

**118. Hisashi Nogami and Tsuneji Nagai: Studies on Powdered Preparations. VII.\*<sup>2</sup> Acid Neutralizing Velocity of Antacids.\*<sup>3-5</sup>**

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The antacid properties should be evaluated not only by the acid-consuming capacity, but also by the neutralizing velocity. The neutralizing velocity might be influenced by many factors, i. e., the specific surface area of the antacid, the reaction rate per unit surface area (reactivity), and the wettability of the surface, that is, the effective surface area. Consequently, the reaction velocity is not only related to physical and chemical properties of the antacid, but also can be effectively changed by the method of preparation or formulation. The antacid properties of dried aluminum hydroxide gel (DAHG) vary widely among the different preparations available. It is therefore necessary to formulate an adequate method for evaluating this property.

Numerous useful methods have been presented for the evaluation of antacids.<sup>1-15)</sup> However, few investigations have been made which deal with antacids on the standpoint of reaction kinetics. The purposes of the present study were to discuss the acid neutralizing velocity of antacids and to establish a method for comparing the antacid reactivities with satisfactory reproducibility. Here, two types of equations were considered useful to express the acid neutralizing velocity; one is the calcium carbonate type and the other the DAHG type. Present experiments were carried out to analyse both types mainly on the procedure to measure pH continuously.

### Theory and Fundamental Concepts

#### Two Types of Fundamental Equations to Express the Acid Neutralizing Velocity of Antacids

The reaction between antacid and acid is a solid-liquid reaction, which is influenced by many complicated factors. It is very difficult to observe microscopically how the reaction progresses on the surface of the antacid powder. In the physiological sense, however, it is more important to observe the reaction with regard to the de-

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\*<sup>4</sup> Presented at the Kanto Local Meeting of Pharmaceutical Society of Japan, Tokyo, January 1961.

\*<sup>5</sup> Outlined in a preliminary communication: This Bulletin, **10**, 434 (1962).

- 1) J. M. Holbert, *et al.*: J. Am. Pharm. Assoc., **36**, 149 (1947); **37**, 292 (1948).
- 2) E. R. Hammarlund, *et al.*: *Ibid.*, **38**, 586 (1949); **41**, 295 (1952).
- 3) R. S. Murphey: *Ibid.*, **41**, 361 (1952).
- 4) A. M. Corrente: *Ibid.*, **43**, 242 (1954).
- 5) J. K. Dale, *et al.*: *Ibid.*, **44**, 170 (1955).
- 6) H. R. Schleif: *Ibid.*, **46**, 179 (1957).
- 7) E. T. Hinkel, Jr., *et al.*: *Ibid.*, **48**, 380, 384 (1959).
- 8) C. Fuchs: Drug & Cosmetic Ind., **64**, 692 (1949).
- 9) N. E. Rossett, *et al.*: Ann. Internal Med., **18**, 193 (1943).
- 10) *Idem*: Gastroenterology, **26**, 490 (1954).
- 11) H. E. Johnson, *et al.*: Quart. J. Pharm. and Pharmacol., **18**, 251 (1945).
- 12) J. Armstrog, *et al.*: J. Pharm. and Pharmacol., **5**, 672 (1953).
- 13) D. N. Core, *et al.*: *Ibid.*, **5**, 686 (1953).
- 14) H. Brindle: *Ibid.*, **5**, 692 (1953).
- 15) P. R. Clemow, *et al.*: *Ibid.*, **6**, 610 (1954).

crease of hydrogen ion concentration in bulk liquid, which may be determined by several methods. The fundamental equations of the following two types, which concern with such a decrease of hydrogen ion concentration, are considered to be helpful for analyzing the acid neutralizing velocity of antacids.

The calcium carbonate type equation is of the first order in the acid neutralizing reaction with respect to the hydrogen ion concentration in bulk liquid. It is frequently reported that the reaction between metals and dilute aqueous acids are of the first order with respect to the acid, though the reports on the reactions of higher order were found.<sup>16)</sup> But such a higher order reactions are considered to be rather exceptional in the reaction between antacid powder and acid, and therefore it was not taken into consideration in this study. Then the acid neutralizing velocity is given by

$$-\frac{dH}{dt} = kSH \quad (1)$$

where  $H$  is the hydrogen ion concentration in bulk liquid after time  $t$ ,  $k$  the velocity constant and  $S$  the surface area of antacid powder. Equation (1) is similar to those derived by Noyes and Whitney,<sup>17)</sup> Nernst,<sup>18)</sup> and Berthoud,<sup>19)</sup> concerning the velocity of dissolution of solid into liquid. The velocity of the reaction is governed ordinarily by diffusion or activated collision.<sup>20)</sup>

Nextly, the DAHG type equation shows that the acid neutralizing reaction is of fractional order with respect to the hydrogen ion concentration in bulk liquid. Then the acid neutralizing velocity is represented by

$$-\frac{dH}{dt} = kSH^r \quad (0 \leq r < 1) \quad (2)$$

where  $r$  is the order of reaction and the other symbols denote the same significances as indicated in equation (1). In this type, the surface reaction is considered to be the slowest of all, thus having the greatest influence on the net velocity of acid neutralizing reaction. Equation (2) indicates that the velocity is proportional to the amount of acid adsorbed on the surface of antacid powder, which is empirically related by the Freundlich type isotherm. Similar proportionality is found in some of the heterogeneous catalytic reaction.<sup>21)</sup>

#### Reaction between Powdered Calcium Carbonate (Powdered Marble) and Hydrochloric Acid

Marble parallelepipeds are so convenient to examine the reaction between solid and acid that several investigators had chosen them as the test samples.<sup>22-25)</sup> However, little work had been done to investigate such reaction in the powder state.<sup>26)</sup> Since the surface area of powder is larger than that of parallelepiped of the same weight, the reaction is faster, henceforth a rapid method is required to measure the velocity

16) M. Centnerszwer : Z. phys. Chem., A, **141**, 297 (1929).

