

Kinetics of Calcium Carbonate Neutralization

First-Order Case of the Cube-Root Law

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The rate of neutralization of HCl by dispersed calcium carbonate powder has been studied as a function of pH, temperature, and particle size. The results can be explained using the Hixon-Crowell cube-root law under the limiting condition of constant hydrogen-ion concentration. The process is first order throughout the whole of the reaction at pH 2.8, whereas only 50 per cent of the reaction is first order at pH 5.1. The apparent first-order rate constant is directly proportional to hydrogen-ion concentration. The first-order rate constant, k , for a sample of mixed particle sizes can be described by $k = \sum k_i f_i$, where k_i is the individual rate constant for an isolated particle size, and f_i is its fraction by weight of the original sample.

THE RATIONAL design and evaluation of an ideal antacid formulation requires an understanding of the rate and mechanism by which neutralization occurs. Relatively little is known about the kinetics and mechanisms of antacid activity, even though many *in vitro* evaluations have been reported. In their investigation, Steinberg *et al.* (1, 2) also reviewed the methods and discussed several of their limitations. The studies done previous to their work either (a) included the addition of hydrochloric acid at some arbitrary rate in an effort to simulate *in vivo* conditions (3-5) or (b) measured the change in pH as a function of time (4-6). Neither of these approaches has provided the proper data necessary to establish the complete kinetics of antacid activity.

Many workers have pointed out the clinical significance of the velocity of neutralization by antacids (2-5). Several observations, including that of the relatively selective inhibition of aluminum antacids by polypeptides (3, 4), remain uninterpreted. The differences between the kinetics or the rate-determining step of the various antacids may supply satisfactory explanations for such behavior. Aside from the antacid case in point, Higuchi *et al.* (7) emphasized the general importance of understanding the kinetics of dissolution of acidic or basic drugs in nonneutral media. The current studies are intended to establish the kinetics and mechanisms of neutralization by antacids and to quantify the effects of those variables which previously have been only qualitatively observed.

Nogami (6) has developed equations for the reaction of calcium carbonate with acid. The rate of decrease in hydrogen-ion concentration, $[H^+]$, in the bulk solution may be described by

$$-d[H^+]/dt = kS [H^+] \quad (\text{Eq. 1})$$

where t is time, k the rate constant, and S the

surface area of the solid antacid. Applying the Hixon-Crowell cube-root law to Eq. 1 results in

$$-d[H^+]/dt = \frac{k\alpha W^{1/3}/\rho d_0}{\{W - h(H^+ - H^+)_{t=0}\}^{2/3} [H^+]} \quad (\text{Eq. 2})$$

where W is the quantity of antacid, H^+ the initial hydrogen-ion concentration in the bulk solution, h the factor to convert the concentration to quantity and α , ρ , and d_0 are the usual shape factor, density, and mean volume-surface diameter of test sample, respectively.

Nogami studied the change in pH with time and used the initial slopes to evaluate the rate constants from the relationship

$$[d(\text{pH})/dt]_{t=0} = 0.4343 k\alpha W/\rho d_0 \quad (\text{Eq. 3})$$

which follows from Eq. 2. However, he was able to obtain a linear relationship between $[d(\text{pH})/dt]_{t=0}$ and W only for the special case where W/H^+ was a constant ratio. Since the hydrogen-ion concentration varied throughout his reactions, the effect of hydrogen-ion concentration on the rate was not determined. Two particle sizes were examined and found to differ in rate. No work was reported for mixed particle sizes. The pH values in his studies were limited to the range of 1 to 2. No work was carried out to

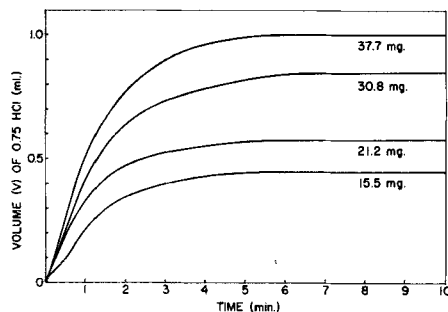


Fig. 1.—A pH-stat recording showing the volume of HCl consumed as a function of time by various initial weights (mg.) of calcium carbonate powder at pH 3.01, 25°.

