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Coordination Chemistry Reviews
149 (1996) 1–9

COORDINATION CHEMISTRY REVIEWS

Aluminium and biological systems: an introduction

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Received 26 April 1995

Abstract

The involvement of aluminium in biological systems is very slight. The chemistry of this element indicates that it and in fact all simple trivalent cations with no redox properties are avoided since they are too powerful as Lewis acids and their reactions are in slow exchange relative to those of the divalent ions such as magnesium and zinc. There is also an interactive chemistry with silicon and this could limit aluminium availability in some waters and even protect within organisms. The toxicity of aluminium in cellular systems is well documented but its involvement in specific diseases such as Alzheimer's, remains uncertain.

Keywords: Aluminium; Biological systems; Silicon

1. Introduction: essential elements

It is now commonly accepted that all the living systems we have discovered including the most primitive archaebacteria require some 15 to 20 essential elements. There is no known life without this degree of complexity [1]. It is immediately interesting to compare these requirements with the Periodic Table of the Chemical Elements, Fig. 1. This table represents similarities between elements in eighteen Groups so that for example sodium is more like lithium and potassium than any other elements. Maximum chemical diversity is then expressed in the eighteen Groups. A chemical system such as a biological cell which needs to undertake selectively a huge variety of chemical tasks within its structures and metabolism can in principle achieve this end best by making use the diversity of seventeen of these groups. We exclude the inert or noble gases, for obvious reasons. Before we examine this expectation there is a restriction upon biological systems — element availability which becomes very much reduced down the Groups of the Table but is also low for Li, Be and B. The availability is partly due to element abundance (on Earth) and partly due to solubility in water (of salts) of the elements or to formation of gas molecules. The elements in and after the second long period of the table become extremely rare through low abundance and most elements in this period are also of

TABLE 1 — IUPAC PERIODIC TABLE OF THE ELEMENTS

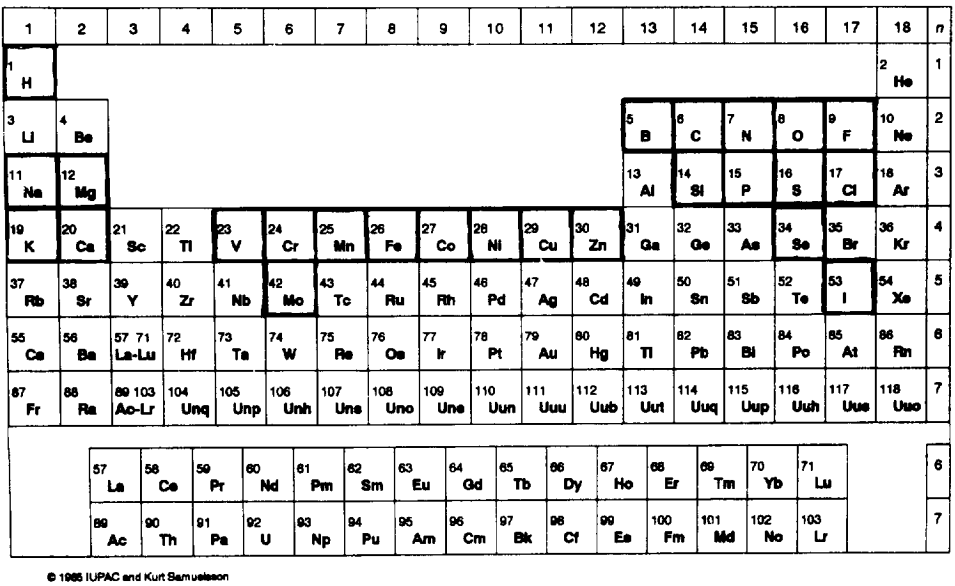


Fig. 1. The Periodic Table. The elements in heavily lined boxes are those known to be essential for the majority of organisms.

low availability through the form in which they occur. Exceptions include Sr, Mo and I. We now look at the elements found in functional use in biology. The list of elements is

Na (K), Mg (Ca, Sr, Ba), B, V, Mo (W), Mn, Fe, Co, Ni, Cu, Zn,

C (Si), N (P, As), O (S, Se), Cl (F, Br, I).

The underlined elements probably have functional use in all organisms, making a total of some 18. Some elements are only rarely of functional value e.g. Ba, As and Br. The conclusion is that expectation is borne out in that biological systems make full use of the Periodic Table's diversity in 17 groups with four exceptions, see below, and that limited availability down Groups does not allow access to many heavy elements.

