Review

Reflections upon and recent insight into the mechanism of formation of hydroxyaluminosilicates and the therapeutic potential of silicic acid

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ABSTRACT

The chemistry of mono or ortho silicic acid $(Si(OH)_4)$ is barely considered in most chemistry texts. Mention is usually only made of its autocondensation in forming hydrated amorphous silica and its reaction with ammonium molybdate in forming the molybdosilicic acid complex. Reference should now be made to its unique inorganic chemistry with aluminium (Al) and specifically aluminium hydroxide $(Al(OH)_{3(s)})$ in forming hydroxyaluminosilicates $(HAS_{(s)})$. The competitive condensation or substitution of $Si(OH)_4$ into a framework of $Al(OH)_{3(s)}$ results in the formation of either HAS_A or HAS_B. Which type of $HAS_{(s)}$ predominates depends upon the ratio of Si:Al in preparative solutions with the formation of HAS_B requiring a two-fold excess of $Si(OH)_4$ over Al. The Si:Al ratio of HAS_A is 0.5 and the existence of HAS_A is a prerequisite to the formation of HAS_B in which the ratio of Si:Al is 1.0. HAS_A is composed of only octahedrally co-ordinated Al, Al^{VI}, whereas HAS_B is composed of equal quantities of Al^{VI} and tetrahedrally coordinated Al, Al^{IV}, and is formed by a $Si(OH)_4$-fuelled dehydroxylation reaction. $HAS_{(s)}$ are significantly more 'kinetically' stable than $Al(OH)_{3(amorphous)}$ with HAS_B predicted to predominate at pH > 4.0 and $[Si(OH)_4]$ > 0.1 mmol/L. $HAS_{(s)}$ are critical secondary mineral phases in the biogeochemical cycle of Al and $Si(OH)_4$ and the formation of $HAS_{(s)}$ have played a major role in precluding $Al^{3+}_{(aq)}$ from biochemical evolution. In the future $Si(OH)_4$ and the formation of $HAS_{(s)}$ are predicted to be of significant importance in providing protection for humans against a potentially burgeoning exposure to biologically available Al.

1. Preface

Silicon and aluminium are the second and third most abundant elements of the Earth's crust after oxygen [1]. Paradoxically neither element has any known essentiality in man. The non-selection of Al was due to a geochemically controlled infinitesimally low biological availability while the non-selection of silicon was the result of the inert nature of silicic acid, $Si(OH)_4$, its only biologically available form [2]. The abundance of $Si(OH)_4$ over geological and evolutionary time has been the major influence upon the natural history of Al both through limiting its biological availability and by aiding in the selection of alternatives to Al, such as magnesium, in essential biochemistry [3]. The significance of the latter is that at the present time in evolutionary history, with the man-made emergence of more and more biologically available Al being concomitant with increasingly lower concentrations of environmental $Si(OH)_4$, essential metal-based biochemistry, such as involving $Mg^{2+}_{(aq)}$, is coming under selection pressures from Al with potential

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consequences for human health [2]. Almost nothing is understood about chronic Al toxicity in man [4] though there are many anecdotal reports of the putative health benefits of $Si(OH)_4$. One consistent example concerns individuals whose health has been blighted by adverse reactions to vaccinations which included Al-based adjuvants [5]. Several such affected individuals have contacted the author to say that their health has improved markedly (if not fully) following the inclusion of a silicon-rich mineral water in their everyday diet. While such reports are anecdotal and there is as yet no unequivocal explanation of the reported health benefits of silicon it is intriguing to explore if they might be partially or fully explained by the unique inorganic chemistry of the reaction of $Si(OH)_4$ with Al.