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TABLE I.—EXPERIMENTAL CONDITIONS, MEAN VALUES FOR APPARENT FIRST-ORDER RATE CONSTANTS (k IN MIN.⁻¹), AND THE PER CENT OF REACTION BEHAVING FIRST ORDER (%) FOR THE NEUTRALIZATION OF HCl BY DISPERSED CALCIUM CARBONATE POWDER AT 25°

Observed pH	Calcd. 10 ⁴ [H ⁺]	No. Runs	Sample Range, mg.	$\bar{k} \pm \text{A.D.}^a$	% $\pm \text{A.D.}^a$
2.82	15.13	6	13.2-54.4	1.79 \pm 0.42	90 \pm 6
2.85	14.13	3	25.0-25.4	1.24 \pm 0.03	85 \pm 3
2.90	12.59	4	15.6-30.4	0.957 \pm 0.055	89 \pm 6
3.01	9.772	5	15.5-37.7	0.790 \pm 0.028	82 \pm 6
3.10	7.943	1	17.7	0.545	83
3.20	6.310	1	22.9	0.454	91
3.35	4.467	11	19.5-283.5	0.459 \pm 0.058	79 \pm 7
3.65	2.239	1	29.4	0.225	88
3.83	1.479	4	15.5-41.0	0.194 \pm 0.009	62 \pm 4
4.30	0.5012	7	20.9-43.0	0.0785 \pm 0.0106	62 \pm 8
4.60	0.2512	1	21.0	0.0214	50
5.10	0.07943	2	24.4-24.6	0.00926 \pm 0.00010	48.5 \pm 0

^aA.D., average deviation.

examine possible changes in kinetic behavior at higher pH values, such as the range 3.0 to 5.0, which is considered appropriate for a good antacid (1).

Our work has established the kinetics for the pH region 2.8 to 5.1, the effect of hydrogen-ion concentration on the reaction rate, and a quantitative treatment for the kinetic behavior of heterogeneous and relatively homogeneous particle sizes.

For the case where the hydrogen-ion concentration is constant throughout an entire reaction, Eq. 2 becomes

$$-d[\text{H}^+]/dt = k\alpha W[\text{H}^+]_0/\rho d_0 \quad (\text{Eq. 4})$$

where $[\text{H}^+]$ ' is the acid being neutralized, and $[\text{H}^+]_0$ is the initial hydrogen-ion concentration. For a given pH, Eq. 4 may be written

$$-d[\text{H}^+]/dt = k'W \quad (\text{Eq. 5})$$

where $k' = k\alpha[\text{H}^+]_0/\rho d_0$. Thus, maintaining a constant pH and measuring the acid required to be added as a function of time should produce data which is first order in weight of calcium carbonate, W . Examination of several pH values would then allow an evaluation of the effect of hydrogen-ion concentration. These studies were accomplished by using a pH-stat apparatus.

EXPERIMENTAL

Constant-pH Neutralization of HCl by Calcium Carbonate.—The Sargent recording pH stat S-30240, equipped with the Corning pH meter, model 12, was standardized with thermally equilibrated buffers of pH 7.00 and 4.01. Twenty milliliters of distilled water was adjusted to the desired pH and temperature in the titration vessel. Samples of calcium carbonate powder, A.C.S. reagent (B & A code 1506), varying from 13 to 300 mg., were weighed on a small watch glass and transferred to the titration vessel. The volume of titrant required to maintain a constant pH was recorded as a function of time by the automatic recorder (Fig. 1). (See Table I for experimental conditions.)

A 2.5-ml. buret was used. The range of total volume delivered was 0.1 to 2.0 ml. The usual volume increase, due to dilution with titrant, was 2%; the maximum increase possible was 10%.

Effect of Stirring Speed.—The magnetic stirrer was run at various speeds from a setting of 5 to 10. The actual velocity was not known. The pH and sample weight were held constant. A region where neutralization velocity was independent of stirring speed existed above settings of 9. All studies were run at a setting of 10 thereafter. (See Table II for experimental conditions.)

Effect of Temperature.—The Sargent recording pH stat has a temperature regulator with specifications of $\pm 0.05^\circ$ from 15 to 50°. The temperature was varied from 15 to 45° at constant pH and stirring. (See Table III for experimental conditions.)

TABLE II.—EFFECT OF STIRRING VELOCITY ON THE APPARENT FIRST-ORDER RATE CONSTANT (k IN MIN.⁻¹) FOR THE NEUTRALIZATION OF HCl BY DISPERSED CALCIUM CARBONATE POWDER^a AT pH 2.9 AND 25°

Stirrer Setting	k
5.5	0.385
6.0	0.414
7.0	0.486
8.0	0.556
9.0	0.899, 0.812
9.10	0.956
9.25	0.990
9.50	0.860
9.75	0.958
10.00	0.809, 0.877

^a Sample size range: 19.8-21.0 mg.