The striking feature of this list in the context of this special issue of Coordination Chemistry Reviews is the exception. No metal element from group 3, 4, or 13 and 14 is essential for any known living system. (Note that non-metals are used in Groups 13 (B), 14 (C) — and it is their metals which are avoided.) This includes aluminium, scandium, titanium and tin and all their nearest chemical relations lower in same groups. Thus high valent metal ions are rejected by biology. What is it that is particularly nasty about such elements that they find no functional use. In particular, what is biology's case against aluminium? It is not that it is not available. We look to chemistry for an explanation.

2. The chemistry of aluminium

This special issue contains all the relevant aluminium chemistry in some detail and here I need give only the briefest of summaries. Aluminium is available in the sense that in water it is much more available than iron(III), an element which all biological cells contain. Biological systems could have obtained aluminium since although its concentration is low, 10^{-11} M at pH = 7.0, that of iron(III) is much lower, 10^{-17} M. Again aluminium could be stored in vesicles, say approaching 10^{-3} M at pH = 4. Iron is readily stored by many cells. The transport of aluminium is greatly increased by complex ion formation and here we know that ligands such as fluoride, citrate or organic phosphates can mobilise it. A list of the best binding agents [2–4] is given, see Table 1. Much of its binding strength is due to its charge. Availability, transport and storage of aluminium are therefore not problems.

A second feature of aluminium as an ion is that it has a high electron affinity which together with its charge makes it an excellent Lewis acid catalyst. The uses of $AlCl_3$ in organic chemistry are well-known. There does not appear to be good reason for not using it as a catalyst in any chemical system. (In passing, note that all the trivalent ions, Ga^{3+}, Sc^{3+}, Y^{3+}, Ln^{3+} and the ions such as TiO^{2+}, Sn^{4+} could have been obtained from natural sources, much as Al^{3+} could have been obtained, and they too would have made strong catalysts but living cells do not absorb any of them).

The third feature of Al^{3+} chemistry is that it exchanges ligands slowly Fig. 2 even from $[Al(H_2O)_6]^{3+}$.

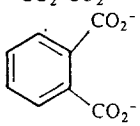
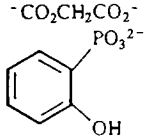
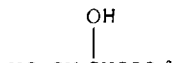
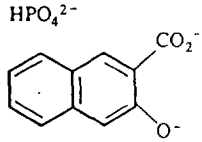
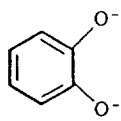
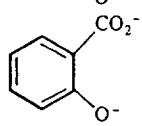
3. The comparative chemistry and biochemistry of magnesium and silicon

In the description of chemical elements it is generally useful to compare neighbours in a period as well as within a Group. This is especially true here since the neighbours of aluminium are much used in living systems. The neighbours of aluminium are Mg and Si. (Boron and related elements of Groups 3 and 13 are not very available, as already stated). Magnesium is very available as a cation $>10^{-3}$ M at all pH values and forms few precipitates but many somewhat weak complexes (Table 1). Silicon is available also at 10^{-3} M as $Si(OH)_4$ in water at pH = 7 but it precipitates as a hydrous gel above this concentration and above pH = 6 readily forms silicates particularly with Al^{3+}. Many plants precipitate $Si(OH)_nO_{2-2n}$, silicas, as opals. No other use is known for silicon.

Magnesium is a weak Lewis acid catalyst, far weaker than Al^{3+}, and magnesium exchanges quite slowly from $Mg(H_2O)_6$, (Fig. 2). Silicon acts as a catalyst only on surfaces and especially with aluminium in zeolites from which it does not exchange.

In all this chemistry there are no redox reactions. We see that while magnesium and silicon are admitted in cells and used there is no admittance or use for aluminium. Why is this? The answer can be looked for at two levels: firstly, in extracted biochemical systems and secondly in biological systems.

Table 1
Values of log K_M for dibasic acid anions[a,c]

		log $K_M(I \rightarrow 0)$		
	pK_a	Na^+	Ca^{2+}	Al^{3+} (unless otherwise stated)
SO_4^{2-}	2.0	0.7	2.3	3.2[b]
$^-CO_2 \cdot CO_2^-$	4.3	–	3.0	7.4
	4.7	–	2.4	4.5
$^-CO_2CH_2CO_2^-$	5.7	0.7	2.4	7.1 (Sc^{3+})
	6.5	–	–	9.5 (Fe^{3+})
	6.6	–	2.1	–
$HOCH_2PO_3^{2-}$	7.0	1.0	2.2	–
HPO_4^{2-}	7.2	1.1	2.7	9.7
	12.8	–	–	13.4
	13.0	–	6.1 (Mg^{2+})	17.4
	13.7	–	4.7	14.1

[a] The data are taken from Ref. [1] unless otherwise stated and corrected to zero ionic strength whenever necessary with the equation

$$\log f_{\pm} = -0.5091\,|z_1 z_2|\left(\frac{I^{1/2}}{1+I^{1/2}} - 0.3I\right)$$

[b] The datum is taken from Ref. [2].