2. A personal perspective

2.1. Silicic acid poisons the growth of aluminium hydroxide

Why is a dialysis membrane with an approximate pore size of 1 nm more permeable to Al (4 μmol/L) at pH 6.0 (though not at pH 4.5 or 7.5) in the presence, as opposed to absence, of $Si(OH)_4$ (>100 μmol/L)? This experimental observation was one of our first indications of a direct interaction between Al and the neutral, monomer, $Si(OH)_4$ and its explanation, which follows, helped us in taking the first steps in elucidating the fundamentals of the unique inorganic chemistry of Al with $Si(OH)_4$ [6]. We began by surmising that in the chosen background medium of 27 mmol/L $NaHCO_3$ the solubility of Al would be approaching its minimum at pH 6.0 and $Al(OH)_{3(amorphous)}$ would be the predominant form of Al in this solution. After allowing the solution to age for 14 days more than 80% of Al had precipitated as $Al(OH)_{3(s)}$ for which the average particle size was in excess of 1 nm. However, in the presence of 500 μmol/L $Si(OH)_4$ a much higher proportion of Al, approximately 50%, had remained at a particle size below 1 nm and had passed through the dialysis membrane. $Si(OH)_4$ had slowed down or inhibited the growth of the solid phase. While the additional presence of $Si(OH)_4$ resulted in more Al passing through the dialysis membrane (porosity ca. 1 nm) it also resulted, for the identical solutions, in less Al being retained by a strongly cationic ion exchange resin (Amberlite 200; sulfonic acid functional group) which had a porosity closer to 100 nm. So in the presence of $Si(OH)_4$ while the mean particle size of the solid phase was smaller and many more particles would have had access to functional groups on the ion exchange resin these particles were sufficiently stable and either uncharged or negatively charged such that Al, as $Al^{3+}_{(aq)}$ or a charged particle, was not retained by the resin. The latter showed that $Si(OH)_4$ was not simply retarding the formation of $Al(OH)_{3(s)}$ by an indirect means as this would not have resulted in less Al being retained by the resin. Instead these preliminary experiments through which we tentatively described the formation of hydroxyaluminosilicates (HAS) under physiologically and environmentally significant preparative conditions allowed us to speculate that HAS were formed by the poisoning of the polymerisation of $Al(OH)_{3(s)}$ through the incorporation of $Si(OH)_4$ into the solid phase.

We tested this hypothesis using membrane filtration (0.04 μm) and a carefully developed protocol for preparation of test solutions [7]. We found that using membrane filtration to discriminate between solutions in which the insoluble phases were either $Al(OH)_{3(s)}$ or $HAS_{(s)}$ was optimal when the original solutions were prepared at pH 3.0 and allowed to equilibrate for 24 h before being slowly titrated with 0.1 mol/L NaOH solution to the desired constant pH. At pH 3.0 Al in solutions was present as $Al^{3+}_{(aq)}$ and there were no known stable interactions with $Si(OH)_4$ (see Fig. 1) which meant that as the solutions were titrated towards less acidic and subsequently alkaline pH and $Al^{3+}_{(aq)}$ began to hydrolyse and

eventually form $Al(OH)_{3(s)}$ then in those solutions which included $Si(OH)_4$ it would be immediately available to 'react' with or 'poison' the earliest stages of the polymerisation and formation of $Al(OH)_{3(s)}$. The careful completion of literally hundreds of titrations of this nature was eventually successful in elucidating a mechanism of $HAS_{(s)}$ formation in which $Si(OH)_4$ was shown to have inhibited the nucleation and growth of $Al(OH)_{3(s)}$. The effectiveness of membrane filtration to identify the formation of $HAS_{(s)}$ in such dilute solutions was greater at higher $[Si(OH)_4]$ and in solutions which were allowed to age for days and weeks. The importance of solution aging probably reflected the slower rate of growth towards a filterable size of $HAS_{(s)}$ relative to $Al(OH)_{3(s)}$ while the significance of $[Si(OH)_4]$ may have been indicative of direct competition between $Si(OH)_4$ and various hydroxylated forms of Al (from $Al^{3+}_{(aq)}$ to $[Al(OH)_3]_n$) at nucleation sites on $Al(OH)_{3(s)}$ frameworks. An important observation which strongly supported the existence of a different insoluble phase in the presence of $Si(OH)_4$ was the shift in the pH of minimum solubility of the solid phase from ca. pH 6.5 for $Al(OH)_{3(s)}$ to ca. pH 5.5 for $HAS_{(s)}$. In addition while the simple presence of a 'new' phase should in itself be sufficient to suggest that it is more sparingly soluble than $Al(OH)_{3(amorphous)}$ the classic solubility curves which can be obtained through membrane filtration of these different solid phases do not immediately suggest as such for solutions aged for only 12 weeks. Thus, while $HAS_{(s)}$ are less soluble than $Al(OH)_{3(s)}$ when formed under the same conditions they are also much slower to achieve a filterable size and such effects could prove to be misleading where membrane filtration is commonly used as an indicator of the 'soluble' fraction of Al in solution [8]. When the pH of minimum solubility for such sparingly soluble solid phases is expressed in the terms of their aggregate size, i.e. using membrane filtration, then this minimum pH is actually a reflection of the gregarious nature of the constituent particles. It is an indicator of how easily they come together and how likely they are to stick to each other following each encounter or collision. The shift in this pH from ca. 6.5 for $Al(OH)_{3(s)}$ to ca. 5.5 for $HAS_{(s)}$ indicated that the formation of $HAS_{(s)}$ lowered the pH at which the resultant particles were capable of being deprotonated and carrying a positive charge. This suggested that the formation of $HAS_{(s)}$ involved the replacement of Al–OH with Si–OH with the latter being much more stable and unlikely to lose a proton until the pH exceeded ca. 9.0. There was also evidence that $HAS_{(s)}$ were unlikely to support as large aggregates as $Al(OH)_{3(s)}$ since when $Si(OH)_4$ was added to preformed aggregates of $Al(OH)_{3(s)}$ it resulted in a significant reduction in the average particle size in solution which suggested that the formation of $HAS_{(s)}$ under these conditions resulted in the break-up of preformed polymers of $Al(OH)_{3(s)}$ [7].

