

K_1 with increasing polarity of the lipid phase was not changed. However, the data demonstrate a relationship between the surface-to-volume ratio and K_1 . Thus, with one exception (Cell II, 10% isoamyl alcohol), the value of K_1 increased as did the surface-to-volume ratio for any one lipid phase employed. Under the same stirring conditions of the aqueous phases [namely, 300 r.p.m. with 2.54-cm. (1-in.) stirring bars] in any one cell, K_2 still showed increasing values with increasing lipid polarity. There was no rank order correlation between the value of K_2 for a particular lipid phase and the surface-to-volume ratio.

The effect of stirring conditions in the aqueous phases was then investigated. While keeping the surface-to-volume ratio constant at 0.148, the stirring conditions of the aqueous compartments were arbitrarily changed from 300 r.p.m. using 2.54-cm. (1-in.) oblong magnetic stirring bars to 400 r.p.m. using 1.27-cm. (0.5-in.) circular magnetic stirring bars. The lipid phase was stirred at the same rate of 60 r.p.m. The data, which were obtained using Cell II, are presented in Table II. It is readily apparent that the size and revolutions per minute of the stirrer did not change the order of the K_1 values, although the magnitude of this rate constant was affected. What is relevant is that, under the second set of stirring conditions, the order of K_2 now is reversed, with K_2 tending to decrease with increasing lipid polarity, as found by Khalil and Martin (1).

In light of these preliminary results, it would appear that the use of the Schulman model cell to correlate *in vitro* with *in vivo* absorption data could produce misleading results if factors such as the size and shape of the stirring bars and the rate of stirring in the various compartments are not closely monitored. The authors have also found further discrepancies between the Schulman cell and the inverted Y-tube apparatus. For example, benzene, when used as the

lipid phase by Khalil and Martin, appeared to be ideal, because there was negligible retention of salicylic acid in this phase over a 24-hr. period. However, when benzene was used as the lipid phase in Cell II, appreciable retention of salicylic acid by this phase was observed over the same time period.

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Effect of pH of Precipitation on Antacid Properties of Hydrous Aluminum Oxide

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Abstract □ The effect of the pH of precipitation on the physical and chemical properties of hydrous aluminum oxide prepared by the reaction of aluminum chloride and strong ammonia solution NF; aluminum sulfate USP, and strong ammonia solution NF; and aluminum chloride, sodium bicarbonate USP, and sodium carbonate USP, was studied. During aging, changes may occur in the hydrous aluminum oxide structure which result in a loss in acid reactivity. This loss followed apparent first-order kinetics. The rate of loss was directly dependent on the pH of precipitation and continued until a constant end-point was reached. The percentage of theoretical reactivity remaining at the end-point was inversely related to the pH of precipitation. X-ray diffraction showed no differences in form, either initially or during aging. Gel stability appears to depend on the presence of anions in the gel structure. The concentration of these anions is related to the pH of precipitation. Data are presented which demonstrate that a stable, completely acid-reactive gel would be obtained if 1 mole of a monovalent anion such as chloride or bicarbonate or 0.5 mole of a bivalent anion such as sulfate is incorporated in the gel structure per mole of aluminum.

Keyphrases □ Hydrous aluminum oxide—antacid properties, preparation □ pH precipitation effect—hydrous aluminum oxide, chemical and physical properties □ Gel stability—anion concentration data, acid reactivity kinetics □ X-ray diffraction—analysis

Alumina gel, which can be described chemically as hydrous aluminum oxide, is widely used in the management of peptic ulcer and gastric hyperacidity. Several

factors, such as the precipitation temperature (1, 2), the order of addition of the reactants (2), and the concentration of the reactants (2, 3), have been shown to affect the properties of the precipitated gel. Although previous authors (4–6) have suggested that the pH of precipitation influences the crystallinity of the precipitated gel, no workers have directly examined the effect of the pH of precipitation on the acid reactivity of the gel. Therefore, the purpose of the present study was to examine the effect of the pH of precipitation on the antacid properties of hydrous aluminum oxide prepared from several reactant systems.

EXPERIMENTAL

Materials—All chemicals used were either official or reagent grade.

