

present in human urine. Further evidence was not obtained for the presence of this conjugate in human urine. However, Wienert and Gahlen (3) reported the presence of only one drug-related spot on the thin-layer chromatogram when they analyzed human urine following an intravenous administration of I.

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Nature of Amorphous Aluminum Hydroxycarbonate

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Abstract □ The titration of sodium carbonate with aluminum nitrate is shown to produce amorphous aluminum hydroxycarbonate. This compound is not stoichiometric, although the maximum carbonate to aluminum ratio appears to be 0.5. The pH conditions for achieving the maximum carbonate content are concentration dependent. A model for the particle surface at the solution interface is proposed. This model accounts for the presence of carbonate directly coordinated to the aluminum and carbonate adsorbed by electrostatic forces. Sodium is present in the diffuse layer and is, therefore, not an integral part of the structure.

Keyphrases □ Aluminum hydroxycarbonate, amorphous—prepared by titration of sodium carbonate with aluminum nitrate, physicochemical nature studied, model for particle surface at solution interface proposed □ Antacids—amorphous aluminum hydroxycarbonate, prepared by titration of sodium carbonate with aluminum nitrate, physicochemical nature studied, model for particle surface at solution interface proposed

Aluminum hydroxide gel used as an antacid usually contains carbonate. Carbonate is part of the structure of aluminum hydroxide gel (1) and contributes significantly to the high rate of acid neutralization (2) as well as gel stability (3). Previously, the term carbonate-containing aluminum hydroxide gel was used to describe the highly reactive gels used as antacids (2, 4, 5). However, this gel is now well enough understood to justify its description as amorphous aluminum hydroxycarbonate.

The production of amorphous aluminum hydroxycarbonate is usually performed in basic media to achieve a high concentration of carbonate in the system during precipitation. However, most studies of the hydrolytic precipitation of aluminum hydroxide are performed in acidic media (6, 7). Therefore, a study of the precipitate produced by titrating sodium carbonate with aluminum nitrate was undertaken. Special emphasis was placed on the precipitation conditions favoring the incorporation of carbonate. Further points of interest were the adsorption of sodium cation by the amorphous aluminum hydroxy-

carbonate and the elution of anions and cations during washing.

Aluminum nitrate was selected as the aluminum salt for precipitation because nitrate does not coordinate with aluminum as does carbonate (5) and, therefore, does not compete with carbonate for adsorption by the gel.

EXPERIMENTAL

Potentiometric titrations were performed by placing 100 ml of either a sodium carbonate or a sodium hydroxide solution in a 400-ml jacketed beaker. The temperature was controlled to $\pm 0.1^\circ$, and the solution was stirred² at 2000 rpm. Aluminum nitrate solution was added at a controlled rate³, 2 ml/min. The solution pH was monitored and recorded continuously.

Preliminary experiments were performed to observe the effect of temperature, addition rate, and reactant concentration. Variation of these precipitation factors did not affect the general shape of the titration curves. However, the position of the inflection points was concentration dependent. Excellent reproducibility of titration curves was obtained.

The equivalent aluminum oxide content was determined by chelometric titration (8). The carbonate content, determined by gasometric displacement using the Chittick apparatus⁴ (9), was expressed as the molar ratio of carbonate to aluminum.

IR analysis⁵ (10) was performed using potassium bromide pellets after the gel was dried under vacuum at room temperature. All samples were amorphous by X-ray diffraction.

Gels were washed with equal volumes of 0.1 M sodium sulfate to determine if the anions in the gel were exchangeable.

The rate of acid reactivity was determined by pH-stat titration at pH 3.0 (11).

The sodium content was determined by atomic absorption spectroscopy⁶.

The effect of washing was determined by adding a volume of deionized water equal to the volume of the gel, mixing, and centrifuging. Successive washes were performed by reconstituting the cake with a volume of water equal to the original volume of the gel and repeating the process.

The charge on the gel particles was determined by observing the direction of motion of the particles during electrophoresis⁷.

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² Stedi-Speed stirrer, Fisher Scientific, Pittsburgh, Pa.

