droxyaluminum ions into stable six-membered rings or multiples thereof. According to Hsu and Bates (12), the inclusion of aluminum ions into rings is complete at a hydroxide to aluminum ratio of about 2. Additional base transforms these rings into larger units. Hsu (11) proposed that the difference between the initial precipitation process and the aging process is the source of hydroxide. Hydroxide added during precipitation is taken up rapidly, whereas the spontaneous hydrolysis is slow, especially in the presence of high salt concentrations (11). This secondary hydrolysis results in the formation of larger particles, which are more highly ordered and resistant to attack by acid, and leads ultimately to the formation of gibbsite (13, 14).

SUMMARY

The aging of aluminum hydroxide gels precipitated at pH 7.0 from aluminum chloride solution and strong ammonia solution was studied by determination of the hydroxide to aluminum ratio as a function of the age of the gel, measurement of gel pH and acid-consuming capacity, determination of the chloride activity of the gel, and X-ray line-broadening measurements. The results are consistent with a 'deprotonation–dehydration polymerization reaction in which positively charged hydroxyaluminum particles are joined at their edges by double hydroxide bridges. This process results in larger particles, which are more highly ordered and resistant to attack by acid. This reaction leads to the eventual formation of microcrystalline gibbsite.

Chloride was found to inhibit the loss of reactivity of aluminum hydroxide gel. The chloride activity increases as the gel ages until it reaches the activity of chloride in aqueous solution. It was concluded that chloride inhibits the loss of reactivity by binding at the positively charged edge of the hydroxyaluminum particles. This inhibits further polymerization of the particles.

A sulfate-containing gel precipitated at pH 7.0 was more stable than a chloride-containing gel precipitated at the same pH. This finding was attributed to stronger binding of the doubly charged sulfate ion by the polymers than the singly charged chloride ion.

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Structure of Aluminum Hydroxide Gel III: Mechanism of Stabilization by Sorbitol

STEVEN L. NAIL *, JOE L. WHITE ‡, and STANLEY L. HEM *ˣ

Abstract □ The effect of sorbitol on the aging of aluminum hydroxide gel, prepared by the reaction of aluminum chloride solution with strong ammonia solution to a final pH of 7.0, was studied by potentiometric titration, acid-consuming capacity, pH, hydroxide to aluminum ratio, chloride activity, X-ray diffraction, and IR spectroscopy. Gels containing sorbitol lost less than 10% of their acid-consuming capacity during a 6-month aging period compared with a loss of more than 60% for an identical gel without sorbitol. The mechanism by which sorbitol stabilizes the gel appears to be inhibition of the secondary polymerization reaction which takes place upon aging. Another polyhydroxy compound, quercetin, also stabilizes aluminum hydroxide gel.

Keyphrases □ Aluminum hydroxide gel—aging mechanism studied, effect of sorbitol □ Gels—aluminum hydroxide, aging mechanism studied, effect of sorbitol □ Aging mechanism—aluminum hydroxide gel, effect of sorbitol □ Antacids—aluminum hydroxide gel, aging mechanism studied, effect of sorbitol □ Sorbitol—effect on aging mechanism of aluminum hydroxide gel

Previous investigations (1, 2) demonstrated that a polymer model can be used to describe the structure and aging characteristics of aluminum hydroxide gel precipitated by the reaction of aluminum chloride or aluminum sulfate solution with sodium hydroxide or strong ammonia solution to a final pH of 7.0. The purpose of this investigation was to study the effect of sorbitol on the initial precipitate and on the aging characteristics of a gel prepared from aluminum chloride solution and strong ammonia solution at pH 7.0.
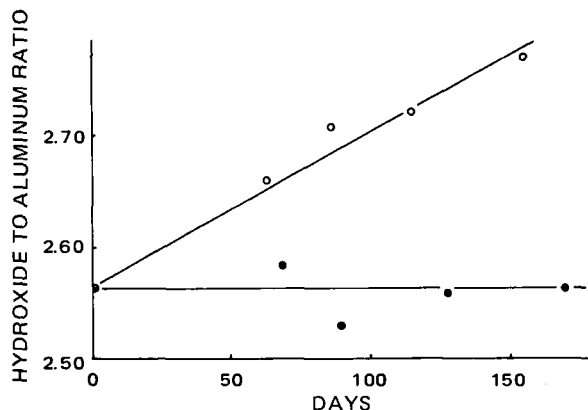
Figure 1—*Change in hydroxide to aluminum ratio during aging at 25°. Key:* O, *Gel I; and* ●, *Gel II.*

EXPERIMENTAL

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

Potentiometric Titrations—One hundred milliliters of a solution of 0.29 M $AlCl_3 \cdot 6H_2O$ and an identical solution containing 1 g of sorbitol were titrated potentiometrically with standard 1.0 N NaOH. The system was allowed to equilibrate after the addition of each aliquot of base until the pH[1] was stable for 30 sec.

