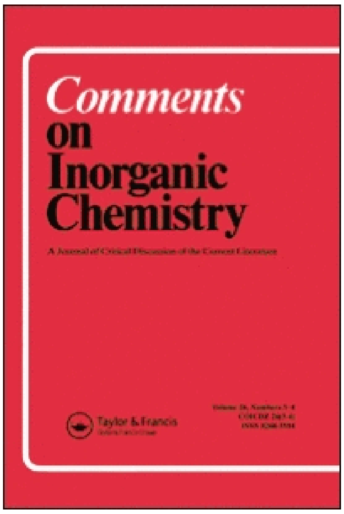

Comments on Inorganic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455155

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To cite this Article Crumbliss, Alvin L. and Garrison, J. Mark(1988) 'A Comparison of Some Aspects of the Aqueous Coordination Chemistry of Aluminum(III) and Iron(III)', Comments on Inorganic Chemistry, 8: 1, 1 — 26
To link to this Article: DOI: 10.1080/02603598808048670
URL: http://dx.doi.org/10.1080/02603598808048670

A Comparison of Some Aspects of the Aqueous Coordination Chemistry of Aluminum(III) and Iron(III)

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The aqueous coordination chemistry of Al^{3+} and Fe^{3+} is compared. The differences in electronegativities (χ_m), ionic radii (r_i) and electron configuration (d^n) for the two ions are shown to influence trends in aquo ion structure and reactivity, hydrolysis, and metal complex stability. Similarities in coordination chemistry result in similarities in distribution and modes of transport for Al^{3+} and Fe^{3+} in a biological system.

Key Words: *aluminum, iron, kinetics, mechanism, stability, hydrolysis, bioinorganic*

INTRODUCTION

In this brief essay we will compare and contrast certain aspects of the aqueous coordination chemistry of aluminum(III) and iron(III). Aluminum is the most abundant metal on the earth's crust and iron, along with calcium and sodium, is nearly as abundant. Their aqueous coordination chemistry is similar in many respects and is important in determining their reactivities and chemical speciation. The utility of an element to a biological system is related to its abundance and its accessibility (bioavailability). Iron is an essential element whose key biological functions involve oxidation/reduc-

Comments Inorg. Chem.
1988, Vol. 8, Nos. 1 & 2, pp. 1–26
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Printed in Great Britain

tion and interactions with O_2. Aluminum plays no essential biological role (except possibly in the case of a few plants) and in many instances has been found to be toxic.

Although there are significant similarities between the aqueous coordination chemistry of aluminum and iron, there are also differences. Most notable are the facile redox reactions and spin state changes possible for aqueous iron(III), but not aluminum(III). Consequently, our comparison will be limited to the spherically symmetrical aqueous metal ions: high spin d^5 iron(III) and d^0 aluminum(III).

An example of the practical application of the similarities in the aqueous coordination chemistry of aluminum(III) and iron(III) is in the use of deferriferrioxamine B as a therapeutic agent. Deferriferrioxamine B is a microbially synthesized chelating agent whose biological function is to make iron bioavailable to certain microorganisms.[1–3] In order to perform this function, deferriferrioxamine B must exhibit a high and relatively specific affinity for environmental iron. Deferriferrioxamine B is currently the US-FDA approved drug (Desferal®, Ciba-Geigy) for use in the treatment of transfusion induced iron overload associated with β-thalassemia (Cooley's Anemia).[4] This same compound has also been used as an aluminum chelator for patients suffering from Alzheimer's disease.[5]

The similarities and differences in the aqueous coordination chemistry of Al^{3+} and Fe^{3+} will be linked to the difference in ionic radii and electronegativities of the two ions, and the resulting effect of these two parameters on aqueous ion structures, hydrolysis, ligand exchange kinetics, complex stability, and distribution in a biological system.

THE AQUEOUS M^{3+} IONS

Information concerning the structure of the primary and secondary coordination shells of M^{Z+}_{aq} in aqueous solution can be obtained from partial molar volumes. If one assumes that the effective volume of a $M(H_2O)^{Z+}_n$ core may be represented by a sphere of radius r_i + 238.5 pm and the solvent electrostriction beyond the primary solvation shell as $1.305Z^2$, then the absolute partial molar volume,

$\overline{V}^0_{\text{abs}}$, may be calculated according to Eq. (1),

$$\overline{V}^0_{\text{abs}} \approx 2.523 \times 10^{-6}\,(r_i + 238.5)^3 - 18.07n - 1.305Z^2 \quad (1)$$

where r_i is the ionic radius of Al^{3+} (53.5 pm) or Fe^{3+} (64.5 pm),[6] n is the primary solvation or coordination number, Z the charge on the ion (+3) and $\overline{V}^0_{\text{abs}}$ the absolute partial molar volume in cm³/mole relative to −5.4 cm³/mole for H^+ at 298°K.[7,8] Calculated values for $\overline{V}^0_{\text{abs}}$ for Al^{3+}_{aq} and Fe^{3+}_{aq} assuming a coordination number (n) of 6 for each ion are -57.4 cm³ mol⁻¹ and -50.0 cm³ mol⁻¹, respectively. These values are in excellent agreement with experimental data[8] and confirm identical coordination numbers of 6 for Al^{3+} and Fe^{3+} in aqueous medium.

Both $Al(H_2O)_6^{3+}$ and $Fe(H_2O)_6^{3+}$ share a strong tendency to form a second hydration shell consisting of 12 water molecules[9–11] as illustrated in Fig. 1. The bound water molecules assume a trigonal orientation with short hydrogen bonds. The small differences

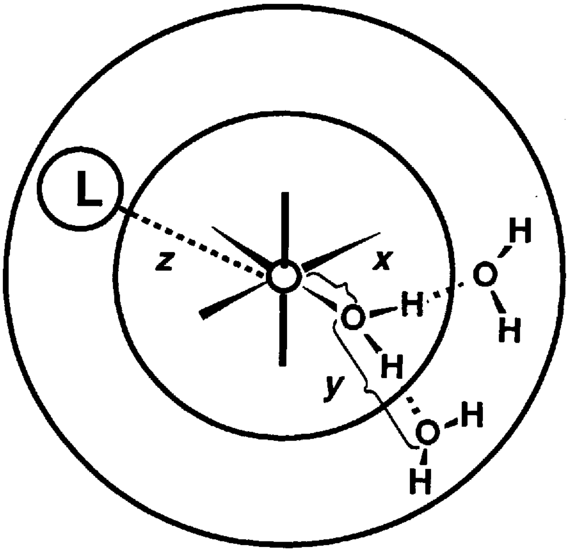


FIGURE 1 Primary and secondary solvation shell structure for $Al^{3+}_{(aq)}$ and $Fe^{3+}_{(aq)}$. For Al x = 190 pm and y = 273 pm (Refs. 9 and 10). For Fe x = 204 pm and y = 270 pm (Ref. 11). When L = Cl^-, z = 383 pm for Al and 384 pm for Fe as calculated from Eq. (7).

TABLE I

Comparison of $Al(H_2O)_6^{3+}$ and $Fe(H_2O)_6^{3+}$ hydrolysis constants

Species Formed From $M(H_2O)_6^{3+}$	pK_h^a	
	M = Al(III)	M = Fe(III)
$M(H_2O)_5(OH)^{2+}$	5.4	2.56
$M(H_2O)_4(OH)_2^+$	9.98	6.19
$M(OH)_3$	15.7	10
$M(OH)_4^-$	23.6	21.9
$M_2(OH)_2^{4-}$	7.7	2.85
$M_3(OH)_4^{5+}$	13.7	6.1

[a] pK_H = −log(hydrolysis constant) for the reaction $xM(H_2O)_6^{3+} + yH_2O \rightleftharpoons M_x(OH)_y^{(3x-y)+} + yH^-$; all data are for 298°K taken from Ref. 12.

in $\overline{V}^0_{abs}$ and size of the primary and secondary coordination shells are a direct consequence of the difference in ionic radii for the two ions.

