-selectivity from 57 to 92% has been reached with DMF as solvent and an increase in the E-selectivity from 67 to 80% has been reached with ethanol as solvent for the same Wittig reaction. Reactions with arenes with bulky substituents which prevent complexation with cyclodextrins are less affected Our results are discussed in the light of recent results on the mechanisms for the Wittig reaction and are best rationalized in terms of Vedejs four-center mechanism

The mechanism(s) of the Wittig reaction have been the topic of many investigations[1] but still no generally accepted picture has emerged. The recent experimental evidence from Vedejs's laboratory that betaines can not be intermediates in the reaction is indeed a very interesting observation.[2] We have addressed the problem of stereoselective Wittig reactions because of a need to form *Z*-double bonds selectively by Wittig reactions with semistabilized ylides i.e. ylides from phosphonium salts of a-halomethyl arenes. Such Wittig reactions give under normal conditions mixtures of *Z*- and *E*-isomers. The *Z*-selectivity depends on a number of factors and it can usually be increased by a proper choice of solvent i.e. N,N-dimethylformamide (DMF) or dimethyl sulphoxide (DMSO) and by keeping the reaction temperature as low as possible. For the synthesis of macrocycles linked by double bonds by Wittig reactions, high *Z*-selectivity in the different steps is a prerequisite.[3] High *Z*-selectivity is of equal importance for the synthesis of isomers of oligo-(paraphenylenevinylenes) for mechanistic studies of photoinduced multiple *Z*/*E*-isomerizations.[4]

Recently, Tsukamoto and Schlosser have presented an elegant method to achieve high *Z*-selectivity in Wittig reactions with semi-stabilized ylides.[5] By the use of tris(2-methoxy-methoxyphenyl)phosphine groups in the ylides and low reaction temperatures in THF *Z*/*E* ratios as high as 95:5 has been achieved. Methods to reach high *Z*-selectivity in Wittig reactions with more reactive ylides as well as with more stable ylides have previously been developed.[6] Parallel to this work we have tried another approach to the same problem which is presented here.

One conceivable way to improve the *Z*-selectivity of a Wittig reaction would be to change the size of the substituents and thus enhance the steric effects in the transition state. This can be effected without a significant change of the reactivity of the substituents by weak host-guest complexation between the substituents in the aldehyde or/and the ylide. It is well known that cyclodextrins form complexes with a wide range of phenyl derivatives and thus it seems as if cyclodextrins could be good hosts for improving the *Z*-selectivity of a Wittig reaction with semistabilized ylides and aromatic aldehydes. In DMF or ethanol, complex formation should occur, which might result in a change of the *Z*-selectivity in a desired way. Besides, a clear effect on the stereoselectivity by the use of cyclodextrin might give some hints to the mechanism of the Wittig reaction A prime target would be to clarify the effect of cyclodextrin on reactions with aromatic aldehydes and semistabilized ylides with the ability to form host-guest complexes. The next step would be to compare these results with results from the same reactions with aromatic groups with bulky substituents which prevent complexation e.g. *t*-butyl groups.

RESULTS

For aldehydes and ylides with the ability to form complexes with cyclodextrin, the addition of cyclodextrin to the Wittig reaction gives a considerable increase of the *Z*-selectivity in DMF reactions at low temperature. When the reactions are run in ethanol, the *E*-selectivity increases. In the reactions with aromatic groups with bulky substituents which prevent complexation, the cyclodextrin does not change the stereoselectivity significantly. The results of the addition of cyclodextrin to the Wittig reactions of the types mentioned above are presented in Tables 1 and 2.

Table 1 The *Z*/*E* ratios for the Wittig reaction run in DMF at -40°.

Benzaldehyde	Benzyltriphenyl phosphonium-bromide	-----		α-CD		β-CD		γ-CD	
		Z	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*
4-methyl	4-methyl	57	43	75	25	85	15	92	8
3,5-ditertbutyl	4-methyl	74	26	–	–	73	27	68	32
4-methyl	3,5-ditertbutyl	54	46	–	–	59	41	57	43
3,5-ditertbutyl	3,5-ditertbutyl	54	46	52	48	39	61	48	52

Table 2 The *Z*/*E* ratios for the Wittig reaction run in ethanol at 20°.

