Zinc: Lewis Acid and Gene Regulator

INTRODUCTION

After iron, zinc is the second most abundant trace element in the human body: an average adult has ~3 g of Zn, corresponding to a concentration of about 0.6 mM. Some 95% of zinc is intracellular. It is essential for growth and development in all forms of life, and has been proposed to have beneficial therapeutic and preventative effects on infectious diseases, including a shortening of the length of the common cold in man.

Zinc is found in more than 300 enzymes, where it plays both a catalytic and a structural role. It is the only metal to have representatives in each of the six fundamental classes of enzymes recognized by the International Union of Biochemistry: oxidoreductases, such as alcohol dehydrogenase and superoxide dismutase; transferases, such as RNA polymerase and aspartate transcarbamoylase; hydrolases, such as carboxypeptidase A and thermolysin; lyases, such as carbonic anhydrase and fructose-1,6-bisphosphate aldolase; isomerases, such as phosphomannose isomerase; and ligases, such as pyruvate carboxylase and amino acyl-tRNA synthetases. Not only is zinc involved in enzymes, where it plays both a catalytic and a structural role, but there are also growing numbers of nucleic acid-binding proteins with essential Zn atoms. This demonstrates that Zn is also widely involved in the regulation of the transcription and translation of the genetic message.

The bioinorganic chemistry of zinc is dominated by a number of factors, the most pertinent of which are summarized here. The divalent zinc ion is redox inactive, in contrast, for example, to manganese, iron and copper. Its d$^{10}$ configuration means that not only does it have no d-d transitions, and therefore no absorption spectroscopy, but also its complexes are not subject to ligand field stabilization effects such that Zn$^{2+}$ has no ligand field constraints on its coordination geometry. Coordination number and geometry are therefore dictated only by ligand size and charge. This means that zinc can, in principle, adopt highly flexible coordination geometry. However, in most zinc proteins there is a strong preference for tetrahedral coordination, frequently slightly distorted, which enhances both the Lewis acidity of the zinc centre and the acidity of a coordinated water molecule. Only Cu(II) is a better Lewis acid. A few cases of zinc in five-coordinate distorted trigonal bipyramidal geometry have been reported. Since zinc is of borderline hardness, it can bind oxygen (Asp, Gu, H$_2$O), nitrogen (His) and sulfur (Cys) ligands.
Three types of zinc-binding sites have been recognized in zinc enzymes (Figure 12.1)—catalytic sites, structural sites and cocatalytic sites. Many of these zinc enzymes are peptidases and amidases, involved in the cleavage of amide bonds—they include peptidases, such as thermolysin and carboxy-peptidases; β-lactamases, which destroy the four-member β-lactam rings in penicillins; and matrix metalloproteinases, which degrade extracellular matrix components such as collagen. Zinc enzymes also participate in the cleavage of the phosphodiester bonds in both DNA and RNA, and their role extends beyond catalysis of hydrolytic reactions to include the important lyase, carbonic anhydrase and the oxidoreductase, alcohol dehydrogenase.

We consider, successively, the catalytic role of several classes of mononuclear Zn\(^{2+}\) enzymes and then discuss enzymes with di- and tri-nuclear cocatalytic zinc centres, some of which include a metal ion other than zinc. We conclude with a presentation of some of the zinc-based motifs found in proteins involved in the regulation of nucleic acid and protein synthesis.

**MONONUCLEAR ZINC ENZYMES**

The first zinc enzyme to be discovered was carbonic anhydrase in 1940, followed by carboxypeptidase A some 14 years later. They both represent the archetype of mono-zinc enzymes, with a central catalytically active Zn\(^{2+}\) atom bound to three protein ligands, and the fourth site occupied by a water molecule. Yet, despite the overall similarity of catalytic zinc sites with regard to their common tetrahedral [(XYZ)Zn\(^{2+}\)-OH\(_2\)] structure, these mononuclear zinc enzymes catalyse a wide variety of reactions, as pointed out above. The mechanism of action of the majority of zinc enzymes centres around the zinc-bound water molecule,
which is best represented as $\text{Zn}^{2+}\cdot\text{OH}_2$. What determines the catalytic properties of each enzyme is not only the nature of the donor ligands, but also the distance that separates them in the amino acid sequence of the protein. Typically (Table 12.1), two of the ligands are separated by only 1–3 amino acids, whereas the third ligand is separated by a longer spacer of between 5 and 196 residues.

