TABLE I

Run	10^3b_0	10^3a_0	p	10^2c_0	10^3c	10^3a	10^3b	u	η	k
13	1.720	1.890	0.91	5.04	1.50	0.716	4.090	2.758	0.621	9.37
14	1.720	1.890	0.91	5.04	1.49	.714	4.094	2.718	.622	9.27
16	1.930	1.593	1.21	6.35	2.87	.442	4.259	2.226	.723	11.53
17	1.930	1.593	1.21	6.35	2.88	.447	4.249	2.230	.719	11.40
18	1.665	1.500	1.11	6.60	2.59	.184	4.354	1.177	.877	16.38
19	1.665	1.500	1.11	6.60	2.57	.176	4.370	1.176	.883	17.16
20	1.665	1.500	1.11	6.60	2.57	.177	4.368	1.179	.882	17.10
21	2.410	1.048	2.30	8.40	5.85	.206	4.119	1.696	.803	14.26
22	2.410	1.048	2.30	8.40	5.85	.208	4.115	1.713	.802	14.25
23	2.124	1.599	1.33	6.40	3.40	.604	4.129	3.385	.622	11.45
24	2.124	1.599	1.33	6.40	3.32	.581	4.176	3.312	.637	11.78
25	1.980	1.492	1.33	6.94	5.55	1.028	2.911	10.143	.311	13.33
26	1.980	1.492	1.33	6.94	5.54	1.026	2.914	10.186	.312	13.45
27	2.666	1.649	1.62	5.92	3.70	0.909	4.151	7.550	.449	12.55
28	2.666	1.649	1.62	5.92	3.78	0.937	4.095	7.581	.432	11.92

tabulation. Although the agreement between these duplicate runs is good there is considerable variation in k over the whole range of measurements. We take this to indicate a real departure of the reaction from the accepted kinetics, and consider the observation of these phenomena to be an important indication of the merit of the flow method for rate studies.

Summary

The approach to the steady state in a stirred flow reactor agrees with theoretical prediction in a complicated reaction, the bromination of acetone. The consumption of reagents in the approach to the steady state is not so large as to be a prohibitive disadvantage in the use of the stirred flow reactor for rate measurements.

Rate constants for the successive steps in a system of consecutive reactions may be computed by substitution of easily accessible experimental quantities in explicit formulas, regardless of the order of the reactions.

The alkaline bromination of acetone in very dilute solutions deviates appreciably from accepted kinetics.

Rate Measurements by Continuous Titration in a Stirred Flow Reactor[1]

BY JEROME SALDICK AND LOUIS P. HAMMETT*

The present investigation is a study of an important advantage of the stirred flow reactor method[2] of investigating reaction kinetics in solution, namely the possibility of applying a scheme of continuous titration to the output of the reactor, thus avoiding the difficulty of quenching and analyzing a considerable volume of reaction mixture at an exactly known time.

The reaction employed for the development of the method was the alkaline hydrolysis of an ester. In the procedure used aqueous solutions of sodium hydroxide and of ester were introduced in separate streams of constant flow rate into a closed stirred reactor (Figs. 1 and 2); the partially reacted mixture overflowed from the reaction cell through a short exit tube to a small titration chamber, where it was mixed with a third *adjustable* flow of the titrating solution,

which was aqueous hydrochloric acid containing acid–base indicator. The flow of the titrating solution was regulated until a visual end-point was observed.

Symbols.—In addition to those of the previous article[2] the following symbols are used. Units are the same as in that article. a refers to sodium hydroxide, b to ester, x to acid anion or alcohol.

x' Concentration of reaction product at point of titration

x'' Concentration of product at a point in the exit tube

t' Time a volume element of reaction mixture has spent in exit tube

V' Volume of exit tube

Experimental

Flow Measurements.—The solutions of reactants were driven from the 0.5-liter reservoirs C,C' through glass capillaries P,P' into the 0.03-liter reaction cell by *independent* constant pressure heads maintained in the air reservoirs B,B' by the hydrostatic pressure between the constant-level device A and the openings of the J-tubes in the air reservoirs (see Fig. 1). The air used to drive the sodium hydroxide solution flow was passed through a soda-lime tube Q, and, when the ester used was volatile, the air used to drive the ester solution flow was passed through a

