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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Kinetics of the Ammonium Acetate-Catalyzed Condensation of Vanillin and Nitromethane[1]

BY THOMAS I. CROWELL AND FAUSTO A. RAMIREZ

In order to study the amine catalysis of the condensation between aldehydes and nitroalkanes the rate of reaction of vanillin with nitromethane to form 3-methoxy-4-hydroxy-β-nitrostyrene has been measured in methanol solution at 25°, using 0.5 M ammonium acetate as catalyst. The rate is decreased both by acid and by base, the maximum being at a pH slightly higher than that of ammonium acetate solutions. A small induction period was observed in the otherwise first-order course of the reaction of vanillin with excess nitromethane. The disappearance of this induction period when vanillin is allowed to react with ammonium acetate, before adding nitromethane, indicates an intermediate tentatively formulated as the imine. Accordingly the acetates of secondary and tertiary amines are shown to be much less effective catalysts than ammonium and n-butylammonium acetates. Ammonium acetate reacts with the above nitrostyrene in dry methanol, forming products which hydrolyze to vanillin.

Various substituted β-nitrostyrenes have been prepared by the action of a strong base on nitromethane and an aromatic aldehyde.[2] The mechanism[3] is probably attack on the carbonyl group by the anion of nitromethane, followed by dehydration. In some cases the intermediate nitroalcohols have been isolated; all the synthetic procedures call for a dehydrating agent in the final step.[4] The condensation also proceeds in less basic or even in acid solution when amines are used as catalysts. Useful conditions range from a trace of a primary amine, without solvent, to ammonium acetate in glacial acetic acid.[2] In order to elucidate the role of the amine, we have studied the rate of condensation of vanillin with nitromethane to form 3-methoxy-4-hydroxy-β-nitrostyrene (VNM), a highly colored acid–base indicator.[5] This particular reaction appeared clean-cut, with stable reactants and product.

The reaction was run in methanol at 25° and in most cases was catalyzed by 0.500 M ammonium acetate. The rate was determined by gravimetric analysis for vanillin as the 2,4-dinitrophenylhydrazone.

Experimental

Materials.—VNM was prepared according to Knoevenagel and Walter.[5a] Nitromethane and the amines used were carefully fractionated in a packed column. Alkylammonium acetates were prepared in solution by adding methanolic acetic acid to a weighed quantity of amine. The solvent was Eimer and Amend reagent methanol.

Eimer and Amend C.P. ammonium acetate was dried about two hours at 0.07 mm. pressure and thereafter handled in a dry-box. Analysis for ammonia by evaporation from standard base gave 22.13% NH_3 (Calcd. 22.09%).

Vanillidene methylamine was prepared by the method of Moffett and Hoehn.[6] The large plates obtained from benzene, m.p. 131–135°, turned yellow in solution or in moist air.

Procedure.—The regular kinetic experiments were started by adding 10 ml. of standard nitromethane solution to 1.927 g. (0.025 mole) of ammonium acetate in 25 ml. of methanol, then adding 10 ml. of standard vanillin solution at zero time and diluting to 50 ml. Samples were withdrawn with a 5-ml. pipet and added to the hot precipitating reagent. (This reagent was prepared by dissolving 1.0 g. of 2,4-dinitrophenylhydrazine in 60 ml. of concd. sulfuric acid and diluting to 1 liter with water. For analysis of a 0.027 M vanillin solution, 40 ml. of this solution was filtered, diluted to 140 ml. and heated to 70°.) The precipitated 2,4-dinitrophenylhydrazone was digested on the hot-plate for ten minutes, then collected in a medium-porosity sintered gooch crucible, dried two hours at 115° and weighed.[7] Five determinations on a known vanillin solution showed an average deviation from the mean of 0.4% (0.17 mg. in weight of precipitate) and an error of 0.05% from the calculated value.

Pure VNM could be obtained by diluting the reaction mixture with water and in one case was isolated in 78% yield, m.p. 166–168°. The nitrostyrene was also obtained by allowing nitromethane to react with vanillidene methylamine in dry methanol, glacial acetic acid or dioxane, then diluting with water.

Effect of pH.—The concentrations of acetic acid and of ammonia were varied in several runs. Acidic solutions were obtained by adding weighed portions of glacial acetic acid. The ammonia concentration was conveniently increased at constant salt concentration by adding sodium methoxide solution to the ammonium acetate solution.