The hydrolytic properties of $Al(H_2O)_6^{3+}$ and $Fe(H_2O)_6^{3+}$ govern the polymerization and solubility of the two metal ions in aqueous media. A comparison of hydrolysis constants is given in Table I. The first hydrolysis constant for iron is about 1000 times larger than for aluminum. The hydrolysis constants of subsequent steps involving Fe^{3+}_{aq} are also greater and iron is polymerized and precipitated from solution at a lower pH than aluminum. The structures of the hydrolytic ions also differ. The important hydrolytic dimer for Fe^{3+}_{aq} is $(H_2O)_5Fe{-}O{-}Fe(H_2O)_5^{4+}$.[13] Rapid hydrolysis of Al^{3+}_{aq} by Na_2CO_3 produces $Al_2(OH)_2(H_2O)_8^{4+}$ and $AlO_4Al_{12}(OH)_{24}(H_2O)_{12}^{7+}$.[14,15]

The greater acidity of $Fe(H_2O)_6^{3+}$ relative to $Al(H_2O)_6^{3+}$ can be correlated with the greater electronegativity of Fe(III) ($\chi_{Fe(III)}$ = 1.96; $\chi_{Al(III)}$ = 1.61[16]). Figure 2 is a plot of pK_h for reaction (2) as a function of the

$$M(H_2O)_6^{z+} \xrightleftharpoons{K_h} M(H_2O)_5OH^{(z\quad 1)+} + H^+ \qquad (2)$$

product of metal ion charge (Z) and electronegativity (χ_m) for a number of spherically symmetrical (d^0, d^{10} and high-spin d^5) aquo ions. The linear correlation shown in Fig. 2 suggests that the ease with which a proton dissociates from a metal bound water molecule is directly related to the polarization of the $M{-}OH_2$ bond (increase

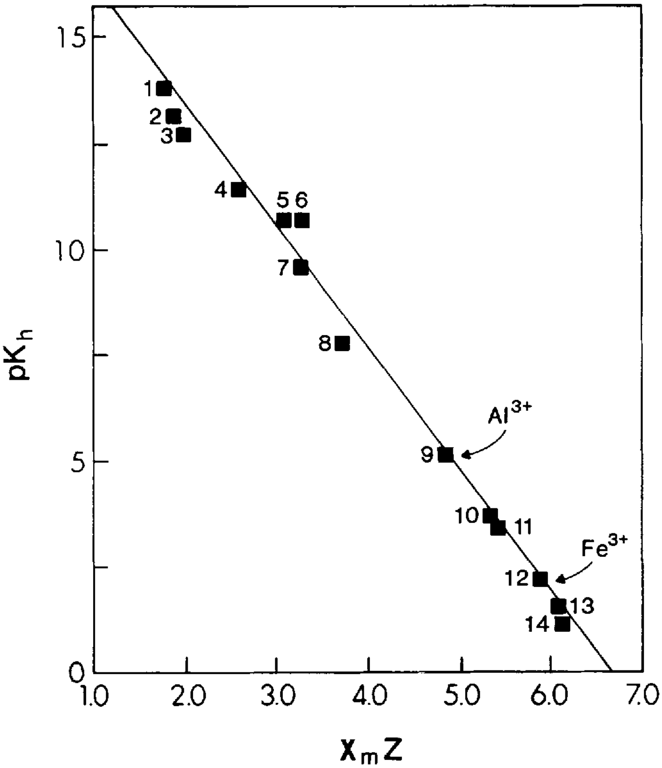


FIGURE 2 Plot of pK_h for reaction (2) as a function of metal ion electronegativity (χ_M) times charge (Z) for d^0, d^{10} and high-spin d^5 metal ions at 25°C. Electronegativity data are from Ref. 16 and pK_h data are from Refs. 12 and 17–20. Symbols: 1, Ba^{2+}; 2, Sr^{2+}; 3, Ca^{2+}; 4, Mg^{2+}; 5, Mn^{2+}; 6, La^{3+}; 7, Zn^{2+}; 8, Pb^{2+}; 9, Al^{3+}; 10, In^{3+}; 11, Ga^{3+}; 12, Fe^{3+}; 13, Bi^{3+}; 14, Ti^{3+}.

in M–O covalent bond character due to an increase in metal ion electronegativity), which results in a greater polarization of the MO–H bonds.

REACTIVITY WITH RESPECT TO LIGAND SUBSTITUTION

Solvent Exchange Reactions

Consideration of the kinetics of solvent exchange is important for an understanding of the intrinsic reactivity pattern of a solvated

TABLE II

Comparison of the kinetic parameters for water exchange on M^{3+}_{aq}

Parameter	$Al(H_2O)_6^{3+}$ [a]	$Fe(H_2O)_6^{3+}$ [b]	$Fe(H_2O)_5(OH)^{2+}$ [c]
$k^{298}_{H_2O}(s^{-1})$	1.29	1.67×10^2	1.4×10^5
$\Delta H^{\ddagger}$ (kJ/mole)	84.7	64.0	42.4
$\Delta S^{\ddagger}$ (J/°K-mole)	+41.6	+12.1	+5.3
$\Delta V^{\ddagger}$ (cm³/mole)	+5.7	−5.4	+7.0

[a] Reference 21.
[b] References 22–24.
[c] References 22 and 23.

metal ion. Aquo exchange rate constants and activation parameters for $Al(H_2O)_6^{3+}$ and $Fe(H_2O)_6^{3+}$ are listed in Table II. The 10^2 increase in water exchange rate constant for Fe^{3+} over Al^{3+} is a result of the increased size of Fe^{3+} (Fig. 1). The influence of size on the water exchange rate constant is illustrated in Fig. 3, which is a plot of log k_{H_2O} for the water exchange reaction (3):

$$M(H_2O)_6^{Z+} + H_2O^* \xrightarrow{k_{H_2O}} M(H_2O)_5(H_2O^*)^{Z+} + H_2O \qquad Z = 2,3 \tag{3}$$

as a function of the charge to ionic radius ratio (Z/r_i) for a series of spherically symmetrical metal ions. A similar plot of log k_{H_2O} as a function of $X_m \cdot Z$ shows no correlation. This plot illustrates that for metal ions where ligand field effects are not important water exchange rates are controlled by cation–water dipole electrostatic interactions as measured by Z/r_i. The markedly enhanced rate of water exchange for $Fe(H_2O)_5OH^{2+}$ (750 times that for $Fe(H_2O)_6^{3+}$; Table II) is consistent with this trend. The overall charge on the monohydroxy ion is reduced to +2, and in addition coordinated OH^- is known to have a labilizing effect. The divalent aquated ferrous ion, $Fe(H_2O)_6^{2+}$, has a lower charge and larger ionic radius (r_i = 78 pm[6]) than $Fe(H_2O)_6^{3+}$ and consequently a larger k_{H_2O} ($4.4 \times 10^6\ s^{-1}$)[30] value.

The symmetrical nature of the solvent exchange process helps in making mechanistic interpretations. First, the influence of thermodynamic driving force is eliminated. Second, the principle of

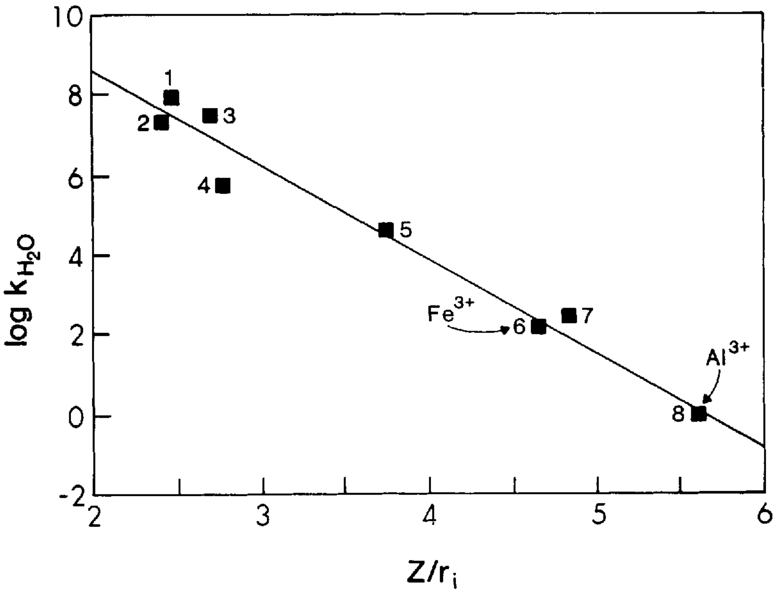


FIGURE 3 Plot of log k_{H_2O} for reaction (3) at 25°C as a function of charge to ionic radius ratio (Z/r_i) for a series of d^0, d^{10} and high-spin d^5 aquo ions. Ionic radii are from Ref. 6 and k_{H_2O} data from Refs. 21, 22 and 25–29. Symbols: 1, La^{3+} [25]; 2, Mn^{2+} [26]; 3, Zn^{2+} [27]; 4, Mg^{2+} [26]; 5, In^{3+} [28]; 6, Fe^{3+} [22]; 7, Ga^{3+} [29]; 8, Al^{3+} [21].

microscopic reversibility requires that the forward and reverse reaction paths be symmetrical. Therefore, the transition states for reactions with discrete intermediates (A or D) will have identical free energies. For interchange processes (I) with no discrete intermediates it is the transition state itself which must be symmetrical.[31–33] Consequently, in a dissociative interchange (I_d) process both entering and leaving ligands will have the same weak interaction with the metal center, while in an associative interchange (I_a) process both entering and leaving ligands will exhibit the same degree of bonding interaction with the metal center.