Aluminum Hydroxide Gel Preparation—Two liters of gel was prepared by the addition of 13% (v/v) strong ammonia solution to a solution of 143.6 g of aluminum chloride hexahydrate in 1670 ml of distilled water at a rate of 120 ml/min. The gel system was stirred throughout the precipitation, and a combination electrode[2] was placed in the system for continuous monitoring of pH. Strong ammonia solution was added until pH 7.0 was reached, and the system was maintained at this pH for 30 min. The gel was then washed with 10 liters of distilled water by draining through a canvas bag. The gel was stirred throughout the washing operation.

After washing, the gel was divided into equal portions, and the volume of each portion was adjusted to 1 liter. For the first portion (I), the final volume adjustment was made with distilled water. For the second portion (II), 10 g of sorbitol was dissolved in distilled water and added to the gel with stirring, and the gel was diluted to 1 liter with distilled water. The gels were prepared in this manner to eliminate any effects of batch-to-batch variation.

Analytical Procedures—The equivalent aluminum oxide content, total chloride content, molar ratio of bound hydroxide to aluminum, pH, acid-consuming capacity, chloride activity, and X-ray diffraction pattern of the gels were determined as previously described (2). The hydroxyl-stretching region of the IR spectrum was recorded using a
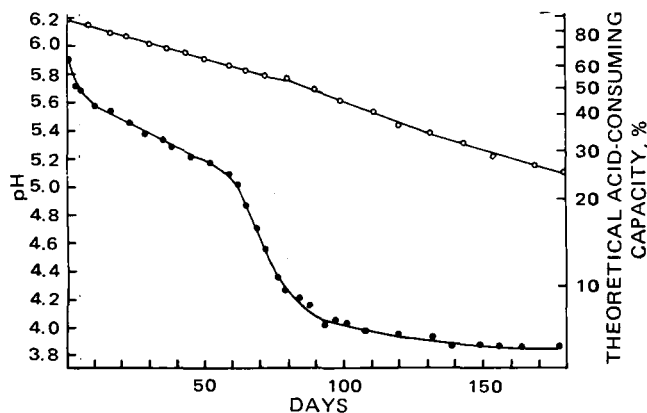

Figure 2—*Change in pH and acid-consuming capacity of Gel I during aging at 25°. Key:* O, *acid-consuming capacity; and* ●, *pH.*
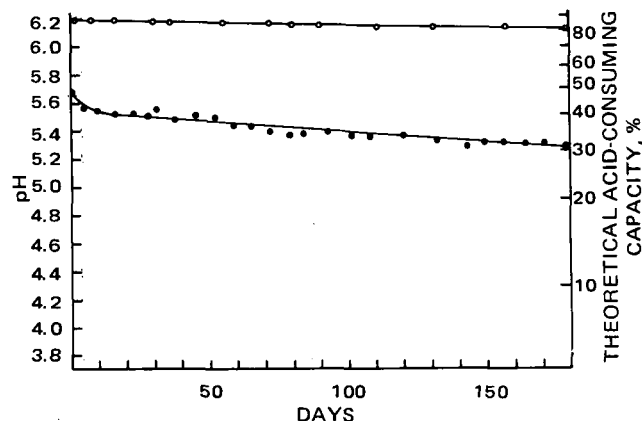
commercial IR spectrophotometer[3]. Samples were prepared by air drying a 0.10-ml sample on a silver chloride window[4]. The concentration on the window was 0.3 mg of aluminum oxide/cm^{2}.

RESULTS AND DISCUSSION

Potentiometric Titrations—Potentiometric titrations of 0.29 M $AlCl_3 \cdot 6H_2O$ and a similar solution containing 1% (w/v) sorbitol with 1.0 N NaOH were performed. The purpose of these titrations was to determine whether any interaction takes place between sorbitol and the hydroxyaluminum complex during gel formation. The two curves were nearly parallel, with the inflection point occurring at a hydroxide to aluminum ratio of 2.51 for both titrations. This result indicates that the primary polymerization reaction is not affected by the presence of sorbitol.