The mechanism of action of mononuclear zinc enzymes depends on the $\text{Zn}^{2+}\cdot\text{OH}_2$ centre, which can participate in the catalytic cycle in three distinct ways (Figure 12.2) – either by ionization, to give zinc-bound hydroxyl ion (in carbonic anhydrase), polarization by a general base (in carboxypeptidase) or displacement of the –OH$_2$ ligand by the substrate (in alkaline phosphatase). In the first two examples of mononuclear zinc enzymes which we consider, the lyases (carbonic anhydrase) and the hydrolases (carboxypeptidase), the zinc ion functions as a powerful electrophilic catalyst by providing some or all of the following properties: (i) an activated water molecule for nucleophilic attack, (ii) polarization of the carbonyl of the bond to be cleaved and (iii) stabilization of the negative charge that develops in the transition state.

**CARBONIC ANHYDRASE**

The carbonic anhydrases of mammalian erythrocytes have been the object of extensive study for the last 68 years, and can be considered as the prototype of zinc enzymes that use...
the hydroxyl ion generated by ionization of the Zn$^{2+}$-OH$_2$ as the nucleophile for hydrolysis or hydration reactions. The Zn$^{2+}$ ion lies at the bottom of a 15 Å conical cavity and is coordinated to the protein by three invariant His residues, with the remaining tetrahedral site occupied by a water molecule. The water molecule is involved in a hydrogen bond with a Thr residue, which in turn is hydrogen bonded to a Glu residue (Figure 12.3a).

The main features of the mechanism of carbonic anhydrase are illustrated in Figure 12.3b, and involve the following steps: (i) deprotonation of the coordinated water molecule with a pK$_a$ ~7, in a process facilitated by general base catalysis involving His 64. This residue is too far away from the Zn$^{2+}$-bound water to directly remove its proton, but it is linked to it by two intervening water molecules, forming a hydrogen-bonded network which acts as a proton shuttle. (ii) The zinc-bound hydroxide then carries out a nucleophilic attack on the carbon dioxide substrate to generate a hydrogen carbonate intermediate [(His)$_3$Zn-OCO$_2$H]$^+$ that (iii) is displaced by H$_2$O to release bicarbonate and complete the catalytic cycle. The key to understanding the role of the Zn$^{2+}$ ion is that its charge makes the bound water molecule more acidic than free H$_2$O. This generates a source of nucleophilic zinc-bound OH$^-$, even at neutral pH.

CARBOXYPEPTIDASES AND THERMOLYSINS

As mentioned earlier, by far the largest number of zinc enzymes are involved in hydrolytic reactions, frequently associated with peptide bond cleavage. Carboxypeptidases and thermolysins are, respectively, exopeptidases, which remove amino acids from the carboxyl terminus of proteins, and endopeptidases, which cleave peptide bonds in the interior of a polypeptide chain. However, they both have almost identical active sites (Figure 12.4) with two His and one Glu ligands to the Zn$^{2+}$. It appears that the Glu residue can be bound in a mono- or bi-dentate manner. The two classes of enzymes are expected to follow similar reaction mechanisms.

Following myoglobin and lysozyme, bovine carboxypeptidase A was the third protein to have its 3-D structure solved at high resolution. The active site zinc is bound to His69, Glu72 and His196 (Figure 12.4), and to a water molecule, which is displaced when
Figure 12.4  Active sites of thermolysin and carboxypeptidases A and B. (Reprinted with permission from Parkin, 2004. Copyright (2004) American Chemical Society.)

Figure 12.5  ‘Zinc-hydroxide’ reaction mechanism for peptide hydrolysis by carboxypeptidase A. (Reprinted with permission from Lipscomb and Sträter, 1996. Copyright (1996) American Chemical Society.)
bidentate ligand such as glycyltyrosine binds to Zn\(^{2+}\) through its carbonyl oxygen and \(-\text{NH}_2\) terminus. The zinc-bound water molecule is itself hydrogen bonded to Glu270. The mechanism of carboxypeptidase has been controversial for almost 50 years. Two proposals have been advanced, which differ as to whether hydrolysis of the peptide bond occurs by attack of a zinc-bound hydroxide anion or by replacement of the zinc-bound water molecule by the oxygen atom of the peptidyl carbonyl group. In the first of these (Figure 12.5), the so-called ‘general base Zn-OH\(^{-}\) pathway’, peptide hydrolysis by carboxy-peptidase A can be described in the following steps: (a) in the Michaelis complex the substrate’s carbonyl oxygen is hydrogen bonded to Arg127, which facilitates nucleophilic attack by a water molecule promoted by zinc and assisted by Glu270; (b) this generates a tetrahedral intermediate that is stabilized by both Zn\(^{2+}\) and Arg127. Glu270 then accepts a proton from a zinc-bound water molecule and transfers the proton to the leaving NH group of the scissile peptide bond to give (c) the final product complex.