Benzaldehyde	Benzyltriphenyl phosphonium-bromide	-----		α-CD		β-CD		γ-CD	
		Z	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*
4-methyl	4-methyl	33	67	44	56	20	80	29	71
3,5-ditertbutyl	4-methyl	17	83	–	–	13	87	–	–
4-methyl	3,5-ditertbutyl	29	71	–	–	29	71	–	–
3,5-ditertbutyl	3,5-ditertbutyl	32	68	23	77	32	68	31	69

DISCUSSION

There are several ways to explain the results when cyclodextrins are added to Wittig reactions with semistabilized ylides. Two obvious ones are: (1) the low basicity of the anions from cyclodextrin, which are formed immediately upon addition of the base to the reaction, prevents the base-catalyzed equilibration of the betaines which could be a major route to *E*-olefins assuming the classical mechanism.

(2) Cyclodextrin and its anions form weak host-guest complexes with the aldehydes and ylides, thus increasing their size and steric requirements. As a result, the reactions are slower and the differences in transition state energies for the various stereochemical routes become larger. One indication that the latter case is valid, is that the presence of cyclodextrin decrease the rate of the Wittig reaction and that the typical ylide colour which usually appears instantaneously on addition of base develops more slowly. From Tables 1 and 2 it can also be seen that there is a correlation between the size of the cyclodextrin and the selectivity, the larger the cyclodextrin the better is the selectivity.

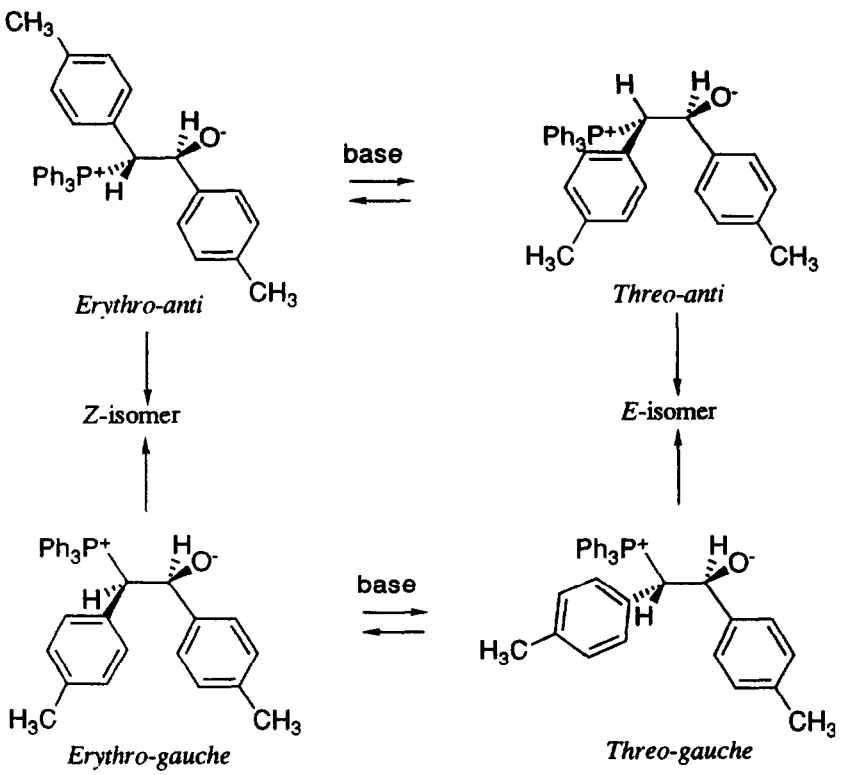

Figure 1 *The base catalyzed equilibration of betaine*

These experimental observations are better rationalized in terms of complex formation than as effects of different bases, cyclodextrin anions, since a base effect should be more or less independent of the type and size of the substituents. From Tables 1 and 2 it can also been seen that, for the reactions with aromatic groups with bulky substituents, the selectivity is small compared to the case of aromatic groups with the ability to form complexes with cyclodextrin. This could be further evidence that the selectivity is due to complex formation, since the *tert*-butyl groups were introduced to prevent complexation. However, weak binding of these bulky groups to cyclodextrins cannot be ruled out.

In order to obtain experimental evidence for complex formation in these reactions we have carried out ^{1}H NMR NOE-experiments. Mixtures of β-CD and *p*-tolualdehyde or the triphenylphosphonium salt from 4-(bromomethyl)toluene in DMF at different temperatures were investigated. A small effect was shown in a NOE-experiment at -40 °C on a mixture of 4-methylbenzyl-triphenylphosphonium bromide and a twofold excess β-CD . Irradiation of one pair of the aromatic protons in the *p*-tolyl ring (δ= 6.9) gave an enhancement of 6 % of signal from the secondary hydroxyl protons. Irradiation of the other pair of aromatic protons (δ=7.05) gave a smaller effect. No NOE effect was observed at room temp. or in the presence of excess α-CD.

