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119. **Hisashi Nogami and Tsuneji Nagai**: Studies on Powdered Preparations. VIII.[1] Reaction between Dried Aluminum Hydroxide Gel and Acid.[*2~4]

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

In the previous paper[1] the neutralizing reaction of antacids was discussed from the standpoint of reaction kinetics and the method was prepared to compare the antacid reactivity. A satisfactory reproducibility was obtained and the process was especially applicable to the evaluation of dried aluminum hydroxide gel (DAHG). In the previous work it was suggested that the velocity of reaction between DAHG and acid was varied with regard to the kind or test samples or acids used.

The clinical application of DAHG has been developed and it is well known that the antacid properties of DAHG are very variable with the manufacture or the lot because various factors in the manufacturing processes have an influence upon the physical and, to a certain extent, the chemical properties of DAHG. The difference in the velocity of reaction between DAHG and acid with regard to the acid used is considered to be related with the anion. Tartar, *et al.*,[2] observed that the presence of a certain anion, such as phosphate, sulfate, or arsenate, affected the velocity of the reaction between colloidal aluminum hydroxide and hydrochloric acid, and assumed that the arrangement and spacing of ions and the electrical potential difference at the interface between the phases might have a dominant influence on the velocity of reaction.

The present study was attempted to investigate the effect of mixed samples of different DAHG or mixed acids on the acid neutralizing velocity of DAHG. The additivity of velocity was observed with respect to the composition of mixed samples of DAHG. The effect of mixed acids on the velocity was remarkable when hydrochloric acid or nitric acid was mixed with sulfuric acid or snlfate ion.

Experimental

Apparatus and Procedure for the Measurement of pH Change——The procedure of the continuous pH measurement during the reaction between DAHG and acid was thoroughly described in the previous paper.[1] In addition, the measurements in almost all cases, except the special examinations, were carried out in the following condition such as 0.600 g. of the test sample, 200 cc. of $0.015N$ acid at 38°.

Test Samples——Samples A, B, C, and D were used. Samples A and B were the same as described in the previous paper.[1] Sample C was that which corresponded to J. P. Ⅶ or U. S. P. XVI. Although the details of the manufacturing methods of samples A, B, and C were not disclosed, it could be stated that each of them was prepared from the reaction between $NaAlO_2$ solution and CO_2. Sample D was prepared by the authors by adding aqueous NH_3 to the solution of $AlCl_3$, immediately centrifuged, being followed by washing the precipitate several times with H_2O, dialyzing, and finally drying it in a desiccator. The powder passing through a 200 mesh sieve was used as sample D, which was contaminated with a negligible amount of chloride, i. e., 1.06×10^{-4} gram-equivalent per gram.

[*1] Hongo, Tokyo (野上　寿，永井恒司).

[*2] Taken in part from the thesis of Tsuneji Nagai for the degree of Doctor of Pharmaceutical Sciences, University of Tokyo, 1961.

[*3] Presented at the Kanto Local Meeting of Pharmaceutical Society of Japan, Tokyo, January 1961.

[*4] Outlined in a preliminary communication: This Bulletin, **10**, 434 (1962).

1) Part Ⅶ: This Bulletin, **10**, 728 (1962).

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

Results and discussion

Effect of Mixed Test Samples of DAHG on the Velocity of Acid Neutralizing Reaction

Mixtures of Samples A and B were selected for this examination. Fig. 1 shows the finished time, t_∞, of reaction between such mixtures and hydrochloric acid with respect to the composition. In the previous paper,[1] finished time, t_∞, was given by

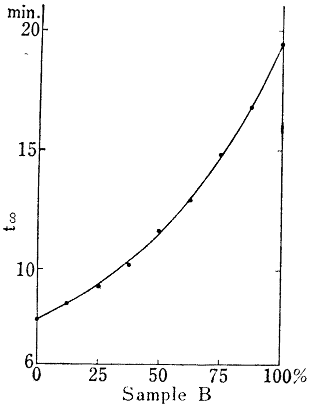

Fig. 1. Mixed Examination of Samples A and B on the Reaction between DAHG and Hydrochloric Acid at 38° under 200 cc. of 0.015N Acid and 0.600 g. of mixed Test Sample

solid symbols : values observed
solid curve : according to equation (2)