Method of Preparation of Hydrous Aluminum Oxide—A series of hydrous aluminum oxides, to be referred to as chloride-containing gels, were prepared at 25° by the addition of a 13% solution of strong ammonia solution NF to an aqueous 8.5% aluminum chloride heptahydrate solution. The method of Papée *et al.* (4) and the conditions described by Lewis and Taylor (2) were followed to ensure reproducible precipitations. Sufficient ammonia solution was added to control the pH of precipitation. Alumina gels were precipitated at pH 4.8, 6.1, 7.7, and 9.2 and washed with deionized water until the concentration of the chloride ion in the filtrate, as determined by the Volhard method (7), was less than 0.1%. The

Table I—Reactants for Precipitation of Chloride-Containing Alumina Gels

pH of Precipitation	Reactants		
	Moles AlCl ₃ /l. Washed Gel	Moles NH ₄ OH/l. Washed Gel	Moles Al ₂ O ₃ /l. Washed Gel
4.8	0.294	0.80	0.144
6.1	0.294	0.84	0.158
7.7	0.294	0.88	0.129
9.2	0.294	1.68	0.129

Table II—Reactants for Precipitation of Sulfate-Containing Alumina Gels

pH of Precipitation	Reactants		
	Moles Al ₂ (SO ₄) ₃ /l. Washed Gel	Moles NH ₄ OH/l. Washed Gel	Moles Al ₂ O ₃ /l. Washed Gel
4.9	0.147	0.88	0.158
6.2	0.147	0.96	0.158
7.9	0.147	1.04	0.158
9.2	0.147	1.49	0.158

concentrations of the reactants required for 1 l. of washed gel and the resultant Al₂O₃ concentration for each alumina gel are listed in Table I.

A series of hydrous aluminum oxides, to be referred to as sulfate-containing gels, were prepared by the reaction of aluminum sulfate USP and strong ammonia solution NF. To ensure reproducible precipitations, the conditions described by Lewis and Taylor (2) were followed. Alumina gels were precipitated at 25° by the addition of a 13% solution of strong ammonia solution NF to an aqueous 12% aluminum sulfate USP solution. Sufficient ammonia solution was added to control the pH of precipitation. Alumina gels were precipitated at pH 4.9, 6.2, 7.9, and 9.2 and washed with deionized water until the concentration of sulfate ion in the filtrate, as determined by the USP gravimetric method (8), was less than 0.1%. The concentrations of reactants required for 1 l. of washed gel and the resultant Al₂O₃ concentration for each alumina gel are listed in Table II.

A series of hydrous aluminum oxides, to be referred to as bicarbonate-containing gels, were prepared by the reaction of aluminum chloride, sodium carbonate USP, and sodium bicarbonate USP. The alumina gels were precipitated at 25° following the conditions of Lewis and Taylor (2). An aqueous 11.4% solution of aluminum chloride heptahydrate was added to an aqueous solution containing 2.8% sodium carbonate USP and 4.5% sodium bicarbonate USP. Sufficient aluminum chloride solution or sodium carbonate USP, and sodium bicarbonate USP, solution was added to control the pH of precipitation. Alumina gels were precipitated at pH 4.8, 6.5, and 8.0 and washed with deionized water until the concentration of chloride ion in the filtrate, as determined by the Volhard method (7), was less than 0.1%. The concentrations of reactants required for 1 l. of washed gel and the resultant Al₂O₃ concentration for each alumina gel in this series are listed in Table III.

Methods of Studying Various Properties of Alumina Gels—The antacid property of each alumina gel was determined by its acid-consuming capacity. The precision of the USP acid-consuming

Table III—Reactants for Precipitation of Bicarbonate-Containing Alumina Gels

pH of Precipitation	Reactants			Moles Al ₂ O ₃ /l. Washed Gel
	Moles AlCl ₃ /l. Washed Gel	Moles Na ₂ CO ₃ /l. Washed Gel	Moles NaHCO ₃ /l. Washed Gel	
4.8	0.864	0.538	1.260	0.386
6.5	0.755	0.570	1.336	0.376
8.0	0.755	0.856	2.012	0.376