[c] At pH = 7 all data for ligands with p$K_a > 1$ need to have log K_M corrected to the effective value to allow assessment of competition.

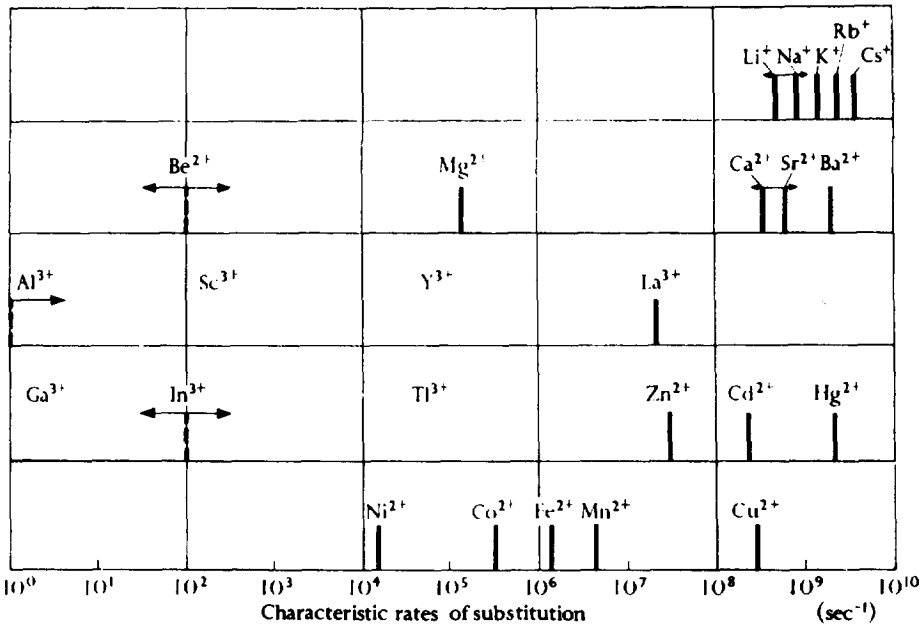
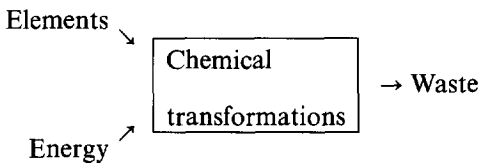


Fig. 2. Characteristic rates of substitution. Rates of water exchange for various cations. The reaction studied was $M(H_2O)_n^q + SO_4^{2-} \rightarrow [M(H_2O)_m SO_4]^{(q-2)+} + (n-m)H_2O$ (from M. Eigen, Seventh International Conference on Coordination Chemistry, Butterworths, London, 1963).

4. Requirements of a cell

A cellular organism of any kind has to be viewed as a flow system. Thus we can write it as a box



Within this box what makes Mg^{2+} so valuable and Al^{3+} fit only for rejection? The answer can be seen by looking at the roles of Mg^{2+}. Firstly it is used to stabilise structures often with a low-binding constant of 10^3 to 10^4. Of overwhelming importance however is its use as a weak catalyst especially in phosphate metabolism and in energy transduction. (We leave aside the use of Mg^{2+} in chlorophyll which is a very special binding to generate the specific absorption spectrum of this pigment). Again without reference to any detail Mg^{2+} binds in its enzymes and to the phosphate groups of nucleotide di- and tri-phosphates NDP and NTP, with a constant of around 10^4. The case of adenosine triphosphate (ATP) is most common. The function of Mg^{2+} with NTP and NDP is to stabilise the terminal P—O—P bond in both free NDP ($\alpha\beta$ bond) and NTP ($\beta\gamma$ bond) until it is bound in say a kinase enzyme

site. Here the Mg^{2+} helps to labilise the terminal γ-β phosphate bond of NTP by moving to the α-β bridge of NDP. The scheme is shown in Fig. 3. These reactions are part of absolutely central kinase transformations which all life is known to use. They have rate constants of around 10^3 per sec which is all that is required given the rates of general biological metabolism. (Remember that biological systems are controlled flows and individual steps do not go as fast as possible but at rates commensurate with many other steps so that the whole system acts cooperatively). In the above it is obvious that the slow association/dissociation of Mg^{2+}, Fig. 2, does not limit phosphate metabolism and all its functions have rate constants of the required speed so that the chemistry of magnesium is not rate limiting in life. Thus Mg^{2+} is an ideal catalyst (weak though it is) for controlling reaction steps where the activation energy for reaction is low. The ligands must all be oxygen donors to remove competition from transition metals. (Aluminium also is favoured by O-donor ligands.)