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

where H_0 is the initial hydrogen ion concentration*[5] of bulk liquid, W the quantity of test sample, n the apparent order of reaction, K the apparent velocity constant, and t_1 the induction period. Under such a condition as 0.600 g. of the test sample, 200 cc. of 0.015N hydrochloric acid at 38°, n was nearly zero and t_∞ of the mixed examination of samples A and B, is, therefore, expected from equation (1) as

$$t_\infty = \frac{K_a W_a t_{1a} + K_b W_b t_{1b} + H_0}{K_a W_a + K_b W_b} \qquad (2)$$

where suffixes, a and b are used for samples A and B, respectively. The solid curve in Fig. 1 was obtained from equation (2), in which $W_a + W_b = 3.000$ g./L., $H_0 = 0.015N$, $K_a = 7.51 \times 10^{-4}N$. L./g. min., $K_b = 3.34 \times 10^{-4}N$. L./g. min., $t_{1a} = 1.2$ min., $t_{1b} = 4.2$ min. were substituted. The values observed were almost in agreement with the calculated values, and the additivity of velocity, i. e., the linear function of the composition, was recognized. It was considered that the mechanism of reaction between DAHG and acid was almost the same, although the velocity was variable according to the kind of samples.

Effect of Mixed Acid on the Velocity of Acid Neutralizing Reaction of DAHG

Hydrochloric acid and nitric acid, both mixed with sulfuric acid, were used for this examination. The concentration of such mixed acids was identical in normality, e. g., $H_0 = 0.015N$, and the ratio of mixture between two original acids is represented as $R = \frac{[SO_4^{2-}]}{2[Cl^-]}$, $R = \frac{[SO_4^{2-}]}{2[NO_3^-]}$, or $R = \frac{[NO_3^-]}{[Cl^-]}$, where the brackets, [ ], denote the molar concentration. Fig. 2 shows the finished time, t_∞, and the pH flexional time, t_v, of reaction between DAHG and hydrochloric acid mixed with sulfuric acid. t_v was fully

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*[5] H_0 is used without discrimination from the initial concentration of acid.

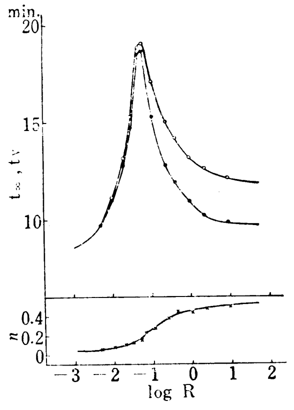

Fig. 2. Finished Time, t_∞, pH Flexional Time, t_v, and Apparent Order of Reaction, n, of the Reaction between DAHG and Hydrochloric Acid mixed with Sulfuric Acid at 38° under 200 cc. of 0.015N Acid and 0.600 g. of Sample A

-○- : t_∞
-●- : t_v

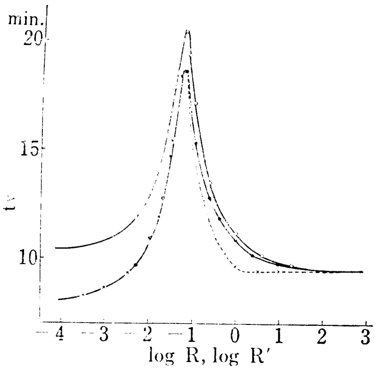

Fig. 3. pH Flexional Time, t_v, of the Reaction between DAHG and Hydrochloric Acid mixed with Sulfate Ion or Nitric Acid mixed with Sulfate Ion under 0.600 g. of Sample A

-●- : hydrochloric acid+sulfuric acid
-○- : nitric acid+sulfuric acid
-×- : hydrochloric acid+sodium sulfate

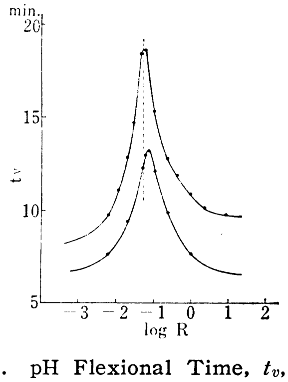

Fig. 4. pH Flexional Time, t_v, of the Reaction between DAHG and Hydrochloric Acid mixed with Sulfuric Acid at 38° under 200 cc. of 0.015N Acid and Two Different Quantities of Sample A

upper : 0.600 g.
lower : 0.800 g.
broken line : log R_m of the upper

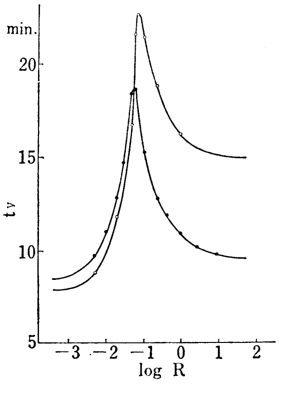

Fig. 5. pH Flexional Time, t_v, of the Reaction between DAHG and Hydrochloric Acid mixed with Sulfuric Acid at 38° under $H_0/W = 5.00 \times 10^{-3} N$. L./g.

