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Dissolution Rate Studies I

Continuous Recording Technique for Following Rapid Reactions in Solution

By PAUL J. NIEBERGALL† and JERE E. GOYAN

An automatic recording apparatus was developed to follow the process of dissolution. Results were obtained as a recording of per cent transmittance *vs.* time. The recorder was equipped with various speed chart drive motors that permitted readings to be taken from the graph at intervals down to 0.375 sec. Several experiments were performed to demonstrate the applicability of this apparatus to the determination of dissolution rates, and constants obtained agreed well with those obtained by the usual method of removing samples with a pipet.

THE FIRST quantitative study of the dissolution process was made by Noyes and Whitney in 1897 (1). Since that time numerous workers have evaluated the effect of different variables on the dissolution rate constant. The majority of these studies have been done using a single large tablet or disk. In a few instances, particularly in attempts to obtain a measure of mixing efficiency, multiparticulate systems have been used.

Initial dissolution rates in multiparticulate systems are rapid, and previous studies have been handicapped by the lack of an accurate method for sampling the solution in the early stages of the process. Therefore, the object of this study was to develop an automatic recording technique which would furnish continuous data and obviate the need for hand sampling in studies of rapid reactions.

THEORY

Calculation of Dissolution Rate Constants.—Hixson and Crowell (2) derived an equation for the dissolution of a single particle in which the surface area was allowed to change with time, using the following form of the Noyes-Whitney equation

$$V\frac{dw}{dt} = -KS(w_s - w_o + w) \quad \text{(Eq. 1)}$$

in which w is the weight of the particle at time t, K is a rate constant, S is the surface area of the particle, w_s is the weight of solid needed to saturate the volume, V, of solvent at a given temperature, and w_o is the initial weight of the particle. Using the property of geometrically similar solids, Hixson and Crowell replaced the surface area by

$$S = kw^{2/3} \quad \text{(Eq. 2)}$$

in which k is a constant containing the shape factor and the density of the particle.[1]

The basic equation of Hixson and Crowell has been extended for use in multiparticulate systems by assuming a system of N equal-sized particles. The total surface area, A, would then be equal to $N \times S$ or

$$A = kNw^{2/3} \quad \text{(Eq. 3)}$$

The total weight, W, for a sample of N equal sized particles would be

$$W = Nw \quad \text{(Eq. 4)}$$

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† Present address: Philadelphia College of Pharmacy and Science, Philadelphia, Pa.

[1] The particles used in this study had a height, h, greater than the diameter, d, which may result in a change in the h/d ratio during the process of dissolution, and the Hixson-Crowell equations would theoretically not be applicable. However, the salicylamide crystals were followed for a total change in weight which was felt to represent a negligible change in the h/d ratio. The benzoic acid crystals were followed to a much greater change in weight. However, the Hixson-Crowell equations did yield straight lines, and it was felt that the apparent rate constants obtained from these equations would be suitable for use in a comparison study of this nature. [See also the paper by Blumberg, *J. Phys. Chem.*, **63**, 1129(1959).]

Substitution of this into Eq. 3, with the condition that the number of particles remains constant, gives

$$A = k_1 W^{2/3} \quad \text{(Eq. 5)}$$

This result, when substituted into Eq. 1, with the weight of a single particle replaced by the total weight of N particles gives

$$V \frac{dW}{dt} = -K_1 W^{2/3} (W_s - W_o + W) \quad \text{(Eq. 6)}$$

Two sets of conditions can be utilized in order to simplify this equation. When the amount of sample used is equal to the amount needed to saturate the solution, W_s equal to W_o, the equation becomes

$$V \frac{dW}{dt} = -K_1 W^{5/3} \quad \text{(Eq. 7)}$$

which upon integration under the condition that W is equal to W_o at time zero, gives

$$W^{-2/3} - W_o^{-2/3} = K_2 t \quad \text{(Eq. 8)}$$

in which K_2 now contains V.

When the amount of solute needed to saturate a given volume of solvent is much greater than the concentration of material in solution, $C_s \gg C$, the equation becomes

$$\frac{dW}{dt} = -K_3 W^{2/3} \quad \text{(Eq. 9)}$$

in which K_3 contains V and W_s. This equation, when integrated under the condition that W is equal to W_o at time zero, gives

$$W_o^{1/3} - W^{1/3} = K_4 t \quad \text{(Eq. 10)}$$

where K_4 is equal to $K_3/3$.

