245. *Condensations of Carbonyl Compounds. A Kinetic Study of the Reaction of Acetophenone with Benzaldehyde.*

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The reaction between acetophenone and benzaldehyde in 90% alcohol in the presence of a constant concentration of sodium ethoxide has been shown to be kinetically bimolecular, the velocity being also proportional to the concentration of catalyst, *i.e.*, v = constant[OEt'][Ketone][Aldehyde]. Substituents in the aldehyde appear to alter principally the energy of activation, whereas substitution in the ketone causes a change in the factor PZ of the equation $k = PZ \cdot e^{-E/RT}$, with little or no change in activation energy. The mechanism of the reaction is discussed in the light of these results.

VARIOUS mechanisms have been suggested to represent reactions of the Claisen, Knoevenagel, and Perkin types, and it is now generally recognised that the formation of the ultimate product is preceded by aldol addition (see *Ann. Reports*, 1939, **36**, 211). Kinetic investigations of these condensations have been few, but Nikitin (*J. Gen. Chem. Russ.*, 1937, **7**, 9, 71, 148) has followed the reactions of benzaldehyde with acetophenone and with acetone in alkaline solution by observations of the colour developed when the solutions were acidified; he finds that the concentration of the aldehyde is involved to the first power and the second power respectively in the two cases, while the square of the concentration of furfuraldehyde appears in the velocity equation for the reaction of this compound with acetophenone. It appeared probable that a fuller kinetic study of certain of these condensations might throw further light upon the mechanisms of reactions of the carbonyl group in general, and this paper describes such a study of the condensation of benzaldehyde and of anisaldehyde with acetophenone and with *p*-methoxyacetophenone in 90% aqueous alcohol in the presence of sodium ethoxide as catalyst. The condensations of benzaldehyde with *p*-chloroacetophenone and of *p*-chlorobenzaldehyde with acetophenone were also studied; in these cases the kinetic experiments were not so accurate as those for the previous compounds, but the results have some qualitative significance.

EXPERIMENTAL.

Materials.—Benzaldehyde was steam-distilled from its suspension in sodium carbonate solution. The aldehyde was run off from the distillate, dried over calcium chloride, and distilled under reduced pressure. Anisaldehyde was washed with sodium carbonate solution, with water, and dried over anhydrous sodium sulphate before distillation in a vacuum; b. p. 116—116·5°/10 mm. A solution of *p*-chlorobenzaldehyde in light petroleum was washed with sodium carbonate solution, water, and then dried over anhydrous sodium sulphate. Most of the solvent was removed, and on cooling, white crystals separated, which after recrystallisation from alcohol had m. p. 48°. Acetophenone was frozen out three times and distilled in a vacuum, m. p. 19·6°. *p*-Methoxyacetophenone was prepared from anisole by Friedel–Crafts synthesis; after crystallisation from light petroleum it had m. p. 37·5°. A similar method was applied for the preparation of *p*-chloroacetophenone, m. p. 20·5°.

The following condensation products were obtained by treating the corresponding aldehydes and ketones dissolved in alcohol containing sodium ethoxide. The crystals which separated on standing were recrystallised from alcohol or aqueous alcohol: benzylideneacetophenone, m. p. 55·6°; ω-4-methoxybenzylideneacetophenone, m. p. 77°; 4-methoxy-ω-benzylideneacetophenone, m. p. 106°; *4-chloro-ω-benzylideneacetophenone*, m. p. 96·4° (Found: C, 74·4; H, 4·6; Cl, 14·4. $C_{15}H_{11}OCl$ requires C, 74·2; H, 4·5; Cl, 14·6%); ω-4-chlorobenzylideneacetophenone, m. p. 103°.

Medium.—The solvent was prepared by suitably diluting absolute alcohol with distilled water. The proportion of alcohol was checked by density determinations.

Catalyst.—An N/10-solution of sodium ethoxide was stored at 25° in a bottle fitted with a semi-automatic 10 c.c. pipette (cf. Davies and Lewis, J., 1934, 1600) suitably guarded with tubes filled with soda–lime.