The volume of activation, $\Delta V^\ddagger$, is the difference in partial molar volume between the transition state and ground state. Partially because of this symmetrical feature of the solvent exchange reaction, $\Delta V^\ddagger$ data are particularly useful for making mechanistic interpretations.[33] The volume of activation may be broken down further into an intrinsic contribution, $\Delta V^{\ddagger}_{\text{int}}$, and a contribution due to the electrostriction of the solvent, $\Delta V^{\ddagger}_{\text{elec}}$; neither of these components are directly measurable.

$$\Delta V^{\ddagger} = \Delta V^{\ddagger}_{\text{int}} + \Delta V^{\ddagger}_{\text{elec}} \tag{4}$$

The intrinsic contribution is a measure of the changes in internuclear distances as the reactants come together to form the transition state and is of importance in making mechanistic assignments. In a solvent exchange process solvent electrostriction may be assumed to be constant; therefore, $\Delta V^{\ddagger}$ is directly related to $\Delta V^{\ddagger}_{\text{int}}$ and is a measure of the compactness of the transition state relative to the reactants. Consequently, $\Delta V^{\ddagger} < 0$ may readily be interpreted as an associative process and $\Delta V^{\ddagger} > 0$ as a dissociative one. Furthermore, consideration of the magnitude of $|\Delta V^{\ddagger}|$ may suggest limiting values which are indicative of A or D processes.[33]

Activation volumes for water exchange are listed in Table II. Based on their signs and magnitudes, water exchange at $Fe(H_2O)_6^{3+}$ is presumed to be associative, while $Al(H_2O)_6^{3+}$ and $Fe(H_2O)_5OH^{2+}$ exhibit dissociative behavior. Both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Table II) are smaller for $Fe(H_2O)_6^{3+}$ than $Al(H_2O)_6^{3+}$ and so are consistent with this interpretation. $Fe(H_2O)_5OH^{2+}$ does not follow this pattern, but this may reflect some degree of H-bonding in the transition state. Since in all three cases $|\Delta V^{\ddagger}|$ is considerably less than Swaddle's[7] estimate of the limiting value 13 $cm^3\ mole^{-1}$ for a D or A process, an interchange process is assigned to these reactions: I_a for $Fe(H_2O)_6^{3+}$ and I_d for $Fe(H_2O)_5OH^{2+}$ and $Al(H_2O)_6^{3+}$. This mechanistic assignment seems to hold for other solvent systems (DMSO, DMF, TMP), although a larger $|\Delta V^{\ddagger}|$ suggests a D mechanism for Al^{3+}.[34]

The difference in activation modes for water exchange may be a direct result of the larger ionic radius for Fe^{3+}, which might be expected to more easily accommodate the increased bonding in the transition state associated with an associative process. However, it is likely that the deciding factor here is electronic structure and not size. Of particular relevance is $Ga(H_2O)_6^{3+}$, whose ionic radius (r_i = 62 pm[6]) is similar to Fe^{3+}, but whose $\Delta V^{\ddagger}$ (+5.0 cm^3/mole[29]) is similar to $Al(H_2O)_6^{3+}$. Hence the d^0 and d^{10} aquo ions $Al(H_2O)_6^{3+}$ and $Ga(H_2O)_6^{3+}$ undergo H_2O exchange via an I_d process while the d^5 ion $Fe(H_2O)_6^{3+}$ reacts via an I_a process. Apparently high-spin aquo ions with d^1 through d^5 electron configurations undergo water exchange via an associative process, with a changeover at d^6 to a dissociative process.[33,34] In the case of $Fe(H_2O)_5OH^{2+}$ the lower charge density and labilizing influence of the OH^- ligand favors bond cleavage and disfavors bond formation; this apparently causes the high spin d^5 hydroxy/aquo ion to undergo water exchange via an I_d process. The divalent $Fe(H_2O)_6^{2+}$ ($\Delta V^\ddagger = +3.8$ cm^3/mole) also undergoes H_2O exchange via an I_d process.[30]

Ligand Substitution Reactions

Consideration of unsymmetrical ligand exchange reactions provides insight into other subtleties of metal ion reactivity. This includes ion-pairing effects, interactions within the encounter complex between the inner and outer coordination shell, and structural influence of the entering and leaving ligand. Swaddle[7] has pointed out that for these unsymmetrical reactions operational classification schemes are too rigid and may obscure such subtleties, and therefore one must consider less restrictive definitions.

The tendency for hydrolysis of the $M(H_2O)_6^{3+}$ ion to occur is sufficiently great that complex formation normally occurs via a parallel path mechanism, even in strongly acidic medium (Eq. (5)). Ligand substitution at either $M(H_2O)_6^{3+}$

$$M(H_2O)_6^{3+} + LH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} M(H_2O)_5L^{2+} + H_3O^+ \qquad (5a)$$

$$K_h \quad H^+ \Big\updownarrow H^+$$

$$M(H_2O)_5OH^{2+} + LH \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} M(H_2O)_5L^{2+} + H_2O \qquad (5b)$$

or $M(H_2O)_5OH^{2+}$ has been described as a two-step process.[35]

$$M(H_2O)_6^{3+} + LH \overset{K_{os,1}}{\rightleftharpoons} M(H_2O)_6^{3+},LH$$

$$\xrightarrow{k_1^*} M(H_2O)_5L^{n+} + H_3O^+ \qquad (6a)$$

$$M(H_2O)_5OH^{2+} + LH \overset{K_{os,2}}{\rightleftharpoons} M(H_2O)_5OH^{2+},LH$$

$$\xrightarrow{k_2^*} M(H_2O)_5L + H_2O \qquad (6b)$$

The first step is the rapid diffusion controlled formation of an encounter complex, which is characterized by an equilibrium constant K_{os}. The second and rate limiting step is the collapse of the encounter complex whereby LH, the entering ligand, penetrates the inner coordination shell. This second step is characterized by the first order rate constant k^*, which is influenced by M and may or may not be influenced by LH.

Within the encounter complex the closest approach of the entering ligand to the metal center is at one of the eight trigonal faces of the $M(H_2O)_6^{3+}$ octahedron. A theoretical distance of closest approach (r_{ML}) may be calculated from the following equation,[7]

$$r_{ML} = \{(r_i + 138)/\sqrt{3}\} + \{(r_L + 138)^2 - 2(r_i + 138)^2/3\}^{1/2} \qquad (7)$$

where the approaching ligand L and metal M are treated as hard spheres of radius r_L and r_i, respectively, and water as a hard sphere of radius 138 pm. A sample calculation for the distance of closest approach for Al^{3+} or Fe^{3+} and Cl^- illustrates that although the two ions have different ionic radii and consequently different secondary solvation shell radii, the distance of closest approach for an entering ligand is essentially the same for the two metals (see Fig. 1). Assuming $r_{Cl^-} = 176$ pm, r_{AlCl} may be calculated as 383 pm and r_{FeCl} as 384 pm. This represents an insignificant difference and implies that for any given entering ligand, K_{os} values for $Al(H_2O)_6^{3+}$ and $Fe(H_2O)_6^{3+}$ (or $Fe(H_2O)_5OH^{2+}$ and $Al(H_2O)_5OH^{2+}$) will be the same.

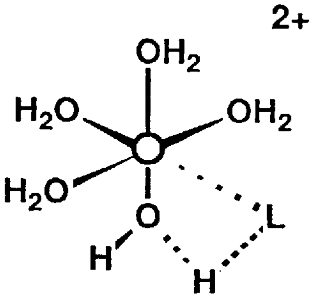
At the conditions where $K_{os}[L] << 1$, the experimental second-order formation rate constant k_f may be related to K_{os} and k^* for either reaction (5a) or (5b) as follows:

$$k_f = K_{os}k^* \qquad (8)$$

For some systems an experimental value for K_{os} may be obtained and in other cases K_{os} can be estimated using the Fuoss equation.[36]

Consequently, a value for k^* may be calculated, which can be compared with the first-order rate constant, k_{H_2O}, for water exchange. This will enable us to say something of the chronology of H_2O leaving group bond cleavage and entering group bond formation.