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(1) Based on part of a dissertation submitted by Jerome Saldick in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(2) Young and Hammett, THIS JOURNAL, **72**, 280 (1950). This contains references to Denbigh's pioneering reports on this technique.
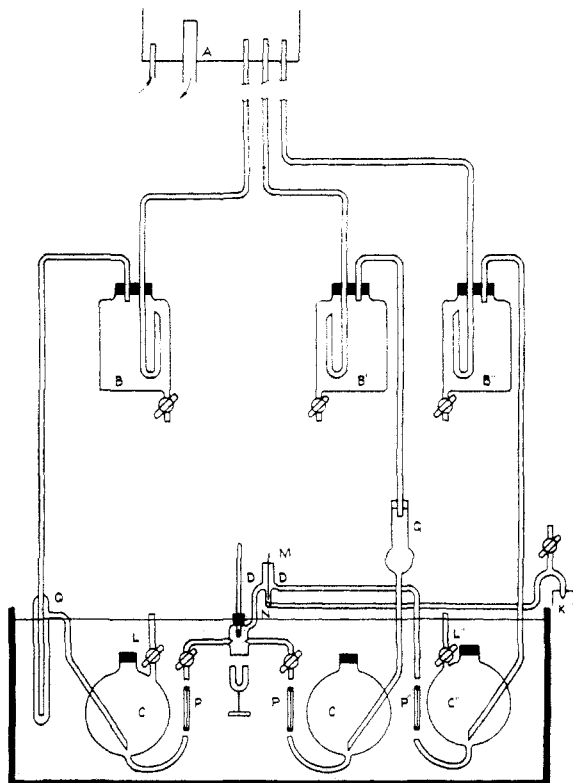
Fig. 1.—Flow apparatus.

Fig. 2.—Reactor, exit tube and titration assembly.

bubbler Q' filled with the same ester solution. The capillaries were 76 mm. over-all length with 30–55 mm. capillary length. Approximate dimensions were: AB 100–350 cm., HD 8 cm. Gum rubber tubing was used to make glass-to-glass connections, where necessary. Flows were measured by weighing the outflow from K over timed periods of 200–600 seconds, using an electric stop-clock. The evaporation shield at K was found to be necessary.

Since the measurements of flows were made after the solutions had passed through the reaction cell, it was necessary to make sure that one flow had no effect on the other. If variations of 0.1% of the flow rates were to be the maximum permissible, then the pressure drop through the exit tube had to be less than 0.05% of that through each of the capillaries. The exit tube, therefore, since it was longer than the capillaries, had to have a diameter of at least ten times that of the capillaries. Since, however, reaction occurring in the exit tube must be corrected for, its volume should be a minimum. A volume of 1 ml. proved satisfactory. Flow additivity was checked for each of the several combinations of capillaries and exit tubes used. All flows had to be measured during each run because even when conditions were carefully reproduced, flows varied up to 2% in different runs on different days.

Stirring in the Reactor.—Thorough mixing of the reactor content is a critical factor in the Denbigh technique. We have used a commercially available magnetized metal bar F, rotated by a rotating magnet external to the reactor. The stirring bar was sometimes used as furnished in a Pyrex enclosure, sometimes without the glass but coated with Saran, and sometimes with small glass plates cemented to the leading edges in such a way as to increase the vertical component of stirring, the whole being then coated with glyptal and baked. These variations produced no observable effect on the results. It was found that the stirring rate affected the flow rate and the stirring speed was held as constant as possible, in the later experiments by a constant speed motor.

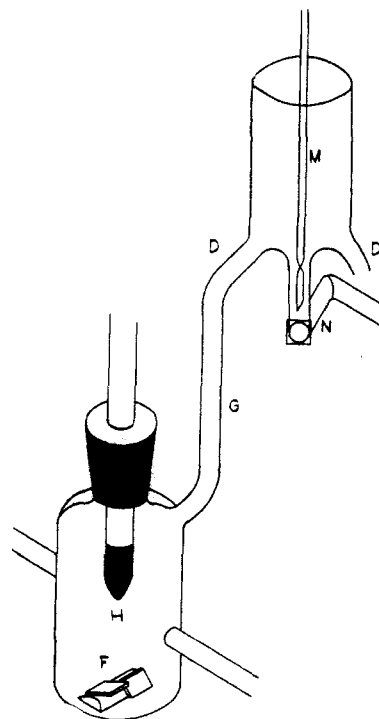An indication of the efficiency of stirring was obtained in

the following experiment. Approximately equivalent flows of 0.1 M sodium hydroxide and hydrochloric acid solutions, each containing thymol blue indicator, were introduced into the reaction cell. The streaks of blue indicated turbulent mixing within the vessel, with no channelling and good vertical component to the mixing. Estimated volume of the blue-streaked portion of the contents was 1–2% of the total volume. This test is more sensitive than one using inert dyestuffs.