The Estimation of Carbonyl in Reactants and Products.—The determination of the concentration of ketone, aldehyde, or condensation product was carried out by estimating the carbonyl group by means of hydroxylamine hydrochloride (Brochet and Cambier, *Compt. rend.*, 1895, **120**, 449; compare Mitchell, " Recent Advances in Analytical Chemistry," 1930, vol. 1, p. 96). Portions of 5 c.c. of the solutions containing the carbonyl compounds and 5 c.c. (excess) of an M/2-solution of hydroxylamine hydrochloride in 90% alcohol were mixed in an all-glass apparatus and heated on a water-bath, under reflux, for a period of time previously determined from experiments with solutions of known concentration (Table I). The benzylideneacetophenones did not break down on heating for these extended periods.

TABLE I.

Carbonyl compound.	Concn. of carbonyl solution (M).	Time required for complete conversion into oxime (mins.).
Benzaldehyde	0·05	10 (at room temp.)
Acetophenone	0·05	20 at the b. p.
Benzylideneacetophenone	0·025	80 ,,
,,	0·0125	45 ,,
ω-4-Methoxybenzylideneacetophenone	0·025	90 ,,
,, ,,	0·01	45 ,,
4-Methoxy-ω-benzylideneacetophenone	0·025	90 ,,
p-Methoxyacetophenone	0·05	60 ,,
4-Chloro-ω-benzylideneacetophenone	0·01	90 ,,
ω-4-Chlorobenzylideneacetophenone	0·01	90 ,,

After refluxing, the solution was cooled, 0·3 c.c. of a 1% solution of bromophenol-blue added, and the liberated hydrochloric acid titrated against N/20-aqueous sodium hydroxide to a green colour matching that of a standard consisting of 5 c.c. of M/2-hydroxylamine hydrochloride (in 90% alcohol), 5 c.c. of alcohol, 3—6 c.c. of water, 0·3 c.c. of bromophenol-blue solution, and sufficient N/20-sodium hydroxide to give an easily distinguishable green shade; the volume of water was equal to that of the expected titre.

Kinetic Measurements.—Stock solutions of M/4-aldehyde, M/4-ketone, and N/10-sodium ethoxide in 90% alcohol were prepared and stored in a thermostat at 25°. 10 C.c. of each of the aldehyde and the ketone solution were transferred by standardised pipettes to a 50 c.c. stoppered, graduated flask, 10 c.c. of N/10-sodium ethoxide added, and the flask filled to the mark with 90% alcohol at 25°. Zero time was taken at half-delivery of the sodium ethoxide. The reaction was then followed by withdrawing 5 c.c. of the mixture at measured intervals, and determination as described above. Suitable correction was made for the sodium ethoxide present in the reaction mixture and for the sodium hydroxide added to the standard. For the measurements at temperatures above 25°, 10 c.c. of stock aldehyde and ketone solutions were added to a 50 c.c. flask and placed in the bath to attain temperature equilibrium. 10 C.c. of N/10-sodium ethoxide solution, measured at 25°, were similarly placed in another small stoppered flask also immersed in the bath. After a suitable interval the ethoxide was run into the mixed solution, the flask washed with 90% alcohol, and the washings were added to the reaction flask. Finally, the latter was filled to the mark at the temperature of the bath, and the reaction was followed as described above.

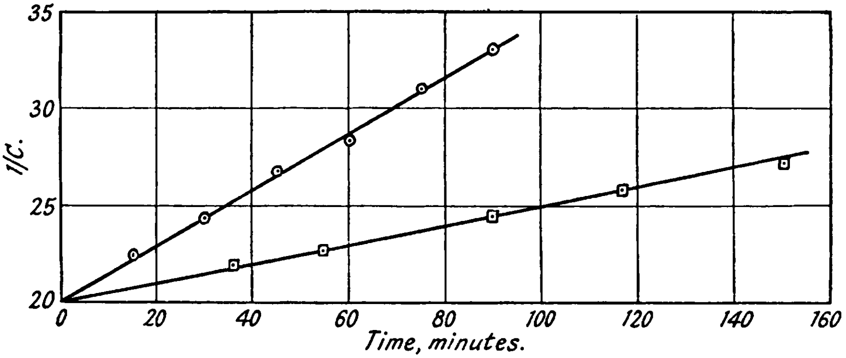
When the initial concentrations of aldehyde and of ketone were equal (c), the velocity coefficient was obtained by graphical means from the slope of the line obtained on plotting $1/c$ against time. In most cases a straight line was obtained, indicating the bimolecular nature of the reaction. The following procedure was adopted to evaluate $1/c$. The reaction measured is represented by

$$\mathrm{Ar{\cdot}CHO + CH_3{\cdot}COAr' \longrightarrow Ar{\cdot}CH{:}CH{\cdot}COAr' + H_2O}$$