2.2. The identification of two discrete forms of hydroxyaluminosilicate

Since our research up to this point had been with environmentally and physiologically significant concentrations of Al then this meant that we had still only been able to identify the formation and presence of $HAS_{(s)}$ by indirect means and primarily by using membrane filtration to show changes in the size distribution profiles of precipitates. One additional indirect way of identifying $HAS_{(s)}$ was to prove a turning point both in adding to our understanding of the conditions under which $HAS_{(s)}$ were formed but also in designing new experiments to investigate the solid phases directly [9]. We prepared treatment solutions which included a range of concentrations of Al and $Si(OH)_4$ and in which the ratio of Al:Si was always 0.5. A set of control solutions contained only Al. All solutions were adjusted to either ca. pH 4.0 or pH 4.5 and then they were 'aged' in the laboratory in the dark for up to 6 months. We then used morin and fluorimetry to compare the 'fast-reactive'

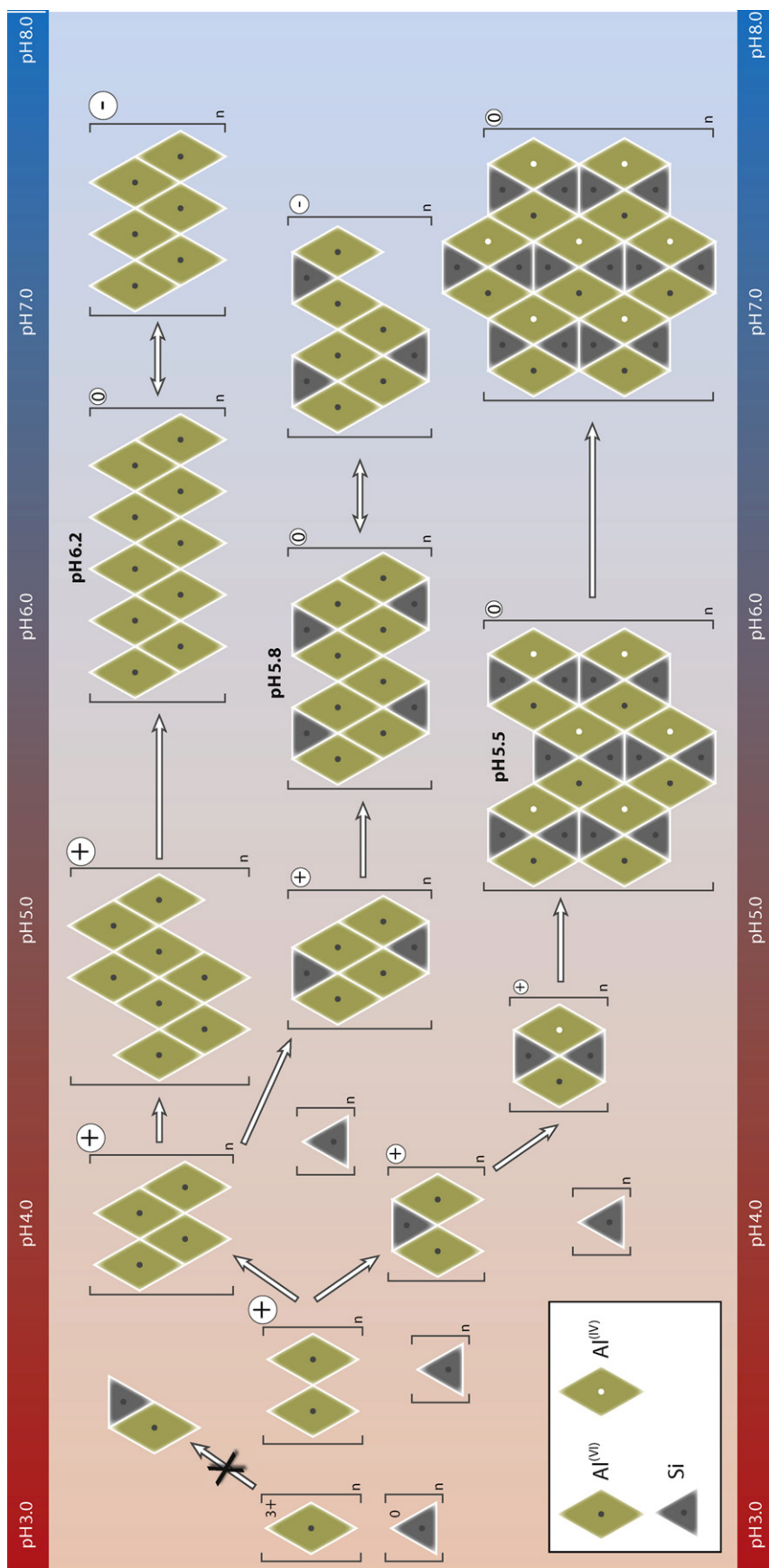**Fig. 1.** Schematic showing pH-dependent formation and stability of Al(OH)$_{3(s)}$, HAS$_A$ and HAS$_B$ with particular reference to their abilities to carry charge, their pH of minimum solubility and their aggregation towards filterable sizes.