TABLE III.—EFFECT OF TEMPERATURE ON THE MEAN APPARENT FIRST-ORDER RATE CONSTANT (\bar{k} IN MIN.⁻¹) FOR THE NEUTRALIZATION OF HCl BY DISPERSED CALCIUM CARBONATE POWDER AT pH 3.35 AND pH 3.83

Temp., °C.	$\bar{k} \pm \text{A.D.}^a$	
	pH 3.35	pH 3.83
15	0.33 \pm 0.03	0.158 \pm 0.005
25	0.46 \pm 0.06	0.194 \pm 0.009
35	0.42 \pm 0.01	...
45	0.43 \pm 0.02	0.204 \pm 0.020

^a A.D., average deviation.

TABLE IV.—MEAN APPARENT FIRST-ORDER RATE CONSTANTS (\bar{k}_i IN MIN.⁻¹) FOR THE NEUTRALIZATION OF HCl BY EQUAL WEIGHTS^a OF DIFFERENT PARTICLE SIZE FRACTIONS, \bar{f}_i ,^b OF CALCIUM CARBONATE POWDER AT 25°, pH 2.85

Screen Size	\bar{f}_i	\bar{k}_i	No. Runs	$\bar{f}_i \bar{k}_i$ ^c
150-200	0.022	0.129	1	0.028
200-250	0.025	0.225	2	0.057
250-300	0.312	0.576	7	0.180
300-325	0.031	1.218	1	0.037
325-Bottom	0.625	1.520	2	0.950

^a Sample size range: 24.9-26.2 mg. ^b Where f_i = weight collection on screen i /total weight based on two separations of about 40 Gm. total weight each. ^c $\sum \bar{f}_i \bar{k}_i = 1.252$; observed value for the apparent first-order rate before screening was $k_{obs} = 1.238$; the difference is 1.13%.

Effect of Particle Size.—Samples of calcium carbonate were weighed and sieved through a series of screens for 10 min. on a Ro-Tap testing sieve shaker (W. S. Tyler Co.). The fractions were collected and weighed. The neutralization reactions for each fraction were studied as described in the previous sections. (See Table IV for experimental conditions.)

CALCULATIONS AND RESULTS

Constant-pH Neutralization of HCl by Calcium Carbonate.—The volume of titrant, V , was recorded as a function of time during the constant-pH neutralization of HCl by dispersed calcium carbonate powder (Fig. 1). According to Eq. 5, the rate may be expressed

$$dNV/dt = k'W \quad (\text{Eq. 6})$$

where NV , the equivalents of titrant added to maintain the pH constant, is equal to the equivalents of acid neutralized by the calcium carbonate. The weight of calcium carbonate, W , remaining at any time, t , is

$$W = N(V_\infty - V)E \quad (\text{Eq. 7})$$

where N is the normality of the titrant, V_∞ is the asymptote of the curve (Fig. 1), and E is the gram-equivalent weight of calcium carbonate. Substitution for W in Eq. 6 gives

$$dV/dt = k(V_\infty - V) \quad (\text{Eq. 8})$$

which on integration yields

$$\log(V_\infty - V) = -2.303kt + \log V_\infty \quad (\text{Eq. 9})$$

Plots of $\log(V_\infty - V)$ versus t were linear as shown in Fig. 2. The apparent first-order rate constants, k , calculated from the slopes of these lines are given in Table I.

Effect of Stirring.—Data showing the effect of stirring speed on the first-order rate constant for the neutralization of acid by calcium carbonate at pH 2.90 are given in Table II. Increasing the magnetic stirrer setting from 5.5 to 8.0 resulted in increased rates. This dependence of rate of reaction on stirring velocity is common in a dissolution controlled process. At settings of 9 through 10 the rate constant was independent of the stirring speed.

Effect of Temperature.—The effect of temperature on the apparent first-order rate constant at pH 3.35 and 3.83 is summarized in Table III. Under the conditions of this study there was no measurable temperature effect. Nogami (6) has reported an activation energy of 6.4 Kcal.

