Tetrahedron Letters No.43, pp. 3801-3804, 1970. Pergamon Press. Printed in Great Britain.

STRUCTURES OF CARBANIONS, I. SOLVENT CONTROL OF PRODUCT GEOMETRIES FROM O-PHOSPHORYLATION OF ENOLATE ANIONS

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(Received in USA 13 July 1970; received in UK for publication 17 August 1970)

The stereochemistry of C-alkylation of enolate anions, particularly anions of cyclohexanone derivatives, has been intensively investigated.[1] In contrast, the factors affecting the geometries of the products obtained from reaction at the oxygen atoms of enolate anions have been essentially ignored. In part, this neglect reflects the fact that reactions of enolate anions with alkylating or acylating agents often give poor yields of the products of attack at oxygen, due to preferential attack at carbon,[2] rearrangement of the initial reaction products,[2] or rapid hydrolysis of O-acylated products. Sulfonyl halides, which should attack oxygen in preference to carbon,[3] often act as halogenating agents rather than sulfonating agents in reactions with enolate anions.[4]

We have studied the reactions of enolate anions with phosphorylating agents, which react solely on oxygen[5] to give very high yields of stable enol phosphates and phosphorothioates.[6] Phosphorylating agents show no tendency to act as halogenating agents in these reactions.

In this paper, we report a study of the effects of changing solvents upon the stereochemistry of the reactions of stable enolate ions with O,O-diethyl phosphorochloridothioate (DECT). We have found that the ratio of geometrical isomers produced changes remarkably as the polarity of the solvent is varied.

The table below records the ratios of trans to cis isomers in the products of the reaction of DECT with the potassium enolates from cyanoacetone, ethyl acetoacetate, and acetylacetone in a variety of solvents. The anions in all cases were obtained by reaction of the ketones with potassium t-butoxide in the solvents listed in the Table. The trans/cis ratios were determined by nmr analysis of the reaction products. (In all cases, cis-isomers are defined as those in which the phosphorothioate group and the polar group - CN, CO_2Et, etc. - are cis to each other).[7] The evidence for the configurations of the products will be discussed below.

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Table

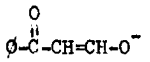
Solvent	Dielectric Constant	Trans/Cis X = -CN	$-CO_2Et$	$-\overset{O}{\overset{\|}{C}}CH_3$
Dimethyl Sulfoxide	46.4[a]	4.0	9.0	6.0
Dimethyl Formamide	37.0[a]	3.6	6.5	
Acetonitrile	36.0[a]	2.6		
Acetone	20 [b]	2.5		
Isopropanol	19 [b]	1.1		
Methyl Isobutyl Ketone	13 [b]	0.63		
t-Butanol	12 [b]	0.25	0.18	0.14
Benzene	2.3[b]	0.145	0.025	

[a] G. Douheret and M. Morénas, Compt. rend., 264, 729 (1967).

[b] Values selected from Landolt-Börnstein, "Funktionen und Tabellen" 6th Ed., Vol. 6, 618-655 (1959)

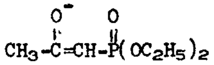
The trans/cis ratio in the products increases markedly as the polarity of the solvent increases. On the other hand, the protonic or non-protonic nature of the solvent appears to have little effect upon the geometries of the products.

The presence of the methyl group on the double bond has little effect on the geometries of the products. The product obtained from reaction of the potassium enolate of benzoylacetaldehyde (I) with DECT in t-butanol had a trans/cis ratio of 0.14, while in DMSO the ratio was 8.2.



$\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-CH=CH-O}^-$

I



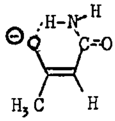
$CH_3\text{-}\overset{O^-}{\overset{|}{C}}\text{=CH-}\overset{O}{\overset{\|}{P}}(OC_2H_5)_2$

II

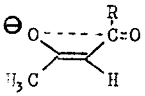
Solvent control of the ratio of isomers obtained is not limited to anions stabilized by carbonyl or nitrile groups. Reaction of DECT with the potassium enolate of diethyl phosphonylacetone (II) gave essentially pure cis-isomer from reaction in t-butanol, while the trans-isomer predominated by a factor of 2.3 in DMSO.