At high stirring speeds and larger driving heads, small bubbles appeared in the reactor, presumably because the liquid had become saturated with air at the higher pressure existing in the reservoirs. These could be removed by stopping the stirrer and momentarily removing the thermometer stopper of the reactor.

Continuous Flow Titration.—The third flow, used for the continuous titration, was a *variable* flow regulated by adjustment of the vertical distance AB″ by a thumbscrew device for raising and lowering bottle B″. When it was lowered, the flow increased to the new higher rate in a few seconds, but when the bottle was raised, it was necessary to vent the *excess* pressure in B″ and C″ by opening stopcock L″ *briefly*, after which the flow increased quickly to the new value.

The stirrer M was the flattened and twisted end of a $^3/_{32}$ in. diameter stainless steel rod, rotated by a small compressed-air turbine at 1000–1600 r. p. m. The alkaline and acid flows overflowed independently at D and D′ and since the stirrer M was not really in either flow stream, its rate of rotation did not affect the flow rates or their measurement.

The hydrochloric acid solution contained phenolphthalein indicator, added as 1 ml. of a 1% alcoholic solution to each 1.2 liters of acid solution (thymol blue was used in some of the early runs with identical results), and the color of the titrated flow was observed against a white background immediately downstream from the point of mixing, in the viewing tube N, which was 4 cm. long, with 4 mm. inside diameter, and to which small pieces of plane glass had been cemented at each end.

Obviously an electrometric end-point could have been used instead of the visual one, and the general method can

be used with any titration method of determining the extent of a reaction which employs an indicator or electrometric endpoint.

Maintenance of the equivalence point during the continuous titration showed that the steady state was stable, and if it was disturbed (by removing the thermometer and/or stopping the stirring in order to remove the air bubbles), the same equivalence point was reattained as had existed before the displacement. The end-point color in the viewing tube was as steady when a reacting system was being titrated as when only sodium hydroxide solution was flowing through the reactor.

Flow titrations of sodium hydroxide solutions against indicator-containing hydrochloric or acetic acids, at either 0.1 M or 0.01 M concentrations, gave results reproducible on different days within a range of 0.2% and agreeing to about 0.1% or better with buret titrations.

Procedure.—It has been shown[1,2] that the steady state in the reactor is attained to within 0.1% when the total flow through the reactor amounts to from seven to eight times the reactor volume in the most unfavorable case, and frequently with a considerably smaller expenditure of reagents. It has also been shown[1] that this conclusion is only slightly affected by the choice taken between the following procedures: (1) the reactor contains the reagent solution in the ratio of their flow rates when the flow is started; (2) the reactor is empty when the flow is started; (3) the reactor is initially full of one reagent solution; (4) the reactor is initially full of inert liquid.

Our usual procedure has been the following: After the solutions have come to thermostat temperature the flow of sodium hydroxide is started and its rate measured. The ester flow is next started. (It saves a little time and solution to open the cell, pipet out its content, and refill with a mixture of alkali and ester solutions in the ratio of the flow rates.) The combined flow of ester and alkali is then measured, giving the ester flow rate by difference. By this time the reactor is usually at steady state. Flow of titrating solution is started and adjusted to the end-point indication. The alkali is then turned off, and the reactor emptied. While the reactor fills with ester solution the flow of titrating liquid is measured. Finally with the titrating liquid flow turned off the ester flow is measured as a check on its constancy. The density of each solution is determined.

The steady state temperature was determined by the calibrated thermometer which served as stopper to the cell, and could be read to 0.01°. This temperature was 0.10 to 0.18° higher than thermostat temperature when the entering solutions were 0.1 M in ester and alkali, and proportionately lower with more dilute reagents.

Materials and Instruments.—Selection and purification of materials, standardization of solutions for titration, and calibration of thermometers and volumetric glassware met customary standards for precision work. Thermostat temperature was 25.00°. A commercial sample of ethyl α-hydroxyisobutyrate kindly supplied by the Rohm & Haas Co. was fractionated in a good column. It analyzed by saponification at 100.1 and 99.9%.

