were drawn during a period of time equal to two half-lives. The samples were then hydrolyzed by immersing the tightly sealed bottles in an oil-bath at 60° to the water level within the bottles. After 24 hours, the bottles were removed from the bath and cooled to room temperature. Isoöctane (25.00 ml.) added from a buret was mixed with the contents of each bottle. The caps were again placed securely on the bottles, the contents shaken thoroughly for several minutes and allowed to stand 24 hours. (The time of standing could be shortened probably by more frequent shaking.) At this point, the ketone was dissolved in the isoöctane layer, and the substituted aniline salt and acetic acid in the aqueous layer. The samples were then analyzed by measuring the optical density of the isoöctane layer relative to a blank of pure isoöctane at the wave length of maximum absorption of the ketone. The log of the optical density plotted *vs.* time gave a straight line indicative of a pseudo first-order rate. The slope of the straight line was obtained by the method of least squares which, multiplied by 2.303, gave k. These results are summarized in Table VII.

Further Comments on Kinetic Work.—All analytical operations were conducted in an air-conditioned room. Any rate given is highly precise (standard deviation 10^{-3} to 10^{-4}) but probably is reproducible only to the extent of ±1% among different operators. A better idea of the reproducibility in this paper can be obtained by comparison of duplicate rates given in the half-life column of Table VII. A more thorough check of kinetic data was made with acetophenone oxime using different sources of oxime for each run: the half-lives found at 50.77° were 509, 509 and 516 minutes and at 51.37° were 475, 465, 474 and 479 minutes. The above method of analysis did not succeed in determination of the rate of rearrangement of 3,4,5-triethylacetophenone oxime. The abnormality was detected by the non-linearity of the log concentration *vs.* time curve, and its cause was found to be loss of carbonyl concentration in the hydrolysis step—possibly by rearrangement of oxime undergoing hydrolysis. The abnormality was remedied by hydrolyzing the samples at 50° for at least 36 hours rather than at 60° for 24 hours. Lesser periods of time showed incomplete hydrolysis of the anilide. The length of time of hydrolysis did not affect the concentration of ketone. Greater detail of any experiment is recorded in the thesis of P. J. M.[2]

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Carbonyl Reactions. VII. The Effect of Substituents upon the Rate of Condensation of Substituted Benzaldehydes with Acetophenone[1]

BY DONALD S. NOYCE AND WILLIAM A. PRYOR[2]

RECEIVED AUGUST 11, 1958

The rates of condensation of anisaldehyde, *p*-chlorobenzaldehyde and *p*-nitrobenzaldehyde with acetophenone have been measured in acetic acid with sulfuric acid as the catalyst. The modest effect of the substituent upon the rate of condensation is interpreted as the result of two nearly counterbalancing factors, the change in basicity of the aldehyde and the change in the ease of condensation of the protonic salt of the aldehyde with the enol of acetophenone. Comparison with the corresponding base-catalyzed reaction is made.

Introduction

In continuation of studies of the acid-catalyzed condensation of benzaldehyde with acetophenone as typical of the acid-catalyzed aldol condensation[3] we have examined the effect of substituents upon the rate of condensation. The number of reactions of aromatic aldehydes for which ρ–σ correlations have been reported[4] is somewhat limited, but there are examples of both positive and negative ρ-values. We have previously reported on the situation prevailing in the formation of semicarbazones[5] and have commented upon possible reasons for the failure to obtain a linear ρ–σ correlation.

The condensation reaction of substituted benzaldehydes with acetophenone is additionally valuable, since Coombs and Evans[6] have measured the rates of the corresponding base-catalyzed reaction in 90% ethanol. It is thus possible to compare the rates of acid- and base-catalyzed reactions of the same compounds.

Results and Discussion

The kinetic measurements were carried out under conditions which were known from the results with benzaldehyde and acetophenone to give simple kinetic behavior. These conditions obtain when the concentrations of both benzaldehyde and acetophenone are reasonably low, so that the unimolecular dehydration step following the bimolecular condensation step is fast. For the compounds studied here, the plotted data of any individual kinetic run revealed no evidence of an induction period in the formation of the final unsaturated ketone.

The kinetic results obtained are summarized in Table I.