**ALCOHOL DEHYDROGENASES**

Alcohol dehydrogenases are a class of zinc enzymes, which catalyse the oxidation of primary and secondary alcohols to the corresponding aldehyde or ketone by the transfer of a hydride anion to NAD\(^{+}\) with release of a proton:

\[
\begin{align*}
\text{RCH(OH)R'} + \text{NAD}^+ & \xrightarrow{\text{ADH}} \text{RC(=O)R'} + \text{NADH} + \text{H}^+ \\
\end{align*}
\]

The most extensively studied alcohol dehydrogenases are those of mammalian liver. They are dimeric proteins, with each subunit binding two Zn\(^{2+}\) ions, only one of which is catalytically active. This catalytic Zn\(^{2+}\) ion has distorted tetrahedral geometry, coordinated to one histidine and two cysteine residues. The non-catalytic zinc plays a structural role and is coordinated tetrahedrally to four cysteine residues.

The essential features of the catalytic cycle are summarized in Figure 12.6. After binding of NAD\(^{+}\) the water molecule is displaced from the zinc atom by the incoming alcohol substrate. Deprotonation of the coordinated alcohol yields a zinc alkoxide intermediate, which then undergoes hydride transfer to NAD\(^{+}\) to give the zinc-bound aldehyde and NADH. A water molecule then displaces the aldehyde to regenerate the original catalytic zinc centre, and finally NADH is released to complete the catalytic cycle.

Thus, the role of zinc in the dehydrogenation reaction is to promote deprotonation of the alcohol, thereby enhancing hydride transfer from the zinc alkoxide intermediate. Conversely, in the reverse hydrogenation reaction, its role is to enhance the electrophilicity of the carbonyl carbon atom. Alcohol dehydrogenases are exquisitely stereo specific; and by binding their substrate via a three-point attachment site (Figure 12.7), they can distinguish between the two-methylene protons of the prochiral ethanol molecule.
OTHER MONONUCLEAR ZINC ENZYMES

We have already seen the diversity of function in the lyases, hydrolases and oxidoreductases. Several other types of zinc coordination are found in a number of other enzymes, illustrated in Figure 12.8. These include enzymes with the coordination motif [(His)_2(Cys) Zn^{2+}-OH], illustrated by the lysozyme of bacteriophage T7; this group also includes a peptidyl deformylase.

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**Figure 12.6** (a) The catalytic site of liver alcohol dehydrogenase and (b) the essential features of its catalytic cycle. (Reprinted with permission from Parkin, 2004. Copyright (2004) American Chemical Society.)

**Figure 12.7** Specific attachment of a prochiral centre to an enzyme-binding site enables the enzyme to distinguish between prochiral methylene protons in ethanol. (From Voet and Voet, 2004. Reproduced with permission from John Wiley & Sons., Inc.)
The 5-aminolaevulinate dehydratase (or porphobilinogen synthase), which catalyses the condensation of two molecules of 5-aminolaevulinate to form the pyrrole precursor of the porphyrins (haem, chlorophyll, cobalamines), has the motif [(Cys)$_3$Zn$_2$/H$_{11001}$]-OH$_2$. As pointed out earlier (see Chapter 1), this enzyme is the target for saturnism, the Pb toxicity frequently observed among inner city children.

Tetrahedral structural sites typically only involve coordination by the protein, frequently by cysteine residues, as illustrated by the [Cys$_4$Zn$^{II}$] structural site in liver alcohol dehydrogenase. More recently, a class of zinc proteins and enzymes with tetrahedral ‘non-aqua’ functional zinc sites have started to emerge in which the activity centres upon the reactivity of a zinc thiolate linkage rather than that of a zinc-bound water molecule. The first to be discovered was the Ada DNA repair protein (Figure 12.8), which has a [(Cys)$_4$Zn] motif and whose function is to repair damage to DNA as a result of methylation. The Ada protein achieves the repair by undergoing sacrificial alkylation of one of the zinc cysteine thiolate ligands (Figure 12.9); this indicates that Ada is not acting as an enzyme, but rather as a reagent (hence its description as a DNA repair protein). Other examples that involve reactivity of zinc cysteine thiolate linkages include methionine synthase and the farnesyl- and geranylgeranyl-transferases, which participate, respectively, in the transfer of farnesyl and geranylgeranyl groups to target proteins.