17) A.A. Noyes, W.R. Whitney : J. Am. Chem. Soc., **19**, 930 (1897).

18) W. Nernst : Z. phys. Chem., **47**, 52 (1904).

19) A. Berthoud : J. chim. phys., **10**, 633 (1912).

20) E. A. Moelwyn-Hughes : "The Kinetics of Reactions in Solution," 2nd ed., p. 357 (1947), Oxford University Press, London.

21) E. A. Moelwyn-Hughes : "The Kinetics of Reaction in Solution," 2nd ed., p. 52 (1947), Oxford University Press, London.

22) J.G. Boguski, M. Kajander : Ber., **10**, 34 (1877).

23) W. Spring : Z. phys. Chem., **1**, 209 (1887).

24) E. Brünner : *Ibid.*, **47**, 56 (1904).

25) C.W. King, C.L. Lin : J. Am. Chem. Soc., **55**, 1928 (1933).

26) E. Suito, *et al.* : Nippon Kagaku Zasshi, **72**, 714 (1951).

of the reaction. In this study, powdered marbles of different mean particle diameters were examined. Though it is possible to keep surface area constant during the reaction in the case of parallelepiped as investigated by Spring,<sup>23)</sup> it is impossible in the case of a powdered sample. Applying the Hixon-Crowell cube root law<sup>27)</sup> to equation (1), the velocity of acid neutralizing reaction of powdered marble may be described to

$$-\frac{dH}{dt} = k \frac{\alpha W^{1/3}}{\rho d_0} \{W - h(H_0 - H)\}^{2/3} H \quad (3)$$

where  $W$  is the quantity of test sample,  $H_0$  the initial hydrogen ion concentration<sup>\*6</sup> in bulk liquid,  $h$  the factor to convert the concentration into the quantity, and  $\alpha$ ,  $\rho$ , and  $d_0$  denote the shape factor, the density and the mean volume-surface diameter<sup>28)</sup> of test sample, respectively. The influence of either the concentration or the ionic strength upon the activity coefficient of hydrogen ion is not taken into consideration. Hence the change of pH,  $X$ , will be represented by

$$\frac{dX}{dt} = 0.4343 k \frac{\alpha W^{1/3}}{\rho d_0} \{W - h(H_0 - H)\}^{2/3} \quad (4)$$

Since the induction period was not observed at the beginning of the reaction in this experiment, the initial increase of pH is given by

$$\left(\frac{dX}{dt}\right)_{t=0} = 0.4343 k \frac{\alpha W}{\rho d_0} \quad (5)$$

$\left(\frac{dX}{dt}\right)_{t=0}$  is obtainable graphically either from the pH-time curve or from numerical calculation, and  $k$  is estimated from equation (5).

#### Reaction between DAHG and Acid

It has been evidenced by Tarter, *et al.*,<sup>29)</sup> that the dissolution of colloidal aluminum hydroxide into hydrochloric acid may not be interpreted by such theories as Noyes and Whitney's<sup>17)</sup> and Nernst's.<sup>18)</sup> The reaction between DAHG and acid also does not agree with those theories, therefore a fundamental theory on the velocity has been introduced by equation (2). The equation corresponding to equation (3) is derived as

$$-\frac{dH}{dt} = k \frac{\alpha W^{1/3}}{\rho d_0} \{W - h(H_0 - H)\}^{2/3} H^r \quad (6)$$

Practically, the effective surface area in the reaction can hardly be estimated from such a method as the measurement of particle size; therefore, equation (6) becomes valueless. Moreover, the velocity of reaction between DAHG and acid is so slow that a considerably large excess of antacid is required to be used in the experiment. Therefore, when  $W \gg hH_0$ , it will be possible to approximate the acid neutralizing velocity to

$$-\frac{dH}{dt} = KWH^n \quad (0 \leq n < 1) \quad (7)$$

where  $K$  is the apparent velocity constant influenced by both  $k$  and the specific surface area of test sample, and  $n$  is the apparent order of reaction controlled by  $r$  and the

\*6  $H_0$  is used without discrimination from the initial concentration of acid.

27) A. W. Hixon, H. J. Crowell: *Ind. Eng. Chem.*, **23**, 923, 1002 (1931), A. W. Hixon, G. A. Wilkins: *Ibid.*, **25**, 1196 (1933).

28) J. M. DallaValle: "Micromeritics," 2nd ed. (1948), Pitman Publishing Corp., New York; "Fine Particle Measurement," (1959), The Macmillan Co., New York.

29) H. V. Tartar, *et al.*: *J. Am. Chem. Soc.*, **55**, 2266 (1933).

quantity of test sample. On the contrary to the reaction between powdered marble and hydrochloric acid, it was necessarily to consider an induction period in this experiment. Equation (7) is, therefore, integrated to yield

$$\log H = \log H_0 + \frac{1}{1-n} \log \left| 1 - \frac{(1-n)KW}{H_0^{1-n}}(t-t_1) \right| \quad (8)$$

where  $t_1$  is the estimated induction period. To explain the change of pH,  $X$ , equation (8) is modified to

$$X = X_0 - \frac{1}{1-n} \log \left| 1 - \frac{(1-n)KW}{H_0^{1-n}}(t-t_1) \right| \quad (9)$$

where  $X_0$  is the initial pH in bulk liquid, which depends upon  $-\log H_0$  and the activity coefficient of hydrogen ion. Experimentally, pH increased rapidly in a moment after the sample was added to the acid. The increase of pH at the initial stage seemed to belong to another type of reaction and will be mentioned later.  $t_1$  is, therefore, not distinct on the pH-time curve. Since the observed values of  $K$  are also related to such a circumstance, the calculations of  $K$  are accompanied by troublesome efforts. It is, accordingly, convenient to use the finished time,  $t_\infty$ , as described in the following way.