Can these results be interpreted within the classical mechanism and/or the four-center mechanism?

With the classical mechanism[7] the sterical crowding should be least unfavourable in the *erythro-anti* betaine conformer (see Fig. 1). The *threo-anti* betaine conformer would be insignificant due to the unfavourable energy change on complex formation. Thus, the *erythro-anti* betaine will dominate and a higher yield of Z-olefin will be obtained. For the experiments in DMF the classical mechanism explain our results. However, our results on Wittig reactions with CD in ethanol are more difficult to explain with the classical mechanism. The high *E*-selectivity means that the *threo-gauche* conformer is the most stable conformer but this is difficult to rationalize.

With the four-center mechanism[8] our results for both the ethanol and DMF reactions can be explained. In the four-center mechanism either reaction component could react in an antarafacial mode to comply with the symmetry rules. In Fig. 2 one of the two transition state models , the one with the aldehyde as the antarafacial component has been chosen. The carbonyl and the ylide double bonds are crossed, not parallel. Then four possible remaining geometries for the reaction have to be considered. Two of these with the aryl group pointing upwards are shown in Fig. 2 the remaining two with the aryl groups down are sterically much more crowded and has been omitted.

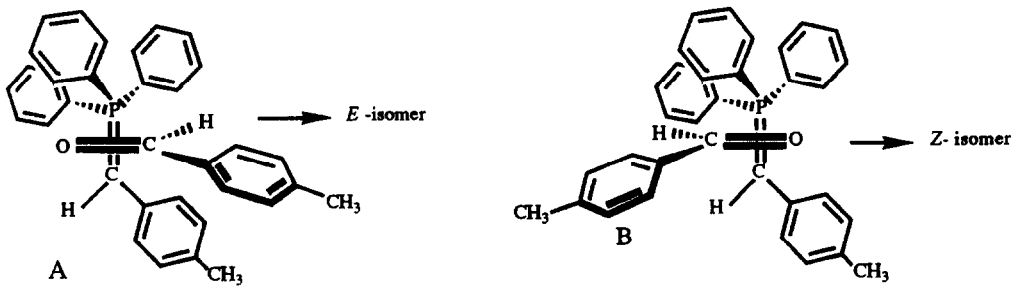

Figure 2 *Hypothetical transition states for the four-center mechanism.*

The first structure for the approaching reactants, A in Figure 2, leads to the *E*-isomer and the second structure (B) leads to the *Z*-isomer. Structure B should be energetically more favorable than A, whereas the reaction path from B to the product (the oxaphosphetane) is sterically less demanding than the reaction path from A. This is schematically shown below (Fig. 3).

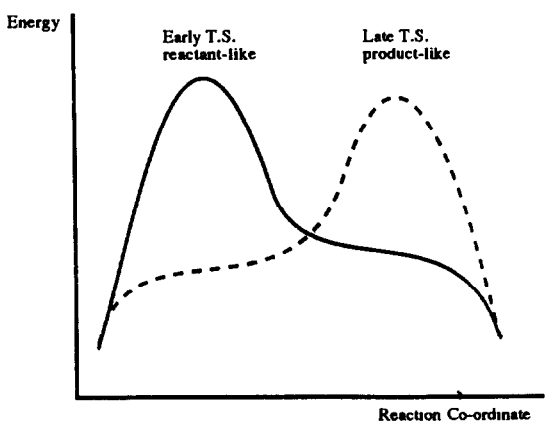

Figure 3 *Hypothetic energy profile for the reactions in the two types of solvent, nonpolar or polar aprotic solvent* (——) *and protic, polar solvent* (----).

This model for the Wittig reaction can be used to rationalise the effect of the solvent and the steric crowding caused by CD-complexation. In a nonpolar or polar but nonprotic solvent the constraines on the geometry for the TS for a concerted reaction as shown by structure A in Fig. 2 is essential. In a protic, polar solvent like ethanol hydrogen bonding can stabilize the developing charge on the carbonyl oxygen resulting in a less constrains for the still concerted reaction. The rate limiting structure is now found later along the reaction coordinate and it is product like. Thus, the transition state geometry B in Fig. 2 and the dotted energy profile in Figure 3 is preferred.