EXPERIMENTAL

Apparatus.—A model 5800 Beckman energy recording adapter was attached to a Beckman model DU spectrophotometer. The adapter leads were connected to a Varian Associates model G-10 potentiometric recorder. A tube bent into a U shape was made from silica glass, 5-mm. internal diameter. This was fitted into two holes drilled into a cell-compartment cover for the spectrophotometer and the protruding ends painted with black paint. The solution could then be passed through the tube and a continuous tracing of per cent transmittance *vs.* time obtained.

The remainder of the system consisted of a 1-L. beaker equipped with four baffles, a Cenco variable-speed stirrer and a Gordon-Rupp model 1612 centrifugal pump. The width of the baffles represented 10% of the beaker diameter; they were set about 1/8 in. out from the wall and 1/8 in. up from the bottom to eliminate dead pockets. The impeller was a four-blade turbine, 2 1/2 in. in diameter.

The beaker was placed in a constant temperature water bath and the impeller centered by means of appropriately placed markings. A glass filter stick was clamped into the beaker and the open end connected with rubber tubing to one end of the U tube. The other end of the U tube was connected with rubber tubing to the pump and a tube led from the pump back to the beaker.

Assay Procedure.—In this system, the solution coming from the beaker is assayed directly without dilution. Dissolution rates in multiparticulate systems are rapid, and for materials having high absorptivities, concentrations at which large deviations from the Beer-Lambert law occur are reached rapidly. This can be circumvented in some instances by assaying at absorption minima.

A series of dilutions was made for the material to be assayed. The apparatus was assembled as described above and the recorder was balanced at 0% transmittance with the shutter of the spectrophotometer closed. The pump was started and the recorder was balanced at 100% transmittance with the solvent flowing through the system and the shutter open, thus blanking out the absorbance due to the solvent. When the 100% transmittance base line had held steady for 2 minutes, the rubber tubing was clamped shut, and the glass tube cleaned and placed into one of the dilutions. The tubing was released and the solution allowed to flow through the apparatus until a steady transmittance tracing was obtained. The rubber tubing was again clamped and the glass tube placed into the next dilution. When all of the dilutions had been recorded, pure solvent was again passed through the system. If the base line did not level off at 100% transmittance, the calibration was repeated.

The values for per cent transmittance were converted into units of absorbance and plotted in the usual manner to obtain a Beer-Lambert line. The slopes of the resulting lines were calculated using the method of least squares and were used in the usual manner to calculate concentrations. Results for benzoic acid U.S.P. and salicylamide C.P. appear in Table I.

Table I.—Absorbance-Concentration Relationships of Benzoic Acid and Salicylamide in Water

Benzoic Acid		Salicylamide	
Concn., mg./100 ml.	Absorbance 259.5 mμ	Concn., mg./100 ml.	Absorbance 263 mμ
1.00	0.035	1.00	0.015
2.00	0.049	1.50	0.021
5.00	0.131	2.00	0.027
10.00	0.256	2.50	0.034
15.00	0.380	5.00	0.068
20.00	0.527	6.00	0.082
25.00	0.664	7.50	0.102
50.00	1.301	9.00	0.125
60.00	1.569	10.00	0.137
75.00	2.000	...	...
Absorptivity[a] S. D. 0.0002	0.0264	Absorptivity[a] S. D. 0.0001	0.0137

[a] Calculated by least squares as the absorbance of a 0.001% solution.

Dissolution with Return Flow to the Beaker.—In order to determine any systematic error due to the apparatus, the rate constant for the dissolution of salicylamide in water was determined using both the apparatus and the conventional method of sampling.

The salicylamide was carefully screened through a 20-mesh sieve onto a 30-mesh sieve. The particles retained on the latter were used in the study. The solubility of the salicylamide was found to be 2.44 Gm./L. at 25°.

The dissolution apparatus was assembled as described previously, and the total volume of the

glass filter tube, rubber tubing, U tube, and pump was determined by filling the system with water. This was repeated five times with the average being 55 ml. This volume of water was added to 750 ml. of distilled water in the beaker, and the system filled by siphoning. The pump was started with the water being circulated back into the beaker.