Effect of Particle Size.—Weighed samples of calcium carbonate were shaken through a series of sieves for 10 min. and the fractions collected and

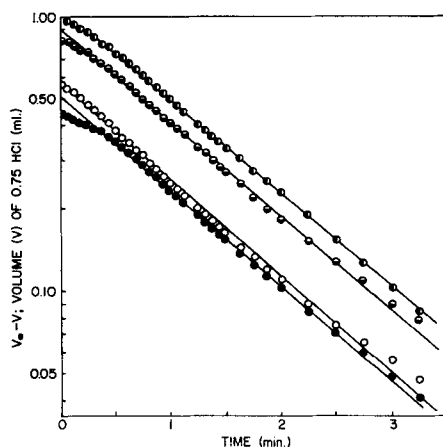


Fig. 2.—First-order plots for the volume of HCl consumed, as a function of time, by various initial weights (mg.) of calcium carbonate powder at pH 3.01, 25°. Key: sample sizes—○, 37.7 mg.; ◐, 30.8 mg.; ○, 21.2 mg.; ●, 15.5.

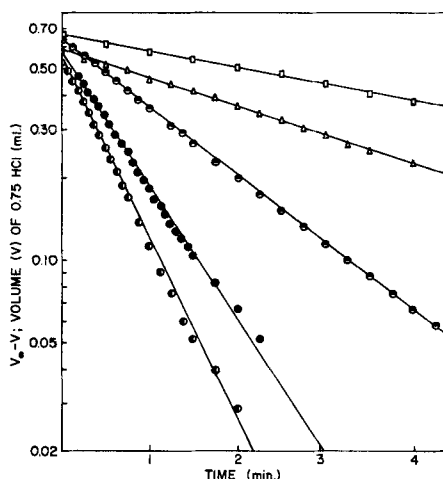


Fig. 3.—First-order plots for the volume of HCl consumed, as a function of time, by equal weights of different mesh sizes of calcium carbonate powder at pH 2.85, 25°. Key: screen sizes—□, 150-200; △, 200-250; ◐, 250-300; ●, 300-325; ●, 325-bottom.

weighed (Table IV). The fraction by weight, f_i , is defined

$$f_i = W_i/W_0 \quad (\text{Eq. 10})$$

where W_i is the weight collected at level, i , and W_0 is the original total sample weight. The apparent first-order rate constants, k_i , for each fraction were calculated from plots based on Eq. 8 (Fig. 3) at 25° and pH 2.85. Average rate constants for each fraction are reported in Table IV. The relationship of the heterogeneous sample, that is, the unscreened analytical calcium carbonate, to its fractions may be expressed as

$$-dW/dt = (\Sigma k_i f_i)W \quad (\text{Eq. 11})$$

where W is the weight of analytical calcium carbonate. Table IV shows the result of applying Eq. 11 to the fractions. The value of $\Sigma k_i f_i$ was 1.252 min.^{-1} in this case. The over-all rate constant for the unscreened sample was 1.238. The difference is +1.13%.

DISCUSSION

Nogami (6), by measuring the change in pH with time, showed that the Hixon-Crowell cube-root law for dissolution of solids is applicable to the neutralization of acid by calcium carbonate. He succeeded in demonstrating first-order kinetics only for the special case where the ratio of sample weight to hydrogen-ion concentration was kept constant. The limit imposed by employing initial slope calculations in his studies (Eq. 3) was that of constant hydrogen-ion concentration. The authors have imposed this same limitation throughout the whole of the reaction time by use of a pH-stat mechanism. The rate of neutralization of acid by calcium carbonate, here, can be expressed

$$-dW/dt = kW \quad (\text{Eq. 12})$$

where W is the weight of calcium carbonate at time, t , and k is the apparent first-order rate constant which includes α , ρ , and d_0 as defined in Eq. 2.

The per cent of reaction giving a linear first-order plot varied with the pH studied (Table I). About 87% of the reaction is first-order in the pH range 2.85 to 3.20. At a pH of 5.1 only 50% of the reaction was linear. The apparent first-order rate constants, calculated from plots based on Eq. 9, were directly proportional to hydrogen-ion activity:

$$k = k_{H^+}(a_{H^+}) \quad (\text{Eq. 13})$$

where the activities of the hydrogen ion, a_{H^+} , were calculated from the observed pH. The catalytic rate constant, $k_{H^+} = 83 (\text{min.})^{-1}$, was calculated from the slope of the plot of observed k versus a_{H^+} (Fig. 4). The apparent convergence of this plot at the origin is indicative of no significant solvent effect. A plot representing the logarithmic transformation of Eq. 13 is given in Fig. 5. The slope of this plot is 0.92 in agreement with the theoretical expectation of unity. The small temperature effect is consistent with a dissolution process as compared to a chemical one. This is in agreement with the low activation energy reported by Nogami (6 Kcal.). Our studies were carried out at a region independent of stirring speed also in agreement with Nogami, who reported independence of reaction rate at speeds greater