Figure 12.8 Some other active-site coordination motifs in mononuclear zinc enzymes: from left to right bacteriophage T7 lysozyme, 5-aminolaevulinate dehydratase, Ada DNA repair protein. (Reprinted with permission from Parkin, 2004. Copyright (2004) American Chemical Society.)

Figure 12.9 Repair of damaged DNA by sacrificial alkylation of one of the zinc cysteine thiolate ligands of the Ada DNA repair protein. (Reprinted with permission from Parkin, 2004. Copyright (2004) American Chemical Society.)
MULTINUCLEAR AND COCATALYTIC ZINC ENZYMES

It was clear for some time that a number of zinc enzymes required two or more metal ions for full activity, but in the absence of X-ray structural data the location of these metal centres with regard to one another was often uncertain. When the first 3-D structures began to appear, it became clear that the metals were in close proximity. A particular feature of many of these enzymes was the presence of a bridging ligand between two of the metal sites, usually an Asp residue of the protein, which is occasionally replaced by a water molecule. While some of the sites contain only Zn ions, several contain Zn in combination with Cu (in cytosolic superoxide dismutases) Fe (in purple acid phosphatases) or Mg (in alkaline phosphatase and the aminopeptidase of lens).

We will discuss the Cu-Zn superoxide dismutases in greater detail in Chapter 14. Suffice to say here that this is the only cocatalytic site to have a bridging His ligand, and that the role of the Zn ion is thought to be structural, whereas the Cu undergoes redox cycling during catalysis. The importance of the Zn atom is underlined by the observation that the zinc-deficient enzyme is thought to participate in both the sporadic and familial forms of the neurodegenerative disease amyotrophic lateral sclerosis, which is discussed in Chapter 18.

Among the enzymes that contain dinuclear zinc sites we can include the metallo-β-lactamases, a number of aminopeptidases (Figure 12.10) and alkaline phosphatase. β-lactams are the most important class of antibiotics, but bacterial resistance to β-lactams is increasingly observed, severely compromising their efficacy. In many cases, the bacterial resistance is achieved by the production of β-lactamases, enzymes that cleave the four-membered β-lactam ring of many classes of β-lactam antibiotics, including penicillins, cephalosporins and carbapenems. There are four classes of β-lactamases, the most recent to be discovered are the metallo-β-lactamases which have a dinuclear zinc centre. One of the zinc atoms is tetra-coordinate with a [(His)_3(Zn(μ-OH))] motif in which the hydroxide ion serves as a bridge to the second Zn site, which has trigonal bipyramidal geometry with a [(His)(Asp)(X)Zn(OH)_2(μ-OH)] motif. Whereas most β-lactamases have maximum activity with both Zn sites occupied, the enzyme from Aeromonas hydrophila is fully active with only one Zn site occupied. This zinc site has a dissociation constant lower than 20 nM. Binding of a second zinc atom inhibits the enzyme, with a $K_i$ of 46 μM. The mechanism

![Metal coordination sites in dinuclear zinc enzymes.](image)

Figure 12.10 Metal coordination sites in dinuclear zinc enzymes. (Reprinted with permission from Parkin, 2004. Copyright (2004) American Chemical Society.)
of β-lactamases remains unknown, but it is thought to be analogous to that described above for carboxypeptidases, with the presence of one Zn\(^{2+}\) ion that has the characteristics of a catalytic zinc site, while the role, and even the essentiality of the second zinc atom, is not clear.

Aminopeptidases are counterparts to carboxypeptidases, removing N-terminal amino acids. However, unlike the carboxypeptidases, they seem to require two Zn\(^{2+}\) ions, which are typically linked by a bridging carboxylate ligand (Figure 12.10).