Hence, if a denotes the initial concentration of aldehyde and of ketone and x is the fall in concentration at time t, the concentration of ketone or aldehyde is $a - x$ and the total carbonyl compound present at this time is $2a - x$. The reaction with hydroxylamine hydrochloride is $\mathrm{>CO + NH_2OH,HCl \longrightarrow >C{:}N{\cdot}OH + H_2O + HCl}$. Therefore if V represents the volume of N/20-sodium hydroxide used in the neutralisation of the free acid in the actual titration, the amount of N/20-sodium hydroxide equivalent to the total carbonyl in the 5 c.c. of reaction mixture is $Z = (V + E - y)$ c.c., where E c.c. represents the equivalent of the sodium ethoxide in the reaction mixture and y is the number of c.c. of N/20-sodium hydroxide added to the standard. Hence: total concentration of carbonyl $= (2a - x) = 0{\cdot}05 \times Z/5$ g.-mols. per l., and $1/c = 1/(a - x) = 1/\{(2a - x) - a\} = 1/(0{\cdot}1Z - a)$. Figures for two typical runs are given in Table II.

TABLE II.

Time (mins.).	V, c.c., for 5 c.c. of mixture.	Z, c.c.	$1/c$.	Time (mins.).	V, c.c., for 5 c.c. of mixture.	Z, c.c.	$1/c$.
$[C_6H_5{\cdot}CHO] = [C_6H_5{\cdot}CO{\cdot}CH_3] = 0{\cdot}05$; [NaOEt] = 0·02; temp. 45°; y = 0·55 c.c. of 0·05441N-NaOH; V and Z are in terms of 0·05441N-NaOH.							
15	7·38	8·67	22·5	60	6·55	7·84	28·3
30	7·09	8·38	24·3	75	6·26	7·55	31·1
45	6·74	8·03	26·8	90	6·09	7·38	33·0
k from graph in figure = 8·7 (l. g.-mol.$^{-1}$ hr.$^{-1}$).							
$[C_6H_5{\cdot}CHO] = [C_6H_5{\cdot}CO{\cdot}CH_3] = 0{\cdot}05$; [NaOEt] = 0·01; temp. 45°; y = 0·71 c.c. of 0·05441N-NaOH.							
36	8·56	8·77	22·0	117	7·94	8·15	25·8
55	8·44	8·65	22·7	150	7·78	7·99	27·1
90	8·14	8·35	24·5				
k from graph in figure = 3·0.							



In order to determine the effect of concentration, the reaction between benzaldehyde and acetophenone was studied at various concentrations at 45°. In those cases where the concentrations of aldehyde and ketone were not equal, the velocity coefficients were evaluated by means of the usual expression for the bimolecular coefficient $k = [2{\cdot}303/t(a - b)] \log b(a - x)/a(b - x)$, where a = [aldehyde] and b = [ketone] or *vice versa* according to which was in excess. The results are in Table III.

TABLE III.

Ph·CHO	0·05	0·05	0·05	0·10	0·025	0·05	0·05	0·025
Ph·COMe	0·05	0·05	0·05	0·05	0·05	0·10	0·025	0·025
NaOEt	0·01	0·02	0·04	0·02	0·02	0·02	0·02	0·02
k (l. g.-mol.$^{-1}$ hr.$^{-1}$)...	3·2	8·7	14·4	8·5 *	8·4	8·4 †	8·9	8·5

* In order to prevent precipitation of the benzylideneacetophenone, 25 c.c. of alcohol were added in the estimation before the sodium hydroxide was run in.

† 5 C.c. of alcohol were similarly added. In both these cases the standard was suitably adjusted.

After about one-third of the reaction between acetophenone and *p*-anisaldehyde had been completed, the reaction mixture became slightly yellow, and this was more pronounced at higher temperatures, *e.g.*, 65°; therefore, in this reaction, readings were taken only for the first third of the whole change. A summary of the results for the velocity coefficients (in l. g.-mol.$^{-1}$ hr.$^{-1}$), together with the activation energies (obtained from the plot of log k against $1/T$) and log PZ, are included in Table IV. In all these reactions the initial concentration of aldehyde and of ketone was 0·05M and of condensing reagent 0·02M.

TABLE IV.