form of Al in control and treatment solutions and we were able to show that this form of Al was unchanged at pH 4.0, regardless of the presence of $Si(OH)_4$, while it was significantly reduced in solutions which included $Si(OH)_4$ at pH 4.5. Essentially, $HAS_{(s)}$ were only formed in saturated solutions of Al, those solutions in which the solubility of $Al(OH)_{3(amorphous)}$ was exceeded, and these observations confirmed our expectation that the formation of $Al(OH)_{3(s)}$ was a prerequisite to the formation of $HAS_{(s)}$. In some of the treatment solutions at pH 4.5 we noticed by eye the formation of precipitates and their presence gave us the idea that we might be able to collect sufficient weights of $HAS_{(s)}$ (ca. 200–500 mg) to undertake a range of physical characterisations. To achieve these weights of precipitates we needed to make up 10 L of each type of solution and these volumes were adjusted to pH 6.2 and aged in the laboratory in the dark for 3 months before they were filtered through a polycarbonate membrane filtration system (maximum volume 250 mL!) to collect the precipitates. We prepared 7 different treatments ranging from 2.0 mmol/L $Si(OH)_4$/0.25 mmol/L Al to 0.5 mmol/L $Si(OH)_4$/2.0 mmol/L Al and 3 replicates of each and this titanic effort was eventually rewarded with an exciting and completely unexpected finding. Solid state Al and Si NMR of the collected precipitates demonstrated the existence of two discrete forms of $HAS_{(s)}$ with the Si:Al ratio in preparative solutions being the major determinant of which type of $HAS_{(s)}$ was formed. One major difference between the two forms was that when Al was in excess in preparative solutions the resulting precipitates were dominated by octahedrally coordinated Al, (Al^{VI}), while when $Si(OH)_4$ was in excess the precipitates contained approximately equal amounts of Al^{VI} and tetrahedrally coordinated Al, (Al^{IV}). Further, the precipitates which only contained Al^{VI} were shown by SEM-EDX to have Si:Al ratios of 0.5 while those which included Al^{VI} and Al^{IV} had Si:Al ratios close to 1.0. We had identified two discrete forms of $HAS_{(s)}$ which we called HAS_A (Si:Al = 0.5) and HAS_B (Si:Al = 1.0). While the existence of HAS_A had been predicted from earlier research the identification of HAS_B with its equal composition of Al^{VI} and Al^{IV} was completely unexpected [9]. The presence of silicon-enriched HAS_B in solutions at pH 6.2 might begin to explain why its particles had aggregated to sizes which could be collected by filtration through a 2.0 μm membrane while those particles that were formed in solutions in which HAS_A was predicted to predominate remained sub-micron and had to be collected using a 0.2 μm membrane. Particles of HAS_A were very likely able to undergo further deprotonation at pH 6.2 to result in potentially negatively charged particles while particles of HAS_B remained neutral under the same conditions due to the replacement of Al–OH groups with more stable Si–OH groups (see Fig. 1).