The Reverse Reaction.—To a solution of 2.037 g. of ammonium acetate in dry methanol was added 0.0245 g. of VNM. The first sample produced no precipitate with hot DNP reagent, but a sample taken after five days yielded 7 mg. of vanillin 2,4-dinitrophenylhydrazone, m.p. 269–271°. VNM also formed products hydrolyzing to vanillin when treated with butylamine in methanol or ammonium acetate in acetic acid. An aqueous solution of VNM at 100°, red because of increased ionization at the high temperature, slowly produced vanillin. This hydrolysis was retarded if enough HCl was added to turn the indicator yellow.

Results

The course of a typical run is shown in Fig. 1 and on a larger scale in the lower curve of Fig. 2. The ordinate, w, is $[1/(b - a)] \ln [a(b - x)/b(a - x)]$, where a and b are the initial concentrations of vanillin and nitromethane, and $a - x$ the concentration of vanillin at time t. After a short induction period the plot is linear up to about 65% reaction. When a larger excess of nitromethane was used, the linear relation held for 90% or more of the reaction;

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[1] Presented before the Division of Organic Chemistry, Chicago, September 6, 1950.

[2] W. S. Emerson, *Chem. Revs.*, **45**, 347 (1949).

[3] J. F. Bourland and H. B. Hass, *J. Org. Chem.*, **12**, 704 (1947); G. Hahn and K. Stiehl, *Ber.*, **71**, 2154 (1938).

[4] See L. Canonica, *Gazz. chim. ital.*, **79**, 192 (1949).

[5] (a) E. Knoevenagel and L. Walter, *Ber.*, **37**, 4506 (1904); (b) M. G. S. Rao, C. Strikantia and M. S. Iyengar, *Helv. Chim. Acta*, **12**, 581 (1929); (c) R. Stewart and R. H. Clark, *Can. J. Research*, **26B**, 7 (1948).

[6] R. B. Moffett and W. M. Hoehn, THIS JOURNAL, **69**, 1792 (1947).

[7] H. A. Iddles and C. E. Jackson, *Ind. Eng. Chem., Anal. Ed.*, **6**, 454 (1934).

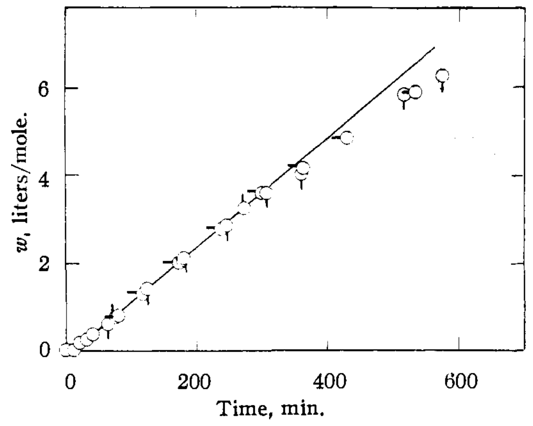

Fig. 1.—Course of the reaction (four runs), $a = 0.0270$, $b = 0.296$.

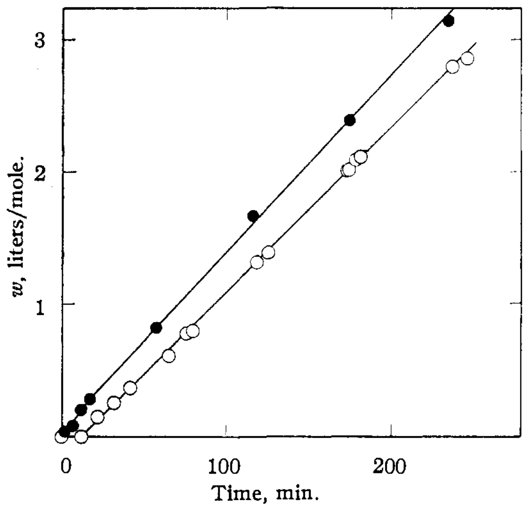

Fig. 2.—Course of the reaction; ○, normal procedure (same data as Fig. 1); ●, vanillin added 19 min. before CH_3NO_2.

with equivalent quantities of vanillin and nitromethane it held for only the first 25% reaction. The rate is measured by *k*, the slope of the straight portion of the curve. The results were reproducible provided fresh solutions were used: three values of *k* from runs at the concentrations of Fig. 1, using three different batches of ammonium acetate, were 0.0127, 0.0127 and 0.0125 l./mole-min. Equilibrium was reached at 92% reaction at this concentration. Table I shows the results obtained at different concentrations of vanillin and nitromethane. The reaction is approximately second order (third order if ammonium acetate concentration is considered), although there is considerable variation of *k* with concentration.