For both Al^{3+} and Fe^{3+}, ligand substitution in acidic medium increases with increasing pH, suggesting that $M(H_2O)_5OH^{2+}$ reacts significantly faster than $M(H_2O)_6^{3+}$ and that water exchange energetics are dominant. As a consequence of the larger hydrolysis constant for $Fe(H_2O)_6^{3+}$, reactivity via the hydroxide complex (reaction (5b)) is relatively more important for iron. The tendency for $M(H_2O)_6^{3+}$ to hydrolyze can also result in internal H-bonding in the outer sphere complex for reactions with basic incoming ligands. This can enhance substitution rates by increasing K_{os}. The rate constant for the actual ligand substitution process, k^*, may also be accelerated in the case of basic multidentate ligands since strong hydrogen bonding may effectively produce a coordinated –OH in the inner coordination sphere.[37] Furthermore, dissociation of a conjugate base ligand can occur via an acid dependent and acid independent path, as shown in Eq. (5). The relative importance of these dissociation paths for Al^{3+} and Fe^{3+} for a given ligand can be influenced by the greater acidity of a H_2O bound to Fe^{3+} over Al^{3+}. Consequently, dissociation via an acid independent path (Eq. (5b)) may be a relatively more important process for Fe^{3+} complexes due to the relative ease of internal hydrolysis as shown below in I.[38,39]



I

Aquo ions whose water exchange mechanism is dissociative are observed to experience a greater rate acceleration upon hydrolysis to $M(H_2O)_5OH^{2+}$ than aquo ions whose water exchange mechanism is associative.[7] On this basis one might expect the hydrolysis of $Al(H_2O)_6^{3+}$ to produce a more enhanced H_2O exchange rate for ligand substitution than found for $Fe(H_2O)_6^{3+}$; i.e., $k_{H_2O}^{Al(H_2O)_5OH}/k_{H_2O}^{Al(H_2O)_6} > k_{H_2O}^{Fe(H_2O)_5OH}/k_{H_2O}^{Fe(H_2O)_6}$. Unfortunately, good water exchange data for $Al(H_2O)_5OH^{2+}$ are not available in the literature to test this hypothesis. However, complex formation rate constants (k_1, k_2; Eq. (5)) for a series of hydroxamic acid ligand substitution reactions at $M(H_2O)_6^{3+}$ and $M(H_2O)_5OH^{2+}$ provide a relevant data set for comparison. The ratio k_2/k_1 for Fe^{3+} is 10^3,[40-44] consistent with the ratio of water exchange rate constants at $Fe(H_2O)_5OH^{2+}$ and $Fe(H_2O)_6^{3+}$ (Table II). The corresponding ratio for Al^{3+} is a factor of 10 larger at 10^4.[39,45] If water exchange dynamics are dominating in these ligation reactions then this larger ratio for Al^{3+} is expected, since water exchange is an I_d process for $Al(H_2O)_6^{3+}$ [21] and an I_a process for $Fe(H_2O)_6^{3+}$.[22]

One criterion for assessing activation modes at the Al^{3+} or Fe^{3+} center is to compare k^* with the water exchange rate constant: $k^* > k_{H_2O}$ suggests entering ligand participation in the transition state and hence an I_a mechanism, while $k^* < k_{H_2O}$ suggests an I_d mechanism. However this exchange rate criterion often fails for $Fe(H_2O)_6^{3+}$ reactions with simple negative ligands. For example, formation rate constants for Cl^- and Br^- are 4.8 and 1.6 $M^{-1}s^{-1}$,[46] respectively, and consequently the calculated k^* value is less than k_{H_2O} as expected for an I_d process. However, $\Delta V^‡$ values are -5 and -19 $cm^3\ mol^{-1}$,[47] consistent with an I_a process. Most of the data in the literature which includes $\Delta S^‡$ and $\Delta V^‡$ values support a mechanistic picture whereby ligand substitution at $Fe(H_2O)_6^{3+}$ occurs by an I_a process and at $Fe(H_2O)_5OH^{2+}$ by an I_d process. In some cases where activation parameters are available for reaction at $Fe(H_2O)_5OH^{2+}$, $\Delta S^‡ < 0$ suggesting bond formation in the transition state.[40-42] However, in these cases H-bonding between the entering group and coordinated –OH may occur.

Sasaki and Sykes have suggested using the relative discriminating ability of an aquo ion towards NCS^- and Cl^- as an indication of associative or dissociative character in ligand substitution reactions.[48] When $k^{NCS}/k^{Cl} \sim 1$ (assuming N coordination by NCS^-)

a dissociative mode of activation is suggested. Rate constant ratios deviating from this value by an order of magnitude or more suggest an associative mode. Rate constant ratios (k^{NCS}/k^{Cl}) for $Fe(H_2O)_6^{3+}$ and $Fe(H_2O)_5OH^{2+}$ are 14 and 0.6, respectively.[48] This suggests an I_a process for $Fe(H_2O)_6^{3+}$ and I_d for $Fe(H_2O)_5OH^{2+}$, consistent with water exchange activation assignments. There are other reports in the literature which show ample evidence of entering group selectivity for $Fe(H_2O)_6^{3+}$.[49-53]

Much fewer kinetic data are available for Al^{3+} reactions in aqueous medium. This is undoubtedly largely due to the fact that: (1) complex stability is relatively low in strongly acidic medium; (2) hydrolysis of $Al(H_2O)_6^{3+}$ becomes a problem at lower acidity; and (3) there is a lack of convenient specific absorbance bands in the UV-visible region of the spectrum with which to monitor reaction progress. However, it has been proposed that $Al(H_2O)_6^{3+}$ and $Al(H_2O)_5OH^{2+}$ react via an I_d mechanism, based on a lack of influence of entering ligand on k^*, and $k^* < k_{H_2O}$.[21]

Due to the known water exchange rates, identical charge, and similar distance of closest approach, some details of the intimate mechanism for ligand substitution may be discernible by directly comparing formation rate constants for Al^{3+} and Fe^{3+} complexes for the same entering ligand. By considering the ratio k_f^{Fe}/k_f^{Al} (where $k_f = K_{os}k^*$ for Path 1 or 2 in Eq. (5)), uncertainties in assessing K_{os} by the Fuoss equation due to size and orientation effects will be eliminated and we will in effect be comparing ratios of k^* values for Al^{3+} and Fe^{3+}. That is, for a given ligand reacting with both Al^{3+} and Fe^{3+} $K_{os}^{Al} \approx K_{os}^{Fe}$ and Eq. (9) applies.

$$\begin{aligned} k_1^{Fe}/k_1^{Al} &= k_1^{*Fe}/k_1^{*Al} \\ k_2^{Fe}/k_2^{Al} &= k_2^{*Fe}/k_2^{*Al} \end{aligned} \tag{9}$$

If for a series of entering ligands $k_f^{Fe}/k_f^{Al} = R$ (R is a constant) is true, then parallel reactivity trends at Al^{3+} and Fe^{3+} apply. If $R \neq k_{H_2O}^{Fe}/k_{H_2O}^{Al}$ a ligand influence is apparent: for $R > k_{H_2O}^{Fe}/k_{H_2O}^{Al}$, Fe^{3+} is exhibiting more electrophilicity towards the entering ligand than Al^{3+}, and conversely, for $R < k_{H_2O}^{Fe}/k_{H_2O}^{Al}$, Al^{3+} is exhibiting the greater electrophilicity. If the ratio k_f^{Fe}/k_f^{Al} is not constant then different metal–ligand reactivity patterns are indicated for each entering ligand, and for Fe^{3+} and Al^{3+}.

The problem with such an analysis of kinetic data is the severe lack of data for common ligands reacting with both Fe^{3+} and Al^{3+} at similar experimental conditions so that a direct comparison can be made. Table III is a summary of data available in the literature. Any interpretation of these data must be made with caution, however, due to the number of different techniques and experimental conditions involved. Footnotes to Table III indicate where results were recomputed to compensate for differing experimental conditions. Ionic strength corrections were made by adjusting K_{os} using the Fuoss equation[36] and assuming $k_f/K_{os} = k^*$. Key observations to be made based on data in Table III are as follows:

(1) $k_1^{*\mathrm{Fe}}/k_1^{*\mathrm{Al}} = 6 \rightarrow 600$ and $k_2^{*\mathrm{Fe}}/k_2^{*\mathrm{Al}} = 0.2 \rightarrow 5$: The reactivity patterns of the hydroxy ions $M(H_2O)_5OH^{2+}$ are more similar than those of the aquo ions $M(H_2O)_6^{3+}$.

(2) $k_2^{*\mathrm{Fe}}/k_2^{*\mathrm{Al}} < k_1^{*\mathrm{Fe}}/k_1^{*\mathrm{Al}}$ for each L: The ratio $k_2^{*\mathrm{Fe}}/k_2^{*\mathrm{Al}}$, which hovers around 1, is smaller than expected based on the ratio $k_1^{*\mathrm{Fe}}/k_1^{*\mathrm{Al}}$. This suggests that $Al(H_2O_5)OH^{2+}$ is more reactive towards L than expected since in most cases $k_2^{\mathrm{Fe}}/k_1^{\mathrm{Fe}} \sim 10^3$, as expected from water exchange data.

(3) $k_1^{*\mathrm{Fe}}/k_1^{*\mathrm{Al}} \sim 10$ for positive and uncharged ligands: This ratio is relatively constant and less than what would be expected based on water exchange rates ($k_{H_2O}^{\mathrm{Fe}}/k_{H_2O}^{\mathrm{Al}} = 130$, Table II). This suggests similar reactivity patterns for the two metals and a higher degree of electrophilicity exhibited by $Al(H_2O)_6^{3+}$.