Although the hydrogen ion concentration can not become zero, it may be assumed mathematically to become zero in equation (9). Using  $t_\infty$  for the finished time, when  $H=0$  or  $X \rightarrow \infty$ , hence  $t_\infty$  is given from equation (9) as

$$t_\infty = \frac{H_0^{1-n}}{(1-n)KW} + t_1 \quad (10)$$

Substituting from equation (10), equation (9) becomes

$$X = X_{t=0} - \frac{1}{1-n} \log \left| 1 - \frac{1}{t_\infty} t \right| \quad (11)$$

where  $X_{t=0}$  is the estimated pH in bulk liquid at  $t=0$ , depending upon  $X_0$  and  $\log \left| 1 - \frac{(1-n)KW}{H_0^{1-n}} t_1 \right|$ . Denoting  $X$  at  $t(X)$ , and  $X+\xi$  at  $t(X+\xi)$  and  $\xi = \text{constant}$ , the linear relationship between  $t(X)$  and  $t(X+\xi)$  is given by

$$t(X+\xi) = t_\infty \{ 1 - 10^{-(1-n)\xi} \} + 10^{-(1-n)\xi} \cdot t(X) \quad (12)$$

Values of  $t(X)$  or  $t(X+\xi)$  are obtainable graphically from the pH-time curve, and the plot of these values, except the initial and the final stage of reaction, is in accordance with equation (12).  $n$  is obtained from the slope of this plot and  $t_\infty$  is obtained from the intersection of this plot and the bisector  $t(X+\xi) = t(X)$ . Such  $n$  and  $t_\infty$  are very useful to compare the antacid reactivity of DAHG.

Aluminum ion is produced in bulk liquid with the progress of reaction between DAHG and acid, influencing the pH of bulk liquid caused by the hydrolysis.<sup>30-33)</sup> Accordingly, the pH-time curve is flexed at a certain pH, and as the rate of pH increase becomes smaller, the reaction will finish at another certain pH; thus, the curve after

30) C. Brosset : Acta Chem. Scand., **6**, 910 (1952).

31) C. Brosset, *et al.* : *Ibid.*, **8**, 1917 (1954).

32) R.K. Shofield, A.W. Taylor : J. Chem. Soc., **1954**, 4445.

33) J. Kenttämaa : Suomen Kemistilehti (Helsinki), **B**, **28**, 172 (1955).

such flexion is not in accordance with equation (11). The time and the pH at the flexion point, where the rate of pH increase became maximum, are called the pH flexional time (represented by  $t_v$ ) and the flexional pH (represented by  $X_v$ ), respectively. The relationship between  $t_\infty$  and  $t_v$  is given by

$$\log \left| \frac{t_\infty - t_v}{t_\infty - t_1} \right| = -(1-n)(X_v - X_0) \quad (13)$$

Since  $X_v$  is related to  $X_0$  as described in the experimental part,  $\frac{t_v - t_1}{t_\infty - t_1}$  becomes almost identical when  $X_0$  is identical. Consequently,  $t_v$  is also useful to compare the antacid reactivity. Details on the change of pH at the initial and the final stage will be learned in the results and discussion.

### Experimental

**Apparatus and Procedure for the Measurement of pH Change**—The apparatus shown in Fig. 1 is consisted of a flask containing 200 cc. of the acid solution, a water bath with heating unit, a pH

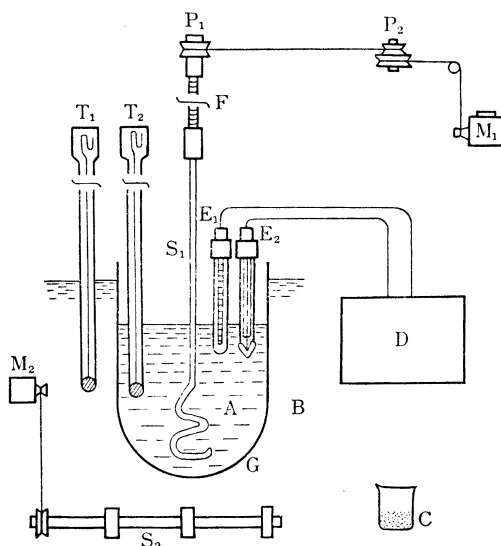


Fig. 1. Apparatus for the Measurement of Change pH

- A : acid solution to be tested
- B : thermally controlled water
- C : sample in a small beaker
- D : pH meter
- E<sub>1</sub> : calomel electrode
- E<sub>2</sub> : glass electrode
- F : flexible junction
- G : flask
- M<sub>1</sub> : single phase induction motor
- M<sub>2</sub> : series motor
- P<sub>1</sub> and P<sub>2</sub> : pulleys
- S<sub>1</sub> and S<sub>2</sub> : stirrers
- T<sub>1</sub> and T<sub>2</sub> : Beckmann's thermometers

meter, stirrers, Beckmann thermometers, and a small beaker containing test sample. Both a Beckmann Model G pH meter and a Hitachi-Horiba Model P pH meter, with calomel and glass electrodes, gave the same results. A single phase induction motor, M<sub>1</sub>, was used to move the stirrer, S<sub>1</sub>, at a constant speed of 500 r.p.m. At the speed of 350 r.p.m. and above the stirring did not make the test sample rest on the bottom of the flask, thus reproducible data were obtained. The flask and acid were kept in a water bath thermostatically controlled at the desired temperature with a maximum deviation of 0.08°. A given amount of the test sample was added to the acid, while stirring constantly, and the pH was measured at adequate intervals. The phthalate buffer at pH 4.01 (J.I.S.) was used as the pH standard. The acid solution contained 0.05% of Tween 80 which sufficiently wetted the test sample. Such a wetting agent was especially useful in the reaction between powdered marble and acid which was accompanied by the evolution of carbon dioxide, because gases should be removed instantly from the surface, in order to keep a good contact between surface and solution.