³ Solution metering pump, model 746, Beckman Instruments, Fullerton, Calif.

⁴ Sargent-Welch Scientific Co., Skokie, Ill.

⁵ Model 180, Perkin-Elmer Corp., Norwalk, Conn.

⁶ Model 290B, Perkin-Elmer Corp., Norwalk, Conn.

⁷ Zeta meter, Zeta Meter, Inc., New York, N. Y.

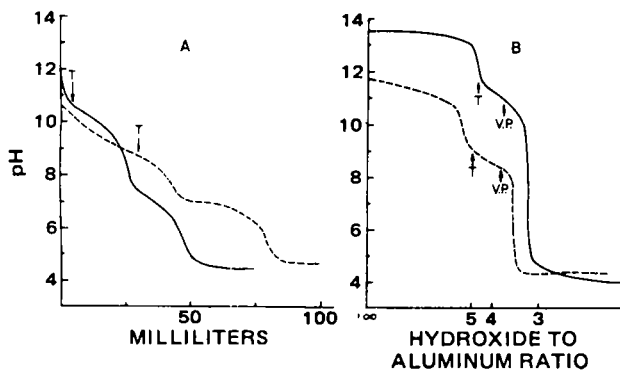


Figure 1—Effect of concentration on the titration of sodium carbonate (A) or sodium hydroxide (B) with aluminum nitrate. Key: —, 0.5 M; and - - -, 0.01 M.

RESULTS AND DISCUSSION

Titration Curve—The titration curve of sodium carbonate and aluminum nitrate is shown in Fig. 1A. The curve contains three plateaus and several concentration-dependent inflection points. To establish the role of carbonate in the basic titration curve, a similar titration was conducted with sodium hydroxide and aluminum nitrate (Fig. 1B). Comparison of the curves suggests that the initial decrease in pH observed in the sodium carbonate system was due to the partial neutralization of carbonate anion. A visible precipitate was observed during the first plateau for the sodium carbonate system, but no distinction could be made between turbidity and precipitation.

In contrast, turbidity was noted at the beginning of the second plateau in the sodium hydroxide system, and a visible precipitate was not observed until the end of the second plateau. This result suggests that carbonate was competing with hydroxide during the formation of the initial structure. Thus, when the titration was conducted using a lower concentration of sodium carbonate, the point of precipitation shifted and approached the turbidity point in the sodium hydroxide system. On the other hand, both systems showed the same general titration curve, suggesting that the precipitation mechanism was similar.

Since the hydroxide to aluminum ratio can be determined easily in the titration of sodium hydroxide by aluminum nitrate, an interpretation of the titration curve was based on this system. In basic media, aluminum exists as the aluminate anion, $\text{Al}(\text{OH})_4^-$ (12). Consequently, during the first plateau, which extended to a hydroxide to aluminum ratio of 5, the aluminate anion predominated.

Because a large excess of hydroxides was present in the system during the initial phase, a relatively small pH change was observed. As the hydroxide concentration was further reduced by the addition of aluminum

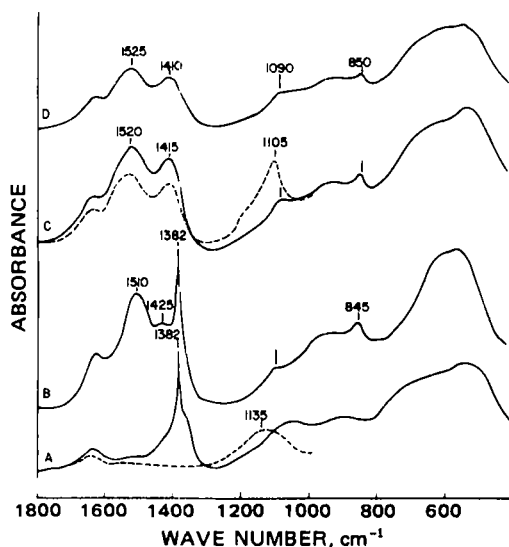


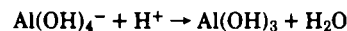
Figure 2—IR spectra of precipitates at different pH values during titration of 0.5 M sodium carbonate with 0.5 M aluminum nitrate. Key: A, pH 4.3; B, pH 4.5; C, pH 6.4; D, pH 9.15; and - - -, IR spectra after three washings with 0.1 M sodium sulfate.