Calculation.—The flow titration yielded a value of x' from which k was obtained by successive approximations. In the exit tube $dc''/dt = k(a_0 - x'')(b_0 - x'')$ in any volume element of the liquid moving through the tube. When $t' = 0$, $x'' = x$; when $t' = V'/u$, $x'' = x'$. The well-known form of the solution

$$\frac{1}{b_0 - a_0} \ln \frac{(b_0 - x')(a_0 - x)}{(b_0 - x)(a_0 - x')} = \frac{kV'}{u} \qquad (1)$$

may be rearranged to

$$x = x' - \frac{(p - 1)(a_0 - x')(b_0 - x)}{(p - 1)x' + b_0 - a_0 p} \qquad (2)$$

where $p = \exp(b_0 - a_0)kV'/u$, giving a more convenient form for calculation, especially when $b_0 -$

a_0 is small. Using an estimated value of k (2) led to a value of x, and this by insertion in the equation given by Denbigh

$$k = ux/V(a_0 - x)(b_0 - x) \qquad (3)$$

yielded a better value of k, which could be used to obtain a better value of x from (2), etc. Two of these successive approximations were usually sufficient, since only about 3% of the total reaction took place in the exit tube.

Precision.—In most runs, successive flow measurements agreed to ±0.06% or better. Accuracy of flow measurements (considered satisfactory when three out of four successive measurements all agreed within a range of about 0.1%) was estimated at = 0.1%. Over the duration of a run, flows were usually constant to 0.1%. Special precautions were not taken to free the solutions completely from *all* solid particles, and partial temporary plugging of the capillaries was possible. A large or a permanent partial plugging could be detected by the flow rate measurements, but small transient plugging was a possible source of error whose magnitude could not be estimated. Better flows, in general, were obtained with the acid and alkali solutions made up in large batches and allowed to stand for several days before using. It was, however, sometimes necessary to use freshly-made sodium hydroxide solutions, and the ester solutions were always freshly made or well-shaken.

The volumes of the reactor H and of the exit tube could be measured to 0.1%. However, it was necessary to decide somewhat arbitrarily where the reactor ended and the exit tube began. Fortunately an error in V' of as much as 50% with the compensating error in V would lead under typical conditions to an error in k of only 1%.

It was also found that under typical conditions of concentration and flow an error of 0.1% in each of the experimental measurements would lead to an over-all precision measure expectation for the rate constant of 1.0%, the loss in precision arising from the fact that the computation involved differences in flow rates and concentrations. The estimate of a probable error of 0.1% for each of the experimental measurements made during a run was a reasonable estimate for a majority of the runs. In some, however, the check on "additivity" of flows indicated that one or more of the flows had changed at some time during the run, and calculations were made assuming that all but one of the measurements were correct. Almost always, the double flow of the steady state mixture was assumed to be correct, since its measurement directly preceded the flow titration, and one of the single flows was assumed to have changed. The actual dispersion of the results was therefore greater than the optimum predicted for a series of "perfect" runs, and the results are presented as an indication of the reliability of the actual method used. Only one run was arbitrarily rejected because the calculated rate constant (for ethyl acetate) was 41% higher than the average. Other runs were re-

jected *only* if the flows were obviously unreliable. Questionable runs were *included* in the average if the flow data permitted reasonable calculation. Deviations from the averages in these cases were about evenly high and low.

Results

The experimental results are summarized in Table I. The rate constants were calculated to 25.00°, using 10.9 kcal./mole for the energy of activation of ethyl acetate,[3] and 11.5 kcal./mole for ethyl α-hydroxyisobutyrate.[4] The corrections amounted to less than 0.4% in most cases, since the steady state temperature was usually kept within 0.06° of 25.00° by presetting the bath temperature at the proper lower value.

TABLE I

SUMMARY OF EXPERIMENTAL DATA

Concentration of ester, M	Number of runs	η	V/u	k	% a. d.[j]	Note
			Ethyl acetate			
0.01	7	0.27-0.32	65-80	6.86	3.2	b
.1	10	.58- .80	41-94	7.18	2.3	a
.1	4	.59	42.5-43.0	7.22	0.5	c
			Ethyl α-hydroxyisobutyrate			
0.01	3	.31- .36	63-84	8.53	1.4	d
.01	6	.31- .32	67-86	8.91	1.4	e
.01	4	.30- .31	64-66	8.93	1.6	f
.01	4	.28- .35	62-72	8.74	1.0	g
.01	13	.29- .31	60-63	8.80	1.0	h
.01	1	.28	53.5	8.90		i
.03	5	.27- .28	16.5-18.3	8.95	0.9	h
.03	8	.35- .39	28-32	8.79	1.4	h
.03	1	.50	64.3	8.74		h
.03	4	.60- .65	125-136	8.87	1.2	h
.03	18			8.85		j
.1	11	.52- .65	24-35	8.94	2.8	h