Hydroxide to Aluminum Ratio—The change in the molar ratio of bound hydroxide to aluminum with time is shown in Fig. 1 for Gels I and II. For Gel I, the ratio increased from 2.57 to 2.75 after 150 days. After the same aging time, the ratio for Gel II was between 2.55 and 2.60.

The increase in the hydroxide to aluminum ratio of Gel I indicates that further polymerization occurred during aging (2). The fact that the ratio for Gel II remained relatively constant indicates that secondary polymerization did not take place. Since the gels were precipitated and washed as one batch, the observed difference must be attributed to the presence of sorbitol in Gel II. Sorbitol apparently inhibits the secondary polymerization reaction.

pH and Acid-Consuming Capacity—Plots of the change in pH and acid-consuming capacity with time are shown in Figs. 2 and 3 for Gels I and II, respectively. During 180 days of aging, the pH of Gel I decreased from 5.70 to 3.85 while the acid-consuming capacity decreased from 88 to 25% of the theoretical capacity (Fig. 2). During the
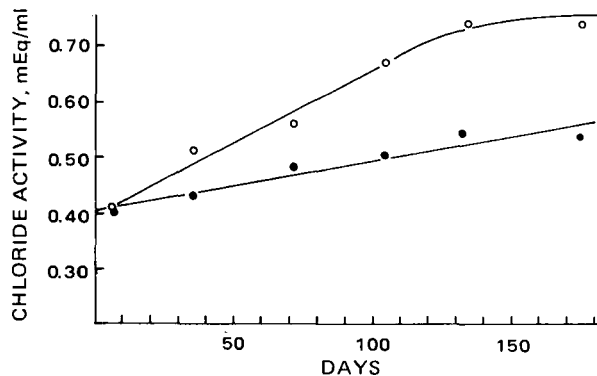

Figure 3—*Change in pH and acid-consuming capacity of Gel II during aging at 25°. Key:* O, *acid-consuming capacity; and* ●, *pH.*

Figure 4—*Change in chloride activity during aging at 25°. Key:* O, *Gel I; and* ●, *Gel II.*

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[1] Model NX, Sargent-Welch Scientific Co., Skokie, Ill.
[2] Sargent-Welch Scientific Co., Skokie, Ill.
[3] Model 421, Perkin-Elmer Corp., Norwalk, Conn.
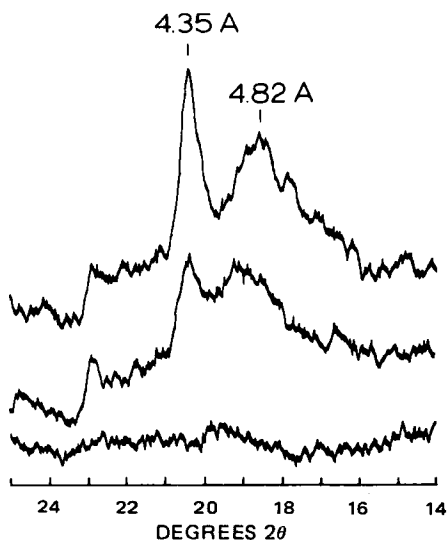[4] Harshaw Chemical Co., Cleveland, Ohio.

Figure 5—*Change in X-ray diffraction pattern of Gel I during aging at 25°. Key: bottom, 38 days; middle, 94 days; and top, 143 days.*

Figure 7—*Change in acid-consuming capacity during aging at 25°. Key: □, gel containing quercetin; and △, gel without quercetin.*

same period, the pH of Gel II decreased from 5.67 to 5.38 and the acid-consuming capacity decreased from 87 to 81% of the theoretical capacity.

The pH decrease with age is predicted by the deprotonation–dehydration reaction (2) leading to larger, more ordered particles. Increased order with age is consistent with lower acid reactivity. The stability of the pH of Gel II relative to that of Gel I is strong evidence for inhibition of the deprotonation–dehydration reaction by sorbitol.