Several zinc enzymes that catalyse the hydrolysis of phosphoesters have catalytic sites, which contain three metal ions in close proximity (3–7 Å from each other). These include (Figure 12.11) alkaline phosphatase, phospholipase C and nuclease P1. In phospholipase C and nuclease P1, which hydrolyse phosphatidylcholine and single-stranded RNA (or DNA), respectively, all three metal ions are Zn\(^{2+}\). However, the third Zn\(^{2+}\) ion is not directly associated with the dizinc unit. In phospholipase C, the Zn–Zn distance in the dizinc centre is 3.3 Å, whereas the third Zn is 4.7 and 6.0 Å from the other two Zn\(^{2+}\) ions. All three Zn\(^{2+}\) ions are penta-coordinate. Alkaline phosphatase, which is a non-specific phosphomonoesterase, shows structural similarity to phospholipase C and P1 nuclease; however,
the third metal ion is Mg$^{2+}$. One of the Zn$^{2+}$ sites shares a common Asp ligand with the Mg$^{2+}$ site, which is typically hexa-coordinate. The main features of the mechanism of alkaline phosphatase are illustrated in Figure 12.12.

The first step involves binding of the substrate monophosphate [ROPO$_3$$^2^-$], which is coordinated by both Zn$^{2+}$ ions, accompanied by dissociation of the two bound water molecules. The two remaining oxygen atoms of [ROPO$_3$$^2^-$] that are not coordinated to the Zn$^{2+}$ ions interact with an Arg residue. The phosphorus of the substrate undergoes nucleophilic attack by a Ser-O$^-$ in an S$_{N}$2 manner, cleaving the P–OR bond with the formation of a phospho-serine intermediate. It is thought that the two Zn$^{2+}$ ions play several roles—by coordinating the RO group one of the zinc atoms activates the RO–P bond, while by coordinating the Ser–OH group, the other zinc centre facilitates deprotonation to generate the highly nucleophilic Ser–O$^-$. The zinc alkoxide group is hydrolysed, releasing ROH and generating a zinc hydroxide species. This carries out a nucleophilic attack on the phosphoenzyme intermediate, cleaving the phosphorus–enzyme bond with the formation of a bridging phosphate [HOPO$_3$$^2^-$] complex. This catalytic cycle is completed by the displacement of [HOPO$_3$$^2^-$] by water. The importance of the Ser residue is underlined by the observation that its mutation to Gly or Ala decreases activity by 10$^4$ or 10$^5$ fold. The two-step reaction sequence explains the retention of configuration, in agreement with experimental observations.

Finally we should briefly mention the purple acid phosphatases, which, unlike the alkaline phosphatases, are able to hydrolyse phosphate esters at acid pH values. Their purple colour is associated with a Tyr to Fe(III) charge transfer band. The mammalian purple acid phosphatase is a dinuclear Fe(II)-Fe(III) enzyme, whereas the dinuclear site in kidney bean purple acid phosphatase (Figure 12.13) has a Zn(II), Fe(III) centre with bridging hydroxide and Asp ligands. It is postulated that the iron centre has a terminal hydroxide ligand, whereas the zinc has an aqua ligand. We do not discuss the mechanism here, but it must be different from the alkaline phosphatase because the reaction proceeds with inversion of configuration at phosphorus.

**Figure 12.12** Principal steps in the mechanism of alkaline phosphatase. (Reprinted with permission from Parkin, 2004. Copyright (2004) American Chemical Society.)
ZINC FINGERS – DNA- AND RNA-BINDING MOTIFS

Aaron Klug discovered the first of the eukaryotic DNA-binding motifs in *Xenopus* transcription factor IIIA (TFIIIA), a protein that binds to the 5S rRNA gene. The resulting complex subsequently binds two other transcription factors and RNA polymerase III, which leads to the initiation of transcription of the 5S rRNA gene. The TFIIIA molecule contains 9 similar ~30 residue long, tandemly repeated modules. Each of these modules contains two invariant Cys residues, two invariant His residues and several conserved hydrophobic residues (Figure 12.14), and a Zn$^{2+}$ ion, which is tetrahedrally coordinated by the invariant Cys and His residues. These so-called Cys$_2$–His$_2$ Zinc Fingers occur from 2 to at least 37 times each in a family of eukaryotic transcription factors. In some zinc fingers, the invariant His residues are replaced by Cys residues (Cys$_2$–Cys$_2$ Zinc Fingers), while in others six Cys residues bind two Zn$^{2+}$ ions (Dinuclear Cys$_6$ Zinc Fingers). Structural diversity is a hallmark of zinc finger proteins, and it appears that the Zn$^{2+}$ ion(s) allow(s) formation of a relatively compact globular DNA-binding domain, precluding the requirement for a much larger hydrophobic core. The zinc finger proteins constitute a super family, and ~1% of all mammalian proteins contain this motif.

