Tetrahedron Letters No. 21, pp. 22-26, 1959. Pergamon Press Ltd. Printed in Great Britain.

ON THE MECHANISM OF THE FORMOSE REACTION

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(Received 25 November 1959)

IN 1861 Butlerow[1] first noted the formation of sugar-like substances when formaldehyde is treated with mild base. Since that time numerous investigations of this reaction have been undertaken,[2] and many mechanisms have been suggested for the process, but to date no mechanism appears to have been formulated which does not employ "active formaldehyde" or some other ill-defined species. It is the purpose of this communication to call attention to the considerable body of data available on this reaction and to point out a mechanism which is consistent with such data and which is also consistent with chemical experience.

Although a heterogeneous mixture of products is usually obtained on treatment of formaldehyde solutions with base, conditions have been realized in which as much as 50% of the original formaldehyde has been converted to glycolaldehyde.[3] Furthermore, trioses, tetroses, etc., could easily arise

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[1] A. Butlerow, C. R. Acad. Sci., Paris **53**, 145 (1861).

[2] For a short review with leading references, cf. W. Langenbeck, Tetrahedron **3**, 185 (1958).

[3] W. Langenbeck, Angew. Chem. **66**, 151 (1954).

from aldol condensations involving glycolaldehyde as the active methylene component and formaldehyde, glycolaldehyde, etc., as the carbonyl component. For this reason it has long been obvious that the formation of glycolaldehyde from formaldehyde is the process to be explained, and we will not further consider the subsequent condensation reactions in this paper.

The reaction of two formaldehyde molecules by an "aldol condensation" mechanism is of course very unlikely, and the finding that there is a long induction period in the formose reaction[4] suggests that if such a direct process does occur it must be very slow. However, kinetic studies have shown that after this induction period a rapid reaction ensues.[4] This suggests an autocatalytic process, and this has been confirmed by the finding that the addition of glycolaldehyde, glyceraldehyde, or dihydroxyacetone causes the induction period to disappear, the reaction starting immediately but at the same rate as that observed in the fast part of the normal formose reaction. This has led to the suggestion that there are two processes by which the formaldehyde condensation occurs: (1) a slow direct condensation, possibly involving a formyl anion, but forming glycolaldehyde at an indetectable rate. (2) a fast reaction, catalyzed by glycolaldehyde, in which formaldehyde condenses to a second molecule of glycolaldehyde.

The first reaction is certainly interesting, but it is relatively inacessible for study if it proceeds at an indetectable rate, and if the rate is slow the reaction is not inconceivable as formulated, being related

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[4] Careful kinetic studies, with references to the earlier work, are reported by E. Pfeil and G. Schroth, Ber. **85**, 293 (1952).

to other cases in which some moderate acidity of hydrogens on a double bond has been observed.[5] The high rate of the second process strongly indicates, however, that some more usual types of reaction are involved in its mechanism. We wish to point out that, although minor modifications in details are possible, the following series of simple condensations and tautomerizations suffice to rationalize the process:

(1) $CH_2O + HOCH_2\text{-}CHO \longrightarrow HOCH_2\text{-}CHOH\text{-}CHO$

(2) $HOCH_2\text{-}CHOH\text{-}CHO \rightleftharpoons HOCH_2\text{-}CO\text{-}CH_2OH$

(3) $CH_2O + HOCH_2\text{-}CO\text{-}CH_2OH \longrightarrow HOCH_2\text{-}CHOH\text{-}CO\text{-}CH_2OH$

(4) $HOCH_2\text{-}CHOH\text{-}CO\text{-}CH_2OH \rightleftharpoons HOCH_2\text{-}CHOH\text{-}CHOH\text{-}CHO$

(5) $HOCH_2\text{-}CHOH\text{-}CHOH\text{-}CHO \longrightarrow HOCH_2\text{-}CHO + HOCH_2\text{-}CHO$

The first aldol condensation is unexceptionable, and the tautomerization of glyceraldehyde to dihydroxyacetone through the common enol is also well known. This can of course undergo a second aldol condensation to form the keto tetrose. The crucial step is the next one, in which this keto tetrose tautomerizes to the aldotetrose. This is simply the aldol condensation product of two glycolaldehydes, and by a simple reverse aldol reaction can regenerate the original glycolaldehyde and liberate the new one, which has thus been synthesized from two formaldehyde molecules.

This mechanism is certainly consistent with the operation of small amounts of glycolaldehyde, glyceraldehyde, or dihydroxyacetone in eliminating the induction period but not affecting the rate of the fast process, assuming that a steady state concentration of these intermediates would be established because of the competing further condensations.

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[5] R. Breslow, J. Amer. Chem. Soc. **80**, 3719 (1958).

Furthermore, this mechanism explains why benzoylcarbinol can give both an immediate reaction and a faster reaction when it is added as catalyst to the formaldehyde reaction mixture,[3] for it can function in place of glycolaldehyde, thus eliminating the induction period, and condensation reactions involving benzoylcarbinol might well be even faster than those involving glycolaldehyde, a presumption which is supported by the observation that m- and p-cyanobenzoylcarbinol are still better catalysts, while the p-methoxy compound is somewhat worse.

Many other catalysts are known for this reaction,[2] and most of them, e.g. benzoin, could not function in place of glycolaldehyde in our mechanism, a factor which has undoubtedly contributed to the overlooking of this mechanism previously. However, in all these cases the effect is to shorten the induction period only, and the eventual reaction rate is not accelerated, but is identical with that in the fast part of the normal reaction. Thus we suggest that many of these other catalysts facilitate the formation of the first molecule of glycolaldehyde, but that the catalysts are not involved in the fast section of the reaction. It is possible to suggest reasonable mechanisms for all of these cases by which the first glycolaldehyde molecule might be produced more rapidly, but these will not be outlined here since our prime concern is with the second fast part of the reaction.

It has also been found that the reaction is very dependent on the metal ion involved in the base,[5] being rapid with thallium or lead hydroxides, relatively fast with calcium hydroxide, and of negligible importance with sodium or potassium hydroxide. It has even been found that in the presence of an appropriate metal ion the reaction can be acid catalyzed. All of this is explicable in terms of the well known stabilizing effect of chelating ions on enediols, which are postulated intermediates in the tautomerization and condensation steps of our mechanism. Finally, the uniqueness of formaldehyde in this reaction derives from the fact that it alone among the aldehydes can condense to an acyloin with an active methylene group, and therefore, it alone can lead to an autocatalytic reaction.

The function of glycolaldehyde in this mechanism is clearly analogous to that of cyanide ion in the benzoin condensation. A carbonion is involved (in this case the enolate ion of glycolaldehyde) whose carbon also has carbonyl-like character (in this case by tautomerization to a true carbonyl group). The prediction of other catalyses of this type and some other predictions based on our suggested mechanism are currently under investigation.