[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Kinetics of the Base-catalyzed Condensation of Benzaldehyde with Phenacyl Chloride

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The rate of the base-catalyzed condensation between benzaldehyde and phenacyl chloride has been measured in dioxane-water mixtures at 0° under conditions leading to a high yield of benzalacetophenone epoxide. The reaction is of the third order, the rate-determining step involving benzaldehyde, phenacyl chloride and hydroxyl ion. This fact is interpreted as indicating that enolization of phenacyl chloride and epoxide formation from the chlorohydrin are both much more rapid than the attack of phenacyl chloride anion on benzaldehyde.

It is generally agreed[1] that condensation reactions involving a hydrogen atom in the α-position to the carbonyl group of an aldehyde, ketone or ester have enolization of that carbonyl compound as an essential first step. The enolization of this compound, commonly called the B-component in an aldol reaction, may or may not be the rate-determining step in the reaction as observed. In the base-catalyzed aldolization of acetaldehyde[2] and in that of glyceraldehyde with itself or with dihydroxyacetone[3] kinetic and tracer evidence indicates that the A-component is so reactive toward the enolate ion of the B-component that essentially every enolization is followed immediately by attack of the enolate anion upon the carbonyl group of the A-component. In other cases studied, including the especially carefully investigated aldolization of acetone[4] the enolization step is found to be so much more rapid than the attack upon the carbonyl group that the B-component and its enol essentially establish equilibrium during the reaction.

Aldolization is a highly reversible reaction; kinetic and mechanistic conclusions concerning the forward reaction in the general case must be drawn from a study of the reverse reaction and a knowledge of the position of the equilibrium. In the Darzens condensation and related reactions[5] the primary product of aldolization is a halohydrin anion which is converted irreversibly into an epoxide by an intramolecular displacement. The Darzens condensation accordingly appears to be a favorable case for the observation of the kinetics of aldol condensation with active and inactive reactants alike. For this reason we have undertaken to explore the kinetics of the Darzens condensation and have chosen as a first example the reaction of benzaldehyde with phenacyl chloride catalyzed by sodium hydroxide. After ascertaining that this condensation could be carried out in dioxane–water mixtures under the conditions projected for the kinetic study with a yield of 94.5% of the epoxide of benzalacetophenone, an investigation was made of possible ways of following the reaction.

Experimental

Analytical Method.—In 50% aqueous dioxane even at 0° the reaction between benzaldehyde and phenacyl chloride in the presence of equivalent concentrations of hydroxyl ion was so rapid that it was necessary to find an analytical method which permitted dilution of the phenacyl chloride to concentrations between 5×10^{-4} and 10^{-3} molar. It was found that self-condensation of phenacyl chloride[6] could be rendered inappreciable by the use of a 9- to 20-fold excess of benzaldehyde over phenacyl chloride. The use of this excess required that the benzaldehyde be exceptionally pure with no detectable amount of benzoic acid and that the reaction be protected completely from the possibility of atmospheric oxidation. The benzaldehyde was accordingly prepared for use by distillation and storage under nitrogen. Storage vessels and reaction vessels were kept stoppered at all times and all transfers of reagents and solutions were made through stainless steel needles.

Attempts to titrate either the benzaldehyde[7] or the chloride ion[8] were abandoned because all the methods tried either were too insensitive for the concentration required or, in the case of chloride ion, were interfered with by either benzaldehyde or dioxane. It was found possible to obtain check analyses by the potentiometric titration of the chloride ion using silver and tungsten electrodes,[9] but the best method of following the reaction proved to be after all the titration of the hydroxyl ion with standard acid. The sodium hydroxide was always used in moderate excess over the phenacyl chloride so that its concentration changed to a conveniently measurable extent during the reaction. In the early runs it was established that the amount of phenacyl chloride initially taken, the amount of chloride ion liberated, and the amount of hydroxyl ion consumed during the course of a run were all identical. In the kinetic calculations the initial concentration of phenacyl chloride was always taken as the difference between the initial hydroxyl ion titer and that after the reaction solution had stood for about two days.

Procedure.—The reaction was initiated by rapidly injecting with a hypodermic syringe a small amount of concentrated solution of phenacyl chloride in dioxane into the solution of the other components previously cooled to 0°. At suitable intervals aliquot portions of the mixture were pipetted out for analysis of the sodium hydroxide. Each aliquot was added to a convenient excess of standardized sulfuric acid solution and the excess acid was back-titrated with standard base.