![Figure 12.13](image1.png) Coordination of the dinuclear site in kidney bean purple acid phosphatase. (Reprinted with permission from Parkin, 2004. Copyright (2004) American Chemical Society.)

![Figure 12.14](image2.png) (Left) Schematic representation of tandemly repeated zinc finger motif with their tetrahedrally coordinated Zn$^{2+}$ ions. Conserved amino acids are labelled, and the most probable DNA-binding side chains are indicated by balls (from Klug and Rhodes, 1988). (Right) A ribbon diagram of a single zinc finger motif in a ribbon diagram representation. (From Voet and Voet, 2004. Reproduced with permission from John Wiley & Sons., Inc.)
The global structural details of how zinc fingers bind to double-stranded DNA are well understood. One isolated Cys$_2$-His$_2$ zinc finger, consisting of two β-strands joined by a β-bend followed by an α-helix (Figure 12.14) held together by a tetrahedrally coordinated Zn$^{2+}$ ion, can span three or four consecutive base pairs of the DNA sequence. The multiple zinc fingers follow a right-handed helical path as they wrap around the double helix, with multiple contacts being made with particular nucleotide bases in the major groove. The contacts are frequently made by the side chains of amino acid residues at positions −1, +2, +3 and +6 of the α-helix.

Among the strong preferences that have been observed, it seems that Arg prefers binding to guanosine, Asp to adenosine and cytosine and Leu to thymidine. However, we are not yet sufficiently advanced to define a set of coding rules (i.e. to define the amino acid sequence of one or more zinc fingers, which would bind to a specific DNA sequence).

The *Xenopus* transcription factor IIIA not only acts as an essential RNA polymerase transcription factor for the expression of the 5S rRNA gene, it also binds to the 5S rRNA to form a 7S ribonucleoprotein particle that stabilizes the RNA until it is required for ribosome assembly and facilitates nuclear export of the 5S rRNA. Indeed, it was originally shown to be the protein component associated with 5S rRNA in the 7S particle in *Xenopus* oocytes before it was recognized as a transcription factor. How, we may ask, can this protein not only recognize specific DNA sequences in the 5S rRNA gene upstream region, but also recognize different, but equally specific, sequences in 5S rRNA?

Both biochemical and X-ray crystallographic data show that binding of TFIIIA to the 5S rRNA gene internal control region utilizes all but the fourth and sixth of the nine zinc fingers of the transcription factor (Figure 12.15).

Fingers 1–3 bind to a 10-base-pair ‘box C’ sequence, wrapping around the major groove of the DNA. Finger 5 binds to a 3-base-pair ‘intermediate element’ (IE) sequence. Fingers 4 and 6 act as non-DNA-binding spacers to allow recognition of the separated elements. This allows fingers 7–9 to interact with an 11-base-pair ‘box A’ sequence.

By using a very clever strategy, Klug and his colleagues were able to design a truncated 5S rRNA that binds to zinc fingers 4–6. The resulting X-ray structure shows that finger 4 binds to sequences in loop E, finger 5 binds to backbone atoms in helix V, while finger 6

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**Figure 12.15** (a) TFIIIA binds to 5S rRNA promoter sequences using zinc fingers 1–3, 5 and 7–9 which recognize box C (green), the IE sequences (red) and box A (orange), respectively. (b) TFIIIA binds to 5S rRNA using primarily zinc fingers 4–6. Finger 4 binds to sequences in loop E, finger 5 to backbone atoms in helix V and finger 6 to sequences in loop A. (From Tanaka Hall, 2005. Copyright 2005, with permission from Elsevier.)
binds to sequences in loop A. The three fingers are associated with identical sequences in their DNA and RNA complexes, but in quite different ways. This is illustrated in Figure 12.16, which compares the binding of the unique member of the three zinc fingers, finger 5, which binds to both DNA and RNA, in its complexes, respectively, with the 5S rRNA promoter DNA and with the 5S rRNA. Whereas in the DNA structure, the interactions are mostly in the major groove and include both specific interactions with bases of the DNA (e.g. Leu148 with a thymine residue of the DNA), in the RNA interactions there are no direct interactions with the bases, and the interactions are essentially with the phosphate groups of the 5S rRNA. Some residues in finger 5, such as Ser150, Lys144, Arg154 and His155, bind to both RNA and DNA, but to different sites in each case. This is in marked contrast to the zinc finger 4 in which a His binds directly to a guanosine and possible also to a second guanosine, and finger 6 in which a Trp stacks onto an adenosine.

REFERENCES