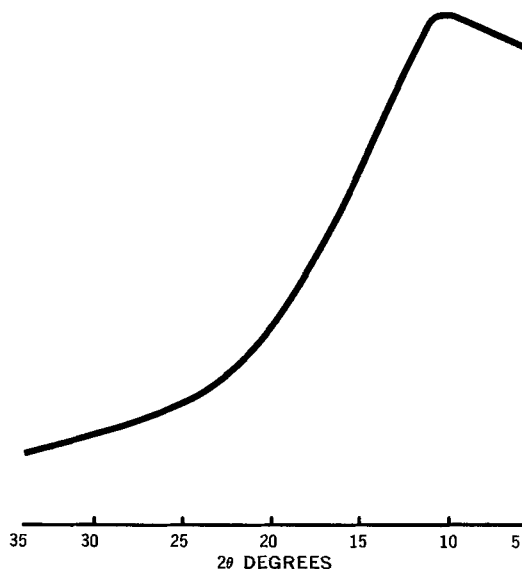


Figure 1—Initial X-ray diffraction pattern of the chloride-containing alumina gel precipitated at pH 7.7.

capacity test (9) was improved by titrating to pH 3.5 rather than using bromophenol blue T.S., as given in the USP.

The theoretical acid-consuming capacity of each alumina gel is based on the stoichiometric reaction of the aluminum oxide in the alumina gel and 0.1 N HCl. The antacid property of the aged alumina gel is given as a percentage of the theoretical acid-consuming capacity.

The X-ray diffraction pattern of each alumina gel was determined in the colloidal state by irradiating a sample in dialyzer tubing.

The Al₂O₃ content of each washed alumina gel was determined by the ethylenediaminetetraacetic acid titration (10).

The concentration of chloride ion was determined by the Volhard method (7). Total chloride was determined by dissolving the gel in nitric acid and assaying for the chloride ion as described. The amount found in the filtrate and the amount which could be eluted with deionized distilled water from an equal quantity of untreated gel were determined. The difference was regarded as representing the chloride content of the gel structure.

The concentration of sulfate ion in the gel structure was determined by the USP gravimetric method (8). The total sulfate in the alumina gel was determined by dissolving the alumina gel in nitric acid prior to sulfate assay. The amount found in the filtrate and the amount which could be eluted with deionized distilled water from an equal quantity of alumina gel was also determined. The

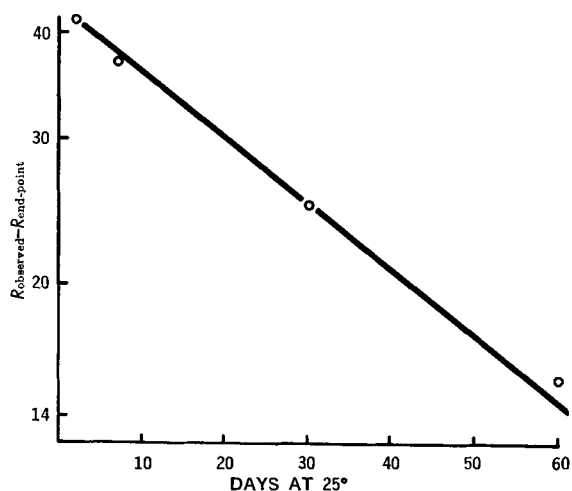


Figure 2—Change in acid reactivity during aging of the chloride-containing alumina gel precipitated at pH 6.1.

Table IV—Effect of Aging at 25° on the Acid Reactivity of Chloride-Containing Alumina Gels Precipitated at Various pH Conditions

pH of Precipitation	% of Theoretical Acid-Consuming Capacity after Storage at 25° for							
	1 Day	2 Days	7 Days	1 Month	2 Months	6 Months	1 Year	2 Years
4.8	85	—	—	82.5	—	75	70	70
6.1	—	91.5	87	75	66	50	50	50
7.7	59	—	—	37	27	25	25	25
9.2	27.5	24.3	20	10	—	10	9	10

difference was regarded as representing the sulfate content of the gel structure.

The amount of CO₂ which was evolved from the gel structure was determined by the gasometric determination of carbon dioxide (11). A volume of gel was filtered and washed with previously boiled deionized distilled water. The CO₂ which resulted from the addition of hydrochloric acid USP to the retained solids was taken as the CO₂ evolved from the gel structure.

