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THE CHEMICAL MODEL FOR THE CLASS II ALDOLASE. CUPRIC-ION CATALYZED ALDOL CONDENSATION OF AROMATIC ALDEHYDES WITH ACETONE

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The aldol condensation of several aromatic aldehydes with acetone was specifically catalyzed by cupric ion and the additional effect of zinc ion on the cupric-ion catalyzed condensation was substantiated.

The novel results reported in the precedent paper1) prompted us to survey the generality of the catalytic activity of cupric ion for the condensation of aldehydes with ketones. To our great surprise there has been no report concerning the transition metal-ion catalyzed aldol condensation.2) The investigation of the condensation seems to serve for the extension of synthetic means and for the elucidation and the understanding of the reaction mechanism of the class II aldolase.3) We wish to report here the preliminary results of the aldol condensation of aromatic aldehydes with acetone in the presence of cupric ion alone and also in the coexistence of cupric and zinc ions.

In a typical procedure, 8 mmol of cupric chloride dihydrate and 5 mmol of aromatic aldehyde were stirred in 30 ml of acetone at ambient temperature for two or three days. After the completion of the reaction, the mixture was hydrolyzed and filtered. The filtrate was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvents were evaporated. The residue was chromatographed on a silica gel column to give products.

By the procedure described above, benzaldehyde (1), o- (2) and p-anisaldehydes (3), and 2,6-dimethoxybenzaldehyde (4) were treated. In every case, the corresponding benzalacetone was produced in a low yield. The results obtained are summarized in Table I. On the basis of the analogy with the enhancement effect of nucleophilic attack by the addition of zinc ion,4) we added equimolar amounts of zinc chloride to cupric ion to the reaction system above. The yield of the condensation product was then strikingly increased (Table I). The aldol condensation never proceeded in the presence of zinc ion alone. In addition, neither cobaltous, manganese, nor magnesium chloride alone, all of which were selected in relation to the prosthetic metal ions for the class II aldolase,3b) catalyzed the aldol condensation. These metal ions only resulted in the self condensation of acetone.

These results lead us to conclude that the Claisen-Schmidt type condensation is specifically catalyzed by cupric ion. Moreover, since the addition of imidazole completely inhibited the cupric-ion catalyzed condensation, it was suggested that the reaction occurred at the coordination sites of cupric ion. The additional effect of zinc ion may come from the contribution to the stabilization of the transition state of the cupric-ion catalyzed aldol condensation. In order to elucidate the reaction mechanism, the spectroscopic studies of the reaction and the application of this condensation method to other types of aldehydes and ketones are undertaken.

Present results are of interest in relation to the enzymatic reaction, for which the postulated reaction mechanism has been afforded by Rutter et al.3b) According to their hypothesis, metal ions serve as an electrophile to promote the enolization of ketone. The catalytic specificity substantiated by cupric ion in our results suggests the importance of the stereochemistry of coordination in metal ions. In the enzymatic reaction, zinc ion shows the predominant activity, while cupric ion shows the specific activity in the non-enzymatic reaction. Increasing evidence concerning the state and the role of metal ion in metallo-enzymes indicates the special function of the protein chain.5) Accordingly, it may be considered that the difference of the active metal ions in enzymatic and non-enzymatic processes will be caused by that of the stereochemical change of the coordination surroundings of metal ion.

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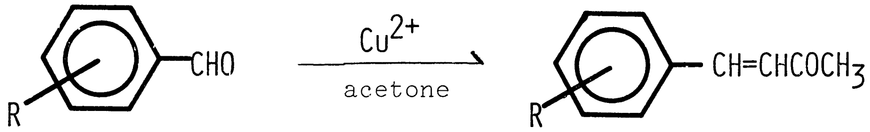

Table I. The condensation of aromatic aldehydes with acetone in the presence of cupric ion alone and in the coexistence of cupric and zinc ions.

R		configuration of double bond of product	Yield %	
			$CuCl_2$	$CuCl_2$ + $ZnCl_2$
H	(1)	E	2	26
2-OCH_3	(2)	E	trace	12
4-OCH_3	(3)	E	4	20
2,6-di-OCH_3	(4)	E	34	73

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