Now let us consider the consequences of replacing Mg^{2+} by Al^{3+} in an enzyme such as a kinase. The binding to NDP and NTP is now much stronger $>10^7$ but

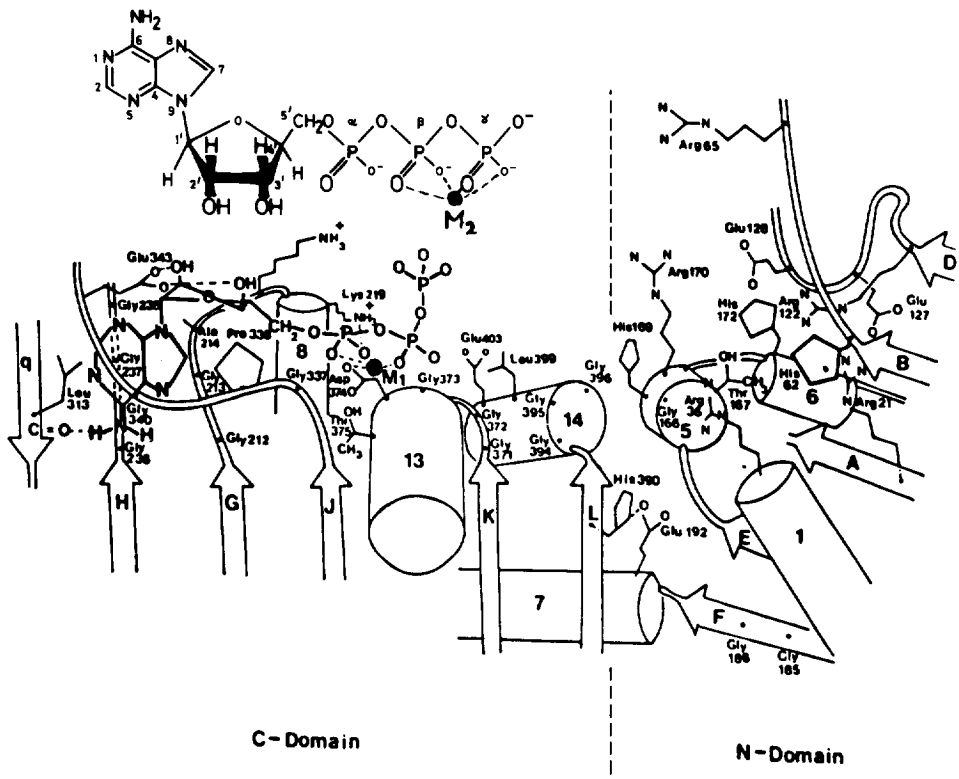


Fig. 3. (top, left) The formula of magnesium bound to free adenosine triphosphate, ATP. (below) The structure, in part, of a kinase, phosphoglycerate kinase, showing the activated form of Mg·ATP in which the Mg^{2+} ion sits between the α,β phosphates.

certainly if the aluminium bound to the $\beta\gamma$ groups of NTP and then moved to the $\alpha\beta$ site it would readily hydrolysis NTP. However if the aluminium is bound initially to the $\beta\gamma$ groups (which is probable) on an enzyme, the required displacement of the Al^{3+} to the $\alpha\beta$ phosphates is inhibited by the very slow rate at which Al^{3+} leaves any ligand, e.g. H_2O, and the even slower rate at which it leaves a ligand such as NTP with a strong binding constant. In fact the Al^{3+} ion is not active in kinases in all probability because of its movement with a restricted rate constant of seconds. Here lies the problem with high valent ions. In themselves they are not useful catalysts because of slow exchange while once in a system they would block binding of ions such as magnesium because they have higher binding constants. Thus quite probably aluminium must be excluded because of its affinity for phosphates. How this situation is affected by the presence of other anions, e.g. fluoride, is a matter of intensive study in several papers.