In addition to their potential to carry charge there were also clear differences in the morphologies of HAS_A and HAS_B and these were observed for the very first time using atomic force microscopy (AFM) [9,10]. Those particles collected from solutions in which HAS_A was predicted to predominate were rectangular in appearance, approximately 1–2 nm thick, 40–45 nm in width and 80–180 nm long while particles collected from solutions in which HAS_B was predicted to predominate were discoid, again about 1–2 nm thick and 20–25 nm in diameter. These differences in particle shape, rectangular for HAS_A versus discoid for HAS_B, gave further support to the idea that condensation of $Si(OH)_4$ across hydroxyl groups on adjacent Al atoms 'poisoned' the further growth of individual $HAS_{(s)}$ units with the additional incorporation of $Si(OH)_4$ into the structure of HAS_B preventing its continued growth through reactions with hydroxylated Al or $Si(OH)_4$. These varied observations on their physical and chemical properties allowed us to propose specific structures for $HAS_{(s)}$ and to elucidate more detailed mechanisms of their formation. We were confident that HAS_A was formed by competitive condensation of $Si(OH)_4$ with a framework of $Al(OH)_{3(s)}$. In addition we speculated that for-

mation of HAS_A was a prerequisite to formation of HAS_B and that the additional condensation of $Si(OH)_4$ into HAS_A in forming HAS_B resulted in a dehydroxylation reaction, not normally seen in metal hydroxides at room temperature and pressure, and a subsequent rearrangement of the coordination of Al in the structure to accommodate 50% of both Al^{VI} and Al^{IV}. This $Si(OH)_4$-driven dehydroxylation of Al^{VI} in HAS_A to give HAS_B is, to our knowledge, unique under the conditions in which it is known to occur [9,10].

To test the hypothesis that the pre-existence of HAS_A was a prerequisite to the formation of HAS_B we designed an experiment in which small quantities of $HAS_{(s)}$ materials could be collected by membrane filtration from treatment solutions in which the predominant form of $HAS_{(s)}$ could be reliably predicted [11]. We collected precipitates after allowing solutions to 'age' for between 0.5 h and 336 h and we determined their Si:Al ratio using electron microprobe analysis. We also measured molybdate-reactive silicon (essentially $Si(OH)_4$) at each timepoint in each of the filtered solutions and it was remarkable that for every ratio of Si:Al in solution, in which the $[Al_T]$ was always 800 μmol/L, the change in $[Si(OH)_4]$ at the earliest sampling point (T = 0.5 h) was always a drop of ca. 400 μmol/L, as would be expected if HAS_A was the first reaction product. The solid state analyses of the collected precipitates also supported this indirect evidence that HAS_A is an absolute prerequisite to HAS_B. For example, for an initial solution ratio of Si:Al of 1.0 (expect HAS_A to be the predominant solid phase) the ratio of Al to Si in the precipitate after aging for 12 h was 0.44 (HAS_A) rising to 0.57 ($HAS_A > HAS_B$) after 336 h. Also for an initial solution ratio of ca. 1.9 (expect HAS_B to be the predominant solid phase) the ratio of Al to Si in the precipitate after aging for 12 h was 0.61 ($HAS_A > HAS_B$) rising to 0.84 ($HAS_B > HAS_A$) after 336 h. Finally for an initial solution ratio of 2.5 (expect only HAS_B) the ratio of Al to Si in the precipitate after aging for 0.5 h was 0.60 (HAS_A), rising to 0.64 ($HAS_A > HAS_B$) at 12 h and 0.92 (HAS_B) after 336 h. These data confirmed to us that HAS_B was formed from the reaction of HAS_A with $Si(OH)_4$ though for HAS_B to be the main product a significant excess of $Si(OH)_4$, a Si:Al ratio of >2, was required in the preparative solution to fuel the additional condensation reactions and the partial dehydroxylation of the Al^{VI} framework [11]. Intriguingly, HAS_B is only formed from the reaction of $Si(OH)_4$ with HAS_A in situ. This means that if HAS_A are collected from solution, dried and then incubated in a 2 mmol/L solution of $Si(OH)_4$ there are no further condensation reactions and HAS_A remains stable as HAS_A. The latter observation clearly demonstrates that there are chemical and physical differences between precipitates which are formed in solution and remain in situ and those same products following their collection by filtration and air drying for solid state analyses. Air-dried HAS_A will not accommodate further $Si(OH)_4$ upon its 'rehydration' in $Si(OH)_4$-rich medium. This also applied to $Al(OH)_{3(s)}$ in that following its precipitation, collection by filtration and air drying it does not form $HAS_{(s)}$ when it is rehydrated in a solution of $Si(OH)_4$. This might go some way towards explaining why the suggested structure of $HAS_{(s)}$ does not include double hydroxy-bridges as are always indicated in the structures of crystalline $Al(OH)_{3(s)}$ such as gibbsite and some clays such as kaolinite [12]. The mechanism of formation of $HAS_{(s)}$ and their known physical structures and elemental compositions all point towards the possibility that in the continuum which exists between the rapidly formed $Al(OH)_{3(amorphous)}$ and the rarely encountered crystalline $Al(OH)_{3(gibbsite)}$ the amorphous or least crystalline forms of $Al(OH)_{3(s)}$ do not include double hydroxy-bridges. It is perhaps the existence of such quasi-stable forms of fully hydrated $Al(OH)_{3(s)}$ and latterly HAS_A and their increased lability which enables their reactions with $Si(OH)_4$ in forming HAS_A and HAS_B. In support of such, as yet ill-defined phenomena, we have exciting recent data which concerns the thermal behaviour of $Al(OH)_{3(amorphous)}$ and HAS_A and which suggest an hitherto unrecognised form of $Al(OH)_{3(s)}$ being involved