TABLE I

RATE CONSTANT *k*, IN 0.500 *M* AMMONIUM ACETATE

Vanillin concn., m./l.	Nitromethane concn., m/l.	*k*, l./mole/min.
0.00774	0.296	0.020
.0117	.296	.0174
.0270	.296	.0127
.0442	.0745	.0154
.0461	.0368	.0204
.0587	.0655	.0180
.0901	.0466	.0121
.0270	.296	.0188[a]

[a] 0.0322 *M* ammonium acetate, *k* cor. to 0.5 *M*.

The induction period is small but definite, and outside experimental error. In all runs using neutral ammonium acetate the straight portion of the curve could be extrapolated to about +20 minutes on the time axis. When the vanillin was added to the ammonium acetate solution 19 minutes before the nitromethane, the reaction showed no induction period, but a fast initial reaction upon addition of the nitromethane, soon slowing to the normal rate (upper curve, Fig. 2; nitromethane added at zero time). The effect of adding the vanillin 107 minutes before the nitromethane is shown in Fig. 3. Adding the nitromethane one hour before the vanillin had no effect on the rate. Vanillin is unstable in 0.5 *M* methanolic ammonium acetate, forming yellow products even in the absence of oxygen. The decomposition proceeds about 3% in the first hour and 10% after a day, and accounts for the small *w*-intercept of the upper curves in Figs. 2 and 3. Aqueous ammonia has a similar action on vanillin.

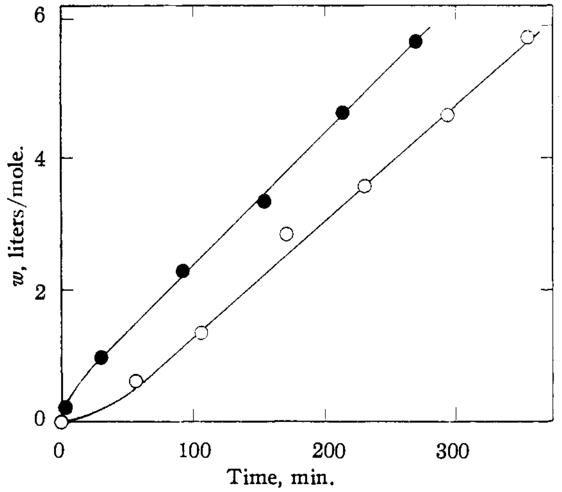

Fig. 3.—Course of the reaction: ○, normal procedure; ●, vanillin added 107 min. before CH_3NO_2: $a = 0.117$, $b = 0.296$.

The effect of increased acidity was to decrease *k* and to eliminate the induction period. In concentrations up to 0.06 *M* sodium methoxide increased *k* (Fig. 4). Larger amounts decreased *k* and lengthened the induction period.

The data of Table II prove that the condensation is catalyzed much faster by ammonium and butylammonium acetates than by the acetates of certain stronger bases. The results are similar to the qualitative rate data of Cope[8] for the Knoevenagel

TABLE II

CATALYSIS BY VARIOUS ACETATES

Acetate	Molarity	*k*, l./mole/min.
NH_4OAc	0.500	0.0127
$BuNH_3OAc$	.493	.018
Et_2NH_2OAc	.492	.0003
Et_3NHOAc	.508	.00003
NaOAc	.500	.00017

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[8] A. C. Cope, THIS JOURNAL, 59, 2329 (1937).

condensation, except that the nitrostyrene condensation was not catalyzed appreciably by acetamide under our conditions.