[a] First runs done with a somewhat cruder apparatus; stirring speed about 350 r. p. m.   [b] Some difficulty experienced in routine analysis of ethyl acetate solutions at first; stirring speed about 350 r. p. m.   [c] Stirring speed reduced to 175 r. p. m. in one of these runs, which gave k of 7.22. In the same run, increasing stirring speed to 350 r. p. m. did not change steady state.   [d] Stirring speed about 350 r. p. m.   [e] Stirring speed 800-1000 r. p. m.   [f] Stirring speed 1500-2000 r. p. m.; variations ±10%.   [g] Stirring speed 1500-1800 r. p. m.; modified stirring bar.   [h] Stirring speed about 1700 r. p. m. using constant speed motor; modified stirring bar.   [i] Direct drive stirring by propeller on shaft passing through stuffing box; apparatus unsatisfactory because of variable heat production in the packing.   [j] Average of all runs at 0.03 M concentrations.   [j] The % a. d. values of column 6 are averages of absolute deviations from the mean.

(3) Moelwyn-Hughes, "Kinetics of Reactions in Solutions," Oxford Press, 1933, p. 87, gives 11.2 kcal./mole. Calculation from the data of Salmi and Liemu, *Suomen Kemistilehti*, 20B, 43 (1947), gives 10.4-10.5 kcal./mole.

(4) Salmi and Leimu, *ibid.*, 17B, 19 (1940). Their rate constant for 25° is 7.74, significantly lower than the rate constant reported in this study. The energy of activation of 11.5 kcal./mole, calculated from their data, however, is a reasonable one for an aliphatic ethyl ester in aqueous solution.

A very careful determination of the rate constant for ethyl acetate has been made[5] at initial concentrations of about 0.01 M, giving a value of 6.750 ± 0.75%. A summary of the older literature[6] gives the average value of 6.46 for results of different investigators which ranged up to 6.94. Denbigh[7] reports 6.60 from measurements using the stirred flow reactor with batchwise titration.

While our value for the hydroxyisobutyrate differs considerably from that of Salmi and Leimu[4] it is in satisfactory agreement with the value 9.02 obtained from careful measurements by the batch technique and reported in the following article.[8]

The observed variability in the rate constants determined from measurements on the flowing system was not appreciably greater than that to be expected from random experimental errors. When an attempt was made to keep concentrations and flow rates constant over a series of consecutive runs, the variability, as shown by the average deviation, was slightly lower than otherwise.

The first three runs made with ethyl α-hydroxyisobutyrate, at stirring speed of about 350 r. p. m., gave slightly lower rate constants than the other runs. This was contrary to earlier findings with ethyl acetate in which lowering the stirring speed from about 350 to 175 r. p. m. produced no change in rate constant. Nevertheless, higher stirring speeds were used from then on.

The increase in the rate constant for ethyl acetate with increase in concentration is probably real, but the variations with concentration found with the isobutyrate are within the probable experimental error.

Summary

Apparatus and techniques have been developed for the continuous titration of the output from a continuously flowing stirred reactor for the measurement of reaction rates. The output from the reactor, in which the concentration of reaction product directly measures the rate of reaction, is mixed with a continuous, measured flow of titrating reagent, whose flow rate is adjusted to obtain an indicator end-point. The method is particularly advantageous for relatively rapid reactions, and has the more general merit that the instantaneous rate is determined directly.

Second order rate constants for the alkaline hydrolysis of ethyl acetate and ethyl α-hydroxyisobutyrate determined in this way under varying conditions of concentration, rate of stirring, and extent of reaction, were reproducible to 1-2% and agreed within experimental error with those obtained or extrapolated from determinations by the standard batch method. This was true even with average times of reaction as low as 100 seconds.

(5) Terry and Stieglitz, THIS JOURNAL, 49, 2216 (1927).
(6) Skrabal and Hugetz, *Monatsh.*, 47, 17 (1926).
(7) Denbigh, *Faraday Soc. Discussions*, No. 2, 263 (1947).
(8) Rand and Hammett, THIS JOURNAL, 72, 287 (1950).