Isolation Experiment.—Benzaldehyde (1.5 g., 0.014 mole), 0.2 g. (0.005 mole) of sodium hydroxide and 0.387 g. (0.0025 mole) of phenacyl chloride were dissolved in 125 ml. of dioxane and 125 ml. of water previously cooled to 0°. Two hours later the solution was diluted with water to 1 liter

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[2] R. P. Bell, *J. Chem. Soc.*, 1637 (1937).

[3] K. F. Bonhoeffer and W. D. Walters, *Z. physik. Chem.*, **A181**, 441 (1938).

[4] W. D. Walters and K. F. Bonhoeffer, *ibid.*, **A182**, 265 (1938), and references there cited.

[5] G. Darzens, *Compt. rend.*, **139**, 1214 (1904); **141**, 766 (1905); M. S. Newman and B. J. Magerlein in Adams,' "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 413-440.

[6] Z. Fritz, *Ber.*, **28**, 3028 (1895); O. Widman, *Ann.*, **400**, 86 (1913).

[7] H. Schultes, *Angew. Chem.*, **47**, 258 (1934).

[8] J. R. Caldwell and H. V. Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935); W. Clark, *J. Chem. Soc.*, 749 (1926); B. Cunningham, P. L. Kirk and S. C. Brooks, *J. Biol. Chem.*, **139**, 11 (1941); P. L. Kirk, "Quantitative Ultramicro Analysis," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 191; J. Pinkhoff, *Chem. Weekblad*, **16**, 1163 (1919); C. G. Swain and S. D. Ross, THIS JOURNAL, **68**, 658 (1946).

[9] F. Daniels, J. H. Mathews and J. W. Williams and staff, "Experimental Physical Chemistry," Fourth edition, McGraw-Hill Book Co., New York, N. Y., 1949, p. 222.

and left at 0° for 12 hours. Then the mixture was rendered slightly acid with acetic acid and salted out with sodium chloride. After several more hours at 0°, filtration and drying yielded 0.531 g. of benzalacetophenone epoxide melting at 88.5 to 89.0°. This is a 94.5% yield.

Other Preliminary Experiments.—It was ascertained by titration of chloride ion that in 20 hours at 25° phenacyl chloride liberated about 0.5% of its chloride ion when present alone in 50% aqueous dioxane, about 0.35% when present with benzaldehyde, and not over 0.75% in the presence of benzaldehyde and 2 drops of concentrated sulfuric acid in 25 cc. of solution. In a buffer containing 0.1 *N* sodium acetate and 0.1 *N* acetic acid in five days at 28° only 9% of the chloride ion was liberated. Considering the rapidity with which the Darzens condensation takes place at 0°, these experiments serve to establish the absence of appreciable acid catalysis, of general basic catalysis from acetate ion and of spontaneous or "water" reaction.

Results

All the runs were made at 0° since solubilities became a limiting factor much below this temperature and the speed of the reaction precluded accurate measurement above it. All runs were made in the presence of 0.01 *M* sodium perchlorate to maintain a constant ionic strength. The benzaldehyde concentrations varied from 4.77×10^{-3} to 9.74×10^{-3}, the phenacyl chloride concentrations from 0.47×10^{-3} to 1.04×10^{-3}, and the sodium hydroxide concentrations from 1.06×10^{-3} to 1.54×10^{-3}. In all these runs up to 70–80% the reaction was of third order over-all, first order with respect to aldehyde, first order with respect to phenacyl chloride and first order with respect to hydroxyl ion. Beyond 70–80% the curves showed a departure from third-order kinetics in the direction of a slower reaction or a higher order. Table I summarizes the conditions of the runs and the values of the third-order rate constants obtained.

TABLE I

KINETIC EXPERIMENTS AT 0°, IONIC STRENGTH, 0.01

	Concentrations, moles per liter × 10^3			
Run	Benzaldehyde	Phenacyl chloride	Sodium hydroxide	$k \times 10^{-3}$
1	9.05	0.956	1.300	5.77
2[a]	9.54	0.474	1.064	5.81
3	9.74	1.041	1.540	5.81
4	9.08	0.522	1.544	6.08
5	4.77	0.521	1.544	6.16

Average $k = 5.93 \times 10^3$ liters² moles⁻² min.⁻¹

[a] The concentrations of the reactants reported in run 2 are those of the first aliquot.