The recorder was balanced at 0% and 100% transmittance. When the contents of the beaker had reached temperature equilibrium, the end of the rubber tubing through which the water was passing into the beaker was placed into a 100-ml. graduated cylinder. An accurately weighed sample of salicylamide was simultaneously poured into the beaker. When the volume of liquid needed to fill the system (55 ml.) had been removed, the end of the rubber tubing was again placed so the solution would be returned to the beaker keeping the volume constant at 750 ml. It was felt that by this time (15 sec.) the concentration of the solution in the beaker was great enough that the dilution due to the returning solution would be negligible. The total time for the run was 30 sec. The stirring rate was 500 r.p.m. and the flow rate 350 ml. per minute.

The amount of salicylamide used was just sufficient to saturate the 750 ml. of water; Eq. 8 was applicable. Therefore, $W^{-2/3} - W_0^{-2/3}$ was plotted against time, resulting in a straight line which is shown in Fig. 1. The positive intercept represents a lag of 1.2 sec. This lag is not a factor of circulation time since time zero was taken as being the instant before the recording pen started to move. This lag will be discussed further in a future publication. The rate constant was evaluated using the method of least squares on the data shown in Table II.

TABLE II.—DISSOLUTION RATE OF 20/30-MESH SALICYLAMIDE CRYSTALS IN WATER AT 25° USING THE AUTOMATIC RECORDING APPARATUS

Time, sec.	Concn., mg./100 ml.	Weight Remaining (W), mg.	$W^{-2/3} \times 10^3$
0.00[a]	0	1830	6.733
3.75	2	1810	6.759
7.50	5	1790	6.838
11.25	9	1770	6.891
15.00	12	1735	6.970
18.75	15	1710	7.022
22.50	18	1690	7.101
26.25	21	1680	7.127
30.00	24	1655	7.206
33.75	27	1640	7.259
37.50	30	1610	7.311
41.25	32	1595	7.364
45.00	34	1585	7.443

$K_1 = 1.79 \times 10^{-2}$ mg.$^{-2/3}$ sec.$^{-1}$ ml.

[a] Time zero point omitted in calculation of the rate constant due to the time lag.

Circulation time should have no effect on the rate constant since it corresponds to frequency of sampling in the hand sampling case. This was verified by running the previous experiment at two other flow rates and calculating the rate constants. The results are given in Table III.

The effect of the dilution resulting from the return of the solution to the beaker could not be determined since the solution was thoroughly mixed while passing through the pump. If it had been serious, however, a break in the line shown in Fig. 1 would have been expected at the point representing the elapsed time of 15 sec.

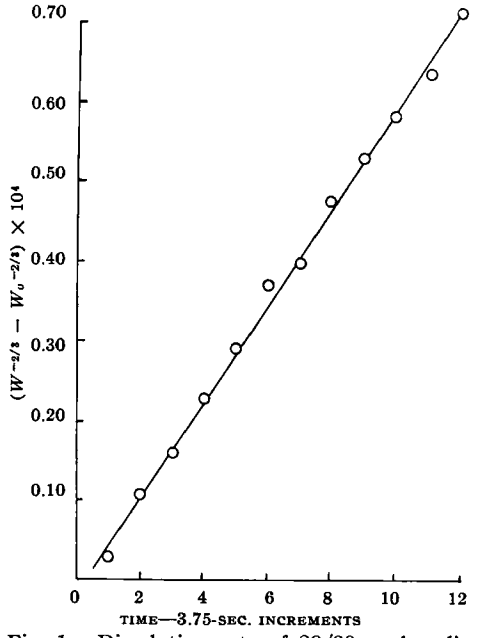

Fig. 1.—Dissolution rate of 20/30-mesh salicylamide in water at 25° using the automatic recording apparatus.

TABLE III. DISSOLUTION RATE CONSTANTS OF 20/30-MESH SALICYLAMIDE CRYSTALS WITH VARYING CIRCULATION TIMES

Flow Rate, ml./min.	Rate Constant (K_1), mg.$^{-2/3}$ sec.$^{-1}$ ml.
350	1.79×10^{-2}
150	1.81×10^{-2}
60	1.80×10^{-2}

The beaker was cleaned, filled with 750 ml. of distilled water, placed in the water bath, and stirred until temperature equilibrium had been reached. The same weight of salicylamide as used in the previous run was added and an electric timer started. Samples of 5 ml. were removed at intervals and assayed spectrophotometrically. The results are shown in Table IV and plotted in Fig. 2.

