138. *The Kinetics and Mechanism of Carbonyl–Methylene Condensation Reactions. Part XII.*[1] *The Elimination Step of the Uncatalysed Condensation in Water.*

By JACOB ZABICKY.

The mechanism and the stereochemistry of the double-bond formation in carbonyl–methylene condensations are discussed, and a possible path for the reversal of the condensation, *i.e.*, the production of the aromatic aldehyde and the active methylene compound from the condensation product, is proposed.

IN Parts VI—IX [2] of this series it was established that condensation of active methylene compounds such as malononitrile, ethyl cyanoacetate, and cyanoacetamide in ethanol or water takes place in three main steps, namely, ionisation of the active methylene compound

$$\mathrm{CH_2XY} \rightleftharpoons {}^{-}\mathrm{CHXY} + \mathrm{H^+} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (1)$$
$$(\mathrm{X, Y = CN,\ CO_2Et,\ CO{\cdot}NH_2})$$

nucleophilic attack of the carbanion formed on the carbonyl group of the aromatic aldehyde

$$\mathrm{Ar{\cdot}CH{:}O} + {}^{-}\mathrm{CHXY} \rightleftharpoons \mathrm{Ar{\cdot}CH(\bar{O}){\cdot}CHXY} \quad . \; . \; . \; . \; . \; . \; . \quad (2)$$

and double-bond formation that may be formally represented as

$$\mathrm{Ar{\cdot}CH(\bar{O}){\cdot}CHXY} \rightleftharpoons \mathrm{Ar{\cdot}CH{:}CXY} + \mathrm{\bar{O}H} \quad . \; . \; . \; . \; . \; . \; . \; . \quad (3)$$

We now suggest for step (3) a mechanism that takes into account observations reported in preceding papers and the stereochemistry of the products, and we explain the mechanism of the reversal of the condensation, *i.e.*

$$\mathrm{Ar{\cdot}CH{:}CXY} + \mathrm{H_2O} \rightleftharpoons \mathrm{Ar{\cdot}CH{:}O} + \mathrm{CH_2XY} \quad . \; . \; . \; . \; . \; . \; . \; . \quad (4)$$

RESULTS AND DISCUSSION

A series of practically insoluble condensation products was prepared in water, in conditions similar to those of the kinetic measurements in Parts VIII and IX.[2] Precipitation of pure condensates began soon after the start of the reaction. Details of the synthesis and properties of the precipitates are given in Table 1.

The m. p.s and infrared spectra of the six precipitates in Table 1 were identical with those described in the preceding paper. It is concluded that in kinetic conditions the products have the configuration of those obtained by ordinary synthetic methods, *i.e.*, *trans* (Ia, Ib).

The alcoholate ion intermediate (II) of step (2) has two asymmetric carbon atoms when the condensation is carried out between an aromatic aldehyde and an active

[1] Part XI, preceding paper.

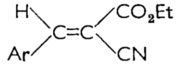
[2] Parts VI—IX, *J.*, 1960, 2020—2044.

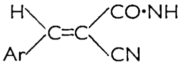
methylene compound with two different activating groups (such as cyanoacetamide and ethyl cyanoacetate). Step (2) may give rise to four diastereoisomeric intermediate ions (II), namely, two *erythro* and two *threo*. The problem is to find the elimination path leading exclusively to the *trans*-condensation product from the mixture of the diastereoisomers.

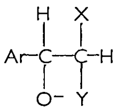
TABLE 1. *Condensation reaction of cyanoacetamide* (CA) *and ethyl cyanoacetate* (EC) *with substituted benzaldehydes* ($Z\cdot C_6H_4\cdot CHO$) *in kinetic conditions*,[2] *in water at* 40°.

Methylenic compound	Z	Time of reaction	Aldehyde reacted (%)	M. p.
CA	*p*-NO_2	2 hr.	4·8	235—236°
CA	*m*-NO_2	2·8 hr.	2·1	162
CA	*p*-Br	3·4 hr.	4·6	219
EC	*p*-NO_2	2 min.	6·2	170—171
EC	*m*-NO_2	15 min.	5·4	134·5—135
EC	*p*-Cl	4 hr.	0·2	92

Initial concentration of active methylene compound 0·01M, of *p*-bromobenzaldehyde 0·003M, and of other aldehydes 0·007M.


(Ia)


(Ib)


(II)

$Ar\cdot CH(OH)\cdot CHXY$ (III)

$Ar\cdot CH(OH)\cdot \bar{C}XY$ (IV)

In preceding papers of this series it was reported that reaction (4) takes place when the condensation product is dissolved in 95% ethanol or water. This hydrolysis of the double bond is catalysed by bases and retarded or even stopped by small quantities of acid. It was also reported that no intermediate was detected in the reaction mixture either during the reaction or at equilibrium, *i.e.*, any intermediate produced will always be in a very small concentration. Owing to the nature of the reaction it was not possible to draw any conclusion from the kinetic results in preceding papers on the reaction constants of steps (1), (2), and (3), and the conclusion reached in this paper are based mainly on qualitative observations.

The following mechanism is proposed for step (3):

$$Ar\cdot CH(\bar{O})\cdot CHXY \overset{+H^+}{\rightleftharpoons} Ar\cdot CH(OH)\cdot CHXY \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (5)$$

$$Ar\cdot CH(OH)\cdot CHXY \rightleftharpoons Ar\cdot CH(OH)\cdot \bar{C}XY + H^+ \quad . \; . \; . \; . \; . \; . \; . \; . \quad (6)$$

$$Ar\cdot CH(OH)\cdot \bar{C}XY \rightleftharpoons Ar\cdot CH{:}CXY + H\bar{O} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (7)$$

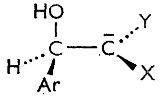
Step (5), being a proton transfer from the solvent (ethanol or water) to the alcoholate ion (II), is probably fast. In the intermediate (III) the hydrogen atom attached to the carbon atom bearing the X,Y groups is strongly activated and is expected to undergo a spontaneous ionisation (6) similar to step (1), giving rise to the carbanion (IV).

