2.13: Selecting Zinc

Zinc has a specific role in bioinorganic processes because of the peculiar properties of the coordination compounds of the zinc(II) ion.

(1) Zinc(II) can easily be four-, five-, or six-coordinate, without a marked preference for six coordination. The electronic configuration of zinc(II) is $3d^{10}$ with two electrons per orbital. In coordination compounds, there is no ligand-field stabilization energy, and the coordination number is determined by a balance between bonding energies and repulsions among the ligands. Tetrahedral four-coordinate complexes have shorter metal-donor distances than five-coordinate complexes, and the latter have shorter ones than six-coordinate complexes (Table 2.2), whereas the ligand repulsion increases in the same order.

Table 2.2 - Average zinc(II)-donor atom distances (A) for some common zinc(II) ligands in four-, five-, and six-coordinate complexes.5

Ligand	Coordination 4	5	Number 6
H_2O	2.00	2.08	2.10
R-COO⁻	1.95	2.02	2.07
Imidazole	2.02	—	2.08
Pyridine	2.06	2.12	2.11
R-NH$_2$	—	2.06	2.15
R, R'NH	2.19	2.27	—

The repulsion can be both steric and electronic. In enzymes, zinc(II) usually has coordination numbers smaller than six, so that they have available binding sites in their coordination spheres. Substrate can in principle bind to zinc by substituting for a coordinated water or by increasing the coordination number. This behavior would be typical of Lewis acids, and, indeed, zinc is the most common Lewis acid in bioinorganic chemistry. Zinc could thus substitute for protons in the task of polarizing a substrate bond, e.g., the carbonyl C-O bond of peptides and esters, by accepting a substrate atom (oxygen) as a ligand. This has been shown to be possible in model systems. Relative to the proton, a metal ion with an available coordination position has the advantage of being a "superacid," 6 in the sense that it can exist at pH values where the H_3O^+ concentration is extremely low. Also, relative to the proton, the double positive charge partly compensates for the smaller electrophilicity due to the smaller charge density.

(2) As a catalyst, zinc in zinc enzymes is exposed to solvent, which for enzymes is almost always water. A coordinated water molecule exchanges rapidly, because ligands in zinc complexes are kinetically labile. This, again, can be accounted for by zinc's lack of preference for a given coordination number. A six-coordinate complex can experience ligand dissociation, giving rise to a five-coordinate complex with little energy loss and then little energetic barrier. On the other side, four-coordinate complexes can add a fifth ligand with little energetic barrier and then another ligand dissociates.[7] The coordinated water has a pK_a sizably lower than free water. Suitable models have been synthesized and characterized in which a solvent water molecule coordinated to various dipositive metal ions has pKa values as low as 7 (Table 2.3).
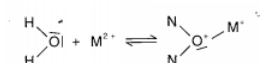
Table 2.3 - The pK_a values of coordinated water in some metal complexes.

a) dacoda = 1,4-diaza-cyciooctane-1 ,4-diacetate.

b) TPyMA = tris(3,5-dimethyl-1-pyrazolylmethyl)amine.

c) TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraaza-cyclotetradecane.

d) CR = Schiff base between 2,6-diacetylpyridine and bis(3-aminopropyl)amine.

e) DMAM-PMHD = 1-[(6(dimethylamino)methyl)-2-pyridyl)methyl]hexahydro-1,4-diazepin-5-one.

f) C-PMHD = 1[(6-carboxy)-2-pyridyl)methyl]hexa-hydro-1,4-diazepin-5-one.

g) [12]aneN$_3$ = 1,5,9-triaza-cyclododecane.

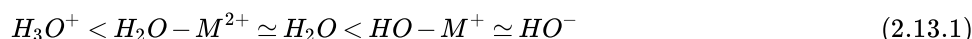h) HP[12]aneN$_3$ = 2-(2-hydroxyphenylate)-1,5,9-triaza-cyclododecane.

i)TImMP = tris(4,5-dimethyl-2-imidazolylmethyl)phosphinoxide.