The values for the rate constants were compared

TABLE IV.—DISSOLUTION RATE OF 20/30-MESH SALICYLAMIDE CRYSTALS IN WATER AT 25° ON SAMPLES WITHDRAWN BY PIPET

Time, sec.	Concn., mg./100 ml.	Weight Remaining (W), mg.	$W^{-2/3} \times 10^3$
0	0	1830	6.696
15	13	1733	6.942
45	34	1575	7.392
75	52	1440	7.855
105	68	1317	8.338
125	80	1224	8.744
160	92	1130	9.223

$K_1 = 1.76 \times 10^{-2}$ mg.$^{-2/3}$ sec.$^{-1}$ ml.

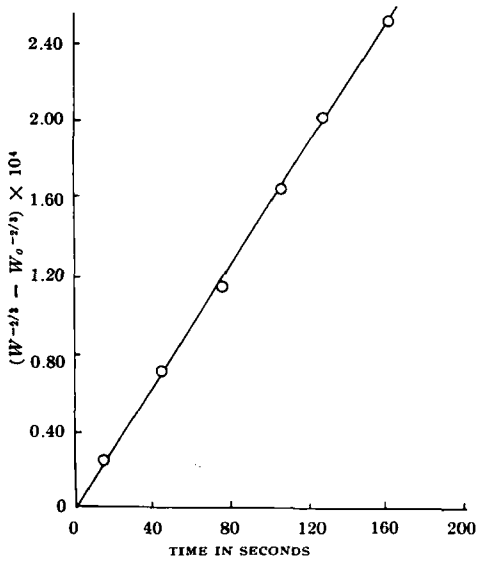

Fig. 2.—Dissolution rate of 20/30-mesh salicylamide in water at 25°. Samples withdrawn by pipet.

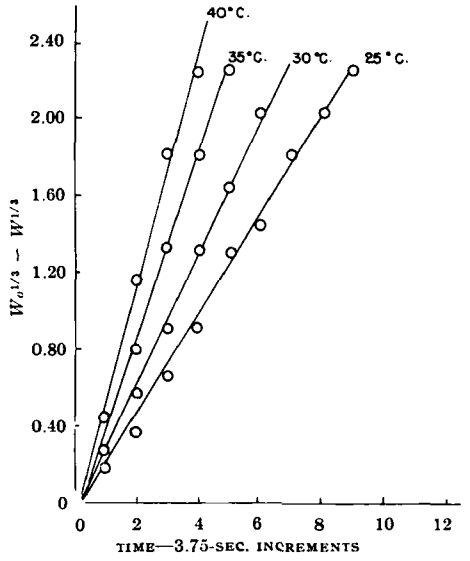

Fig. 3.—Dissolution rate of benzoic acid in water at various temperatures, using the automatic recording apparatus.

using the method described by Davies (3). The value of t was 0.945 with 16 degrees of freedom. The value of t necessary for the difference to be significant at the 95% level is 2.12. Therefore, there is no difference between the two values. It should also be noted that the standard deviation about the regression line was twice as large in the hand sampling case.

Dissolution Rate as a Function of Temperature.—One other experiment was performed to demonstrate the usefulness of the automatic recording apparatus. Reagent grade benzoic acid was screened to collect the 80/100-mesh fraction. The dissolution rate was obtained at four different temperatures using the automatic recording apparatus. In this study, however, the conditions met the requirements for the use of Eq. 10, C_s being much greater than C. The results are plotted in Fig. 3, and the rate constant K_4 was evaluated from the data shown in Table V.

TABLE V.—DISSOLUTION RATE OF 80/100-MESH BENZOIC ACID CRYSTALS IN WATER AT VARYING TEMPERATURES[a]

Time, sec.	Concn., mg./100 ml.	Weight Remaining, mg.
	25°C.	
0.00	0	158
3.75	2	143
7.50	4	128
11.25	7	106
15.00	9	91
18.75	12	68
22.50	13	61
26.25	15	46
30.00	16	38
33.75	17	31
	30°C.	
0.00	0	158
3.75	2	143
7.50	6	113
11.25	9	91
15.00	12	68
18.75	14	53
22.50	16	38
	35°C.	
0.00	0	158
3.75	3	136
7.50	8	98
11.25	12	68
15.00	15	46
18.75	17	31
	40°C.	
0.00	0	158
3.75	5	121
7.50	11	76
11.25	15	46

[a] Time zero point omitted in calculation of the rate constants due to the time lag.