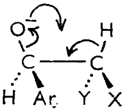
Step (7) is the elimination of a hydroxyl ion from carbanion (IV). This step is aided by the resonance stabilisation occurring on formation of the double bond. The importance of the contribution of the structures involving conjugation of the groups X,Y with the aryl group to the structure of the condensation products is apparent from their ultraviolet spectra (see Parts VI, VIII, and IX of this series).

It remains to show why this elimination path is stereospecific: the elimination path proposed above differs only in detail from an E_2 reaction in which steps (6) and (7) take place in a single step, *i.e.*, at the rate-determining step the proton is removed by a base and at the same time the anion is expelled; in our case a hydrogen ion separates in step (6) owing to the activation by the electronegative groups X, Y, and this process may take place independently of the conformation of the molecule at the time of its occurrence.

The E_2 stereochemical path is well known,[4] and diasteroisomeric compounds that undergo elimination by this mechanism are known to produce mainly one of the possible double-bond compounds, one of the diastereoisomers being used up and the other remaining almost untouched. The transition state of step (7) (as that of E_2) has to have a special conformation in order to permit separation of the hydroxyl group and allow the free-electron pair to form the double bond. For this to occur it is necessary that the groups X, Y take definite positions in the spatial distribution of the groups of intermediate (IV), either staggered between the hydroxyl and aryl groups, or staggered between the hydroxyl group and the hydrogen originally attached to the aromatic aldehyde, as in (V). If intermediate (IV) has to adopt conformation (V), this will be much easier when the group staggered between the phenyl and the hydroxyl groups, say X, is the smaller one of X and Y.

(V)





(VI)

This process of selective elimination, similar to that taking place in E_2, will lead to the condensation product of *trans*-configuration.

This path of elimination is in agreement with the results found for the hydrolysis of the condensation product (4), *i.e.*, the hindering effect of acids on the development of this reaction and the acceleration caused by bases. As hydroxyl ions accelerate the retrograde reaction, it can be concluded, from the principle of microscopic reversibility, that they are eliminated as such in the condensation. This is reinforced by the fact that acids stop reaction (4), and it would be difficult to propose a mechanism for (4) beginning with the attack of a hydrogen ion on the condensation product. (The above arguments exclude an elimination similar to E_1 and its retrogression by electrophilic addition to the double bond.)

There is one alternative path of elimination that may be stereospecific and the retrogression of which may involve base-catalysis. This path is a four-centred elimination from intermediate (II), as described in (VI). The eclipsed conformation necessary for this elimination path gives preference to diastereoisomers (II) where the smaller of X and Y is eclipsed with the phenyl group at the time of elimination. It is hard to believe that the four-centred elimination will be able to compete successfully with the protonation (5) in solvents ethanol or water, but it remains a probable elimination path in aprotic solvents.

The retrogression of step (5), *i.e.*, the splitting of the aldol intermediate (III) into a proton and an alcoholate ion (II), is believed to be a very difficult process in water. This leads us to a new problem: as the reaction is reversible, what will be the path of the retrogression (4) if step (5) is practically irreversible? A probable way is through an internal proton transfer in intermediate (IV), from the hydroxyl group to the carbanion leading to intermediate (II). This process may take place with relative ease owing to the mobility of the free electron pair of the carbanion. The retrogression of this transfer is equivalent to the reversal of the four-centred elimination. From intermediate (II) the completion of reaction (4) follows straightforwardly by the retrogression of step (2) involving the carbon–carbon bond splitting.

The mechanism proposed above is in qualitative agreement with that proposed for the base-catalysed condensation of various substituted benzaldehydes with acetone[5] and butan-2-one.[6] Quantitative differences arise owing to the enhanced activity of the eliminated hydrogen that may be expected in intermediate (III) as compared, for instance,

[3] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, 1953.

[4] Cram, " Steric Effects in Organic Chemistry," edited by Newman, John Wiley & Sons, Inc., New York, 1956, pp. 304 ff.

[5] Noyce and Reed, *J. Amer. Chem. Soc.*, 1959, **81**, 624.

[6] Stiles, Wolf, and Hudson, *J. Amer. Chem. Soc.*, 1959, **81**, 628.

with 4-hydroxy-4-phenylbutan-2-one.[5] The presence of a base in solution helps the hydroxy-ketone to give the corresponding alcoholate ion [5,6] in the retrogression of the condensation, but in the absence of a base the retrogression of step (5) would be very difficult.

Experimental.—Reagents were prepared as described in Parts VIII and IX.[2]

Synthesis in " kinetic conditions." Aqueous solutions of the reagents were placed in a 250 ml. volumetric flask, which was then filled with water to the mark, all being at 40°, shaken, and put in a water-bath at 40°. The precipitate obtained was filtered off, washed with water, and dried in vacuum at room temperature to constant weight (1 day).

Infrared spectra were determined in the solid state the day after the precipitates were obtained, by dispersing the compound in a potassium bromide pellet, in a Baird Associates Inc. spectrophotometer equipped with a sodium chloride prism.

The author is indebted to Professor S. Patai for helpful discussion and criticism and to Mrs. H. Feilchenfeld and Mrs. E. Levi for the infrared spectra.

THE HEBREW UNIVERSITY, JERUSALEM, ISRAEL.

[*Received, April 25th,* 1960.]