Table I—Analysis of the Precipitate at Different Points in the Titration of 0.5 M Sodium Carbonate with 0.5 M Aluminum Nitrate

Parameter	pH			
	9.15	7.50	6.40	4.50
Carbonate to aluminum ratio	0.29	0.34	0.54	0.16
Nonbonded carbonate, %	41	38	35	40
T_{50} , min	3.5	3.0	1.0	14.0
Sodium to aluminum ratio	0.113	0.074	0.050	0.040
Apparent charge	—	—	+	+

nitrate, the pH decreased because the free hydroxides combined with aluminum to form aluminate anion.

Turbidity was observed at the beginning of the second plateau (hydroxide to aluminum ratio = 4.6), indicating that polymerization was occurring (6). Aluminate anions react with protons to produce aluminum hydroxide according to the reaction shown in Scheme I:



Scheme I

Therefore, a visible precipitate was observed at the end of the second plateau (hydroxide to aluminum ratio = 3.8).

Further addition of aluminum nitrate sharply decreased the pH until a hydroxide to aluminum ratio of approximately 3 was reached. The third plateau occurred at this point and continued until enough aluminum nitrate had been added to redissolve the precipitate.

Analysis of Precipitate—The presence of several inflection points and plateaus in the titration curve of sodium carbonate by aluminum nitrate suggests that the precipitate is different at various stages of the titration. Samples were taken at various points in the titration of 0.5 M sodium carbonate with 0.5 M aluminum nitrate, and the solid product was analyzed. As indicated in Table I, carbonate was present in the solid precipitate throughout the pH range studied. However, the carbonate content increased during the titration until pH 6.4. At this point, the precipitate exhibited a carbonate to aluminum ratio of 0.54. Further addition of aluminum nitrate reduced the carbonate content.

The relationship between the pH and carbonate content of the precipitate was apparent in the IR spectra of the precipitate (Fig. 2). An increase in the relative intensity of the absorption bands associated with carbonate (1525, 1410, 1090, and 850 cm^{-1}) was observed from pH 9.15 to 6.4, in agreement with the chemical analysis (Table I). As previously reported, the splitting of the ν_3 vibration of carbonate (1525 and 1410 cm^{-1}) indicates direct coordination between carbonate and aluminum (1).

At pH 4.5, some carbonate was replaced by nitrate; a sharp absorption band associated with nitrate became apparent at 1382 cm^{-1} . However, the nitrate anion did not appear to be affected directly by the aluminum hydroxide surface since the small difference between the position of the ν_3 vibration for the adsorbed nitrate (1382 cm^{-1}) and the free nitrate anion (1358 cm^{-1}) indicates that an electrostatic attraction occurs (5). Therefore, the nitrate anion can be considered to be acting as a counterion in the diffuse layer (13).

The further addition of aluminum nitrate to pH 4.3 virtually eliminated the presence of carbonate in the precipitate. The IR spectrum shows that only nitrate was present. However, in addition to the sharp absorption band at 1382 cm^{-1} , a new shoulder appeared at 1360 cm^{-1} (Fig. 2). This absorption band may have been due to the presence of a more perturbed form of nitrate located within the Stern layer (13).

The loss of carbonate at low pH must be due to the reaction with protons and is reflected first by the appearance of nitrate as a counterion (pH 4.5) and finally by the presence of more perturbed nitrate (pH 4.3). However, carbonate directly coordinated to aluminum cannot be replaced by nitrate (5).

