

The Chemistry of Aluminum and Silicon in Relation to Alzheimer's Disease

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Aluminosilicates have been identified at the core of senile plaques in Alzheimer's disease, and aluminum has been found within neurons bearing neurofibrillary tangles. Here we show that aluminum species interact with silicic acid, $\text{Si}(\text{OH})_4$ —a normal component of plasma—to form aluminosilicate species solubilized by citrate. A switch in the binding of aluminum from silicate to phosphate at pH <6.6 calls attention to the strong binding of cationic aluminum species to proximate phosphate groups, as in the inositol phosphates, and to the potential effect on the activity of the phosphoinositide-derived intracellular messenger system. The chemistry may throw light on the debated relationship between aluminum and Alzheimer's disease.

Additional Keyphrases: *inositol phosphates · citrate · silicic acid*

Amorphous aluminosilicates have been found at the core of senile plaques in Alzheimer's disease (1, 2), and aluminum has been detected in neurons bearing neurofibrillary tangles—both in Alzheimer's disease and in the Parkinson's disease with dementia that is prevalent on Guam and in other Pacific areas (3, 4). Because aluminosilicates are very insoluble, the finding that they are a "consistent feature of the senile plaque core" (5) raises questions as to how they are transported to the brain (6). Also to be determined are whether aluminum has any direct role in the causation or progression of neurological disease and what molecular mechanisms might be involved in the histopathological and neurochemical changes associated with Alzheimer's disease: senile plaques, neurofibrillary tangles, and a decrease in the number of neurotransmitters. Here, we direct attention to hitherto neglected (7) aspects of the chemistry of aluminum and silicon that may be relevant to these questions.

Silicon is a normal component of serum, present as silicic acid, $\text{Si}(\text{OH})_4$, the mean concentration being 21 $\mu\text{mol/L}$ (range 14–39 $\mu\text{mol/L}$) for healthy humans of both sexes (8). After the work of Schwarz and Milne (9) and Carlisle (10), some authorities regard silicon as an essential element for proper growth and development. Its deficiency in rats and chicks leads to a markedly decreased growth rate and to deleterious effects on osteogenesis, with less synthesis of collagen and the polysaccharidic components of the organic matrix of bone (11–13). The mechanisms underlying the suggested essentiality of silicon remain unknown.

Little is known of the factors determining the absorption of aluminum, although it is present in plasma in a concentration of about 0.25 $\mu\text{mol/L}$ (range 0.05–0.54 $\mu\text{mol/L}$) (14). Much higher concentrations may exist (range 0.57–2.2 $\mu\text{mol/L}$) in patients with chronic renal failure (15) and still higher ones in patients who are undergoing hemodialysis with aluminum-rich dialysate (14). These high concentrations are associated with dialysis osteomalacia and dementia (16, 17).

Thus, silicon and aluminum co-exist in serum with, ordinarily, an excess of silicon over the aluminum. From solid-state chemistry and aqueous solution chemistry, we know of a unique association between silicon and aluminum, the result of the similarity between $\text{Si}(\text{OH})_4$ and the aluminate ion, $\text{Al}(\text{OH})_4^-$ (18), the dominant species at pH 7.4. These species are well known to combine to form aluminosilicates under strongly alkaline conditions. However, the interactions between aluminum and silicic acid under pH conditions in the physiological range have been little considered.

In in-vitro experiments (19), the presence of aluminum decreased the activity of prolyl hydroxylase, especially when presented to the enzyme before iron, the essential co-factor of the enzyme. However, the addition of a sixfold excess of silicic acid over aluminum completely suppressed this effect of aluminum, presumably through the formation of aluminosilicate species, which removed aluminum from competition with iron for binding with the enzyme. We have investigated further the suggested formation of aluminosilicates in dilute solution at approximately physiological pH (20).

Materials and Methods

For these filtration and ion-exchange experiments we used dilute solutions of relatively high purity. To filter colloidal solids, we passed the solutions through Millex-GV membrane syringe filters (Millipore Corp., Bedford, MA). These membranes are composed of hydrophilized poly(vinylidene difluoride) and retain particles >0.22 μm . The ion-exchange experiments involved ion-exchange resins with either sulfonate (Amberlite 252) or aminophosphonate (Duolite C-467) functional groups to retain soluble aluminum-based species from solution. We passed these solutions through "mini-columns" containing 0.3 mL of resin, which provided a 10-fold excess of binding groups. Species retained on the resin were extracted by passing 3 mol/L HCl through the column. We then analyzed the extract solutions directly by standard methods of atomic absorption spectroscopy (21), using a Perkin-Elmer ICP instrument ("Plasma 2" model).