This constant contains W_s, the effect of which was canceled by dividing K_4 by the W_s values taken from Edwards' work (4), resulting in a new constant, K_5.

Values for log K_5 were plotted against $1/T$ as shown in Fig. 4. The energy of activation calculated from the data shown in Table VI was 5210 cal./mole. Edwards (4) reported a value of 5162 cal./mole for the dissolution of benzoic acid in water, using a method of sampling similar to the one used in the above study.

DISCUSSION

The good agreement between the dissolution rate constant obtained using the automatic recording technique and the conventional method of withdrawing samples with a pipet indicate that the recording technique is valid for following rapid reactions in solution.

Standard deviations were obtained on the

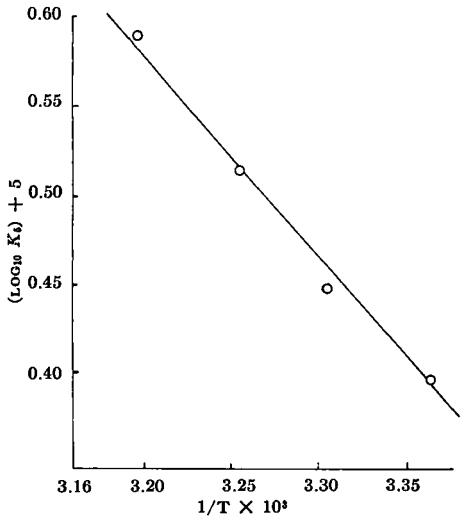

Fig. 4.—Arrhenius plot of the rate constants obtained for the dissolution of benzoic acid in water using the automatic recording apparatus.

values for the energy of dissolution as reported by Edwards' and those obtained in this study. The data from Edwards' paper give a standard deviation of 750 cal./mole, while the results obtained using the recording apparatus gave a standard deviation of 200 cal./mole. Thus, the apparatus appears to be particularly useful for working at elevated temperatures since it eliminates the problem of temperature change during the collection and subsequent handling of samples.

TABLE VI.—RATE CONSTANTS AS A FUNCTION OF TEMPERATURE FOR THE DISSOLUTION OF BENZOIC ACID IN WATER

Temp., °K.	K_4	Weight Needed for Saturation[a]	$K_5 \times 10^5$
298	0.07227	2565	2.818
303	0.09890	3075	3.216
308	0.13410	3623	3.701
313	0.18271	4163	4.389

[a] Taken from Edwards' data (4), and given as mg. needed to saturate 750 ml. of water.

One further advantage for the apparatus is that it can be cleaned and assembled for further use within 15 minutes after the completion of a run. This is a vast saving in time over that generally needed to clean volumetric glassware used in a kinetic study. This apparatus is therefore suggested for use in the study of rapid reactions in which one chemical species can be assayed spectrophotometrically with no interference from other species in solution.

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Investigation of the Mechanism of Urea-Induced Hemolysis

By DALE E. WURSTER and PAUL H. SHAPIRO†

The hemolysis of mammalian erythrocytes in concentrated urea solutions and in isotonic sodium chloride and dextrose solutions containing thirty per cent urea was investigated. Increased concentrations of sodium chloride, dextrose, and other osmotic agents inhibited the urea-induced hemolysis. The existence of urea–dextrose complexes in water, methanol, and methanol–water systems containing high dextrose concentrations were demonstrated.

DURING the last decade, Javid and Settlage, *et al.*, developed a remarkably effective method for reducing elevated intracranial and intraocular pressures. The method involves the intravenous administration of 30 per cent urea solutions (1, 2). In preliminary work with animals they observed that the administration of concentrated solutions caused a hemolysis which was detectable by the resulting hemoglobinuria. This would be expected to happen since the erythrocyte is permeable to urea, and thus the urea solution can exert no osmotic pressure. However, it was found that hemolysis also occurred when the urea was dissolved in an isotonic solution of sodium chloride or dextrose. In experimenting with the addition of various con-

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† Present address. Abbott Laboratories, North Chicago, Ill.