in the formation of HAS$_A$, though, intriguingly, the signatures of this form of Al(OH)$_{3(s)}$, exothermic peaks in the range 260–285 °C, were not found in HAS$_B$ [13]. It may be significant that during heating of precipitates of Al(OH)$_{3(s)}$, HAS$_A$ and HAS$_B$ a transformation (dehydroxylation) occurred, as revealed by solid state NMR, in which Al^{VI} was converted to Al^{IV} and for HAS$_A$ and HAS$_B$, but not Al(OH)$_{3(s)}$, this transformation involved the formation of Al^V as an intermediate. Once again we have additional evidence that the presence of Si(OH)$_4$ within a framework of aluminium hydroxide has significant influence upon the solid-state chemistry of these precipitates.

2.3. Anion-substituted hydroxyaluminosilicates

The appearance of Al^V in thermal transformations of HAS$_{(s)}$ were not the first time that we had observed the apparent existence of an intermediate form of Al in the formation of HAS$_{(s)}$. For example, we have shown that when HAS$_{(s)}$ are formed in the presence of approximately equimolar concentrations of fluoride the final solid phases include significant amounts of fluoride within their structures [14]. Fluoride was found to substitute for hydroxyl groups on Al, i.e. Al–OH is replaced by Al–F, but not on Si, there was no evidence that Si–OH is replaced by Si–F. However, some of the fluoride-substituted solid phases showed Si:Al ratios close to 1.0 while at the same time being made up, not of equal amounts of Al^{IV} and Al^{VI} as expected but predominantly of Al^{VI}. From these data we surmised that under certain conditions the presence of fluoride in HAS$_{(s)}$ delayed or even prevented the Si(OH)$_4$-driven dehydroxylation reactions characteristic of the formation of HAS$_B$ and resulted in an intermediate or transitional phase which we called HAS$_{AB}$. As part of the same study we also investigated how equimolar (to Si(OH)$_4$) concentrations of inorganic phosphate influenced the formation of HAS$_{(s)}$ and, in almost all situations, we found that their formation was inhibited. The exception was where Al was present in preparative solutions to significant excess of both Si(OH)$_4$ and phosphate and in these solutions an hydroxyaluminium phosphate and HAS$_A$ were co-precipitated [14]. The potential for phosphate to prevent the formation of HAS$_{(s)}$ lends support to our view that a particular form of Al(OH)$_{3(s)}$ in which there exists a specific orientation of hydroxyl groups, which is not achieved on forming hydroxyaluminium phosphate, is a prerequisite to the formation of HAS$_{(s)}$. We have obtained additional support for the idea that the hydroxyl groups on Al(OH)$_{3(s)}$ are uniquely orientated to accommodate Si(OH)$_4$ by our attempts to form HAS-like materials using the substituted silicic acids dimethylsilane-diol (DMSD: Si(OH)$_2$(CH$_3$)$_2$) and trimethyldisilane-diol (TMDS: Si$_2$O(OH)$_2$(CH$_3$)$_4$). In the former the hydroxyl groups on silicon are separated by a methyl group while on the latter the hydroxyl groups are on adjacent silicon atoms and in neither case were there any interactions with Al either as Al^{3+}$_{(aq)}$ or as Al(OH)$_{3(s)}$ [15]. There have been several suggestions throughout the scientific literature pertaining to possible reactions of Si(OH)$_4$ with other metals and metal hydroxides as well as other molecules including proteins and carbohydrates but none of these have been supported by the identification, separation, collection and, significantly, physical and chemical characterisation of the solid phases. There is every good reason to talk about the unique inorganic chemistry of Al with Si(OH)$_4$ and to elucidate those characteristics of the reactants (Al(OH)$_{3(s)}$ and Si(OH)$_4$) which define the reaction pathways and products [12,15].