(4) $k_1^{*\mathrm{Fe}}/k_1^{*\mathrm{Al}} >> 10$ and variable for negatively charged ligands: This suggests a variable reactivity pattern for the two metals with negatively charged entering groups. The high value (400) for F^- is indicative of some H-bonding in the transition state for $Fe(H_2O)_6^{3+}$ which would tend to give a transition state with more "$Fe(H_2O)_5OH^{2+}$" character. Fluoride is a relatively basic anion and certainly Fe^{3+}, with its much larger hydrolysis constant, has a greater propensity for internal hydrolysis than Al^{3+}. Similar reasoning may apply for SO_4^{2-}, although in this case the $k_1^{*Fe}/k_1^{*\mathrm{Al}}$ ratio is in the range expected for ligand substitution dominated by water exchange energetics. Although internal H-bonding is possible for $Co(CN)_6^{3-}$, and therefore might explain the large $k_1^{\mathrm{Fe}}/k_1^{\mathrm{Al}}$ ratio, it is not clear why the reactivity ratio for $Fe(CN)_6^{3-}$ is so different from that

TABLE III

Comparison of aqueous aluminum(III) and iron(III) encounter complex collapse rate constants

Entering Ligand (L)	$(k_1^{*Fe}/k_1^{*Al})^a$	$(k_2^{*Fe}/k_2^{*Al})^a$	Comments	Ref.[b]
$(NH_3)_5Co\ (SalH)^{2+c}$	6	4	d	54,55
$CH_3C(CO)N(OH)H$	7	1	e	39,40
$C_6H_5C(O)N(OH)H$	30	2	e	39,40
$CH_3C(O)N(OH)\ (4\text{-}CH_3C(O)C_6H_4)$	5	0.2	e	39,41
$CH_3C(O)N(OH)C_6H_5$	10	0.5	e	39,40
$CH_3C(O)N(OH)\ (4\text{-}CH_3C_6H_4)$	10	0.4	e	39,41
HF	8	–	f	56,57
F^-	400	–	f	56,57
$C_6H_4(2\text{-}OH)COO^-$	–	5	g	58,59
SO_4^{2-}	200	4	h	60,61
$Fe(CN)_6^{3-}$	60	0.5	i	62,63
$Co(CN)_6^{3-}$	600	–	j	64,51

[a] $k_1^* = k_1/K_{os,1}$ and $k_2^* = k_2/K_{os,2}$ where k_1, k_2, $K_{os,1}$ and $K_{os,2}$ are as defined in Eqs. (5) and (6). For ligands in which the ionic strength for the reaction with Al^{3+} and Fe^{3+} are the same, the ratios k_1^{*Fe}/k_1^{*Al} and k_2^{*Fe}/k_2^{*Al} are obtained directly from ratios of the experimental rate constants k_1^{Fe}/k_1^{Al} and k_2^{Fe}/k_2^{Al}. For reactions with two different ionic strengths k_1^* and k_2^* are computed from $k_1/K_{os,1}$ and $k_2/K_{os,2}$ using the Fuoss (Ref. 36) equation and assuming the entering group metal distance to be 500 pm for small ligands and 700 pm for large ligands. All data are at 298°K unless otherwise noted. Values are given to one significant figure.

[b] Reference numbers are for Al and Fe data, respectively.

[c] $SalH^-$ is the mono anion of salicyclic acid.

[d] Al data at $I = 0.1$ M (302°K) and Fe data at $I = 1.0$ M.

[e] Al and Fe data at $I = 1.0$ M.

[f] Al data at $I = 0.1$ M. $Fe(H_2O)_6^{3+}$ data calculated from activation parameters at $I = 0.5$ M; $Fe(H_2O)_5OH^{2+}$ data not available.

[g] $Al(H_2O)_6^{3+}$ and $Fe(H_2O)_6^{3+}$ data not available. Al data at $I = 0.1$ M and Fe data at $I = 1.0$ M.

[h] Al data at $I = 0.6$ M and Fe data at $I = 0.5$ M.

[i] Al data at $I \sim 0$ and Fe data at $I = 0.3$, 0.5, 0.6 and 1.0 M.

[j] $Al(H_2O)_5OH^{2+}$ and $Fe(H_2O)_5OH^{2+}$ data not available. Al data at $I \sim 0$ and Fe data at $I = 0.3$ and 1.0 M.

of $Co(CN)_6^{3-}$, but it is consistent with a variability of reactivity patterns for the two metals.

Two key points regarding ligand exchange reactions should be made. First, additional data for ligand substitution at Al^{3+} and

Fe^{3+} obtained at identical conditions in aqueous medium are needed for definitive conclusions regarding reactivity patterns to be made. Second, as emphasized by Swaddle,[7] it may be a disservice to make general mechanistic assignments or attach I_a, I_d labels to reactions at metal centers other than solvent exchange, since each reaction is best considered on an individual basis.

METAL COMPLEX STABILITY

Stability constants for chelating anions correlate reasonably well with the $X_M \cdot Z$ product for spherically symmetrical metal ions including Al^{3+} and Fe^{3+}.[65] Representative data are given in Table IV for log β_{ML} values, where β_{ML} represents the overall binding constant for the deprotonated ligand with the metal (Eq. (10)).

$$\beta_{ML} = \frac{[ML]}{[M]\,[L]} \tag{10}$$

In each example the ligand binding constant is several orders of magnitude higher for the Fe^{3+} complex than for the Al^{3+} complex, consistent with the higher electronegativity of iron.

Ionic radii may in some cases also influence chelate complex stability. Size influences metal chelate stabilities by matching metal ion radius with chelate bite size. For example, it has been proposed that ferrichrome A (a cyclic trihydroxamic acid siderophore) selectivity for Fe^{3+} over Al^{3+} is partially due to the smaller size of Al^{3+}, which results in more 0 . . . 0 donor repulsion in the inner coordination sphere, resulting in a less stable complex.[70]

Sole consideration of β_{ML} values when evaluating metal complex stability, however, ignores the influence of competing equilibria in aqueous solution. Most notable is competition for the ligand between M^{z+} and H^+ arising from the solution pH, and competition for the metal ion between the ligand and OH^- arising from metal ion hydrolysis. Ligand pK_a values are indicative of competition from H^+ and metal ion hydrolysis constants are indicative of OH^- competition. Ligand pK_a has no influence on the *relative* stabilities of Al^{3+} and Fe^{3+} complexes, but metal ion hydrolysis

TABLE IV

Stability constants for selected aluminum(III) and iron(III) complexes

Ligand	log β[a]		Ref.[b]
	Al^{3+}	Fe^{3+}	
$EDTA^{4-}$	16.5	25.0	17
$EGTA^{4-}$	13.9	20.5	17
$citrate^{3-}$	8.0	11.2	66,67
$catecholate^{2-}$			
mono	16.3[c]	20.0	17
bis	29.3[c]	34.7	17
tris	37.6[c]	43.8	17
$acetohydroxamate^{1-}$			
mono	8.0[c]	11.4[c]	17
bis	15.3[c]	21.1[c]	17
tris	21.5[c]	28.3[c]	17
Tf_C[d]	12.9	22.7	68
Tf_N[d]	12.3	22.1	68

[a] Overall stability constant as defined in Eq. (10). Data at 298°K and $I = 0.1$ M except where noted.

[b] Reference numbers are for Al and Fe data, respectively.

[c] 293°K.

[d] Tf_C, transferrin C-terminal binding site and Tf_N, N-terminal binding site under blood plasma conditions at pH 7.4. Reference 68 also includes a recalculation of data from Ref. 69 for Fe^{3+}.

constants do. For Al^{3+} and Fe^{3+} aqueous equilibria this diminishes the difference in complex stability between the two metals, since metal ion hydrolysis is much more significant for Fe^{3+} than for Al^{3+} (see above). Qualitatively, while metal–ligand interactions are more stable for Fe^{3+} than Al^{3+}, the same is true for metal–OH complex stability, possibly for the same reason(s).

This concept can be quantified by using equilibrium constants for competing reactions to define an effective metal–ligand complex stability constant, K_{eff}. In the absence of competing metal ions, K_{eff} may be defined as follows[65]:

$$\mathrm{Log}\, K_{eff} = \log \beta_{ML} - n\log \alpha_L^{-1} - \log \alpha_M^{-1} \qquad (11)$$

where β_{ML} is the conventional metal–ligand binding constant defined above which is corrected for ligand proton basicity by α_L^{-1}:

$$\begin{aligned} \alpha_L^{-1} &= [1 + [H^+]\beta_1^H + [H^+]^2\beta_2^H + \cdots + [H^+]^n\beta_n^H] \\ \beta_i^H &= \frac{[H_iL]}{[H^+]^i\,[L]} \end{aligned} \tag{12}$$

and corrected for metal ion hydrolysis by α_m^{-1}:

$$\begin{aligned} \alpha_M^{-1} &= \left[1 + \frac{{}^*\beta_1}{[H^+]} + \frac{{}^*\beta_2}{[H^+]^2} + \cdots + \frac{{}^*\beta_n}{[H^+]^n}\right] \\ {}^*\beta_n &= \frac{[M(OH)_n]\,[H^+]^n}{[M]} \end{aligned} \tag{13}$$

The correction for ligand basicity is the same for both Al^{3+} and Fe^{3+} reacting with a particular ligand, and so need not concern us here. Neglecting precipitation and oligomerization reactions, the α_m^{-1} term for Al^{3+} and Fe^{3+} can be calculated from ${}^*\beta_1$, ${}^*\beta_2$, ${}^*\beta_3$, and ${}^*\beta_4$ values available in Table I. Plots in Fig. 4 show that this correction can be large and that for Fe^{3+} the correction to metal–ligand complex stability constants is significant at pH values as low as 3.