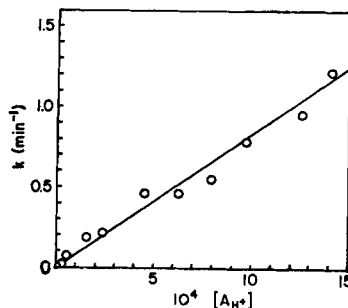


Fig. 4.—Apparent first-order rate constants, k , for constant-pH neutralization of HCl by calcium carbonate powder vs. hydrogen-ion activity, a_{H^+} , at 25°.

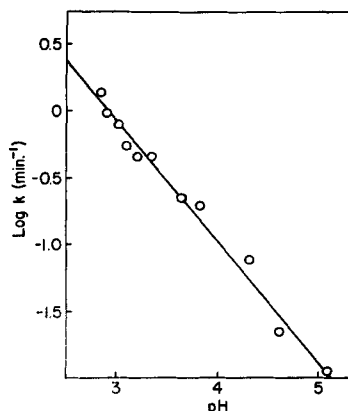


Fig. 5.—Log of the apparent first-order rate constants, k , for the constant-pH neutralization of HCl by calcium carbonate powder vs. pH at 25°.

than 350 r.p.m. and sufficient to maintain the particles suspended.

Steinberg's studies (1, 2) were directed toward the development of a much needed technique by which various commercial antacids could be evaluated. Data were collected strictly for the sake of comparison as opposed to establishing the kinetics of the rate processes. Our studies were made under conditions of sample size and titer appropriate to the collection of kinetically analyzable data throughout the whole of the reaction. The authors have shown the neutralization to be first order. The apparent first-order rate constant, k , for acid neutralization by calcium carbonate powder of mixed particle sizes is the sum of products of the individual first-order rate constants for the isolated particle sizes, k_i , times the fraction by weight of that particle size, f_i ; i.e., $k = \Sigma k_i f_i$. The utilization of fractional contributions to explain an over-all first-order rate constant has been applied by Higuchi (8).

The first apparent pKa of carbonic acid is 6.53. One would therefore expect a 2:1 stoichiometry of total acid neutralized to calcium carbonate sample weight within the pH range 2.85 to 5.3 studied here.

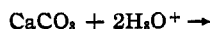


TABLE V.—EXAMPLES OF THE RECOVERY OF CALCIUM CARBONATE (%)^a BASED ON THE TITER CONSUMED IN A CONSTANT-pH NEUTRALIZATION OF THE POWDER

pH	Temp., °C.	CaCO ₃ (meq.) ^b	HCl (meq.)	%
3.35	45	2.878	2.835	98.5
		5.396	5.288	98.0
	35	2.998	2.935	97.9
		4.396	4.323	98.3
		5.596	5.529	98.8
		3.197	3.217	100.6
3.83	45	5.196	5.227	100.6
		3.797	3.719	97.9
	15	5.196	5.083	97.8
		3.177	3.217	101.3
		5.795	5.670	97.8
		4.337	4.262	98.3
4.30	25	6.135	6.313	102.9
		8.593	8.553	99.3

^a Where % = 100 (meq. HCl)/(meq. CaCO₃). ^b Based on Eq. 14.

The authors have found that calcium carbonate neutralizes 98 to 102% of its theoretical capacity in accordance with Eq. 14. Representative data are given in Table V. Steinberg *et al.* (1, 2) have reported that "as the pH stat conditions increase toward pH 5.0, the total acid consuming capacity decreases." Their study used a combination of calcium carbonate and glycine. Since glycine has a pK_a of 2.35, it would be expected that its buffer capacity would be less at pH 5 than at pH 1.5.

Although this over-all process exhibits simple first-order kinetics in the low pH region, the actual mechanism may be quite complex. Since the neutralization of acid by calcium carbonate powder is a rate process, it may be influenced by the acidity of carbonic acid or the relative diffusivity of the various species present. Carbonic acid is a relatively strong acid with a true pK_a of 3.89 (9). This can become important when examining kinetic

data in contrast to the equilibrium situation discussed in the previous paragraph. Because of the complexity of this system, which involves the carbonic acid equilibrium reactions, the rate-limiting process on a microscopic level cannot be defined at this time. Further studies on calcium carbonate and other systems are in progress.

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