Reactants.	k_{65°.	$k_{54\cdot9^\circ}$.	k_{45°.	k_{35°.	k_{25°.	*E*, cals.	log *PZ*.
Benzaldehyde Acetophenone	22·2	—	8·7	—	3·13	9,800	7·7
Anisaldehyde Acetophenone	3·26	2·00	1·2	—	—	10,800	7·5
Benzaldehyde *p*-Methoxyacetophenone	5·85	—	2·4	1·6	0·83	9,800	7·1

In the reactions between (*a*) benzaldehyde and *p*-chloroacetophenone and (*b*) *p*-chlorobenzaldehyde and acetophenone the plots of $1/c$ against time were curved, indicating a tendency towards an equilibrium state. Approximate values for the velocity coefficients were obtained in these cases by drawing tangents to the curves at zero time. These values served to indicate the order of the velocity coefficient and of the energy of activation.

DISCUSSION.

The results obtained in the kinetic measurements show that the speed of the condensation of benzaldehyde with acetophenone is proportional to the concentrations of both reagents (constancy of the bimolecular coefficients in presence of a fixed concentration of catalyst) and also to the concentration of the ethoxide ion (approximate linearity of *k* values when the ethoxide concentration is varied). The velocity is therefore correctly represented by the expression $v = k[\text{aldehyde}][\text{ketone}][\text{OEt}']$. Only its dependence upon the concentration of the aldehyde had been demonstrated previously (Nikitin, *loc. cit.*).

Inspection of the values of the energy of activation and of the non-exponential term of the kinetic equation $k = PZ\,.\,e^{-E/RT}$ leads to the following interesting conclusions. (*a*) The introduction of a *p*-methoxyl group into the aldehyde molecule leads to a decrease in speed, which is to be ascribed to a higher energy of activation (by 1000 cals.), the *PZ* term not being changed to any extent which is outside the limits of precision of the determination of this quantity. The measurements on the velocity of reaction of *p*-chlorobenzaldehyde with acetophenone gave an approximate value for the energy of activation of the order of 8,000 cals. It is quite certain that the value of *E* is increased by *p*-methoxyl and lowered by *p*-chloro-substituents, in accordance with the effect anticipated for a change which is favoured by recession of electrons from the seat of reaction.

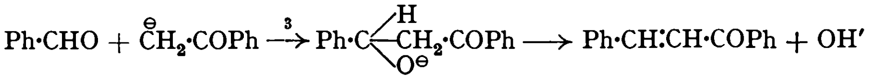
(*b*) Introduction of *p*-methoxyl into the acetophenone molecule has no effect upon the energy of activation, and the lower velocity is to be attributed to a decrease (though not a large one) in the non-exponential term. When *p*-chloroacetophenone reacts with benzaldehyde, accurate values for velocities are difficult to obtain, for the reasons given above; nevertheless, we were able to estimate 10,000—10,500 cals. as an approximate value for the energy of activation. This again is very near to the value found for acetophenone and benzaldehyde. The velocity of the former reaction, however ($k_{45^\circ} = 15\cdot7$), is almost double that of the latter, indicating a definite increase in log *PZ*.

We therefore suggest that the influences of substituents may be described, with some degree of probability at least, as follows: groups in the benzaldehyde molecule influence the velocity mainly by changing the energy of activation, whereas substituents in the acetophenone change principally the non-exponential factor.

In setting up a mechanism for the reaction of benzaldehyde with acetophenone in the presence of a basic catalyst, two alternatives may be envisaged: (*a*) the ethoxide ion may withdraw a proton from the acetophenone in accordance with Hann and Lapworth's mechanism (J., 1904, **85**, 46) for changes of this type, a scheme which has been re-expressed by various later workers; (*b*) the ethoxide ion may form an activated addition complex with the aldehyde (Watson, "Modern Theories of Organic Chemistry," Oxford, 1937, p. 110). These two mechanisms may be written as follows:

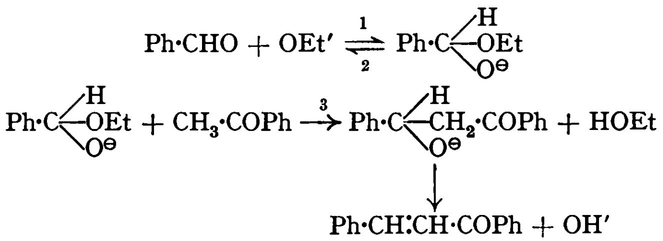
(*a*)

$$\text{CH}_3\text{·COPh} + \text{OEt}' \underset{2}{\overset{1}{\rightleftharpoons}} \overset{\ominus}{\text{C}}\text{H}_2\text{·COPh} + \text{HOEt}$$



$$\text{Ph·CHO} + \overset{\ominus}{\text{C}}\text{H}_2\text{·COPh} \xrightarrow{3} \text{Ph·C}{\overset{\text{H}}{\underset{\text{O}^{\ominus}}{<}}}\text{CH}_2\text{·COPh} \longrightarrow \text{Ph·CH:CH·COPh} + \text{OH}'$$

(*b*)



The production of hydroxyl ion leads to no difficulty, since in our medium (90% alcohol) it will be immediately replaced by ethoxide ion.