**Test Samples**—1) Powdered marble : Marble was powdered and sieved, washed several times with H<sub>2</sub>O to remove finer particles in order to prepare a sample with reasonably uniform particle size, then washed with H<sub>2</sub>O containing 0.05% of Tween 80, and finally dried in a desiccator. This treatment gave two kinds of samples. The mean particle diameter were determined by the microscopic measurement with 400 particles. Table I shows arithmetic mean diameters, standard deviations and mean volume-surface diameter. The density obtained was 257 g./cc. by the pycnometer method.

TABLE I. Particle Sizes of Test Samples of Powdered Marble

	Arithmetic mean diameter ( $\mu$ )	Standard deviation ( $\mu$ )	Mean volume-surface diameter ( $\mu$ )
Sample (1)	323	74	356
Sample (2)	159	46	186

2) DAHG : Two different test samples of DAHG J.P., A and B were selected. The properties of the samples are listed in Table II.

TABLE II. Properties of Test Samples of DAHG

	Sample A	Sample B
Density by the pycnometer method (g./cc.)	2.11	2.15
Apparent density (g./cc.)	0.455	0.441
Sedimentation volume in water (cc./g.)	3.83	3.93
Percentage of aluminum oxide	63.9 <sup>a)</sup>	59.3 <sup>a)</sup>
Acid-consuming capacity (cc.)	336 <sup>a)</sup>	297 <sup>a)</sup>
Specific surface area (m. <sup>2</sup> /g.)	65.5 <sup>b)</sup>	34.1 <sup>b)</sup>

a) These are in accordance with J.P. VII or U.S.P. XVI.

b) Determined by BET gas adsorption method, using nitrogen. The treatment of the sample at a high temperature would change its chemical and geometrical properties; thus, degassing of the sample, before the measurement, was performed at room temperature for about 20hr. at pressure below  $10^{-5}$  mm.Hg, which was thorough enough to obtain the straight line according to BET equation [J. Am. Chem. Soc., 60, 309 (1938)], and the data were satisfactorily reproducible.

Both samples A and B did not give any intensive diffraction by X-ray examination. According to the differential thermal analysis, both samples gave only broad curve of endothermic reaction near 130°, which was different from the curve of crystalline aluminum hydroxide. Therefore, both samples A and B are considered to be amorphous.

#### Colorimetric Determination of Aluminum Ion Produced by Acid Neutralizing Reaction of DAHG

—The method of Goto, *et al.*,<sup>34</sup> was modified partly for the determination of the increase of aluminum ion.

1) Reagents : Oxine solution, prepared by dissolving 2 g. of oxine (8-quinolinol) in 5 cc. of glacial AcOH and adding H<sub>2</sub>O; to make 200 cc. NAcONa; purified CHCl<sub>3</sub>; purified anhyd. Na<sub>2</sub>SO<sub>4</sub>.

2) Procedure : 15 cc. of H<sub>2</sub>O, 2 cc. of oxine solution, and 2 cc. of N AcONa were placed in a glass-stoppered bottle, shaken, and then 20 cc. of purified CHCl<sub>3</sub> was added without shaking. At given intervals, 1 cc. of the suspension (containing less than 80 mg./L. of extractable aluminum) was taken out from the flask shown in Fig. 1 (in which the reaction between DAHG and acid was carried out as described before, and the pH was also measured), added as rapidly as possible to the glass-stoppered bottle just indicated, at once shaken vigorously for 10 sec., and allowed to stand for separation. The aqueous layer was removed by suction, and a small amount of purified anhyd. Na<sub>2</sub>SO<sub>4</sub> was added to the CHCl<sub>3</sub> layer to dehydrate it. The absorbancy was measured at 390 m $\mu$  with the Hitachi Spectrophotometer Model EPU- $\Pi$ . The concentration of aluminum ion was calculated from the standard curve obtained with KAl(SO<sub>4</sub>)<sub>2</sub> of the purest grade.

## Results and Discussion

### Reaction between Calcium Carbonate Powder (Powdered Marble) and Hydrochloric Acid

Typical pH-time curves of the reaction between powdered marble and hydrochloric acid are shown in Fig. 2. The rate of pH change decreased with the progress of the reaction, particularly in the later part of reaction. This was considered to be influenced not only by the decrease of surface area of the sample, but also by the amount of calcium chloride produced; thus, the velocity of reaction was not in accordance with equation (1) over the entire curve as the acid was used up. According to equation (5),  $\left(\frac{dX}{dt}\right)_{t=0}$  is expected to be proportional to  $W$ . Such proportionality was not observed more or less

34) K. Goto, *et al.* : Bull. Chem. Soc. Japan, 31, 783 (1958).