The effect of the substituent upon the rate of condensation is quite small. The change from *p*-nitrobenzaldehyde to anisaldehyde results in a rate change of only a factor of two. This undoubtedly results from two opposing factors. One is the effect of the substituent on the basicity of the aldehyde. Anisaldehyde is distinctly more basic than *p*-nitrobenzaldehyde, and the concentration of the aldehydic oxonium salt will, therefore, be higher for anisaldehyde than for *p*-nitrobenzaldehyde at a given acidity. Such a contributing factor would be expected for anisaldehyde to increase the rate of the condensation step, which we have previously[3] described as involving the oxonium salt of the aldehyde and the enol of acetophenone. The second, opposing factor is the change in the resonance system as carbon–carbon bond formation takes place. This process is unfavorably influenced by the methoxyl substituent, since the resonance interaction between the methoxyl group and the aldehyde group is partly lost at the transition state.

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(2) Union Carbide and Carbon Fellow, 1952–1953; U. S. Rubber Co. Fellow, 1953–1954.

(3) D. S. Noyce and W. A. Pryor, THIS JOURNAL, **77**, 1397 (1955).

(4) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(5) D. S. Noyce, A. T. Bottini and S. G. Smith, *J. Org. Chem.*, **23**, 752 (1958).

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TABLE I

RATE OF CONDENSATION OF SUBSTITUTED BENZALDEHYDES WITH ACETOPHENONE[a]

p-X-	(H_2SO_4)	$(C_6H_5CHO)_0 \times 10^4$	$(CH_3COC_6H_5) \times 10^2$	$k_1' \times 10^6$, sec.$^{-1}$	$k_1^0 \times 10^5$ l. mole^{-1} sec.$^{-1}$
T = 28.00°					
H-[b]	0.699				6.70
NO_2-	.699	3.35	4.37	2.77	6.34
	.699	3.35	2.18	1.38	6.33
	.699	3.35	0.880	0.60	6.82
Cl-	.699	5.38	4.17	3.30	7.91
	.699	5.38	2.08	1.58	7.60
	.699	3.75	4.01	3.12	7.78
CH_3O-	.699	23.9	4.01	5.23	13.04
	.699	5.98	4.01	5.45	13.59
T = 46.30°					
H-[c]	0.699				20.8
NO_2-	.699	8.35	3.98	7.53	19.2
	.699	8.35	1.99	3.48	17.5
	.349	8.87	4.28	2.53	5.91
Cl-	.699	8.99	3.98	9.97	25.0
	.699	8.99	1.99	4.58	23.0
	.349	9.76	4.28	2.93	6.85
CH_3O-	.699	45.2	4.28	17.83	41.7
	.699	22.6	2.14	8.20	38.3
	.349	45.2	4.28	5.30	12.4

[a] Solvent, acetic acid, 0.60 mole H_2O/liter. [b] From ref. 3. [c] Interpolated from ref. 3.

Though the least squares calculation gives $\rho = -0.25 \pm 0.05$ with a satisfactorily small standard deviation, this is a reflection of the small value of ρ. It is to be noted that the rate constant for anisaldehyde and acetophenone lies above the best straight line, and that there is a tendency for the curve to be concave upward. Similar observations have been reported previously, and are discussed by Jaffé.[4]

The corresponding base-catalyzed condensation which was studied by Coombs and Evans[6] shows a rate pattern as the *p*-substituent is varied, in which methoxyl is inhibitory (because of loss of resonance stabilization in the transition state) and chlorine is acceleratory. The estimated value for ρ is now decidedly positive (*ca.* 3.5). Again the rate for anisaldehyde is faster than predicted from the best straight line correlation.

Thus in the condensation of substituted benzaldehydes with acetophenone, the rate of the acid-catalyzed reaction is mildly favored by electron-donating substituents, while the rate of the base-catalyzed reaction is accelerated by electron-withdrawing substituents.