Chloride Activity—Changes in chloride activity for the two gels (Fig. 4) are also consistent with inhibition of the secondary polymerization reaction by sorbitol. Increased activity of chloride with age indicates that the anion is initially bound by the gel (2) and re-
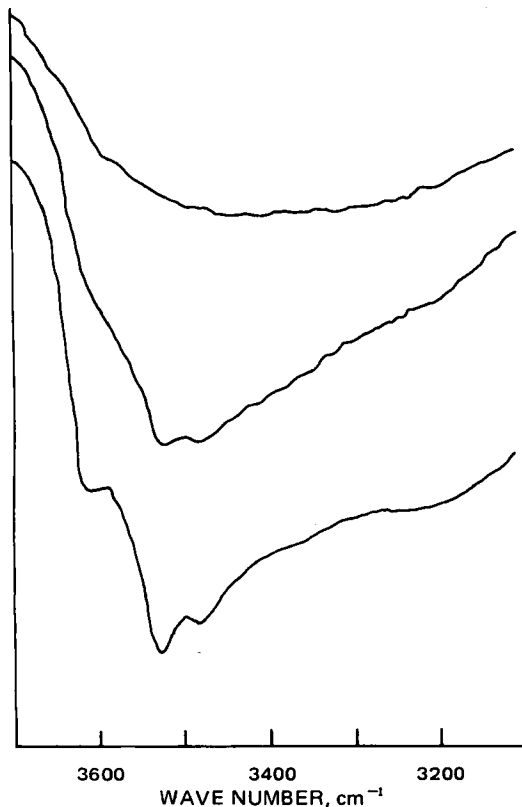
leased during aging. Therefore, the rate of increase in the activity should correspond with the rate of change in the other indicators of secondary polymerization, i.e., pH, acid-consuming capacity, and hydroxide to aluminum ratio. The rate of chloride activity increase in the sorbitol-containing gel was significantly less than for the control gel, which had released virtually all bound chloride after 150 days.

X-Ray Diffraction and IR Spectroscopy—In previous studies (3, 4), X-ray diffraction and IR spectroscopy were employed to detect the formation of microcrystalline gibbsite in aluminum hydroxide gel. Figures 5 and 6 show the change in the X-ray diffractogram and IR spectrum with age for Gel I. Crystalline material is readily detected by both techniques after about 100 days. No significant changes occurred in either the X-ray diffractogram or the IR spectrum of Gel II, which contained sorbitol. This retention of its original amorphous nature is in sharp contrast to the behavior of Gel I.

Other Polyhydroxy Compounds—Various other polyhydroxy compounds such as glycine (5), sucrose (6), disaccharides (7), hydroxypropylcellulose (8), and polyethylene glycol (9) have been reported to stabilize the reactivity of aluminum hydroxide gel.

Another study was carried out under the same conditions of gel preparation with quercetin (3,3′,4′,5,7-pentahydroxyflavone) in solution during precipitation. Since quercetin is only slightly soluble (0.5 g/liter), the aluminum chloride was dissolved in a saturated solution of quercetin. The change in acid-consuming capacity with age was then compared with that of a control gel prepared under the same conditions without quercetin (Fig. 7). The quercetin-containing gel was more stable than the control gel. Some quercetin probably was removed from the gel during washing. A more significant stabilizing effect would probably occur if quercetin was added after the gel was prepared, as is the usual practice with sorbitol.

Figure 6—*Change in hydroxyl-stretching region of Gel I during aging at 25°. Key: top, fresh precipitate; middle, 89 days; and bottom, 147 days.*
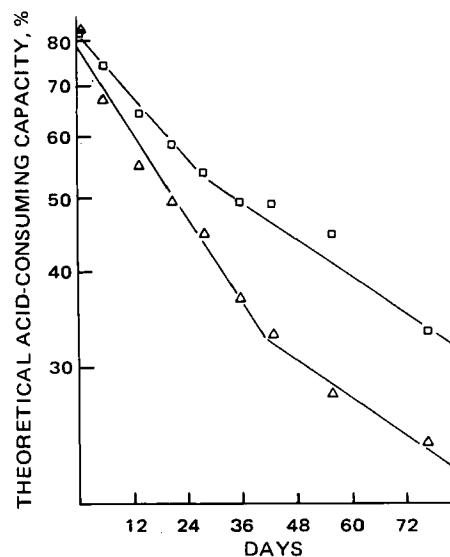
SUMMARY

Comparison of changes in the hydroxide to aluminum ratio, chloride activity, pH, acid-consuming capacity, X-ray diffractogram, and IR spectrum of an aluminum hydroxide gel with an identical gel containing 1% (w/v) sorbitol showed that the mechanism responsible for aging is strongly inhibited by sorbitol. Potentiometric titration curves indicate that sorbitol is not incorporated into the hydroxy-aluminum structure during gel precipitation.

