8: Metal/Nucleic Acid Interactions

I. Introduction

The interest of the bioinorganic community in the field of metal/nucleic-acid interactions has burgeoned in the last decade. This interest and the resulting progress have come about primarily because of the tremendous advances that have occurred in nucleic-acid technology. We can now isolate, manipulate, and even synthesize nucleic acids of defined sequence and structure, as we would other molecules that chemists commonly explore. Furthermore, as may be evident already in other chapters of this book, bioinorganic chemistry has itself been evolving from a field focused on delineating metal centers in biology to one that includes also the application of inorganic chemistry *to probe* biological structures and function. In the past decades it has become clear that nucleic acids, structurally, functionally and even remarkably in terms of catalysis, play active and diverse roles in Nature. Transition-metal chemistry, both in the cell and in the chemist's test tube, provides a valuable tool both to accomplish and to explore these processes.

There are also many practical motivations behind the study of how metal ions and complexes interact with nucleic acids. Heavy-metal toxicity in our environment arises in part from the covalent interactions of heavy-metal ions with nucleic acids. In addition, these heavy metals interfere with metalloregulatory proteins and in so doing disrupt gene expression. We need to understand the functioning of the natural metalloregulators of gene expression and we need to design new metal-specific ligands, which, like the proteins themselves, capture heavy metals before their damage is done. Heavy-metal interactions with nucleic acids indeed have provided the basis also for the successful application of cisplatin and its derivatives as anticancer chemotherapeutic agents (see Chapter 9). The design of new pharmaceuticals like cisplatin requires a detailed understanding of how platinum and other metal ions interact with nucleic acids and nucleic-acid processing. Furthermore, we are finding that metal complexes can be uniquely useful in developing spectroscopic and reactive probes of nucleic acids, and hence may become valuable in developing new diagnostic agents. Finally, Nature itself takes advantage of metal/nucleic-acidchemistry, from the biosynthesis of natural products such as bleomycin, which chelates redox-active metal ions to target and damage foreign DNA, to the development of basic structural motifs for eukaryotic regulatory proteins, the zinc-finger proteins, which bind to DNA and regulate transcription. In all these endeavors, we need first to develop an understanding of how transition-metal ions and complexes interact with nucleic acids and how this chemistry may best be exploited.

In this chapter we first summarize the "basics" needed to consider the interactions of metal ions and complexes with nucleic acids. What are the structures of nucleic acids? What is the basic repertoire of modes of association and chemical reactions that occur between coordination complexes and polynucleotides? We then consider in some detail the interaction of a simple family of coordination complexes, the tris(phenanthroline) metal complexes, with DNA and RNA to illustrate the techniques, questions, and applications of metal/nucleic-acid chemistry that are currently being explored. In this section, the focus on tris(phenanthroline) complexes serves as a springboard to compare and contrast studies of other, more intricately designed transition-metal complexes (in the next section) with nucleic acids. Last we consider how Nature uses metal ions and complexes in carrying out nucleic-acid chemistry. Here the principles, techniques, and fundamental coordination chemistry of metals with nucleic acids provide the foundation for our current understanding of how these fascinating and complex bioinorganic systems may function.

II. The Basics

A. Nucleic-acid Structures[1]

B. Fundamental Interactions with Nucleic Acids
   1. Coordination
   2. Interecalation and Hydrogen Bonding

C. Fundamental Reactions with Nucleic Acids
   1. Redox Chemistry
   2. Hydrolytic Chemistry

III. A Case Study: Tris(phenanthroline) Metal Complexes

A.

Binding Interactions with DNA

B. Techniques to Monitor Binding

IV. Applications of Different Metal Complexes that Bind Nucleic Acids

A. Spectroscopic Probes

B. Metallofootprinting Reagents

C. Conformational Probes

1. Nonspecific Reactions of Transition-metal Complexes
2. Transition-metal Complexes as Shape-selective Probes

D. Other Novel Techniques

V. Nature's Use of Metal/Nucleic-acid Interactions

A. A Structural Role

B. A Regulatory Role

C. A Pharmaceutical Role

D. A Catalytic Role

VI. References

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107. I am grateful to my students and coworkers for their scientific contributions to some of the work described in this chapter and for their critical review of the manuscript. I also thank in particular Dr. Sheila David for preparation of the figures.

Contributors and Attributions

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