However, another factor must be considered. It was shown previously[7] that the rate of dehydration and the rate of reversion of the ketone, 1,3-diphenyl-3-hydroxy-1-propanone, are fairly rapid in dilute solution when compared with the rate of initial condensation. However, in more concentrated solutions, the rates become comparable. The data reported in this paper have been obtained under conditions where the rate of condensation is rate controlling. Nevertheless, alteration of the relative rates of the reversion process and of the dehydration process may still influence any attempted ρ–σ correlations. It is quite likely that the alteration of these rate constants (k_2 for reversion and k_3 for dehydration) are responsible for the failure to observe a smoothly linear correlation of the rate of acid-catalyzed condensation with sigma. This situation is examined in more detail for the condensation of benzaldehyde with methyl ethyl ketone in a subsequent paper.[8]

Finally, it is to be noted that the limited data on acidity dependence presented here (at 46°) indicate the utility of the measured values of the indicator acidity function H_0 in correlating rates of reaction in acetic acid. A change of twofold in the molar concentration of the catalyzing sulfuric acid results in a change of rate of more than threefold in the observed rate of reaction. Such is the expected result from the values of H_0 in this region of concentration of sulfuric acid in acetic acid.[3]

From the data reported in Table I it is possible to calculate apparent heats and entropies of activation (Table II).

TABLE II

APPARENT HEATS AND ENTROPIES OF ACTIVATION

X-C_6H_4CHO	$\Delta H^{\ddagger}$, kcal.	$\Delta S^{\ddagger}$, e.u.
H-	11.6	−53[a]
NO_2-	10.3	−57
Cl-	11.2	−54
CH_3O-	11.0	−55

[a] Incorrectly reported previously[3] as −35 e.u.

The highly negative entropy of activation is expected for a process in which three species are brought together in the activated complex.

Experimental

***p*-Nitrobenzaldehyde** was prepared by the method of reference 9. **Anisaldehyde** was purified by distillation under nitrogen. **The *p*-chlorobenzaldehyde** was purified by crystallization from ethanol. The acid titer of all aldehydes used was less than 0.5%. Anhydrous acetic acid and 100% sulfuric acid were prepared as described previously.[3]

***p*-Nitrobenzalacetophenone.**—A solution of 0.05 mole of *p*-nitrobenzaldehyde and 0.05 mole of acetophenone in 100 ml. of acetic acid containing 0.15 mole of sulfuric acid was stirred for 48 hours at room temperature. The mixture was diluted with water, the sulfuric acid neutralized and filtered. The collected precipitate was carefully washed and then dried, to afford crude *p*-nitrobenzalacetophenone, 12.5 g. (99%), m.p. 155–162°. Two crystallizations from benzene afforded material of m.p. 164.1–164.5° (lit.[10] 163°).

***p*-Chlorobenzalacetophenone.**—In a similar fashion *p*-chlorobenzaldehyde and acetophenone afforded, after crystallizations from ethanol, 70% of *p*-chlorobenzalacetophenone, m.p. 112–114°. Two further crystallizations afforded a sample of m.p. 114.3–115.1° (lit.[11] 113–114°).

***p*-Methoxybenzalacetophenone.**—Likewise a mixture of anisaldehyde and acetophenone afforded a good yield of *p*-methoxybenzalacetophenone, which was isolated by distillation. Crystallization of a small sample from aqueous acetic acid afforded material of m.p. 74.3–74.6° (lit.[12,13] 75°, 78°).

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Kinetic Measurements.—Measurements were carried out as described previously.[3] Thermostated solutions were mixed to give reaction solutions of the appropriate concentrations, and samples were withdrawn periodically and the concentration of the unsaturated ketone determined spectrophotometrically.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Carbonyl Reactions. VIII. The Kinetics of the Acid-catalyzed Condensation of Benzaldehyde and *p*-Nitrobenzaldehyde with Methyl Ethyl Ketone. Some Observations on ρ-σ Correlations[1]

BY DONALD S. NOYCE AND LLOYD R. SNYDER

RECEIVED AUGUST 11, 1958

The condensation of benzaldehyde and methyl ethyl ketone in acetic acid, catalyzed by sulfuric acid, proceeds *via* the intermediate β-hydroxy ketone, 4-phenyl-4-hydroxy-3-methyl-2-butanone (II); II undergoes competitive cleavage, esterification and dehydration in this medium. The condensation of *p*-nitrobenzaldehyde with methyl ethyl ketone proceeds similarly, but with no evidence of cleavage or esterification of the intermediate β-hydroxy ketone. The examination of the ρ-σ correlation gives further insight into situations where such correlations may fail.

Introduction

In continuing the study of the mechanism of acid-catalyzed reactions,[2-6] we have carried out kinetic studies of the condensation of benzaldehyde (I) and of *p*-nitrobenzaldehyde (IV) with methyl ethyl ketone, to supplement the study previously reported[4,5] of anisaldehyde and methyl ethyl ketone. The results obtained are generally similar to those reported earlier. There are, however, differences in degree which make necessary a fairly detailed kinetic analysis for each system. The similarities and divergencies provide additional insight into the reaction processes involved.