Because of the excess of benzaldehyde the data in any run are fitted almost as well by the equation for a second-order reaction between phenacyl chloride and hydroxyl ion. The participation of benzaldehyde in the rate-determining step is shown by the fact that the second-order rate constant in run 5 is only about half as great as in runs 1–4, containing the larger concentration of benzaldehyde. Figure 1, showing the kinetic data for runs 2 and 5 plotted, illustrates this point.

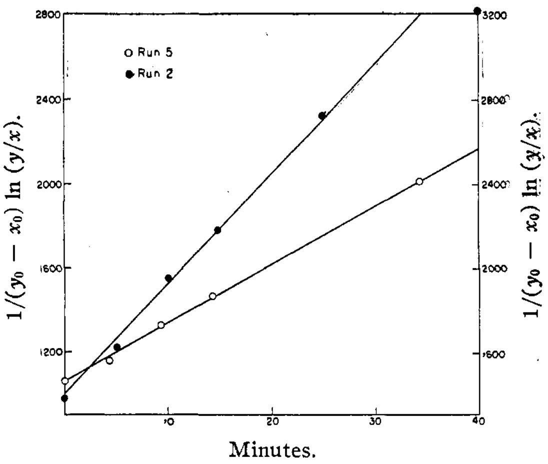
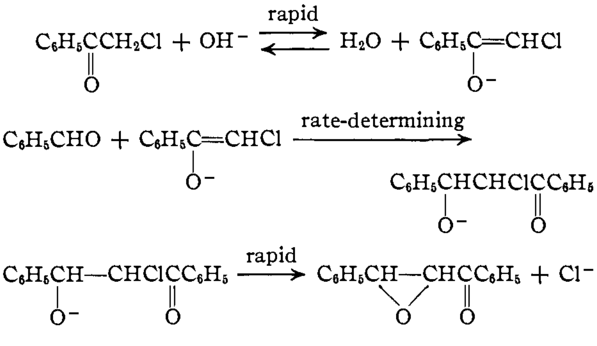


Fig. 1.—Dependence of second-order rate constant (based on phenacyl chloride and hydroxyl ion) upon benzaldehyde concentration: ●, run 2 (right-hand scale); O, run 5 (left-hand scale). $x = [OH^-]$; $y = [C_6H_5COCH_2Cl]$.

Discussion

The kinetics as well as the qualitative course of the haloform reaction[10] shows that halogen in the α-position to a carbonyl group has a powerful accelerating effect upon base-catalyzed enolization. At the same time the anion of a chloroenolate must be both less basic and less nucleophilic in the kinetic sense than that derived from an unhalogenated ketone. Since the base-catalyzed condensation between benzaldehyde and acetophenone involves benzaldehyde in the rate-determining step,[11] it is not surprising that such is also the case with phenacyl chloride, whose enolization should be faster than that of acetophenone.[10] It seems likely, therefore, that the Darzens condensation will afford no example in which enolization is the rate-determining step of the condensation.

The kinetic facts are consistent with the reaction sequence



$$C_6H_5\underset{\underset{O}{\|}}{C}CH_2Cl + OH^- \overset{\text{rapid}}{\rightleftarrows} H_2O + C_6H_5\underset{\underset{O^-}{|}}{C}{=}CHCl$$

$$C_6H_5CHO + C_6H_5\underset{\underset{O^-}{|}}{C}{=}CHCl \xrightarrow{\text{rate-determining}} C_6H_5\underset{\underset{O^-}{|}}{CH}CHCl\underset{\underset{O}{\|}}{C}C_6H_5$$

$$C_6H_5\underset{\underset{O^-}{|}}{CH}{-}CHCl\underset{\underset{O}{\|}}{C}C_6H_5 \xrightarrow{\text{rapid}} C_6H_5CH{-}CH\underset{\underset{O}{\|}}{C}C_6H_5 + Cl^-$$

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(10) P. D. Bartlett, THIS JOURNAL, **56**, 967 (1934); P. D. Bartlett and J. R. Vincent, *ibid.*, **57**, 1596 (1935). See also R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc.* (*London*), **A176**, 88 (1940).

(11) E. Coombs and D. P. Evans, *J. Chem. Soc.*, 1295 (1940).