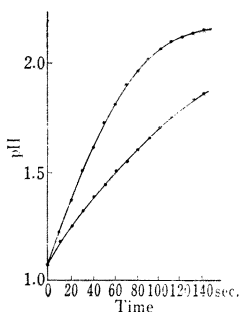


Fig. 2. Reaction between Powdered Marble and Hydrochloric Acid at  $38^\circ$  under 200 cc. of 0.1N Acid and 1.000 g. of Test Sample

upper : smaller particle size ( $d_0=186 \mu$ )  
lower : larger particle size ( $d_0=356 \mu$ )

on the examinations carried out under  $H_0 =$  identical, and this was considered to relate to the circumstances described above. However, the linear relationship between  $(\frac{dX}{dt})_{t=0}$  and  $W$  was ascertained by the examinations carried out under an identical ratio  $W$  to  $H_0$  as shown in Fig. 3. From the slope of this straight line,  $k$  was estimated from

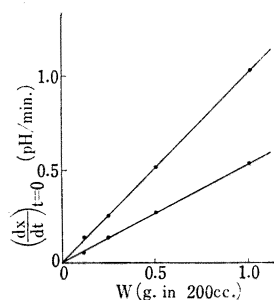


Fig. 3. Linear Relationship between Initial Increase of pH,  $(\frac{dx}{dt})_{t=0}$ , and Quantity of Test Sample,  $W$ , obtained on the Reaction between Powdered Marble and Hydrochloric Acid at  $38^\circ$  under 200 cc. of Acid and  $W/H_0=50.0$  g./N. L.

upper : smaller particle size ( $d_0=186 \mu$ )  
lower : larger particle size ( $d_0=356 \mu$ )

equation (5) (assuming  $\alpha=6$ ). The estimated values of  $k$  at  $28^\circ$ ,  $38^\circ$ , and  $48^\circ$  are shown in Table III. The relationship between  $\log k$  and  $1/T$  is shown in Fig. 4, where  $T$  is the temperature in  $^\circ\text{K}$ . From the temperature coefficient, the activation energy of the reaction was estimated to be about 6,400 calories, which was found similar to Spring's<sup>23)</sup>

TABLE III. Velocity Constant of Reaction between Powdered Marble and Hydrochloric Acid

	$k (\times 10^{-2} \text{ g./cc. min.})$		
	$28^\circ$	$38^\circ$	$48^\circ$
Sample (1) ( $d_0=356 \mu$ )	1.35	1.98	2.69
Sample (2) ( $d_0=186 \mu$ )	1.39	1.81	2.63

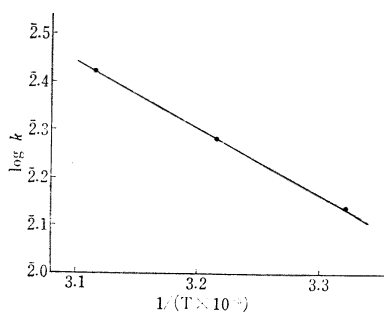


Fig. 4. Relationship between  $\log k$  and  $1/T$  of the Reaction between Powdered Marble and Hydrochloric Acid, where the Means in Table III are used for  $k$

and King's<sup>25)</sup> observations with marble parallelepipeds. Consequently, it may be considered that powdered marble reacts with acid in the same way that mable parallelepiped does, though about the ultrafine powder any examination has not been made.

**Finished Time,  $t_\infty$ , and Apparent Order of Reaction,  $n$ , of the Reaction between DAHG and Acid**

Typical pH-time curve of the reaction between DAHG and acid are shown in Fig. 5, from which values of  $t(X)$  or  $t(X+\xi)$  were obtained. Fig. 6 is an example showing the

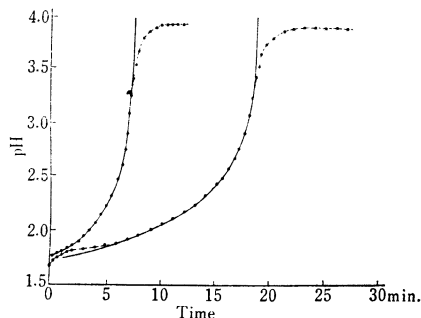


Fig. 5. Reaction between DAHG and Hydrochloric Acid at 38° under 200 cc. of 0.025N Acid and 1.000 g. of Test Sample

left : sample A  
 solid line for sample A :  $X=1.709-1.139 \log(1-0.1295 \cdot t)$   
 right : sample B  
 solid line for sample B :  
 $X=1.710-1.062 \log(1-5.247 \times 10^{-2} \cdot t)$   
 solid symbols : values observed

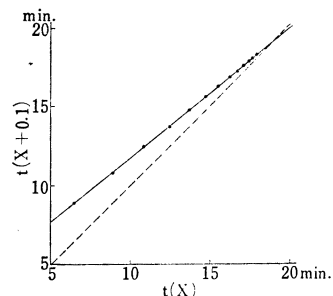


Fig. 6. Finite Differences Diagram of the Reaction between DAHG and Hydrochloric Acid at 38° under 200 cc. of 0.025N Acid and 1.000 g. of Sample B  
 solid line :  $t(X+0.1)=0.805 \cdot t(X)+3.70$   
 broken line :  $t(X+0.1)=t(X)$

linear relationship between  $t(X)$  and  $t(X+\xi)$ ; the slope from the plot is  $10^{-(1-n)\xi}$  and the intersection between the plot and the bisector  $t(X+\xi)=t(X)$  gives  $t_\infty$ , thus,  $n$  and  $t_\infty$  of each experiment were obtained. Using  $n$  and  $t_\infty$ , it was possible to fit equation (11) for the values observed at the main stage of the reaction. The goodness of fit is shown in Fig. 5, in which each point and the solid curve show the observed and the calculated values, respectively. Further investigations at both the initial and the final stages of the reaction, in which pH-time curve is not in accordance with equation (11), will be discussed later. Values of  $n$  obtained at 38° under  $H_0/W=5.00 \times 10^{-3} N. L./g.$  are listed in Table IV. These results show that  $n$  was influenced mostly by the kind of

TABLE IV. Apparent Order of Reaction,  $n$ , of the Reaction between DAHG and Acid, at 38° under 200 cc. of Acid and  $H_0/W=5.00 \times 10^{-3} N. L./g.$