Gettler and Hammett[7] have studied the kinetics of the base-catalyzed condensation of benzaldehyde and methyl ethyl ketone. They have also carefully reviewed and corroborated the evidence showing that the formation of 4-phenyl-3-methyl-3-buten-2-one (III) takes place in acid to the essential exclusion of the isomer, 1-phenyl-1-penten-3-one, which is formed exclusively under basic conditions. Similarly the formation of 4-(*p*-nitrophenyl)-3-methyl-3-buten-2-one occurs under conditions of acid-catalyzed condensation.

From the results to be reported here, it is possible to detail the effect of substitution in the aromatic ring upon the relative rates of the various reactions processes which have been shown to be kinetically important.

Experimental

Preparation of Materials.—The materials used for the study are well-known, and have been carefully purified to give properties concordant with those in the literature. Spectral characterization was also used in purification of the required materials. 4-(*p*-Nitrophenyl)-3-methyl-3-buten-2-one was prepared from *p*-nitrobenzaldehyde and methyl ethyl ketone in 95% sulfuric acid, following the general procedure of Heller.[8] Better yields were obtained using sulfuric acid in acetic acid as solvent. When 4-(*p*-nitrophenyl)-3-methyl-3-buten-2-one was prepared following the procedure of Burckhalter and Johnson[9] material identical to that obtained above (m.p. 94–95°) was obtained, in contrast to the reported value of 108° (Burkhalter and Johnson). Heller reports a value of 96°.

Kinetic Procedures.—Anhydrous acetic acid and sulfuric acid were prepared as described previously.[2] The kinetic procedures were those outlined previously.[2,4] Rate data were obtained by following the appearance of the characteristic absorption bands for the unsaturated ketone and the regenerated aldehyde as appropriate using a Beckman DU spectrophotometer.

Preparation of Intermediate β-Hydroxyketones.—From preliminary kinetic results the following conditions were chosen to isolate the intermediate β-hydroxyketone, 4-phenyl-4-hydroxy-3-methyl-2-butanone (II), from the condensation of benzaldehyde and methyl ethyl ketone. To 156 g. of methyl ethyl ketone was added 10 g. of sulfuric acid. The temperature was adjusted to 23° and 92 g. of benzaldehyde added. After maintaining the resulting solution at 25° for 12 minutes, the mixture was poured into ice, extracted with benzene, and the combined extracts washed with water. The excess solvent and methyl ethyl ketone and unreacted benzaldehyde were removed under reduced pressure below 60°. An oily brown residue (20 g.) resulted, which was approximately 75% ketol II. Crystallization of this oil from pentane at Dry Ice temperature yielded flocculent, colorless crystals, melting well below room temperature.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.12; H, 7.92. Found: C, 74.57; H, 8.21.

The spectral characteristics of the isolated material indicated that it was contaminated with 2% of benzaldehyde and 2% of the unsaturated ketone III.

In a similar fashion following conditions dictated by preliminary kinetic results, an impure sample of 4-(*p*-nitrophenyl)-4-hydroxy-3-methyl-2-butanone (IV) was prepared.

Results

Benzaldehyde and Methyl Ethyl Ketone.—The reaction of benzaldehyde with an excess of methyl ethyl ketone in solutions of sulfuric acid in acetic acid proceeds to the extent of 90%. It is possible to analyze for the appearance of the condensation product as a function of time, and there is observed, as previously with anisaldehyde and methyl ethyl ketone, an apparent initial induction period in the formation of the condensation product. The failure of the reaction to proceed to 100% completion under these conditions precludes the simple analysis of the limiting slope obtained.

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[1] Supported in part by the Office of Ordnance Research, Contract No. DA-04-200-ORD-171.

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[3] D. S. Noyce, W. A. Pryor and A. T. Bottini, *ibid.*, **77**, 1402 (1955).

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[8] G. Heller, H. Lauth and A. Buchwaldt, *Ber.*, **55**, 483 (1922).

[9] J. H. Burckhalter and S. H. Johnson, THIS JOURNAL, **73**, 4835 (1951); M. Stiles has reported a similar observation (private communication).