Due to the higher electronegativity of Fe^{3+}, $\alpha_{Fe}^{-1} > \alpha_{Al}^{-1}$ at all pH values, which makes K_{eff}^{Fe} and K_{eff}^{Al} more similar than β_{ML}^{Fe} and β_{ML}^{Al}. That is, as a result of metal ion hydrolysis the difference in stability between Al^{3+} and Fe^{3+} complexes is much less than expected based on conventional β_{ML} values. Figure 4 also includes a plot of the difference between log α_{Fe}^{-1} and log α_{Al}^{-1} (Δ log α_M^{-1}) as a function of pH. This difference is at its maximum in the pH range from 6 to 8 where it reaches a maximum value of 5.63 log units. Consequently, over the pH range 6–8 the difference in effective stability of Fe^{3+} and Al^{3+} complexes (ΔK_{eff}) is at a minimum. The quantitative significance of the 5.63 log unit maximum in this plot is that if β_{FeL} is less than 6 log units greater than β_{AlL} for a particular ligand, then over the pH range 6–8 the relative stabilities of Fe^{3+} and Al^{3+} complexes will be comparable or even inverted. Examples of such behavior may be seen in Table IV. A

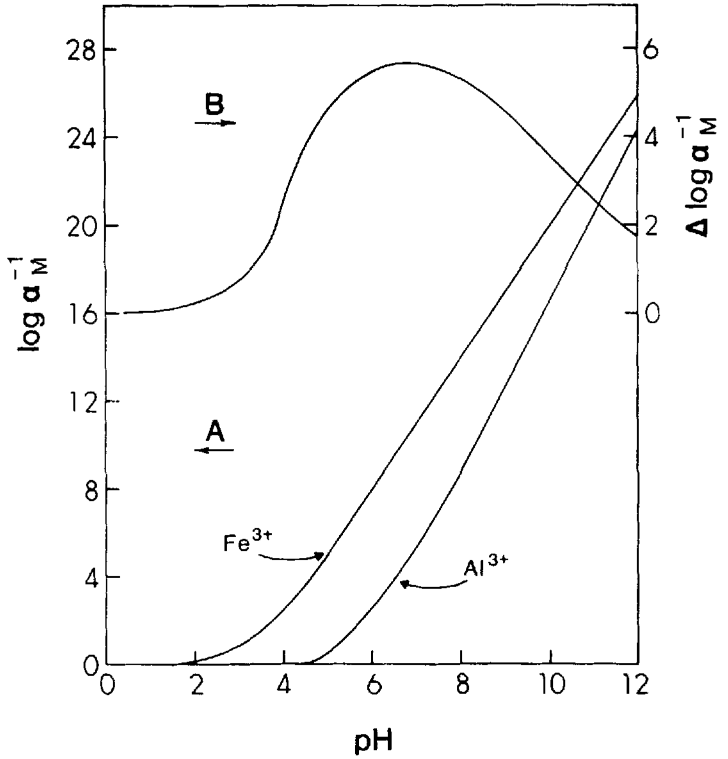


FIGURE 4 (A) Plot of log α_M^{-1} (from Eq. (13)) as a function of pH for Al^{3+} and Fe^{3+}. (B) Plot of $\Delta\log\alpha_M^{-1}$ (= $\log\alpha_{Fe}^{-1} - \log\alpha_{Al}^{-1}$) as a function of pH.

practical application of this phenomenon is in the influence of pH on metal ion separations. It is also of some significance that the pH region for the greatest similarity between Fe^{3+} and Al^{3+} complex stability encompasses physiological pH.

SPECIATION AND DISTRIBUTION OF Al^{3+} and Fe^{3+} IN THE BODY

The aqueous coordination chemistry of Al^{3+} in a biological system is dominated by the insolubility of the hydroxide and phosphate complexes.[71–73] At the physiological pH 7.4 the dominant soluble hydroxy form is $Al(OH)_4^-$. At this pH the concentration of $Al(H_2O)_6^{3+}$ calculated from the solubility of amorphous $Al(OH)_3$ is $10^{-11.5}$ M. (Amorphous $Al(OH)_3$ is somewhat more soluble than crystalline gibbsite $Al(OH)_3$ and is the form likely to be found in a biological system.[71]) Phosphate, present in high concentrations in a biological system, forms an insoluble complex with aluminum, $Al(OH)_2H_2PO_4$. At pH 7.4 and 2 mmol/L total phosphate concentration the free $Al(H_2O)_6^{3+}$ concentration is $10^{-12.9}$ M.

These considerations suggest that most ingested Al^{3+} should be eliminated from the body as insoluble hydroxide and phosphate complexes. However, citrate is present in blood plasma at about 0.1 mmol/L and effectively competes for Al^{3+}, thereby preventing precipitation/elimination by complexation.[66,74] At the physiological pH of 7.4, 0.1 mmol/L citrate and 1 μmol/L Al^{3+}, the free $Al(H_2O)_6^{3+}$ concentration is $10^{-14.0}$ M.[66] Furthermore, citrate may be responsible for the assimilation of Al^{3+} across membranes, since it forms an uncharged complex AlL.

For both Al^{3+} and Fe^{3+} in the plasma, the strongest low molecular weight complex is with citrate, but the complex with the protein transferrin is even stronger.[75] Given enough time (due to the slower ligand exchange rate), plasma Al^{3+} should appear in transferrin.

Transferrin, a glycoprotein of molecular weight 80,000, is the plasma transport protein for Fe^{3+}.[76-79] In addition to human serum transferrin (Tf), two other transferrins are known: ovotransferrin (OTF), and lactoferrin (LTF). The three transferrins exhibit considerable homology. The proteins consist of two lobes, and a large degree of homology exists between the two lobes as well. The transferrins all bind two Fe^{3+} ions, but only in the presence of the synergistic anion CO_3^{2-} (or HCO_3^-). Although there are certain thermodynamic and kinetic differences between the two sites, there is evidence that the ligating groups are identical. The iron binding sites have been investigated by chemical studies, spectroscopy, and in the case of human lactoferrin, by x-ray crystallographic analysis.[80] The protein acts as a tetradentate ligand with two tyrosyl and one aspartic acid oxygen donors, and a histidine nitrogen atom. Octahedral coordination is completed by $CO_3^=$ (or HCO_3^-) and probably a bound H_2O.[76,80] A conformational change is associated with Fe^{3+} binding, with the metal bound structure being more compact.[78] The exact function of the synergistic anion $CO_3^=$ has been the subject of much investigation and is still somewhat an open question. It is necessary for both Fe^{3+} and Al^{3+} binding to transferrin.

The two iron binding sites are designated as the N-terminal and the C-terminal site. The N-terminal site has a lower affinity for Fe^{3+} [77] and dissociates Fe^{3+} more rapidly[81] than the C-terminal site. The Fe^{3+} binding constants for physiological conditions are listed in Table IV, along with the data for Al^{3+} binding. The stability of the Al–Tf complex is less than is expected based on the observed trends in ligand binding to Fe^{3+} relative to Al^{3+}. This may be due to the fact that the smaller Al^{3+} ion cannot achieve hexacoordination in the Tf binding site.[68]

Since Fe^{3+} complexation by transferrin is nearly ten orders of magnitude greater than Al^{3+}, there is no competition between the two metal ions for binding sites on the protein. However, under plasma conditions transferrin is only 30% saturated with Fe^{3+}, leaving many sites to be filled by Al^{3+}. This is based on calculations which show that when the concentration of total Al^{3+} is 1 μmol/L, the free Al^{3+} concentration permitted by transferrin is $10^{-14.6}$ mol/L. This is less than that allowable by insoluble $Al(OH)_3$ or $Al(OH)_2H_2PO_4$, or by complexing with citrate.[71] Transferrin thus emerges as the principal aluminum complexing agent in the blood, binding more strongly than citrate.[68,75]

The major storage depot for iron in the body is ferritin, a protein shell of 24 subunits of MW 20,000 that encapsulates an iron core of up to 4500 Fe^{3+} atoms.[82,83] The iron core has a density about 2.5 times as great as apoferritin and is made up of a ferric-oxy-hydroxy-phosphate complex. The phosphate content varies widely from practically nil to above 1:2 (phosphate:iron) in some bacterioferritins. The core is undoubtedly attached to the inner protein surface. Although there is tight subunit–subunit interaction, there are channels to the iron core which are coincident with the 3-fold and 4-fold symmetry axes.[83] The iron enters and exits the core through these channels. The exact means by which iron is removed from ferritin *in vivo* is not known. *In vitro* iron may be removed as Fe^{3+} by the use of chelators and as Fe^{2+} by using a reductant in combination with a chelator. Reductive mobilization of iron proceeds at a faster rate.