The behavior of the nitrate anion as observed in Fig. 2 suggests that two types of carbonate must be present in amorphous aluminum hydroxycarbonate: directly coordinated to aluminum and as a counterion. This hypothesis was confirmed by washing the precipitate formed at each pH with a solution of 0.1 M sodium sulfate. After three washings, chemical analysis (Table I) showed that approximately 40% of the carbonate was replaced by sulfate in each precipitate. The replaced carbonate is referred to as nonbonded carbonate in Table I.

IR analysis of the precipitate at pH 6.4 after washing with sodium sulfate showed a considerable decrease in the intensity of the absorption bands associated with carbonate at 1520 and 1415 cm^{-1} and the ap-

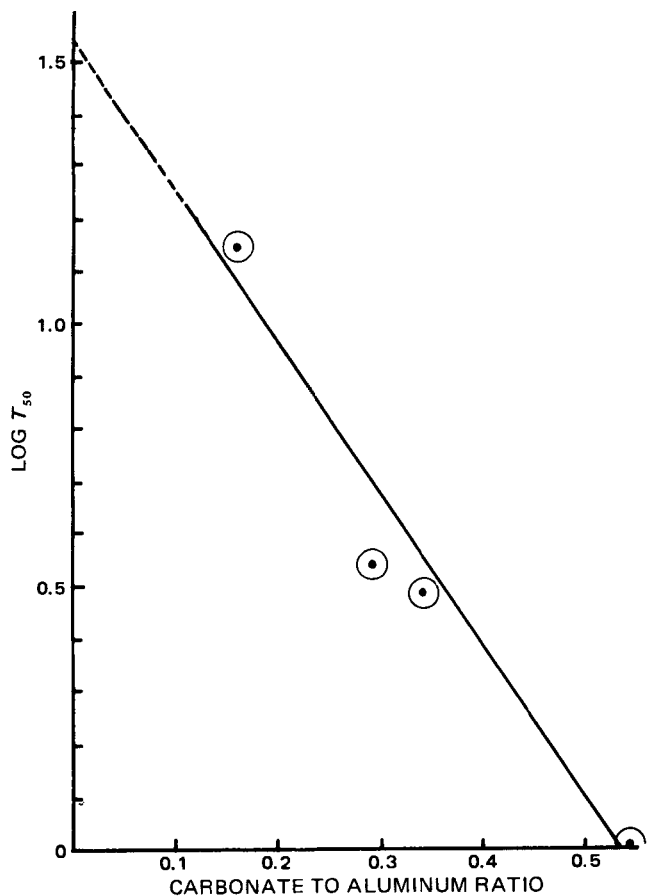


Figure 3—Relationship between carbonate to aluminum ratio and rate of acid neutralization for precipitates at different pH values during titration of 0.5 M sodium carbonate with 0.5 M aluminum nitrate.

pearance of sulfate absorption bands at approximately 1100 cm^{-1} (Fig. 2). However, when the precipitate containing only nitrate anion (pH 4.3) was washed with sodium sulfate in the same manner, complete removal of the nitrate was observed (Fig. 2). Nitrate interacts by electrostatic forces, so it can be replaced by sulfate, which can coordinate to aluminum (5). Thus, the sodium sulfate treatment replaces electrostatically bound anions.

The rate of acid neutralization of each precipitate was determined by pH-stat titration at pH 3.0 (11). The precipitate at pH 6.4 contained the greatest amount of carbonate and exhibited the most rapid neutralization reaction (Table I). The carbonate to aluminum ratio was directly related to the log of the T_{50} of the neutralization reaction (Fig. 3). Extrapolation suggests that a gel in this series containing no carbonate will have a T_{50} of approximately 35 min. This relatively high reaction rate in the absence

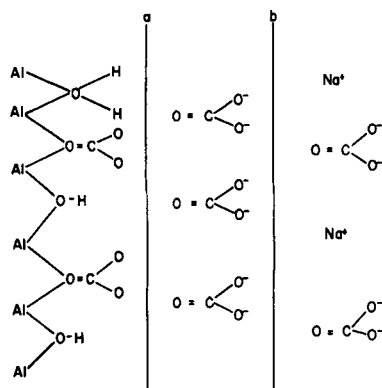


Figure 4—Proposed structure of amorphous aluminum hydroxycarbonate surface/liquid interface. Key: a, inner Helmholtz plane; and b, outer Helmholtz plane. Water, hydroxides, and protons have not been included.