The role of silicon must not go unnoticed in this discussion. It is often taken up by plants, especially grasses, but also primitive plants such as equisetum. The silicon is deposited as opals in leaves and elsewhere. Now aluminium silicates are insoluble and might be expected to precipitate any aluminium associated with it. In fact virtually no Al^{3+} is found in opaline precipitates of plants. This could be due to the nature of plant sap which is at a pH around 5.5 where aluminium silicate does not precipitate. Analysis shows however that effectively aluminium is not taken into plants, despite the fact that plants use citrate as an iron carrier. Silicon is not known to be used inside any cell and is not known to have any catalytic function. Thus inside plants there is no known silicon/aluminium or silicon/iron interaction from chemical studies. This does not exclude indirect interactions.

The possible role of silicon hydroxides as protecting agents against aluminium toxicity suggested by Birchall is under intensive study. There are two levels to these studies.

(1) Removal of Al^{3+} by $Si(OH)_4$ in natural waters. Here there may be little effect at $pH < 6.5$ where aluminium silicates are soluble.

(2) Removal of Al^{3+} on to the surface by mutual Al/Si absorption especially in a biological system. In this second case the question of competitive binding by such ligands such as phosphates and citrate relative to silicate has to be examined in detail. The outside of cells is not so well protected as the inside of course. The critical interest is of course of biological effects interesting though chemical analyses of them may be.

5. Aluminium toxicity

5.1. (a) Plants

We believe that aluminium solubilised by acid conditions is toxic to many plants because of its effects on the surface of roots. It will antagonise calcium binding essential for root cell surfaces under these conditions. The reasons are simple in that the free Al^{3+} ion concentration at equilibrium with precipitates rise as $[H^+]^3$ whereas

free Ca^{2+} in water is not greatly affected by acidity and certainly not more than by $[H^+]$. For a ligand with a low pK_a such as the carboxylate groups of cell surfaces the probability of Al^{3+} binding at a Ca^{2+} site increases as $[H^+]^2$. Unfortunately at a pH value much below about 6.5 the addition of silicic acid may well have little effect (see above). The only real remedy is to keep the pH of soil water high in the presence of silica.

5.2. *(b) Animals*

Animals are very different from plants in two major ways. Their diet is a low in aluminium since they eat plants. Moreover their circulating fluids are high in calcium 3 mM and magnesium 3 mM and are maintained at pH > 7. Thus internally they are well protected from aluminium. Two conditions militate against this. One is the case of animals which live in fresh water and then meet the problem of aluminium contamination from acidified soils. The other is the accidental introduction of aluminium into animals through mal-treatment of drinking water, medical treatment directly into the blood, and abnormal breakdown of physiological barriers, which may well increase in old age and becomes a hazard in some diseases. Let us assume that aluminium succeeds in entering a cell.

Aluminium may now assist in causing cellular damage by the following route. Let the diseased condition be a mutation of a reaction system leading to increased phosphorylation

$$\text{(proteins)Pr} \rightarrow \text{aberrant phosphorylation } PrP_x.$$

The higher level of phosphorylation assists Al^{3+} binding

$$PrP_x + Al^{3+} \rightarrow PrP_x \cdot Al^{3+}$$

This reaction in a cell could cause cell death and exposure of the PrP_xAl outside the cell. There is then the subsequent possibility of further interaction with a large range of cations normally in high concentration outside cells but with which the cell contents now come into contact

$$PrP_xAl^{3+} + M \rightarrow PrP_xAlM\downarrow \text{ (plaque)}$$

Thus aluminium-containing plaques might be formed.

If this outline is true then two approaches to these damaging effects are possible

(a) Total cure by removal of aberrant phosphorylation e.g. by gene therapy.
(b) Reduction of the effect of phosphorylation by keeping $[Al^{3+}]$ low.

These approaches are described in Chapters C 1–2.

Given that we do not understand diseases such as Alzheimer's disease it pays us to study both phosphorylation and aluminium effects carefully. We all believe that we need protection from aluminium and similar elements but how does cell chemistry manage this without interference in normal life? These problems of aluminium are not yet solved but in the following chapters we can see how different investigators see the problems and possible solutions to them.

References

[1] J.R.R. Frausto da Silva and R.J.P. Williams, The Biological Chemistry of the Elements, Oxford University Press, Oxford, 1991.
[2] B.R. Martin in, D.J. Chadwick and J. Whelan (Eds.), Aluminium in Biology and Medicine Ciba Foundation Symposium 169, J. Wiley and Sons, Chichester, UK, 1992, pp. 5–25.
[3] R.M. Smith and A.E. Martell, Critical Stability Constants, Plenum, New York, 1975.
[4] S.C. Tam and R.J.P. Williams, J. Inorg. Biochem. 26 (1986) 35–44.