RESULTS AND DISCUSSION

Chloride-Containing Alumina Gels—When initially precipitated, all the chloride-containing alumina gels were colloidal when examined by optical microscope and amorphous when examined by X-ray diffraction. Figure 1 shows a typical X-ray diffraction pattern. The broad, diffuse band is typical of scattering by amorphous material. The other gels in this series had similar diffraction patterns, indicating that form is independent of the pH of precipitation.

All the alumina gels studied showed a decrease in acid reactivity upon aging at 25° until they reached a constant end-point acid reactivity (Table IV). The data of Table IV were used to construct linear plots from which rate constants were calculated. Figure 2 shows the plot for the gel precipitated at pH 6.1. Each plotted point represents the logarithm of the difference between the reactivity observed at some point in aging (R_{observed}) and that observed at the end-point ($R_{\text{end-point}}$). The plots for all gels were linear, indicating that the loss of acid reactivity follows apparent first-order kinetics.

The rate of loss of acid reactivity is directly dependent upon the pH of precipitation (Fig. 3). Alumina gels which were precipitated at a relatively high pH showed high rates of loss of reactivity. For example, the alumina gel precipitated at pH 9.2 lost reactivity 20 times faster at 25° than the one precipitated at pH 4.8.

The end-point acid reactivity is inversely related to the pH of precipitation (Fig. 4). For example, the gel precipitated at pH 9.2 had an end-point reactivity of only 10% of theory, while the gel precipitated at pH 4.8 was 70% reactive at its end-point.

The end-point acid reactivity does not appear to be a function of the aging temperature, although the rate of loss of activity increases with increasing temperature. The alumina gel precipitated at pH 4.8 reached the same end-point reactivity of 70% of theory

whether aged at 25 or 35°, but it reached it sooner at 35° than at 25°.

The losses in acid reactivity observed in these studies appear irreversible. Samples of an alumina gel, which had been precipitated at pH 7.7 and had reached its end-point reactivity of 25% of theory, did not regain any reactivity when adjusted to pH 5.5 or 4.5 with 0.1 N HCl and aged for 1 month at 25°.

The changes in acid reactivity on aging do not appear to be due to crystallization, since all the end point alumina gels were found to be colloidal by optical microscopy and amorphous by X-ray diffraction.

A probable explanation for the effect of pH on the acid reactivity of these gels lies in the effect of chloride ion in stabilizing the gel

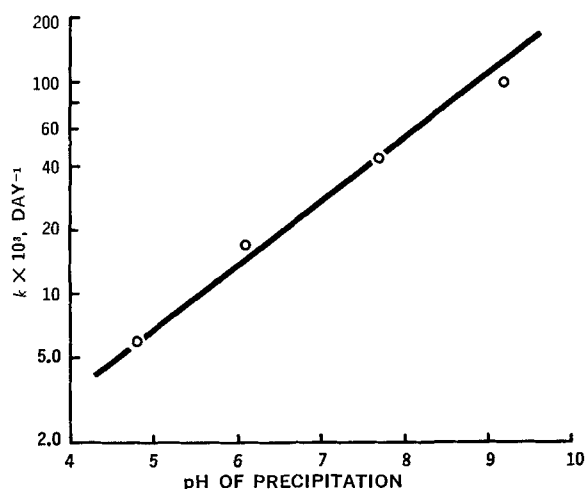


Figure 3—Effect of pH of precipitation of chloride-containing alumina gels on the rate of change of acid reactivity at 25°.

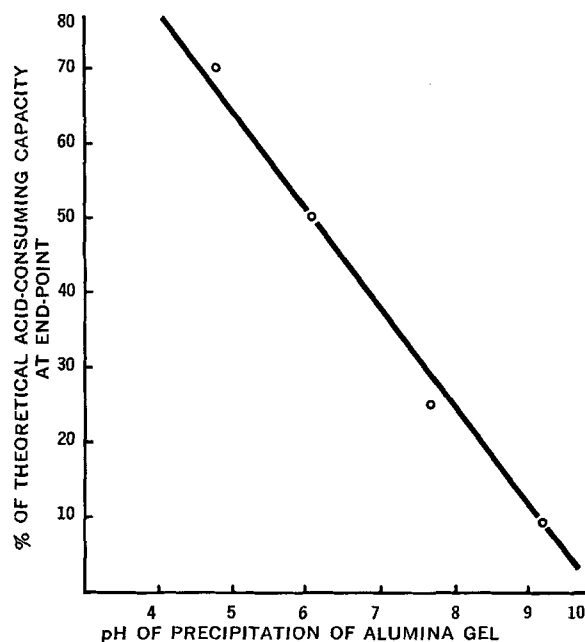


Figure 4—Effect of pH of precipitation of chloride-containing alumina gels on the end-point acid reactivity.