The main function of ferritin is to detoxify, store and transport iron. Ferritin has also been found to bind aluminum, both *in vivo* and *in vitro*.[84–87] The fact that ferritin binds other metals such as aluminum suggests that a secondary role of the protein is in the detoxification of metals.

It is proposed that Al^{3+} enters the ferritin protein shell and binds to the phosphates, and that tight binding requires both the iron core and phosphate.[85,88] Soya ferritin binds more Al^{3+} than do synthetic "iron cores" prepared by the method of Saltman.[85] This is presumably because an iron core of greater surface area is produced in the presence of the protein coating, thus allowing for more Al^{3+} to be bound. A consequence of Al^{3+} binding to ferritin is the inhibition of Fe^{2+} release from the protein.[84,87,89]

Scanning electron microprobe x-ray microanalysis has shown that silicon, aluminum, and iron are present in high concentration in senile plaque cores isolated from the cerebral cortex, hippocampus, and amygdala of individuals afflicted with Alzheimer's disease. The distribution of these elements suggests that their deposition may play an essential role in the genesis of senile plaques associated with Alzheimer's disease.[90] The fact that serum transferrin transports both iron and aluminum suggests that their deposition may occur by a common mechanism. Furthermore, brain ferritin is found to have a high aluminum content in patients with Alzheimer's disease.[84,86,87,89]

Experiments with cultured cells suggest that transferrin-mediated accumulation of aluminum may play a major role in the mechanism of the neurotoxic effects of aluminum.[91] Transferrin receptors present on the lumen of brain capillaries may mediate aluminum uptake into the brain.[92,93] The level of transferrin and density of transferrin-binding sites has been found to be as high in the cerebral cortex of cases with Alzheimer's disease as in cases of elderly patients which are mentally normal. This suggests that the transport of iron and aluminum in the brain is not impaired with patients suffering from Alzheimer's disease[93] and further suggests that aluminum may utilize the iron transport system in the development of plaques.

SUMMARY AND CONCLUSIONS

We have looked at the aqueous coordination chemistry of Al^{3+} and Fe^{3+} and have found that χ_M, r_i, and d^n influence various aspects of the chemistry of each ion. In some cases these parameters can be used to rationalize the similarities and differences between the two ions. While differences in r_i result in different dimensions for the inner and outer coordination shell for the aquo ions and different water exchange rate constants, the distance of closest approach of the entering ligand in an encounter complex in a substitution reaction is the same for the two ions. Although both aqueous ions possess a spherical distribution of electron density, it may be argued that as a result of the d^5 electron configuration water exchange proceeds by an I_a mechanism for Fe^{3+} and an I_d mechanism for the d^0 Al^{3+} ion. Ligand substitution reactions are dominated by water exchange energetics. Parallel or contrasting reactivity patterns are observed for Al^{3+} and Fe^{3+} depending on entering ligand charge, which supports an earlier statement by others that each reaction must be considered on an individual basis. Differences in χ_M relate to differences in metal ion hydrolysis and metal–ligand complex stability. The higher χ_{Fe} leads to more stable Fe^{3+} complexes, but also to a greater tendency towards hydrolysis. Consequently, the higher affinity of Fe^{3+} over Al^{3+} for a particular ligand is reduced through OH^- competition, especially over the pH range 6–8. The similarities in the aqueous coordination chemistry of Al^{3+} and Fe^{3+} result in similarities in the location and mode of distribution of the two ions in the body, one of which is essential to life (in an appropriate concentration range) and the other of which is associated with certain diseases.

Acknowledgment

The authors acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of our research in this area.

References

1. J. B. Neilands, Microbiol. Sci. **1**, 9 (1984).
2. A. J. M. Messenger and R. Barclay, Biochem. Educ. **11**, 54 (1983).
3. K. N. Raymond, G. Müller and B. F. Matzanke, Top. Curr. Chem. **123**, 49 (1984).
4. (a) W. F. Anderson and M. C. Hiller (Eds.), *Development of Iron Chelators for Clinical Use* (Dept. Health, Education and Welfare Publication, U.S. Govt. Printing Office, Washington, D.C., 1977), No. (NIH) 76-994; (b) E. C. Zaino

and R. H. Roberts (Eds.), *Chelation Therapy in Iron Overload* (Stratten Intercontinental, Medical Book Corp., New York, 1977); (c) A. E. Martell, W. F. Anderson and David G. Badman (Eds.), *Development of Iron Chelators for Clincial Use* (Elsevier/North Holland, New York, 1981).

5. D. R. Crapper McLachlan, B. Farnell, H. Galin, S. Karlik, G. Eichhorn and U. DeBoni, in *Biological Aspects of Metals and Metal-Related Diseases*, ed. B. Sarkar (Raven Press, New York, 1983), p. 209.
6. R. D. Shannon, Acta Crystallogr. **A32**, 751 (1976).
7. T. W. Swaddle, in *Advances in Inorganic and Bioinorganic Mechanisms*, Vol. 2 (Academic Press, New York, 1983), p. 96.
8. T. W. Swaddle and M. K. S. Mak, Can. J. Chem. **61**, 473 (1983).
9. R. Caminiti and T. Radnai, Z. Naturforsch A **35A**, 1368 (1980).
10. R. Caminiti, G. Licheri, G. Piccaluga, G. Pinna and T. Radnai, J. Chem. Phys. **71**, 2473 (1979).
11. R. Caminiti and M. Magini, Chemical Physics Letters **61**, 40 (1979) and references therein.
12. J. Kragten, *Atlas of Metal–Ligand Equilibria in Aqueous Solution* (Halstead Press, New York, 1978).
13. J. M. Knudsen, E. Larsen, J. E. Nielsen and O. F. Nielsen, Acta Chem. Scand. **A29**, 833 (1975).
14. J. W. Akitt and A. Farthing, J. Chem. Soc. Dalton Trans. 1609, 1617, 1624 (1981).
15. J. W. Akitt and B. E. Mann, J. Magn. Reson. **44**, 584 (1981).
16. A. L. Allred, J. Inorg. Nucl. Chem. **17**, 215 (1961).
17. A. E. Martell and R. M. Smith, *Critical Stability Constants*, Vol. 4 (Plenum Press, New York, 1976).
18. L. G. Sillén and A. E. Martell, *Stability Constants of Metal-Ion Complexes*, Special Publication No. 25 (The Chemical Society, Burlington House, London, 1971).
19. E. Högfeldt, *Stability Constants of Metal-Ion Complexes, Part A: Inorganic Ligands*, IUPAC Chemical Data Series, No. 21 (Pergamon Press, New York, 1982).
20. C. F. Baes and R. E. Mesmer, *The Hydrolysis of Cations* (Wiley, New York, 1976).
21. D. Hugi-Cleary, L. Helm and A. Merbach, Helv. Chim. Acta **68**, 545 (1985).
22. R. W. Swaddle and A. E. Merbach, Inorg. Chem. **20**, 4212 (1981).
23. M. Grant and R. B. Jordan, Inorg. Chem. **20**, 55 (1981).
24. H. W. Dodgen, G. Liu and J. P. Hunt, Inorg. Chem. **20**, 1002 (1981).
25. J. Feidler and H. B. Silber, J. Phys. Chem. **77**, 1275 (1973).
26. J. P. Hunt and H. L. Friedman, Prog. Inorg. Chem. **30**, 359 (1983).
27. F. Fittipaldi and S. Petrucci, J. Phys. Chem. **71**, 3414 (1967).
28. G. E. Glass, W. B. Schwarzenbach and R. S. Tobias, Inorg. Chem. **7**, 2471 (1968).
29. D. Hugi-Cleary, L. Helm and A. E. Merbach, J. Amer. Chem. Soc. **109**, 4444 (1987).
30. Y. Ducommun, K. E. Newman and A. E. Merbach, Inorg. Chem. **19**, 3696 (1980).
31. F. Basolo and R. G. Pearson, *Mechanisms of Inorganic Reactions* (John Wiley and Sons, New York, 1967).
32. C. H. Langford and H. B. Gray, *Ligand Substitution Processes* (Benjamin, New York, 1965).
33. A. E. Merbach, in *High Pressure Chemistry and Biochemistry*, eds. R. van

Eldik and J. Jona, NATO ASI Series C: Mathematical and Physical Sciences, Vol. 197 (D. Reidel Publ. Co., Boston, 1987), p. 311.