The observed behavior can be explained by hydrogen bonding between the hydroxyl groups of sorbitol and the edge of the hydroxy-aluminum particles, thus inhibiting further polymerization with age. It is believed that the stabilizing effect of other polyhydroxy compounds involves a similar mechanism.

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Kinetics and Mechanisms of Hydrolysis of 1,4-Benzodiazepines I: Chlordiazepoxide and Demoxepam

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Abstract □ Differential absorbance spectroscopy was successfully used to follow the hydrolysis kinetics of chlordiazepoxide and demoxepam from pH 1 to 11. Loss of the methylamino group from chlordiazepoxide produced demoxepam. Demoxepam degraded by a parallel consecutive reaction to 2-amino-5-chlorobenzophenone and a glycine derivative. Two intermediates were observed by TLC for demoxepam hydrolysis. One was assigned the open-ring structure, resulting from amide hydrolysis, which kinetically appears to be the major mechanistic route leading to the benzophenone product. The other intermediate, representing an alternative but minor pathway, presumably results from initial scission of the azomethine linkage. Protonation of the *N*-oxide slightly alters the importance of these two pathways. Recyclization of the carboxylic acid intermediate was facile at pH values below the pKa of this intermediate. The stability parameters involving buffer catalysis, ionic strength effects, and temperature dependence of rate constants are reported.

Keyphrases □ 1,4-Benzodiazepines—kinetics and mechanisms of hydrolysis evaluated by differential absorbance spectroscopy □ Chlordiazepoxide—kinetics and mechanisms of hydrolysis evaluated by differential absorbance spectroscopy □ Demoxepam—kinetics and mechanisms of hydrolysis evaluated by differential absorbance spectroscopy □ Hydrolysis—chlordiazepoxide and demoxepam, kinetics and mechanisms, evaluated by differential absorbance spectroscopy □ Differential absorbance spectroscopy—evaluation of kinetics and mechanisms of hydrolysis of chlordiazepoxide and demoxepam

Little kinetic information is available on the solution stability and mechanisms of hydrolytic reactions of the 1,4-benzodiazepines. This class of nitrogen heterocycles is susceptible to acid–base-catalyzed hydrolysis at two potential sites of scission: the 1,2-amide linkage and the 4,5-azomethine bond. Both bonds undergo heterolysis under appropriate solvolytic conditions, forming a substituted benzophenone product and a glycine derivative (1–3).

Chlordiazepoxide (I) was reported (4) to degrade sequentially in aqueous solution, yielding 2-amino-5-chlorobenzophenone as the final product. An isolated intermediate in the reaction is the corresponding lactam, demoxepam (II); II is formed by hydrolytic

cleavage of the methylamino substituent at the 2-position of chlordiazepoxide. That study (4) described kinetically the hydrolysis of chlordiazepoxide to the intermediate lactam. The purpose of the present study is to describe completely the kinetics and mechanism of hydrolysis from the parent molecule to the product benzophenone. This paper is the first of a series that will describe quantitatively the kinetics and mechanisms of hydrolysis of 1,4-benzodiazepines.

EXPERIMENTAL

Materials—The purity of the compounds was verified by TLC. Chlordiazepoxide[1], demoxepam[1], and 2-amino-5-chlorobenzophenone[1] were used without further purification. All other chemicals were of reagent grade quality. Distilled, deionized water was used for preparing aqueous solutions.

The buffer systems used were: pH 1.0–3.0, hydrochloric acid; pH 3.2–5.6, acetate; pH 4.7–7.4, phosphate; pH 6.9–9.5, borate; and pH 10.1–11, sodium hydroxide. The ionic strength was adjusted to 1.0 with sodium chloride, except for the ionic strength effect studies. The pH values were determined with a digital pH meter[2] at the temperature of the kinetic run.

Kinetic Measurements—The compound to be studied was dissolved in ethanol to make a 10^{-3} M stock solution. It was stored in the refrigerator in a light-protected flask to eliminate reported photolytic reactions (5). A light-protected reaction flask containing appropriate buffer solution was equilibrated at reaction temperature in a constant-temperature oil bath[3]. Less than ±0.05° variation was measured with an iron–constantan thermocouple.

An appropriate amount of stock solution was pipetted into the reaction flask so that the final concentration was about 10^{-5} M. An aliquot was withdrawn and quenched immediately in a light-protected ice water bath. The UV spectrum of the aliquot was measured as the zero-time sample on a recording spectrophotometer[4]. Subsequent aliquots were analyzed similarly at suitable time intervals for at least three half-lives of the slowest reaction. The final measurement, ab-