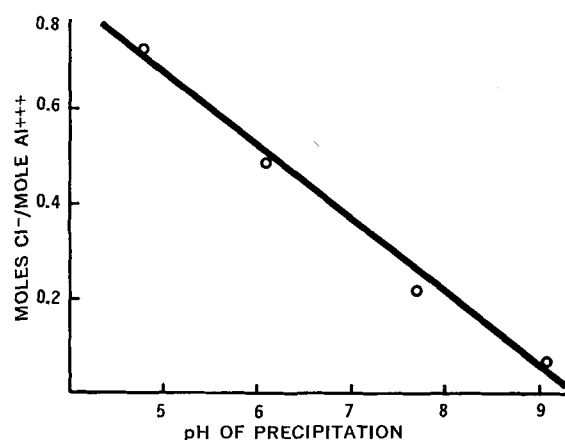


Figure 5—Effect of pH of precipitation on the concentration of chloride ions in the chloride-containing alumina gels.

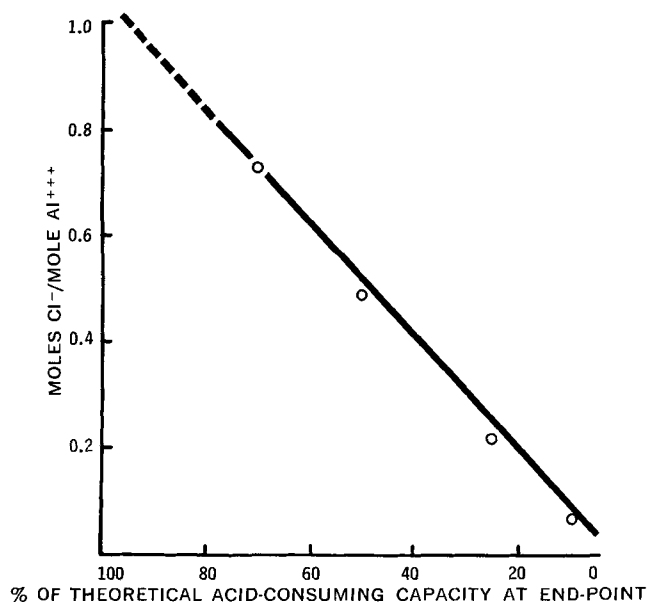


Figure 6—Effect of chloride ion concentration on the end-point acid reactivity.

structure. A varying concentration of chloride ion was found in the gel structure depending on the pH of precipitation (Fig. 5). The concentration did not change during the aging of these gels. A high chloride ion concentration appears to favor stability (Fig. 6). For example, the gel precipitated at pH 4.8, which retained 70% of its theoretical acid-consuming capacity at its end-point, had a high chloride ion concentration, while the alumina gel precipitated at pH 9.2, which lost virtually all its acid reactivity after 1 month at 25°, had little chloride ion in its gel structure. Figure 6 also indicates by extrapolation that a stable 100% acid-reactive gel would be obtained if 1 mole of chloride ion were present in the gel structure for every mole of aluminum. Unfortunately, this ideal gel cannot be produced from this system due to the solubility of the gel at a low pH.

Sulfate-Containing Alumina Gels—This series of alumina gels when initially precipitated were colloidal when examined by optical microscope and amorphous when examined by X-ray diffraction. The X-ray diffraction pattern was similar to that obtained for the chloride-containing gels (Fig. 1).

All the sulfate-containing gels studied showed a decrease in acid reactivity upon aging at 25° until a constant reactivity was reached. This behavior is similar to that observed for the series of chloride-containing gels. The rate of loss of acid reactivity is directly dependent on the pH of precipitation (Fig. 7).