The solutions were prepared with high-quality reagents: aluminum chloride, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ ("Puratronic" grade; Alfa, Danvers, MA); sodium orthosilicate, Na_4SiO_4 (reagent grade; Alfa); sodium chloride, NaCl (Puratronic grade; Alfa); citric acid, $\text{C}_3\text{H}_4(\text{OH})(\text{COOH})_3 \cdot \text{H}_2\text{O}$ (analytical grade; Johnson Matthey, Royston, England); sodium dihydrogen orthophosphate, $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ ("Specpure" grade; Johnson Matthey). The sodium orthosilicate was converted to silicic acid via ion-exchange with Amberlite 252 resin (Alfa) in the H^+ form. The pH of the solutions was adjusted with HCl and NaOH solutions prepared from hydrochloric acid, minimum 30% HCl ("ultrapure" grade; Alfa), and sodium hydroxide, NaOH \cdot H_2O (ultrapure grade; Alfa), respectively.

Results

Besides studies of the interactions of dissolved aluminum and silicic acid as a function of pH, we also investigated the effect of citrate (concentration in plasma, 0.1 mmol/L) and

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phosphate (total concentration in extracellular fluid, 2 mmol/L) on these interactions. Solutions containing 0.1 mmol of aluminum and 0.5 mmol of silicic acid per liter of 0.01 mol/L NaCl solution were prepared at various pH values (solution temperature held at $20 \pm 1^\circ\text{C}$) and passed through filters capable of retaining colloidal solids. Formation of filterable solids took three to five weeks. For solutions in the pH range of 5 to 9, the solids had an Si:Al ratio in the range of 0.3 to 0.6, consistent with those of other workers in soil chemistry (22), who report that aluminosilicates with an Si:Al ratio of 0.25 to 0.5 form in dilute solution at pH <5.5.

By passing 20-hour-old solutions over an ion-exchange resin with sulfonate functional groups, we could isolate aluminosilicate species in solution before the formation of filterable solids. These solution species started to form at about pH 5, their Si:Al ratio rising with pH to around 0.3 at about pH 6.5 and remaining stable to pHs >9 (Figure 1). We suggest that this confirms the view (22) that aluminosilicate solution species exist that are precursors to (or molecular fragments of) poorly crystalline aluminosilicate solids.

We found that such species formed even in the presence of citrate, an aluminum chelator. Solutions containing aluminum (0.1 mmol/L) and equimolar (0.5 mmol/L) concentrations of silicic acid and citrate at pH 7.4 yielded no filterable solid after 12 weeks, even though 20-hour-old solutions passed over an ion-exchange resin revealed species with a Si:Al ratio >0.5. Aluminosilicate solution species are thus formed in the presence of citrate, but their aggregation and eventual precipitation are inhibited.

Aluminum is known to interact with phosphate in DNA (23), membranes (24), and ATP (25). The formation of ATP-Al inhibits the action of hexokinase by blocking, it has been suggested, the ability of the enzyme to transfer the terminal phosphate group to glucose (26). Activity is restored by the addition of citrate, the complex of aluminum with citrate being much more stable than that of ATP with Al (27). It is

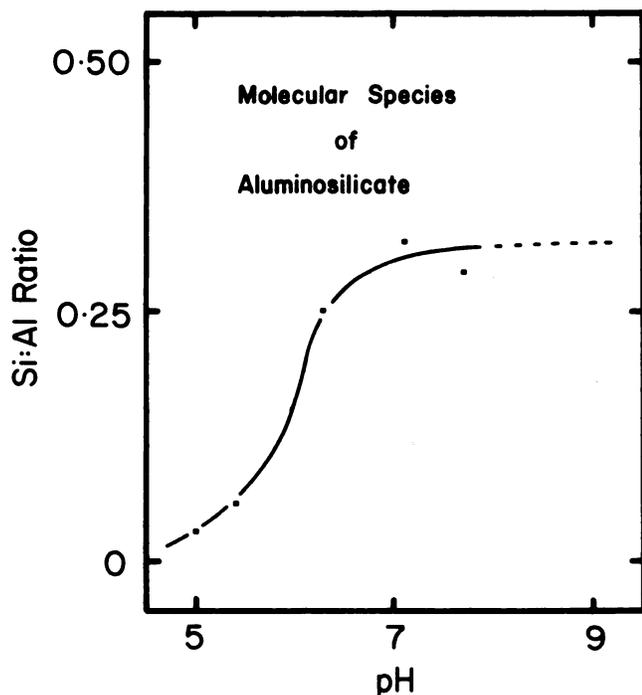


Fig. 1. Observation of molecular species of aluminosilicate as a function of pH

Si:Al ratio is that of the species retained by a sulfonate functional group ion-exchange resin; data points were reproducible among several determinations

thus significant that aluminosilicates are formed in the presence of citrate; i.e., at pH 7.4, the affinity of silicic acid for aluminum is at least similar to that of citrate.