-○- : 200 cc. of 0.005N acid and 0.200 g. of sample A
-●- : 200 cc. of 0.015N acid and 0.600 g. of sample A

described in the previous paper[1] and the relationship between t_∞ and t_v was given by

$$\log\left|\frac{t_\infty - t_v}{t_\infty - t_1}\right| = -(1-n)(X_v - X_0) \qquad (3)$$

where X_0 and X_v are the initial pH and the flexional pH, respectively. As shown in Fig. 2, t_∞ and t_v became maximum at a certain value R (generally represented by R_m), and n changed remarkably near R_m. The difference between t_∞ and t_v was considerably large in the range of $R>R_m$, though it was very small in the other range; this might be related to the remarkable change of n near R_m, expected from equation (3). The similar results were obtained in the mixture of nitric acid and sulfuric acid; in Fig. 3, only t_v is shown with respect to R. R_m in the mixture of nitric acid and sulfuric acid was the same as that in the mixture of hydrochloric acid and sulfuric acid. These results may suggest that the charge of the anion is playing an important role in the velocity of reaction. R_m changed according to H_0 and/or W as shown in Figs. 4 and 5. It seems possible that the total amount of electrolytes and/or DAHG may be an important factor to regulate the velocity of reaction. The difference in R_m was observed with each test sample as shown in Fig. 6; samples A, B, and C had similar values of R_m, but sample D had a fairly different value. The difference may be attributed to the manufacturing method. As shown in Fig. 7, R_m was not observed in the mixture of hydrochloric acid and nitric acid. It is possible that the reaction between DAHG and hydrochloric acid is not very different from the one between DAHG and nitric acid.

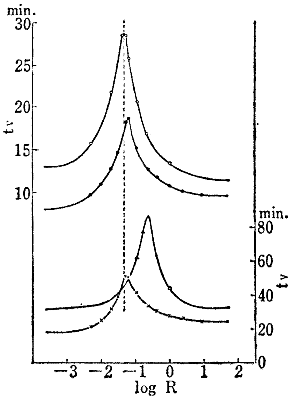

Fig. 6. pH Flexional Time, t_v, of the Reaction between DAHG and Hydrochloric Acid mixed with Sulfuric Acid at 38° under 200 cc. of 0.015*N* Acid and 0.600 g. of Test Sample

-•- : sample A
-×- : sample B
-○- : sample C
-△- : sample D
broken line : log R_m of sample C

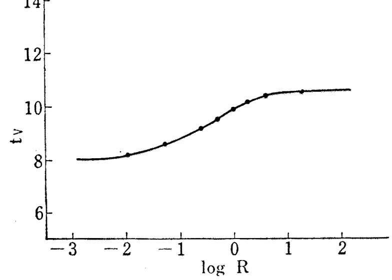

Fig. 7. pH Flexional Time, t_v, of the Reaction between DAHG and Hydrochloric Acid mixed with Nitric Acid at 38° under 200 cc. of 0.015*N* Acid and 0.600 g. of Sample A

The effect of acids by mixture on the velocity of reaction was examined at 28°, 38°, and 48° and the existence of R_m was observed at each temperature as shown in

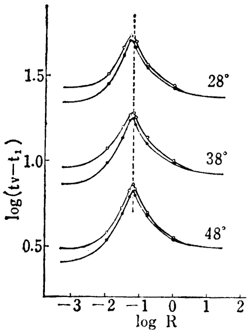

Fig. 8. Temperature Dependence of the Reaction between DAHG and Hydrochloric Acid mixed with Sulfuric Acid or Nitric Acid mixed with Sulfuric Acid under 200 cc. of 0.015*N* Acid and 0.600 g. of Sample A

-●- : hydrochloric acid+sulfuric acid
-○- : nitric acid+sulfuric acid
broken line : $\log R_m$ of the bottom (48°)

Fig. 8. Under $H_0/W=$ identical, (t_v-t_1) was considered to be inversely proportional to the velocity constant according to equations (1) and (3). At a given value, *R*, the linear relationship was observed between $\log(t_v-t_1)$ and 1/T, where T was the temperature in °K. As listed in Table I, the estimated activation energies were more or less different with respect to *R* or the percentage of sulfuric acid, but were in the vicinity of 20,000 calories in almost all cases of *R* and not remarkably changed near R_m. Such phenomena might be characteristic in the reaction between DAHG and acid.