The end-point reactivity is related to the pH of precipitation through an inverse linear relationship (Fig. 8). The changes in

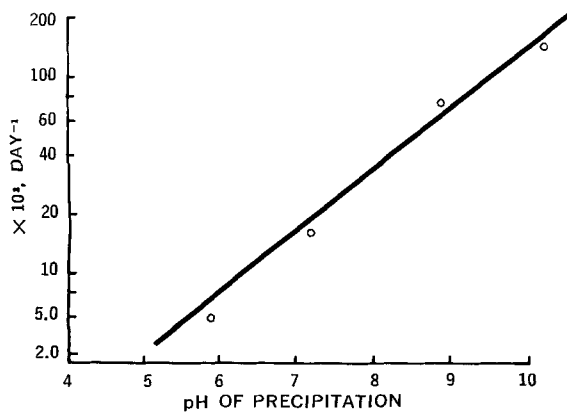


Figure 7—Effect of pH of precipitation of sulfate-containing alumina gels on the rate of change of acid reactivity at 25°.

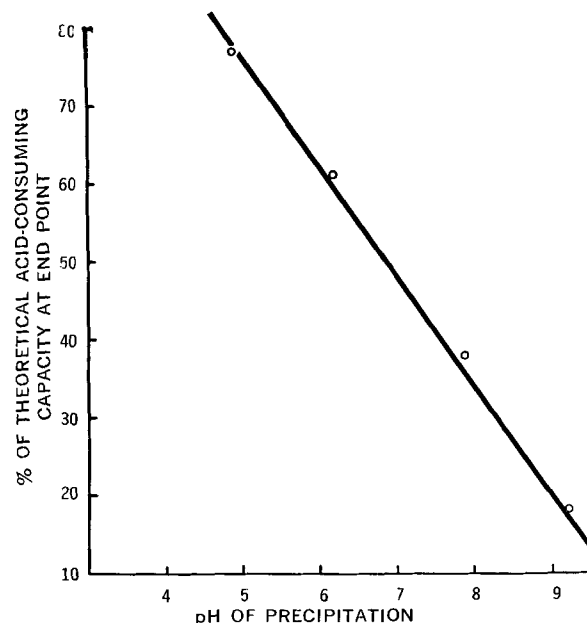


Figure 8—Effect of pH of precipitation of sulfate-containing alumina gels on the end-point acid reactivity.

acid reactivity on aging do not appear to be due to crystallization, since all the sulfate-containing gels at their end point were found to be colloidal when observed by optical microscope and amorphous by X-ray diffraction.

A varying concentration of sulfate ion was found in the gel structure, depending on the pH of precipitation (Fig. 9). As was noted for the chloride-containing gels, a high concentration of sulfate ion in the gel structure favors gel stability (Fig. 10). It is predicted from Fig. 10 that a stable, 100% acid-reactive gel would be obtained if 0.5 mole of sulfate ion was present per mole of aluminum.

Bicarbonate-Containing Alumina Gels—The alumina gels precipitated at pH 4.8, 6.5, and 8.0 by the reaction of aluminum chloride, sodium carbonate USP, and sodium bicarbonate USP, were colloidal and amorphous, similar to Fig. 1, when initially precipitated.

The bicarbonate-containing gels precipitated at pH 6.5 and 8.0 retained complete acid reactivity when stored for 2 years at 25° (Table V). The gel precipitated at pH 4.8 reached an end-point reactivity of 85% of theory. All the gels remained colloidal and amorphous during aging. Less than 0.03 mole of chloride ion per mole of aluminum was found in these gels. However, 1.01 and 1.07 moles of CO₂ per mole of aluminum were evolved when the gels precipitated at pH 8.0 and 6.5 were dissolved in hydrochloric acid USP. The gel precipitated at pH 4.8 evolved 0.72 mole of CO₂ per mole of aluminum. In the pH range of 4.8 to 8.0, bicarbonate ion would be the source of the evolved CO₂. Thus a stable, 100% acid-reactive gel was obtained when 1 mole of bicarbonate ion was present in the gel structure for every mole of aluminum. In this

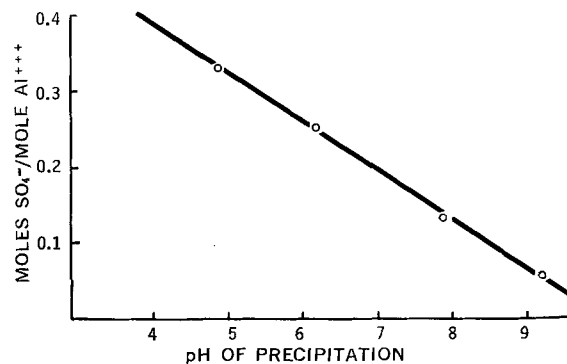


Figure 9—Effect of pH of precipitation on the concentration of sulfate ions in the sulfate-containing alumina gels.