$H_0(N)^{a)}$	Hydrochloric Acid		Nitric Acid		Sulfuric Acid	
	A <sup>b)</sup>	B <sup>b)</sup>	A <sup>b)</sup>	B <sup>b)</sup>	A <sup>b)</sup>	B <sup>b)</sup>
0.050	0.222	0.138	0.154	0.096	0.591	0.549
0.025	0.122	0.047	0.042	0.025	0.494	0.469
0.015	0.058	0.004	-0.013	-0.002	0.502	0.448
0.009	0.015	-0.024	0.004	-0.007	0.462	0.451
0.005	-0.018	-0.040	-0.002	-0.020	0.455	0.389
0.003	-0.046	-0.035	-0.024	-0.035	0.385	0.358

a)  $H_0$  : initial concentration of acid.  
 b) A : sample A; B : sample B.

acid used : in the case of hydrochloric acid and nitric acid  $n$  was nearly zero, but  $n$  is about 0.5 in the case of sulfuric acid. It was, therefore, understood that the kind of anion might be a factor which gave influence on the velocity of reaction between



DAHG and acid.  $n$  had a tendency to increase with the increase in the initial concentration of acid. The negative values of  $n$  seemed to depend on the difference between initial pH,  $X_0$ , and flexional pH,  $X_v$ , which differed with  $X_0$  as shown in Fig. 7;

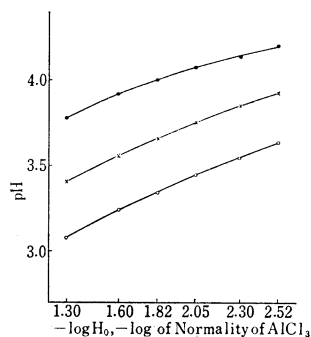


Fig. 7. pH of Bulk Liquid at 38°

—●— : final pH,  $X_e$ , of the reaction between DAHG and hydrochloric acid  
 —×— : pH of aluminum chloride solution  
 —○— : flexional pH,  $X_v$ , of the reaction between DAHG and hydrochloric acid

if the difference is smaller, the curve at the initial stage of reaction had more influence upon the value of  $n$  calculated from equation (12).

It is expected from equation (10) that  $t_\infty$  is related linearly with  $H_0/W$  within such a range that  $1/(1-n)KH_0^n$  is not much changed. Figs. 8 and 9 are examples showing

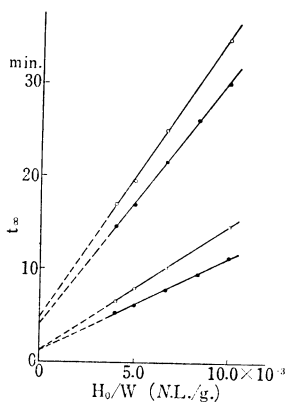


Fig. 8. Finished Time,  $t_\infty$ , of the Reaction between DAHG and Hydrochloric Acid at 38° under 200 cc. of Acid

upper two : sample B  
 lower two : sample A  
 - - - :  $H_0 = 0.015N$   
 - - - :  $H_0 = 0.003N$

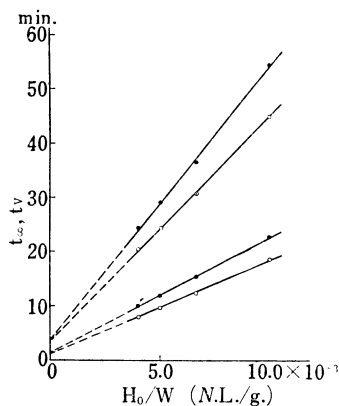


Fig. 9. Finished Time,  $t_\infty$ , and pH Flexional Time,  $t_v$ , of the Reaction between DAHG and Sulfuric Acid at 38° under 200 cc. of 0.015N Acid

upper : sample B  
 lower : sample A  
 - - - :  $t_\infty$   
 - - - :  $t_v$

the linear relationship between  $t_\infty$  and  $H_0/W$  under  $H_0 =$  identical within the appropriate range of  $H_0/W$  to keep  $1/(1-n)KH_0^n$  almost identical; Fig. 8 is the case of hydrochloric acid and Fig. 9 the case of sulfuric acid. Extrapolating such straight line to  $H_0/W=0$ , induction period,  $t_1$ , was estimated by equation (10); the slope,  $1/(1-n)KH_0^n$ , was considered to be inverse ratio to the velocity constant.  $(1-n)KH_0^n$  and  $t_1$  of the reaction between DAHG and hydrochloric acid are shown in Fig. 10, in which a minimum of the former and a maximum of the latter are found. When the measurement was carried out under such a condition that  $t_\infty$  was appropriately long, the difference of  $t_1$  with

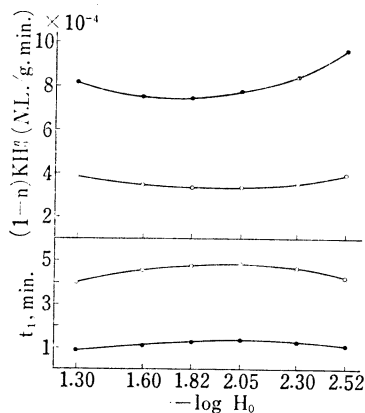


Fig. 10.  $(1-n)KH_0^2$  and  $t_1$  according to Equation (10) of the Reaction between DAHG and Hydrochloric Acid at  $38^\circ$

-•- : sample A  
-○- : sample B

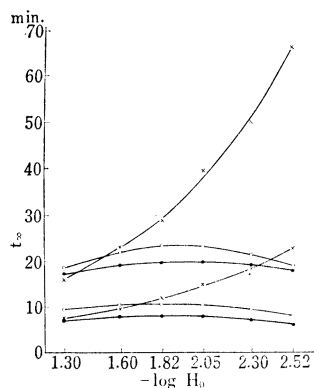


Fig. 11. Finished Time,  $t_\infty$ , of the Reaction between DAHG and Acid at  $38^\circ$  under 200 cc. of Acid and  $H_0/W=5.00 \times 10^{-3}$  N.L./g.