Table II—Analysis of Precipitate at pH 6.4 during Titration of 0.5 M Sodium Carbonate with 0.5 M Aluminum Nitrate after Various Degrees of Washing

Number of Washes	Carbonate to Aluminum Ratio	Sodium to Aluminum Ratio	Particle Charge	T_{50} , min
0	1.22	3.9	—	0.25
1	0.57	0.52	—	0.5
3	0.54	0.05	+	1
5	0.48	0.04	+	1.5
10	0.45	0.03	+	2.5

of carbonate suggests that other factors such as particle size also contribute to the acid neutralization rate.

The sodium content of the precipitates appears to be related to the particle charge (Table I), indicating that sodium is mainly present in the diffuse layer and is, therefore, not specifically adsorbed. This finding is in good agreement with the reported adsorption of divalent cations by aluminum hydroxide from solutions containing 250,000 times more sodium (14).

A model of amorphous aluminum hydroxycarbonate based on the basic titration curve and analysis of the precipitate is presented in Fig. 4. Carbonate is shown coordinated to aluminum by unidentate interaction (5) and present in the Stern layer and the diffuse layer. Sodium is present mainly in the diffuse layer.

Effect of Washing—Previous studies indicated that the washing process had an important effect on the properties of aluminum hydroxide gel (15). The effect of washing on the precipitate containing the greatest carbonate to aluminum ratio (pH 6.4) was studied to test the model structure proposed in Fig. 4. As noted in Table II, a dramatic change occurred in the carbonate content of the precipitate during the first wash. IR analysis also indicated that the nitrate anion was readily removed (Fig. 5). Further washing did not substantially lower the carbonate content of the gel (Table II) and did not alter the carbonate interaction (Fig. 5). This result is in contrast to the behavior of sodium, which was almost completely removed after three washes. Significant amounts of sodium were only present when the particle was negatively charged (up to three washes). The acid neutralization rate decreased during washing. The log of the T_{50} also was related directly to the carbonate to aluminum ratio. This overall behavior agrees well with the model proposed in Fig. 4.

The charge behavior during washing is characteristic of a colloid without permanent charge. This type of colloid has a pH- and concentration-dependent charge that arises from adsorption of ions from solution. The gel particles are positively charged at pH 6.4, but the charge is reversed in concentrated salt solution because of preferential adsorption of anions compressing the double layer (13). As the anions are removed by washing, the gel's positive charge is observed. Therefore the washing process is important because it determines the physical stability of the colloidal particles and, consequently, the rheological properties of the gel.

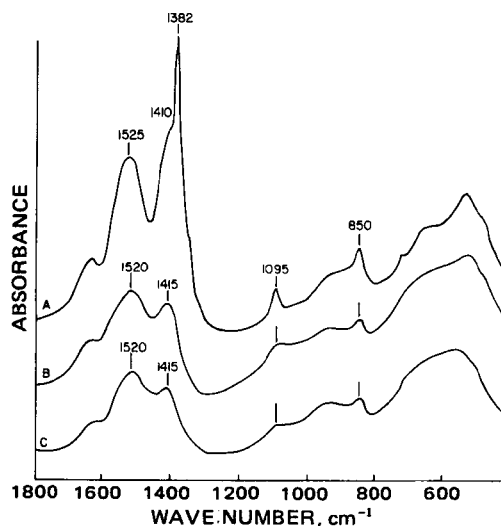


Figure 5—Effect of washing on the precipitate at pH 6.4 during titration of 0.5 M sodium carbonate with 0.5 M aluminum nitrate. Key: A, initial precipitate; B, after three washes; and C, after 10 washes.

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Hepatic Disposition and Biliary Excretion of the Organic Cations Thiazinamium and Thiazinamium Sulfoxide in Rats

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Received July 12, 1977, from the *Department of Pharmaceutical and Analytical Chemistry and the †Department of Pharmacology, State University of Groningen, Groningen, The Netherlands. Accepted for publication December 6, 1977.