2.4. Solubility constants for hydroxyaluminosilicates

It has proven extremely difficult to ascribe quantitative (thermodynamic) constants to the formation and stability of HAS$_{(s)}$. In doing so one would normally describe the formation of a solu-ble complex by applying an effective stability constant (K_a) and then a solubility product (K_{sp}) to its saturation and precipitation from solution. There are no soluble complexes of HAS$_{(s)}$ as they are formed from the reaction between a solid phase (Al(OH)$_{3(s)}$) and a solution species (Si(OH)$_4$). There are, perhaps, theoretical solution species of HAS if one accepts that a dimer of Al(OH)$_3^0$ is a solution species and it could react with one or two molecules of Si(OH)$_4$ and that the resulting 'species' would remain stable in solution (see Fig. 1). It is more realistic to consider the formation of HAS$_{(s)}$ as the competitive condensation of Si(OH)$_4$ at a surface of Al(OH)$_{3(s)}$ and to try to ascribe a solubility-like product to the resulting solid phase. When we investigated the dissolution of HAS$_{(s)}$ at pH 6.5 and 0.1 mol/L ionic strength it was immediately clear that this process was non-stoichiometric with Si(OH)$_4$ being released steadily over an 18 month period while Al was only released in detectable amounts after 12 (HAS$_A$) and 18 months (HAS$_B$). Al was similarly only slowly released by equivalent preparations of Al(OH)$_{3(s)}$ being detectable in bulk solutions after 12 months. None of the solid phases reached any sort of 'equilibrium' with the solution phase during 18 months though their rates of dissolution with respect to Al were different with HAS$_B$ being kinetically the most stable and Al(OH)$_{3(s)}$ the least [16]. We postulated that this kinetic stability could be quantified by means of a solubility constant which reflected the quasi-equilibrium between the solid phase and a fast-reactive form of Al, Al$_r$, which could be determined fluorimetrically using morin. When we applied this method to the determination of a solubility constant for Al(OH)$_{3(s)}$ we obtained a value for K*Al(OH)$_{3(s)}$ of $10^{-30.8\pm0.27}$ which compared favourably to the literature value for Al(OH)$_{3(gibbsite)}$ of $10^{-33.9}$. Using the same approach we determined a solubility constant for HAS$_B$ of $10^{-40.6\pm0.15}$ which, again, seemed to accurately reflect the increased kinetic stability of HAS$_B$ relative to Al(OH)$_{3(s)}$. One purpose of defining such a quantitative expression is to use it to predict Al solubility control in the natural and, potentially, physiological environment. This solubility constant predicts that HAS$_B$ will be the predominant secondary mineral phase controlling the solubility of Al in natural waters in which the pH > 4.0 and the [Si(OH)$_4$] > 0.1 mmol/L. While this cannot be considered a classical solubility product it has been tested for a wide range of natural waters and it has proved to be a realistic estimate of Al solubility control in such waters [17–20]. The geochemical significance of HAS$_{(s)}$ will not be elaborated upon herein as it was alluded to in one of our early publications and it has been expanded upon in our previous review in this journal [9,12]. However, while it does seem clear that HAS$_{(s)}$ have analogues in the natural environment, HAS$_A$ being identified as protoimogolite and HAS$_B$ as allophane, this has not been demonstrated unequivocally by experiment. It is important to stress that HAS$_{(s)}$ are not the product of the weathering or dissolution of minerals they are the product of the reactions of products of mineral weathering and dissolution. They are an integral component of the lithospheric cycling of Al in that their formation shifts the solubility control for Al from Al(OH)$_{3(s)}$ to the more sparingly soluble HAS$_{(s)}$. In this way the lithospheric cycling of Al ensures that only a negligible fraction of the Al in the Earth's crust is accessible to biota [1].

3. Silicic acid therapy in human disease

We have recently reviewed the role of HAS$_{(s)}$ in controlling the biological availability and hence toxicity of Al [15]. What perhaps is less well understood at this time is whether the protective effect of the formation of HAS$_{(s)}$ might extend to humans and human physiology. For example, what did Louis Pasteur have in mind when he said that; "Effects of silicic acid are destined to play a great and major role in therapy"? Whatever it was in the mid-nineteenth

century that heightened Pasteur's interest in the therapeutic possibilities of $Si(OH)_4$ has today remained largely unexplained though the therapeutic potential of $Si(OH)_4$ continues to be of significant interest [21]. The fascination with $Si(OH)_4$ and health probably originates from the reputed health benefits of both bathing in, and partaking of, mineral or spa waters rich in $Si(OH)_4$. Such purported health benefits have received scientific support in the latter half of the twentieth century from experiments which demonstrated the nutritional essentiality of silicon in laboratory animals [22]. Indeed research using both animals and plants continues to this day to strongly support the notion that living things grow better and are healthier when their environment is replete with silicon [23,24]. If it is generally agreed that silicon is beneficial there is no such consensus concerning the mechanism of silicon's essentiality. Myriad experiments over decades of research have failed to identify any silicon biochemistry. There are no silicon complexes in any biochemical system. There are no Si–C, Si–N, Si–O–C/N bonds in any biological process. $Si(OH)_4$ is a neutral monomer under almost all possible physiological conditions. How can such a molecule, whose closest analogue in biological systems is water, be beneficial to life [2]?