upper three : sample B  
lower three : sample A  
-•- : hydrochloric acid  
-○- : nitric acid  
-x- : sulfuric acid

respect to  $H_0$  was ignored and  $t_\infty$  was sufficient to discuss the velocity of reaction. Fig. 11 shows  $t_\infty$  in the cases of three acids at  $38^\circ$  under  $H_0/W=5.00 \times 10^{-3}$  N.L./g.  $t_\infty$  was not quite dependent upon  $-\log H_0$  in the case of hydrochloric acid and nitric acid, but it increased with  $-\log H_0$  in the case of sulfuric acid. This was expected from equation (10), because  $n$  was nearly zero in the former cases and about 0.5 in the latter one. A possible explanation for the existence of a maximum or minimum in Figs. 10 and 11 seemed to lie in the difference in the total amount of electrolyte and/or DAHG. This might be acceptable as one of the phenomena which were often observed with colloidal or colloid-like substances.  $t_\infty$  of sample A was about one half of that of sample B, though both the samples were in accordance with J.P. VII or U.S.P. XVI as shown in Table II. It was interesting to note that the specific surface area of sample A was about twice as much as that of sample B, but it was very difficult to state that the specific surface area was most directly related to the acid neutralizing reactivity of DAHG. Further investigations should be made in order to know why such reactivity differ with the kind of samples.

It appears well established that the difference of antacid reactivity of DAHG with regard to the products can be compared quantitatively by  $t_\infty$  measured under the same condition, e.g., 0.600 g. of test sample and 200 cc. of 0.015N hydrochloric acid at  $38^\circ$ , and in some cases the examination of DAHG by such measurement of  $t_\infty$  may be more sufficient and reasonable than that by the "acid-consuming capacity" in J.P. VII or U.S.P. XVI.

#### Correlation between Finished Time, $t_\infty$ , and pH Flexional Time, $t_v$ , of the Reaction between DAHG and Acid

The flexional pH,  $X_v$ , was related to the initial pH,  $X_0$ , as shown in Fig. 7; thus,  $(X_v - X_0)$  was identical when  $X_0$  was identical.  $n$  and  $t_1$  were respectively identical when the same sample and the same acid under  $H_0 =$  identical were used for the examination.  $t_\infty$  was, therefore, correlated to  $t_v$  according to equation (13). The correlation between  $t_\infty$  and  $t_v$  is shown in Table V, Figs. 9 and 12.  $t_v$  was coincident with the time when the rate of increase of pH was maximum; thus, it was obtained graphically from

TABLE V. Examples Showing the Correlation between  $t_\infty$  and  $t_v$  of the Reaction between DAHG and Acid, at  $38^\circ$  under 0.600 g. of Test Sample and 200 cc. of 0.015N Acid

Acid	Test sample of DAHG	$n$	$X_0$	$X_v$	$t_\infty$ (min.)	$t_v$ (min.)	$t_1$ (min.)	$\left(\frac{t_v-t_1}{t_\infty-t_1}\right)_c^a$	$\left(\frac{t_v-t_1}{t_\infty-t_1}\right)_o^b$
HCl	A	0.058	1.88	3.34	7.9	7.7	1.2	0.96	0.97
	B	0.004	1.88	3.34	19.4	19.0	4.7	0.96	0.97
H <sub>2</sub> SO <sub>4</sub>	A	0.502	1.97	3.32	11.9	9.6	1.1	0.79	0.79
	B	0.448	1.97	3.32	28.8	24.2	4.7	0.82	0.81

a)  $\left(\frac{t_v-t_1}{t_\infty-t_1}\right)_c$  : calculated according to equation (14)

b)  $\left(\frac{t_v-t_1}{t_\infty-t_1}\right)_o$  : observed

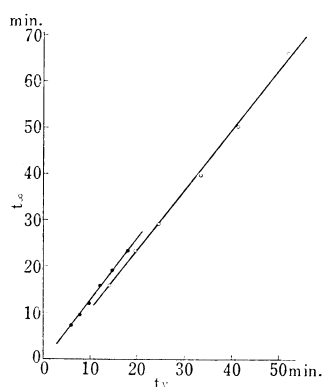


Fig. 12. Correlation between Finished Time,  $t_\infty$ , and pH Flexional Time,  $t_v$ , of the Reaction between DAHG and Sulfuric Acid at  $38^\circ$  under 200 cc. of Acid and  $H_0/W=5.00 \times 10^{-3}$  N. L./g.

-•- : sample A  
- - - : sample B

the pH-time curve or by a simple numerical calculation, and could be used conveniently instead of  $t_\infty$ . It seems that  $t_v$  measured under the same condition is another characteristic with which the antacid reactivity of DAHG can be compared quantitatively. This is useful in testing a number of samples in succession.

#### Activation Energy of Reaction between DAHG and Acid

It was mentioned before that  $1/(1-n)KH_0^n$  was considered to be inverse ratio to the velocity constant and was obtained by such a measurement as shown in Figs. 8 and 9. To obtain  $1/(1-n)KH_0^n$ , the experiments were carried out at  $28^\circ$ ,  $38^\circ$ , and  $48^\circ$  under  $H_0=0.015N$  and  $H_0/W=4.0 \times 10^{-3}N. L./g.$  to  $10.0 \times 10^{-3}N. L./g.$ , i. e., as shown in Fig. 9. The relationship between  $\log(1-n)KH_0^n$  and  $1/T$  is shown in Fig. 13, where  $T$  is the temperature in  $^\circ K$ . As listed in Table VI, the estimated activation energies were more or less different with regard to the kind of sample and acid used, but were in the