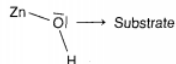| Complex	Note	Donor Set	pK$_a$	Reference
Ca(NO$_3$)$_2$(OH$_2$)$_4^{2+}$		O$_6$	10.3	8
Cr(OH$_2$)$_6^{3+}$		O$_6$	4.2	8
Cr(NH$_2$)$_5$OH$_2^{3+}$		N$_5$O	5.1	8
Mn(OH$_2$)$_6^{2+}$		O$_6$	10.5	8
Fe(OH$_2$)$_6^{3+}$		O$_6$	1.4	8
Co(OH$_2$)$_6^{2+}$		O$_6$	9.8	8
Co(dacoda)OH$_2^{2+}$	(a)	N$_2$O$_3$	9.4	9
Co(TPyMA)OH$_2^{2+}$	(b)	N$_4$O	9.0	10
Co(TMC)OH$_2^{2+}$	(c)	N$_4$O	8.4	11
Co(CR)OH$_2^{2+}$	(d)	N$_4$O	8.0	12
Co(NH$_3$)$_5$OH$_2^{3+}$		N$_5$O	6.2	8
Ni(OH$_2$)$_6^{2+}$		O$_6$	10.0	8
Cu(OH$_2$)$_6^{2+}$		O$_6$	7.3	8
Cu(DMAM-PMHD)OH$_2^{2+}$	(e)	N$_3$O$_2$	7.1	13
Cu(C-PMHD)OH$_2^{+}$	(f)	N$_2$O$_3$	6.6	14
Zn(OH$_2$)$_6^{2+}$		O$_6$	9.0	8
Zn(DMAM-PMHD)OH$_2^{2+}$	(e)	N$_3$O	9.2	13
Zn(C-PMHD)OH$_2^{+}$	(f)	N$_3$O$_2$	7.1	14
Zn(CR)OH$_2^{2+}$	(d)	N$_4$O	8.7	12
ZN([12]aneN$_3$)OH$_2^{2+}$	(g)	N$_3$O	7.3	15, 16
Zn(HP[12]aneN$_3$)OH$_2^{+}$	(h)	N$_3$O$_2$	10.7	16
Zn(TImMP)OH$_2^{2+}$	(i)	N$_3$O	< 7	17
Co(TImMP)OH$_2^{2+}$	(i)	N$_3$O	7.8	17

This is the result of the formation of the coordination bond. The oxygen atom donates two electrons to the metal ion and formally becomes positively charged:

Under these conditions a proton is easily released. The nucleophilicity of coordinated water is, of course, decreased with respect to free water, owing to the decreased electronic charge on the oxygen atom, but a significant concentration of M-OH species may exist in neutral solution. In turn, the coordinated hydroxide is a slightly poorer nucleophile than the free OH⁻ ion, but better than water. On the basis of recent MO calculations,[18] the order of nucleophilicity for solvent-derived species can be summarized as follows:

$$H_3O^+ < H_2O - M^{2+} \simeq H_2O < HO - M^+ \simeq HO^- \tag{2.13.1}$$

Therefore, at neutral or slightly alkaline pH, the small decrease in efficiency of coordinated vs. free hydroxide ions is more than compensated for by the higher concentration of reactive species available (i.e., HO-M$^+$ vs. HO$^-$). Another common role for zinc enzymes is thus to provide a binding site at which the substrate can be attacked by the metal-coordinated hydroxide:

$$Zn-\overline{\underline{O}}| \longrightarrow \text{Substrate}$$
$$\quad\quad | $$
$$\quad\quad H$$

The pK$_a$ of coordinated water in zinc complexes is controlled by the coordination number and by the total charge of the complex, in the sense that it decreases with decreasing coordination number and with increasing positive charge, because a zinc ion, bearing in effect a more positive charge, will have greater attraction for the oxygen lone pair, thus lowering the pKa. Charged ligands affect water pK$_a$'s more than does the number of ligands.[18] The pK$_a$ in metalloproteins is further controlled by the presence of charged groups from protein side chains inside the cavity or by the binding of charged cofactors. The coordinated water may have a pK$_a$ as low as 6, as in carbonic anhydrase (see later). On the other hand, the pK$_a$ of the coordinated water is 7.6 in liver alcohol dehydrogenase (LADH) when NAD$^+$ is bound, 9.2 in the coenzyme-free enzyme, and 11.2 in the presence of NADH (see Section V.C).

(3) As mentioned before, Zn complexes show facile four- to five-coordinate interconversion. The low barrier between these coordination geometries is quite important, because the substrate may add to the coordination sphere in order to replace the solvent or to be coordinated together with the solvent. If the interconversion between four- and five-coordination is fast, catalysis is also fast.

Thus, to summarize, zinc is a good Lewis acid, especially in complexes with lower coordination numbers; it lowers the pK$_a$ of coordinated water and is kinetically labile, and the interconversion among its four-, five-, and six-coordinate states is fast. All of these properties make zinc quite suitable for biological catalysis.[19]

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