We find the competitive binding of aluminum by silicic acid and phosphate to be highly pH-dependent. Solutions containing 0.1 mmol of aluminum and 0.5 mmol each of silicic acid and phosphate per liter gave precipitates in which the Si:Al ratio varied with pH. At pH 7.4, the Si:Al ratio was 0.44, whereas at pH 6.4 the silicon content was negligible and this ratio was 0.02. Experiments in which similar solutions were passed over a resin having aminophosphonate functional groups confirmed this variability, a switch in the binding of aluminum from phosphate to silicate being indicated at about pH >6.6 (Figure 2).

These results indicate that, at pH 7.4, aluminum will be bound to silicate in molecular species of Si:Al ratio 0.25–0.5, and that the presence of citrate will prevent these species from aggregation and eventual precipitation as amorphous aluminosilicate solids. However, at about pH <6.6, silicic acid becomes a weak ligand and aluminum will be bound to phosphate. The binding is thus delicately balanced around the pH of the extra- and intracellular environment. The observed switch in binding from silicate to phosphate probably reflects the transition in the speciation of aluminum from the tetrahedral anion, $\text{Al}(\text{OH})_4^-$, which interacts strongly with silicic acid, to octahedral cationic species, such as $\text{Al}(\text{OH})_2^{2+}$ and $\text{Al}(\text{OH})_2^+$, which preferentially interact with negatively charged phosphate groups. Interestingly, the aluminosilicates of Alzheimer plaque cores show both octahedral and tetrahedral aluminum (1), with the aluminosilicates being extracellular while the aluminum is bound to chromatin in the neuron.

Discussion

The results presented here suggest that, in mildly acidic intracellular conditions, aluminum will be bound to phos-

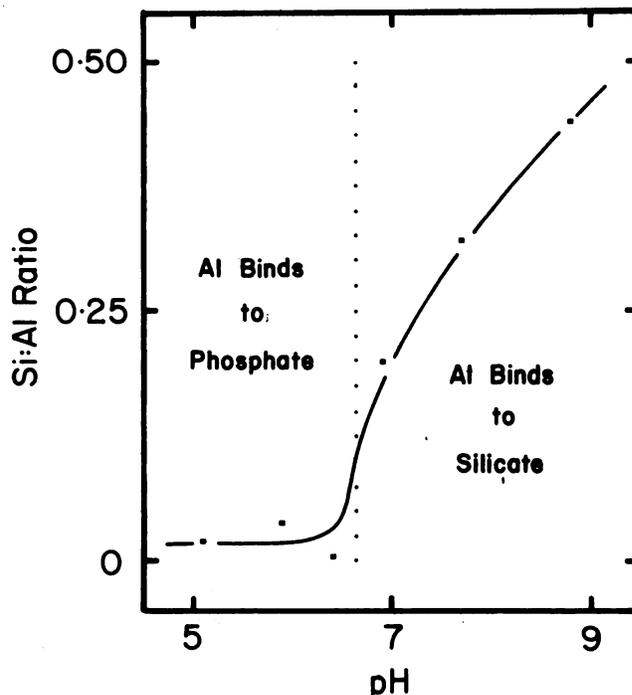


Fig. 2. Transition in binding of aluminum with phosphate and silicate as a function of pH

Shown is the Si:Al ratio of the species retained by an aminophosphonate functional group ion-exchange resin; dotted line indicates approximate pH at which the switch in binding of aluminum occurs

phate and certain geometrically favorable phosphate-binding sites will be of special interest. A computer simulation of binding suggests that proximate phosphate groups such as in inositol phosphates will bind aluminum more strongly than the linear phosphates of ATP. Such binding could have far-reaching consequences in the manipulation of the phosphoinositides, which are important in cellular signal transduction (28, 29). For example, we would expect that the conversion of inositol-1,4,5-triphosphate, responsible for Ca^{2+} mobilization, to inositol-1,4-bisphosphate would be blocked by the stability imposed on the binding of aluminum across the 4,5-phosphate groups. The recycling of the inositol phosphates and thus, eventually, the production of 1,2-diacylglycerol and the activation of protein kinase c (EC 2.7.1.37) would be affected. Such effects may be responsible for some of the biochemical disturbances characteristic of Alzheimer's disease.

In conclusion: the interactions in aqueous systems containing aluminum, citrate, phosphate, and silicic acid are extraordinarily pH-dependent, changing within the pH range experienced in human physiology. The formation of aluminosilicate species at pH 7.4 and their solubilization by citrate may be relevant in aluminum transport. The switch in aluminum binding from silicate to phosphate at pH <6.6 may be significant in the transition from the extra- to the intracellular environment and may be related to the finding of extracellular aluminosilicate deposits and the intracellular binding of aluminum to chromatin. The chemistry described may throw light on the transportation of aluminosilicates, the formation of aluminosilicates at the core of senile plaques, and the molecular site of aluminum-induced biochemical lesions.

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