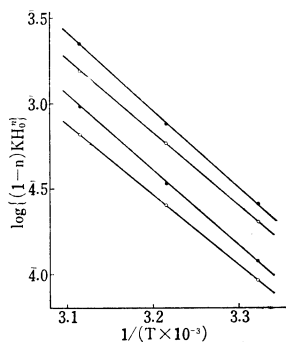


Fig. 13. Temperature Dependence of the Reaction between DAHG and Acid under 200 cc. of 0.015N Acid

upper two : sample A  
lower two : sample B  
-•- : hydrochloric acid  
-○- : sulfuric acid

TABLE VI. Activation Energy,  $E_A$ , of the Reaction between DAHG and Acid

Acid	Test sample of DAHG	$E_A$ (calories)
HCl	A	20,800
	B	20,200
H <sub>2</sub> SO <sub>4</sub>	A	19,700
	B	18,900
HNO <sub>3</sub>	A	21,200 <sup>a)</sup>

a) This value was calculated from the relationship between  $\log(t_0 - t_1)$  and  $1/T$  as described in the following paper [H. Nogami, T. Nagai : This Bulletin, 10,741 (1962)].

vicinity of 20,000 calories. It follows as a result that the reaction between DAHG and acid is considered different from such a reaction as governed by the diffusion.

The temperature dependence of  $t_1$  was also observed by the experiments just indicated; generally,  $t_1$  decreased with temperature, and the values estimated are listed in Table VII.

TABLE VII. Estimated Induction Period,  $t_1$ , according to Equation (10) of the Reaction between DAHG and Acid, under 200 cc. of 0.015N Acid and  $H_0/W = 4.0 \times 10^{-3} N. L./g.$  to  $10.0 \times 10^{-3} N. L./g.$ 

Acid	Temperature	$t_1$ (Sample A) (min.)	$t_1$ (Sample B) (min.)
HCl	28°	3.5	14.2
	38°	1.2	4.7
	48°	1.1	1.5
H <sub>2</sub> SO <sub>4</sub>	28°	3.2	15.0
	38°	1.1	4.2
	48°	1.0	1.0

### Initial Stage of the Reaction between DAHG and Acid

As shown in Fig. 5, the pH increased rapidly in a moment after the test sample was brought into contact with the acid, and then it hardly changed before the reaction was shifted to the main stage. Fig. 14 shows the decrease of hydrogen ion concentration and the increase of aluminum ion concentration in the reaction between DAHG and hydrochloric acid, observed by turns. The former was estimated from pH in reference to the activity coefficient of hydrochloric acid,<sup>35)</sup> and the latter was determined by the colorimetric method. It was observed that the dissolution of DAHG did not compare with the decrease of hydrogen ion at the initial stage of the reaction. When each sample was suspended in the distilled water, pH in the bulk liquid was 7~8, thus showing that the contamination of the test sample with alkaline substances was negli-

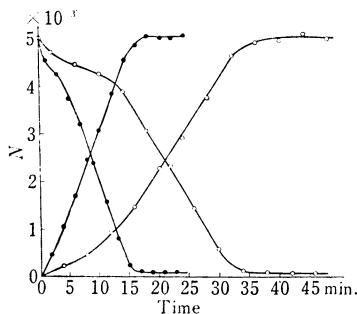


Fig. 14. Reaction between DAHG and Hydrochloric Acid at 38° under 200 cc. of 0.005N Acid and 0.100 g. of Test Sample  
down-curves : hydrogen ion concentration  
up-curves : aluminum ion concentration  
--·-- : sample A  
--○-- : sample B

35) H. S. Harnned, B. B. Owen : "The Physical Chemistry of Electrolytic Solution" 2nd ed., (1950), Reinhold Publishing Corp., New York.

gible. These results may indicate that the rapid increase of pH at the initial stage is due primarily to the absorption of acid by the test sample.

#### Final Stage of Reaction between DAHG and Acid

From Fig. 5, the pH-time curve was shown to be flexed discontinuously at the pH flexional time,  $t_v$ , and as the rate of pH increase became smaller, the reaction began to finish with the constant pH which will be called final pH represented by  $X_e$ . Such property, to which the availability of DAHG as antacid is well attributed, is considered to depend, upon the hydrolysis<sup>30-33)</sup> of aluminum ion produced. The final pH was maintained within a deviation of 0.1 by standing for 24 hours and any difference of the circumstances were not observed between samples A and B. It was expected from the theoretical viewpoint that  $X_e$  related to the final concentration of aluminum salt produced, which could be estimated from  $H_0$  (because  $W > hH_0$ ); pH of each solution of aluminum chloride, equivalent to  $H_0$  in normality unit, was measured and shown in Fig. 7. Such pH was lower than  $X_e$ , but became close to  $X_e$  when the test sample was suspended in solution. It seems possible that  $X_e$  is not only related to the final amount of aluminum salt produced in the reaction, but also influenced by the adsorption effect of the test sample.

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#### Summary

1. Two types of equations expressing the velocity of acid neutralizing reaction of antacids were discussed. One was the calcium carbonate type, for which the initial increase of pH,  $\left(\frac{dX}{dt}\right)_{t=0}$ , was convenient to compare the velocity of reaction. The other was DAHG type, for which the apparent order of reaction,  $n$ , the finished time,  $t_\infty$ , and the pH flexional time,  $t_v$ , were convenient to compare the antacid reactivity quantitatively.

2. The activation energy of reaction between powdered marble and hydrochloric acid was estimated to be about 6,400 calories.

3. The velocity of reaction between DAHG and acid depended upon the kind of samples or acids used.

4. The activation energy of reaction between DAHG and acid was estimated to be about 20,000 calories.

5. The rapid increase of pH at the initial stage of reaction between DAHG and acid was considered to be due primarily to the absorption of acid by the test sample.

6. The change of pH at the final stage of reaction between DAHG and acid was considered to be dependent upon the hydrolysis of aluminum ion produced and the adsorption effect of the test sample.

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