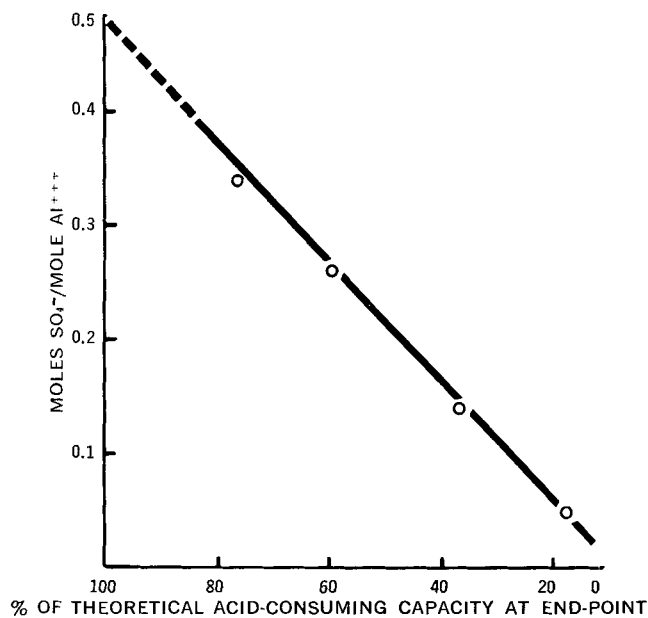


Figure 10—Effect of sulfate ion concentration on the end-point acid reactivity.

system the optimum concentration of bicarbonate ion was incorporated into the gel structure when the pH of the reaction mixture was 6.5 to 8.0. Effervescence occurred when the pH of the reaction mixture was below pH 5.5. Thus CO₂ was driven from the reaction mixture of the gel precipitated at pH 4.8, which resulted in a lower bicarbonate concentration in the gel structure.

It is concluded that the chloride-, sulfate-, and bicarbonate-containing gels studied may be in a highly unstable form when initially precipitated. The degree of instability is a function of the pH of precipitation. During aging, changes may occur in the gel structure which result in a loss in acid reactivity. Anions such as chloride, sulfate, and bicarbonate present in the reaction mixture are incorporated into the gel structure and act to stabilize the gel. A stable, completely reactive gel is expected if 1 mole of a monovalent anion such as chloride or bicarbonate or 0.5 mole of a bivalent anion such as sulfate is present in the gel structure per mole of aluminum.

SUMMARY

Hydrous aluminum oxide prepared by the reaction of aluminum chloride and strong ammonia solution NF; aluminum sulfate USP and strong ammonia solution NF; and aluminum chloride, sodium bicarbonate USP, and sodium carbonate USP, may exhibit an apparent first-order decrease in acid reactivity upon aging until a constant end-point is reached. The rate of loss of reactivity and the end-point reactivity are related to the pH of precipitation. The end-point reactivity is independent of storage temperature and was found to be irreversible. According to X-ray diffraction, these

Table V—Effect of Aging at 25° on the Acid Reactivity of Bicarbonate-Containing Alumina Gels Precipitated at Various pH Conditions

pH of Precipitation	Moles CO ₂ Evolved/ Mole Al ⁺⁺⁺	% of Theoretical Acid-Consuming Capacity after Storage at 25° for		
		Initial	30 Days	2 Years
4.8	0.72	100	85	85
6.5	1.07	100	100	100
8.0	1.01	100	100	100

changes are not related to changes in form. It is concluded that anions present in the reaction mixture are incorporated into the gel structure, depending on the pH of precipitation, and act to stabilize the gel. A stable, completely acid-reactive gel is obtained if 1 mole of a monovalent anion such as chloride or bicarbonate or 0.5 mole of a bivalent anion such as sulfate is incorporated in the gel structure per mole of aluminum.

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