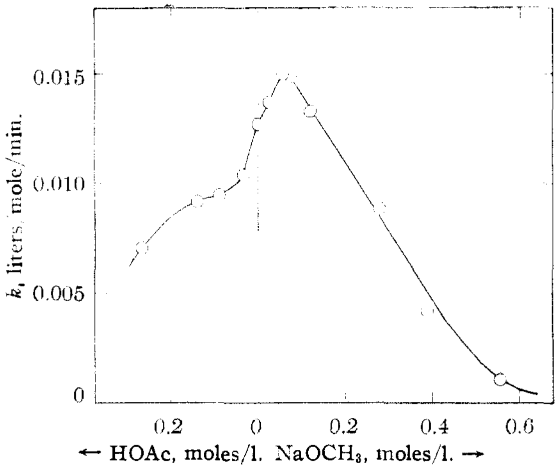

Fig. 4.—Effect of added acid or base on rate.

Discussion

The existence of an induction period which is eliminated by a preliminary reaction of vanillin with ammonium acetate indicates that this reaction is the first step in the condensation mechanism. Ammonia is involved in this step, for acetate ion and ammonium ion are both relatively ineffective catalysts, even in the presence of acetic acid. It is therefore reasonable to postulate reaction of vanillin with ammonia to form the imine as the first step, followed by condensation of the imine with nitromethane

$$RCHO + NH_3 \rightleftarrows RCH{=}NH + H_2O \qquad I$$

$$RCH{=}NH + CH_3NO_2 \longrightarrow RCH{=}CHNO_2 + NH_3 \qquad II$$

This mechanism, proposed early for the Knoevenagel condensation,[9] is consistent with the observed kinetics if the two forward reactions proceed at comparable rates. Since the imine would hydrolyze to vanillin in our analysis, Step I would not be detected and the reaction would appear to proceed only as Step II began to take place. It is easily verified that for certain relative rates, the consecutive reactions would give rise to a fairly linear second-order plot after the induction period. Preliminary mixing of the vanillin with ammonium acetate allows more imine to form than is normally present near the start of the reaction, causing a faster condensation than normal. It also follows that the values of *k* will vary with the initial concentrations *a* and *b;* however, the decomposition of vanillin and the reversibility of the condensation prevented the exact description of this set of reactions. In the variation of *k* with concentration and in the induction period, our kinetics resemble those of Alexander and Underhill in their study of the Mannich reaction.[10]

The high reaction rate induced by ammonium and *n*-butylammonium acetates, contrasted with the low catalytic power of the secondary and tertiary amine acetates, supports our assignment of this special function to the primary amine and ammonia. The data of Table II are not in themselves conclusive, however; the decrease in rate might be a steric effect contrary to the Brönsted catalysis law.

The rapid reaction of aldehydes with primary amines in alcohol solution is well known[11] and the resulting aldimines combine with nitromethane to form nitrostyrenes.[12] Our preparation of VNM from nitromethane and vanillidene methylamine verifies the latter observation. The reaction of benzylidene aniline with nitromethane to give the nitroamine[13] possibly illustrates a difference between aromatic and aliphatic amines, or a *p*H effect.

Step I is probably acid catalyzed and at first sight the rate–*p*H curve (Fig. 4) appears typical of an acid-catalyzed reaction of a base. The decrease in rate at high *p*H could however be caused by ionization of vanillin to a less reactive anion. The only evidence for acid catalysis is the absence of an induction period in the reactions in acid solution. Step II is obviously abbreviated: our experiments give no information about the detailed mechanism. The existence of a mechanism not involving elimination of water is proved by the reversal of the condensation under anhydrous conditions, as described in the experimental section. The same path must be available to the forward reaction.

The mechanism involving the Schiff base has been refuted for the nitrostyrene condensation on the grounds that secondary and tertiary amines function as catalysts.[12] We believe that the older view should be reconsidered and are conducting experiments to evaluate the rates of the consecutive reactions which determined the over-all course of the condensation.

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[9] E. Knoevenagel, *Ber.*, **31**, 2596 (1898).

[10] E. R. Alexander and E. J. Underhill, THIS JOURNAL, **71**, 4014 (1949).

[11] C. W. C. Stein and A. R. Day, *ibid.*, **64**, 2569 (1942).

[12] D. E. Worrall, *ibid.*, **56**, 1556 (1934).

[13] C. D. Hurd and J. S. Strong, *ibid.*, **72**, 4813 (1950).