The measured speed is that of the decrease in concentration of carbonyl group, and this process occurs in reaction 3. Since reaction 3 is followed immediately by loss of water we may regard it as irreversible and we may consider two extreme types of relationship between the relative speeds of reactions 1, 2, and 3.

(i) v_3 may be small enough compared with v_1 and v_2 to permit the establishment and maintenance of the equilibrium concentration of the ketone ion in (*a*) or the complex ion in (*b*). For the former mechanism we then have

$$\begin{aligned}\text{Measured velocity} = v_3 &= k_3[\text{Ph·CHO}][\overset{\ominus}{\text{C}}\text{H}_2\text{·CO·Ph}]\\ &= k_3K[\text{Ph·CHO}][\text{CH}_3\text{·CO·Ph}][\text{OEt}']/[\text{EtOH}]\\ &= \text{constant} \times [\text{Ph·CHO}][\text{CH}_3\text{·COPh}][\text{OEt}']\end{aligned}$$

A similar expression may be derived for mechanism (*b*).

(ii) v_3 may be very large compared with v_1 and v_2, so that none of the ketone ion returns to the original reagents and the measured velocity is $v_1 = \text{constant} \times [\text{CH}_3\text{·COPh}][\text{OEt}']$. In this case the measured velocity is independent of [Ph·CHO] in (*a*) and of [CH_3·COPh] in (*b*). This state of affairs probably exists in the aldol condensation of acetaldehyde studied by Bell (J., 1937, 1637; cf. Watson, *Ann. Reports*, 1939, **36**, 215).

If the speeds of reactions 1, 2, and 3 were of the same order we should obtain a more complicated velocity equation which certainly would be very different from that found experimentally.

In both mechanisms (*a*) and (*b*) the first stage consists in a reaction between a neutral molecule and an ion, and reactions involving an ion usually have a *P* factor of about unity (Grant and Hinshelwood, J., 1933, 258). Now the value of *P* for the reaction between acetophenone and benzaldehyde is of the order 10^{-4}, and it is therefore probable that only one of many ions proceeds to reaction 3; the vast majority either revert to the original state or stay in the form of the ketone ion (*a*) or the complex ion (*b*). The condition (i) in which an equilibrium is established is therefore the probable one and is in harmony with the observed kinetics. The last stage requires, *inter alia*, collision with a suitably orientated benzaldehyde molecule in (*a*) or an acetophenone molecule in (*b*), and the probability of this collision is apparently small. It is this stage which determines the extent to which the value of *P* differs from unity. On the basis of the assumption that v_3 is much smaller than v_1 or v_2, it therefore appears that either mechanism is in accord with the observed kinetics.

Mechanism (*a*) presumably needs its energy of activation almost entirely for the removal of the proton from the ketone, since the anion so formed will be highly activated, possessing, in all probability, sufficient energy to bring about the next stage (reaction with the aldehyde molecule). This mechanism therefore demands that substituents in the acetophenone should change the value of *E*. Mechanism (*b*), on the other hand, requires its energy for the reaction of the catalyst with the aldehyde, and here the complex ion formed will possess the energy required for the subsequent reaction with the ketone. According to this scheme, therefore, substituents in the benzaldehyde should change the energy of activation for the reaction. The *P* factor will depend, to some extent at least, however, upon the facility with which the ketone can react with the complex, and hence substituents in the acetophenone would be expected to lead to a variation in the *P* factor. The latter conclusions are in harmony with our experimental results.

Although we do not claim that this work provides a conclusive proof or disproof of either mechanism, we suggest that the results are best interpreted in the light of mechanism (*b*), and that they tend to the conclusion that the first step in the complete series of changes is a reaction of the aldehyde with the basic catalyst. The work appears, in fact, to offer for the first time a means of distinguishing between mechanisms of the types set out above.

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