Abstract □ The disappearance from plasma and the excretion in bile of the monoquaternary thiazinamium (administered as the iodide) and one of its polar metabolites, thiazinamium sulfoxide (also administered as the iodide), were studied in the rat after intravenous injection to obtain more information on hepatic transport mechanisms for organic cations. Both compounds exhibited an extremely rapid plasma disappearance, partly due to a rapid liver uptake. After injection of thiazinamium iodide and thiazinamium sulfoxide iodide, 36 and 47%, respectively, of the administered dose were excreted in bile during 1 hr. TLC analysis of the bile showed at least two unidentified polar metabolites in addition to thiazinamium sulfoxide and only 3.8% unchanged thiazinamium after administration of thiazinamium iodide. The same metabolites were found after injection of thiazinamium sulfoxide iodide. Urinary excretion and intestinal secretion were 18 and 12%, respectively, for thiazinamium sulfoxide iodide and 27 and 9%, respectively, of the dose for thiazinamium iodide. It is concluded that, in spite of unequal physicochemical features, thiazinamium iodide and thiazinamium sulfoxide iodide differ only slightly in hepatic uptake and metabolism.

Keyphrases □ Thiazinamium—tissue distribution and biliary excretion in rats □ Distribution, tissue—thiazinamium in rats □ Excretion, biliary—thiazinamium in rats □ Phenothiazine derivatives—thiazinamium, tissue distribution and biliary excretion in rats

Factors such as molecular weight, polarity, molecular structure, lipophilicity, protein binding, and metabolism were reported (1-3) to influence biliary excretion of drugs. It was suggested (4) that biliary excretion of quaternary ammonium compounds requires a polar organic cation group and a relatively nonpolar ring structure in the molecule.

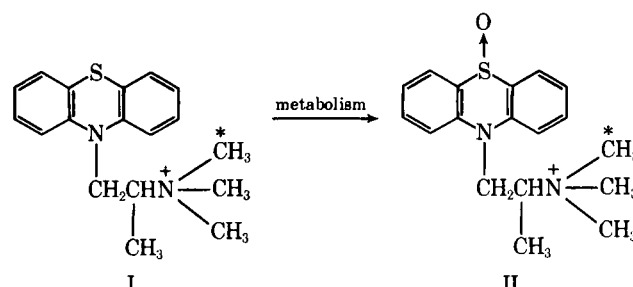
Thiazinamium (I) iodide is a phenothiazine derivative containing a quaternary ammonium group. No metabolites were detected in rats; no details were provided on biliary excretion of thiazinamium and its metabolites (5). In humans, dogs, and monkeys, one metabolite was detected (6)

in bile and urine: thiazinamium sulfoxide (II) (Scheme I, asterisks indicate ¹⁴C-label). Introduction of the oxygen in the phenothiazine nucleus results in a much more polar compound (Table I). Therefore, it was of interest to study whether this structural and physicochemical change would result in different hepatic disposition.

¹⁴C-Thiazinamium iodide and ¹⁴C-thiazinamium sulfoxide iodide were prepared and were used to investigate the distribution, biotransformation, and elimination in rats, with special reference to biliary excretion.

EXPERIMENTAL

Synthesis of ¹⁴C-Thiazinamium Iodide—Synthesis of ¹⁴C-thiazinamium iodide according to the reaction conditions described by Huang *et al.* (5) resulted in a radiochemical yield of only 8%. The conditions were modified, resulting in the following procedure. Promethazine, 500 mg, was allowed to react for 72 hr at 21° with 251 mg of ¹⁴C-methyl iodide (100 μCi total activity) in 25 ml of acetone. After the acetone was removed, the substance was recrystallized (24 hr) in 20 ml of a hot mixture of dichloromethane-benzene (10:9). After drying, a chemically pure product (>99.5%) was obtained (95% yield). TLC analysis showed no radio-



Scheme I