In the late 1980s we made the serendipitous discovery that $Si(OH)_4$ protected salmon from the toxicity of Al in acid waters [25]. Al is the chief antagonist of the devastation which is wreaked on fish and forests by acid rain and while we were trying to understand the mechanism of toxicity of Al in fish we stumbled upon the protective effects of $Si(OH)_4$. We were able to show that the benefits of $Si(OH)_4$ were accrued through its unique inorganic chemistry with Al in forming $HAS_{(s)}$. We went on to define $Si(OH)_4$ as a geochemical control of the biological availability of Al and to propose that the mechanism of silicon essentiality in life was through its exclusion of Al [26]. Put simply, many if not all of the symptoms of purported silicon deficiency might be explained as Al toxicity. The ecotoxicology of Al is well known though our understanding of how exposure to Al impacts upon human health is far less well understood [4]. Following our work on salmon we immediately hypothesised that $Si(OH)_4$ would act so as to reduce human exposure to Al. Evidence supported a role for $Si(OH)_4$ in reducing the gastrointestinal absorption of Al [27] and more recently for $Si(OH)_4$ to facilitate the urinary excretion of systemic Al [28,29]. However, the chemistry which potentially underlies such effects, the formation of $HAS_{(s)}$, is not easy to understand in the context of human physiology and most likely relies upon concentrations of $Si(OH)_4$ which are higher than are normally found in, for example, potable waters and, consequently, human blood and tissues. Indeed there is evidence that lower concentrations of $Si(OH)_4$ could increase the biological availability of Al which in humans could be manifested as greater absorption of Al across the gut [30]. Epidemiological studies have, for example, suggested that potable waters with concentrations of $Si(OH)_4$ above 0.2 mmol/L show some protection against Alzheimer's disease [31]. We would suggest that any such protection afforded by $Si(OH)_4$ would be much greater for concentrations in excess of 0.5 mmol/L. We make this suggestion based upon our research with silicon-rich mineral waters in which it has become clear that such greatly facilitate the urinary excretion of Al and that the mechanism seems to involve a pulse of $Si(OH)_4$ at high concentration entering the blood and thereby purging Al from the body via the kidney [29]. As was mentioned previously, the closest chemical, and indeed biological, analogue to $Si(OH)_4$ is water and it is probably true to say that the body's natural level of $Si(OH)_4$, the concentration in plasma, is roughly in dynamic equilibrium with $Si(OH)_4$ in the environment. Populations living in geographical regions in which the environmental $Si(OH)_4$ concentrations are low due to geological processes in the catchment will have lower 'background' levels of $Si(OH)_4$ in the body [32] and this may increase their susceptibility to exposure to Al. They may be more prone to the absorption and retention of Al as well as the potential biological effects, toxicity, of systemic Al. We believe that any such enhanced exposure to Al could be countered by including a $Si(OH)_4$-rich mineral water in the everyday diet. While this is an obvious way to boost one's protection against environmental Al it might be that herein also lies the secret of $Si(OH)_4$-rich bathing waters? We have stated in previous work that biology is permeable to $Si(OH)_4$ [33] and it would be a very interesting study to find out if regular bathing in $Si(OH)_4$-rich waters resulted in higher blood levels of $Si(OH)_4$ and reduced susceptibility to Al-related disease?

4. Conclusions

I would argue that the reaction of $Si(OH)_4$ with $Al(OH)_{3(s)}$ is fundamental to life on Earth as we experience it today. While a lack of clear biological essentiality for silicon might otherwise be equated with a lack of biological significance I would suggest that there has not been any more an influential role in the natural selection of the elements of life than that of $Si(OH)_4$ in keeping $Al^{3+}_{(aq)}$ out of biota for the majority of biochemical evolution. It is only very recently that we have begun to understand this unique inorganic chemistry and the majority of that understanding has, to-date, been obtained in synthetic systems. I am confident that there is much more to be understood and, in particular in physiological milieu. I share Pasteur's prescient understanding of the therapeutic potential of $Si(OH)_4$ and I look forward, with some hope, towards being able to put such an hypothesis to the test.

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