34. (a) Y. Ducommun and A. E. Merbach, in *Inorganic High Pressure Chemistry: Kinetics and Mechanisms*, ed. R. van Eldik (Elsevier, Amsterdam, 1986), Chap. 2. (b) A. E. Merbach, Pure and App. Chem. **59**, 161 (1987).
35. M. Eigen and R. G. Wilkins, Adv. Chem. Ser. **49**, 55 (1965).
36. R. M. Fuoss, J. Am. Chem. Soc. **80**, 5059 (1958).
37. D. B. Rorabacher, Inorg. Chem. **5**, 1891 (1966).
38. A. L. Crumbliss and J. M. Garrison, Rec. Trav. Chim. Pays-Bas **106**, 404 (1987).
39. J. M. Garrison and A. L. Crumbliss, Inorg. Chem. **26**, 3660 (1987).
40. B. Monzyk, and A. L. Crumbliss, J. Am. Chem. Soc. **101**, 6203 (1979).
41. C. P. Brink and A. L. Crumbliss, Inorg. Chem. **23**, 4708 (1984).
42. L. L. Fish and A. L. Crumbliss, Inorg. Chem. **24**, 2198 (1985).
43. B. Monzyk and A. L. Crumbliss, Inorg. Chem. Acta, Bioinorg. Chem **55**, L5 (1981).
44. B. Monzyk and A. L. Crumbliss, J. Am. Chem. Soc. **104**, 4921 (1982).
45. J. M. Garrison and A. L. Crumbliss, Inorg. Chim. Acta, Bioinorg. Chem. **138**, 61 (1987).
46. B. B. Hasinoff, Can. J. Chem. **54**, 1820 (1976).
47. B. B. Hasinoff, Can. J. Chem. **57**, 77 (1979).
48. Y. Sasaki and A. G. Sykes, J. Chem. Soc. Dalton Trans. 1048 (1975).
49. See, for example, Refs. 22, 23, 40–42, 50–53, and references cited therein.
50. E. Mentasti, F. Secco and M. Venturini, Inorg. Chem. **21**, 602 (1982).
51. E. Mentasti, F. Secco and M. Venturini, Inorg. Chem. **21**, 2314 (1982).
52. B. Perlmutter-Hayman and E. Tapuhi, J. Coord. Chem. **6**, 31 (1976).
53. R. G. Wilkins, in *The Biological Chemistry of Iron*, eds. H. B. Dunford, D. Dolphin, K. N. Raymond and L. Sieker (D. Reidel Publ. Co., Dordrecht, Holland, 1982), p. 13.
54. A. C. Dash, Inorg. Chem. **22**, 837 (1983).
55. A. C. Dash and G. M. Harris, Inorg. Chem. **21**, 2336 (1982).
56. B. J. Plankey and H. H. Patterson, Env. Sci. Tech. **20**, 160 (1986).
57. D. Pauli and W. MacF. Smith, Can. J. Chem. **38**, 567 (1960).
58. B. Perlmutter-Hayman and E. Tapuki, Inorg. Chem. **18**, 875 (1979).
59. A. C. Dash and G. M. Harris, Inorg. Chem. **21**, 2336 (1982); G. Saini and E. Mentasti, Inorg. Chim. Acta **4**, 585 (1970); E. Mentasti, F. Secco and M. Venturini, Inorg. Chem. **21**, 602 (1982).
60. J. Miceli and J. Stuehr, J. Am. Chem. Soc. **90**, 6967 (1968).
61. F. P. Cavasino, J. Phys. Chem. **72**, 1378 (1968).
62. M. Matušek and H. Strehlow, Ber. Bunsenges Phys. Chem. **73**, 982 (1969).
63. D. L. Singleton and J. H. Swinehart, Inorg. Chem. **6**, 1536 (1967); R. G. Walker and K. O. Watkins, Inorg. Chem. **7**, 885 (1968); E. Mentasti, F. Secco and M. Venturini, Inorg. Chem. **21**, 2314 (1982).
64. C. Kuehn and W. Knoche, Trans Faraday Soc. **67**, 2101 (1971).
65. A. E. Martell, in *Development of Iron Chelators for Clinical Use*, eds. A. E. Martell, W. F. Anderson and D. G. Badman (Elsevier, New York, 1981), p. 67.
66. R. B. Martin, J. Inorg. Biochem. **28**, 181 (1986).
67. T. B. Field, J. L. McCourt and W. A. E. McBryde, Can. J. Chem. **52**, 3119 (1974).
68. R. B. Martin, J. Savory, S. Brown, R. L. Berthoff and M. R. Wills, Clin. Chem. **33**, 405 (1987).

69. P. Aisen, A. Leibman and J. Zweiser, J. Biol. Chem. **253**, 1930 (1978).
70. D. van der Helm, J. R. Baker, R. A. Loghry and J. D. Ekstrand, Acta. Cryst. **B37**, 323 (1981).
71. R. B. Martin, Clin. Chem. **32**, 1797 (1986).
72. R. J. P. Williams, Rec. Trav. Chim. Pays-Bas **106**, 401 (1987).
73. S. C. Tam and R. J. P. Williams, J. Inorg. Biochem. **26**, 35 (1986).
74. M. Venturini, G. Bethon and P. M. May, Rec. Trav. Chim. Pays-Bas **106**, 406 (1987).
75. M. Cochran, J. Coates and S. Neoh, FEBS Letters **176**, 129 (1984).
76. E. N. Baker, S. V. Rumball and B. F. Anderson, TIBS **12**, 350 (1987).
77. J. H. Brock, in *Metalloproteins (Part 2)*, eds. P. M. Harrison (MacMillan, 1985), pp. 183–262.
78. P. Aisen and I. Listowsky, Annu. Rev. Biochem. **49**, 357 (1980).
79. (a) N. D. Chasteen, in *Advances in Inorganic Biochemistry*, Vol. 5, eds. E. C. Theil, G. L. Eichhorn and L. G. Marzilli (Elsevier, New York, 1983), Chap. 8. (b) N. D. Chasteen, C. P. Thompson and D. M. Martin, in *Frontiers in Bioinorganic Chemistry*, ed. A. V. Xavier (VCH Publ. Co., Deerfield Beach, FL, 1986), p. 278.
80. B. F. Anderson, H. M. Baker, E. J. Dodson, G. E. Norris, S. V. Rumball, J. M. Waters and E. N. Baker, Proc. Nat'l. Acad. Sci. (USA) **84**, 1769 (1987).
81. S. A. Kretchmar and K. N. Raymond, J. Am. Chem. Soc. **108**, 6212 (1986).
82. (a) E. C. Theil, in *Advances in Inorganic Biochemistry*, Vol. 5, eds. E. C. Theil, G. L. Eichhorn and L. G. Marzilli (Elsevier, New York, 1983), Chap. 1. (b) E. C. Theil, in *Frontiers in Bioinorganic Chemistry*, ed. A. V. Xavier, (VCH Publ. Co., Deerfield Beach, FL, 1986), p. 259. (c) E. C. Theil, Ann. Rev. Biochem. **56**, 289 (1987).
83. P. M. Harrison, Biochem. Educ. **14**, 154 (1986).
84. J. G. Joshi, J. Fleming and A. Zimmerman, J. Neurol. Suppl. **232**, 61 (1985).
85. J. G. Joshi, S. Cho, J. T. Fleming, S. Sczekan and A. Zimmerman, in *Trace Metals, Aging and Alzheimer's Disease*, Proceedings of the Conference held at NIH September 22–25, 1986, ed. Z. S. Khachaturian (National Institutes of Health, Washington, D.C., 1988.
86. J. Fleming and J. G. Joshi, Proc. Natl. Acad. Sci. (USA) **84**, 7866 (1987).
87. J. G. Joshi and A. Zimmerman, Toxicology **48**, 21 (1988).
88. J. G. Joshi, D. J. Price and J. Fleming, in *Protides of the Biological Fluids*, **31**, 183 (1983), ed. H. Peters, Proceedings of the 31st Colloquium, 1983 (Pergamon Press, Oxford, 1983).
89. J. Fleming and J. G. Joshi, Fed. Proc. **44**, 1425 (1985).
90. J. M. Candy, A. E. Oakley, F. Watt, G. W. Grune, J. Klinowski, R. H. Perry, and J. A. Edwardson, *Modern Trends in Aging Research* (Colloque INSERMEURAGE) **147**, 443 (1986).
91. C. M. Morris, J. M. Candy, J. A. Court, C. A. Whitford and J. A. Edwardson, Biochem. Soc. Trans. **15**, 498 (1987).
92. W. A. Jefferies, M. R. Branden, S. V. Hunt, A. F. Williams, K. C. Gatter and D. Y. David, Nature (London) **312**, 162 (1984).
93. C. M. Morris, J. A. Court, A. A. Moshtaghie, A. Skillen, J. M. Candy, R. H. Perry, J. A. Edwardson and A. Fairbairn, Biochem. Soc. Trans. **15**, 891 (1987).