The Aldol Condensation: Influence of Solvent and Cation on Stereoselectivity

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THE transition state for the aldol condensation, as well as that for the Reformatsky and Ivanov reactions, has been described as involving a perpendicular attack of an electrophile on an enolate double bond.[1] The stereochemistry of the aldol condensation has, however, been little studied. We report that by an appropriate choice of cation and solvent the condensation can be directed into two radically opposed stereochemical paths.

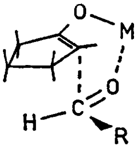
When the condensation of cyclopentanone and isobutyraldehyde is performed without special precautions the isomeric *threo*- and *erythro*-2-(1-hydroxy-2-methylpropyl)cyclopentanones are obtained in the thermodynamically determined proportions: 68% *erythro* and 32% *threo*. The Table, however, shows the results obtained when the reaction is performed under kinetic control.†

Percentage of threo-*isomer in the cyclopentanone–isobutyraldehyde condensation at* −20°; [aldehyde] = [ketone][a] *ca.* 3M; [OH$^-$] *ca.* 0·1N.

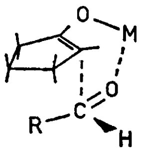
Cation	Cyclopentanone ($D_{-20°}$ *ca.* 15)[b] Li$^+$	K$^+$	Me$_4$N$^+$	Methanol ($D_{-20°}$ = 40)[b] Li$^+$	K$^+$	Me$_4$N$^+$
% *threo*	>95	>95	30±10	30±10	30±10	30±10

[a] In methanol as solvent only; [b] Dielectric constant.

In the weakly solvating media generally used in Reformatsky and Ivanov reactions, ether or ether–benzene mixtures, the enolate is not dissociated in the transition state.[2,3] For the cyclopentanone–acetaldehyde condensation performed under conditions of kinetic control, using cyclopentanone itself as the solvent and K$^+$ as the cation, we showed earlier that the major product is the less stable *threo*-isomer.[4] Since the enolate must also exist here in a covalent form or as an ion pair, we suggested structures A and B for the transition states leading to the *threo*- and *erythro*-isomers, respectively (R = Me). The steric interactions between the methylene groups and the methyl being less in A than in B, the *threo*-isomer predominates.



(A)



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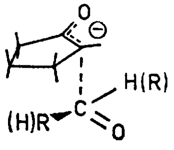

(C)

In a solvent of low dielectric constant, two factors, amongst others, are responsible for the relative orientations of the cyclopentanone enolate and the aldehyde molecules, and hence for the

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† The acetols produced were determined by g.l.c., the reaction being stopped after a very short time, about 15 sec. in the case of cyclopentanone and 1—15 min. for methanol. When the *threo*-isomer is formed stereospecifically, kinetic control is self-evident; in the event of *erythro*-stereoselectivity we have verified that no appreciable equilibration of the products could have occurred subsequent to the condensation.

product stereochemistry. Firstly, the two molecules must lie in roughly parallel planes and the line of attack, perpendicular to these planes, is determined by the need for maximum overlap of the π-orbitals of the reacting bonds. Secondly, the relative orientation of the two C–O bonds is determined by the existence of the "cationic bridge" involving the metal ion M^+. Should complete dissociation of the enolate occur, the transition state would be more labile and the final geometry considerably modified.

Our results show that the effects of cation and solvent are very important. For Me_4N^+ in cyclopentanone and various ions in methanol where extensive dissociation of the enolate is to be expected,† the "normal" stereoselectivity is reversed, and the *threo* : *erythro* ratio approaches that obtained under thermodynamic control. These results, therefore, tend to confirm the structure proposed for the transition state in the case of a weakly dissociating solvent and a cation of small ionic radius. However, the "quasi-thermodynamic" value found in the *erythro*-stereoselective reactions suggests a very different type of interaction in the transition state. It seems therefore reasonable to suggest, as limits of a plurality (or a continuum) of reaction mechanisms, two competing mechanisms.

(a) The enolate, covalent or as an ion pair, *is linked* with the carbonyl compound most likely through a "cationic bridge"; the reaction leads then to *threo*-products (transition state of type A and B).

(b) The enolate *is dissociated* and reacts without significant intervention of a cation, *via* a more open transition state such as C, leading to a kinetic stereoselectivity close to the thermodynamic norm.

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† We assume that the enolates behave in much the same way as the picrates whose anion is also mesomeric, and for which electrochemical data are available. In acetone, tetramethylammonium picrate is ten times as dissociated as the lithium salt; in methanol, potassium picrate is ten times more dissociated than in acetone (G. Charlot and B. Tremillon, "Les réactions chimiques dans les solvants et les sels fondus", Gauthier-Villars, Paris, 1963, p. 305; E. Price in "The Chemistry of Non-aqueous Solvents", ed J. J. Lagowsky, Academic Press, New York, 1966, p. 87).

[1] E. Toromanoff, *Bull. Soc. Chim. France*, 1962, 1190.
[2] M. Mousseron, J. Neyrolles and Y. Beziat, *Bull. Soc. Chim. France*, 1963, 1483.
[3] H. E. Zimmerman and M. D. Traxler, *J. Amer. Chem. Soc.*, 1957, **79**, 1920.
[4] J. E. Dubois and M. Dubois, *Tetrahedron Letters*, 1967, 4215.