The modification of the Vedejs four-center mechanism for the Wittig reaction presented here is consistent with our results on the effect of CD-complexation on the selectivity in Wittig reactions.

CONCLUSIONS

It is clear that the addition of CDs to certain Wittig reactions affects the *Z/E*-selectivity in an interesting way. The *Z*-selectivity increases in DMF and the *E*-selectivity increases in ethanol. The results are best explained as steric effects due to host-guest complexation rather than as due to the influence of the base. Although the data are interpreted as due to steric effects they can not unambigously discriminate between different mechanisms for the Wittig reaction,i.e. the "classical" mechanism and Vedejs's more recent concerted mechanism although our results presented here favours the latter. From a preparative point of view the addition of CDs to Wittig reactions in DMF at low temperatures is one method to increase the *Z*-selectivity in reactions with semi-stabilized ylids.

EXPERIMENTAL

The Wittig reactions have been performed at room temperature (21 °C) with abs. ethanol as the solvent and at low temperature (-40 °C) with freshly distilled DMF as the solvent. In both cases has lithium ethoxide been used as the base. The investigated aldehydes are 4-methyl- and 3,5-di-*tert*-butylbenzaldehyde[9] and the ylides investigated are the corresponding triphenylphosphonium salts,[10] (*i.e.* 4-methyl- and 3,5-di-*tert*-butylbenzyltriphenylphosphonium salt). The cyclodextrins used where α-,β- and γ-cyclodextrin, which were always vacuum dried for at least 4 h prior to use. ^{1}H NMR spectra were recorded on a Varian XL 400 Spectrometer.

General procedure for the Wittig reaction

A mixture of aldehyde (0.25 mmol), phosphonium salt (0.25 mmol) and cyclodextrin (0.50 mmol) in 50 ml solvent was left to stand for 1h at the desired reaction temperature to give complexation. A solution of lithium ethoxide in ethanol (2.5 ml, 0 75 M, 1.8 mmol) was added and the reaction mixture was stirred over night. The reaction was worked up by the addition of water (200 ml) and dichloromethane (50 ml). The organic phase was washed with water (3x100 ml) and dried over $MgSO_4$. The solvent was removed in a rotary evaporator to give a white-yellow residue on which the *Z/E* ratio was measured on NMR. The isomers were separated by preparative HPLC (hexane as eluent and a medium polar column, Spherisorbe nitrile)

Data for the substituted stilbenes

4,4'-dimetylstilbene, Z: ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.31(6H,s) 6.51(2H,s) 7.17-7.40(8H,d,J 8Hz). MS (m/Z):208 (M^+, 15%) 193(47) 178(60) 165(15) 115(20)

4,4'-dimetylstilbene, E: ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.36(6H,s) 7.05(2H,s) 7.17-7.40(8H,d,J 8Hz). MS (m/Z):208 (M^+, 16%) 193(49) 178(64) 165(15) 115(22)mp. 180-182°.

3,5-di-tert-butyl-4'-metylstilbene, Z ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.22(18H,s) 2.31(3H,s) 6.54(2H,s) 7.15-7 43(4H,d,J 8Hz) 7 34(1H,s) 7.36(2H,s).MS (m/Z).306 (M^+,0%) 220(20) 205(100) 57(60)

3,5-di-tert-butyl-4'-metylstilbene, E·^{1}H-NMR (400MHz, $CDCl_3$) δ 1.36(18H,s) 2.36(3H,s) 7.08(2H,s) 7.15-7.43(4H,d,J 8Hz) 7.34(1H,s) 7.36(2H,s). MS (m/Z):306 (M^+,0%) 220(14) 205(100) 57(54).

3,3',5,5'-tetra-tert-butylstilbene, Z.^{1}H-NMR (400MHz, $CDCl_3$) δ1.20(36H,s) 6.66(2H,s) 7.00(4H,s) 7.22(2H,s). MS (m/Z): 404 (M^+,30%) 187(15) 57(100).

3,3',5,5'-tetra-tert-butylstilbene, E:^{1}H-NMR (400MHz, $CDCl_3$) δ1.37(36H,s) 7.12(2H,s) 7.34(2H,s) 7.38(4H,s). MS (m/Z): 404 (M^+,30%) 187(15) 57(100).mp. 149-151°.

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