Table I. Activation Energy, E_A, of the Reaction between DAHG and Hydrochloric Acid mixed with Sulfuric Acid or Nitric Acid mixed with Sulfuric Acid, at 38° under 0.600 g. of Sample A and 200 cc. of 0.015*N* Acid

0.015*N* H_2SO_4 (%)	$E_A(HCl+H_2SO_4)$ (calories)	$E_A(HNO_3+H_2SO_4)$ (calories)
100	19,700	19,700
50	19,800	19,900
15	18,900	19,400
7	19,000	19,100
6	19,400	19,200
5	20,300	20,100
3	20,400	21,000
1	20,600	21,700
0	20,400	21,200

Effect of Salt added to the Acid on the Velocity of Acid Neutralizing Reaction of DAHG

In the same category as described earlier, the ratio of mixture between acid and salt under $H_0=$ identical is represented by $R'=\frac{[SO_4^{2-}]}{2[Cl^-]}$, $R'=\frac{[SO_4^{2-}]}{2[NO_3^-]}$, $R'=\frac{[NO_3^-]}{[Cl^-]}$, or $R'=\frac{\text{salt in normality}}{\text{acid in normality}}$, where brackets, [ ], denote the molar concentration. The pH flexional time, t_v, of reaction between DAHG and hydrochloric acid mixed with sulfate or nitric acid mixed with sulfate became maximum at a certain value R' (generally represented by R'_m). For example, the result in the case of hydrochloric acid mixed with sodium sulfate is shown in Fig. 3. R'_m was all the same to R_m. In the range of $R'>R'_m$, the curve observed in the case of hydrochloric acid mixed with sodium sulfate was different from that of hydrochloric acid mixed with sulfuric acid. This may be attributed to the difference in the total amount of electrolytes. It must be considered that sulfate ion has a remarkable influence on the velocity of the reaction between DAHG and such mixed acids.

As shown in Fig. 9, R'_m was not observed when the salt of original acid was added; the velocity of reaction showed a little change owing to the amount of salt added, and

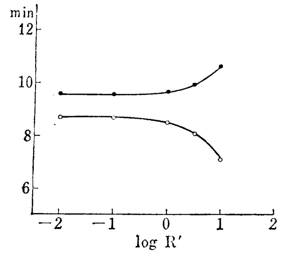

Fig. 9. pH Flexional Time, t_v, of the Reaction between DAHG and Acid mixed with Sodium Salt at 38° under 200 cc. of 0.015N Acid and 0.600 g. of Sample A

-○- : hydrochloric acid+sodium chloride
-●- : sulfuric acid+sodium sulfate

the circumstances varied according to the kind of anions. Distinct differences in velocities were not observed with regard to the kind of cations as shown in Table II, in which values of t_v at $R'=1$ are listed; t_v at $R'=1$ was similar to the case when the acid contained the same equivalent of sulfate ion.

Table II. pH Flexional Time, t_v, of the Reaction between DAHG and Acid mixed with Salt, at 38° under 0.600 g. of Test Sample and 200 cc. of 0.015N Acid containing the Salt in the Concentration of 0.015N, i. e., $R'=1$

Acid	Salt	Sample A (min.)	Sample B (min.)
HCl	nothing	7.9	19.2
	NaCl	8.1	18.9
	$MgCl_2$	7.9	18.9
	$AlCl_3$	7.8	18.7
	Na_2SO_4	9.7	24.6
	$MgSO_4$	9.7	24.2
	$CuSO_4$	9.6	24.8
	$KAl(SO_4)_2$	9.5	24.3
H_2SO_4	nothing	9.6	24.4
	NaCl	9.6	24.2
	$MgCl_2$	9.5	24.1
	$AlCl_3$	9.5	24.5
	Na_2SO_4	9.7	24.3
	$MgSO_4$	9.8	24.5
	$CuSO_4$	9.7	23.9
	$KAl(SO_4)_2$	9.5	24.5

Only such mixed acids can not show remarkable properties near R_m or R'_m. It is, therefore, considered that the interaction of electrolytes at the solid-liquid interface gives an influence on the velocity of the reaction between DAHG and acid.

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Summary

1. The velocity of reaction between DAHG and acid showed the additivity with respect to the composition of mixed test samples of DAHG, i.e., the linear function of the composition.

2. In the reaction between DAHG and hydrochloric acid mixed with sulfuric acid or nitric acid mixed with sulfuric acid, the finished time, t_∞, and the pH flexional time, t_v, became maximum at a certain mixing ratio, R_m, between the two original acids. R_m was different with regard to the kind of test samples and the total amount of electrolytes and/or DAHG. The estimated activation energies were not remarkably changed near R_m, i.e., 20,000 calories and almost the same as the values of different R.

3. The examinations of hydrochloric acid mixed with sulfates and of nitric acid mixed with sulfates gave about the same results as described above. The velocity of reaction between DAHG and acid mixed with salt was dependent upon the kind of anions, but fairly independent of the kind of cations.

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