One exception was found to the rule that product geometries change from cis to trans as the polarity of the solvent increases. Reaction of DECT with the enolate of acetoacetamide in either DMSO or t-butanol gave a single isomer, to which we assigned the cis-configuration. In contrast, reaction of the enolate of N,N-dimethylacetoacetamide with DECT showed the usual solvent effect. Reaction in t-butanol gave mainly the cis-isomer, while reaction in DMSO gave almost pure trans-isomer.

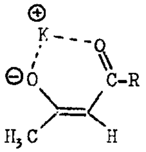
The geometries of the phosphorothioates obtained by reaction of the enolate anions with DECT are presumably related to the configurations[8] of the ions in solution. Thus, we believe that formation of a single isomer from phosphorylation of the anion of acetoacetamide in solvents of markedly different polarities is due to hydrogen bonding between the enolate anion and the amide protons, which holds this anion in the cis-configuration (III) regardless of the solvent.



III



IV



V

Two explanations might account for the unusually marked influence of solvent polarity upon the geometries of the products of all the other reactions we have studied. 1.) In non-polar solvents, the anion might be stabilized by proximity of the negatively charged oxygen atom to the positive pole of the carbonyl, nitrile, or phosphonyl groups, thus maintaining a *cis*-configuration, such as IV. Normal solvation of the oxygen atom in polar solvents should reduce the value of this sort of interaction. Normal repulsion between the polar groups and the enolate oxygen should therefore favor the *trans*-configurations. 2.) The enolate anions might exist as potassium "chelates" (such as V) in non-polar solvents, but as free anions in more polar solvents. Again, normal repulsions between the two groups bearing the negative charge in the free anions should favor the *trans*-configuration.

In the following paper we will offer evidence to show that chelation of enolate anions with metal cations is indeed the cause of the high *cis*/*trans* ratios found in non-polar solvents.

The assignment of configuration to the reaction products was based on their nmr spectra. All compounds assigned *trans*-configurations (that is, those with vinyl protons *cis* to the oxygen of the phosphorothioate group) have vinyl proton resonances appearing *ca*. 0.2-0.5ppm downfield from those assigned *cis*-configurations. This is consistent with previous work which has shown that vinyl protons *cis* to oxygen atoms have resonances which appear at lower fields than those for protons *trans* to oxygen atoms. Since peaks for vinyl protons *cis* or *trans* to methyl groups appear at similar fields,[9] the geometry of the proton relative to the oxygen of the phosphorothioate group should be the predominant influence on the position of its adsorption. A similar conclusion can be drawn from the position of the methyl proton resonances in the phosphorothioates prepared in this work, since these resonances uniformly appear at lower fields in compounds assigned the *trans*-configurations (that is, those with the methyl groups *cis* to the carbethoxy, cyano, acetyl, or phosphonyl groups) than in those assigned the *cis*-configurations. Peaks for allylic methyl groups *cis* to electron withdrawing groups normally appear at lower fields than do those *trans* to electron withdrawing groups.[10] Finally, the vinyl protons in the product obtained from reaction of the enolate anion I in *t*-butanol had a coupling constant of 6.8Hz, while in the product obtained from reaction in DMSO, the coupling constant is 11.8Hz. Thus, the combined nmr data offers convincing evidence for the geometries of the products of these reactions.

References

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2. H.O. House, "Modern Synthetic Reactions", W.A. Benjamin, Inc., New York, 1965, Chap. 9.

3. R.G. Pearson, J. Am. Chem. Soc., 85, 3533 (1963).

4. E.v. Meyer and T.v. Findeisen, J. Prakt. Chem. [2], 65, 529 (1902).

5. a) J.E. Casida, Science, 122, 597 (1955);
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6. Reactions in very non-polar solvents (e.g. benzene), however, give poor yields[5b] due to the insolubility of the enolate anions.

7. As has been pointed out,[5] the literature names in some cases refer to the reverse geometries.

8. Although interconversion of the cis and trans forms of the anions is presumably facile, we prefer to call them configurations, rather than conformations, in view of the presence of the double bond and the relationship to the configurations of the products.

9. See C. Pascual, J. Meier and W. Simon, Helv. Chim. Acta, 49, 164 (1966).

10. L.M. Jackman and R.H. Wiley, J. Chem. Soc., 2881, 2886 (1960).