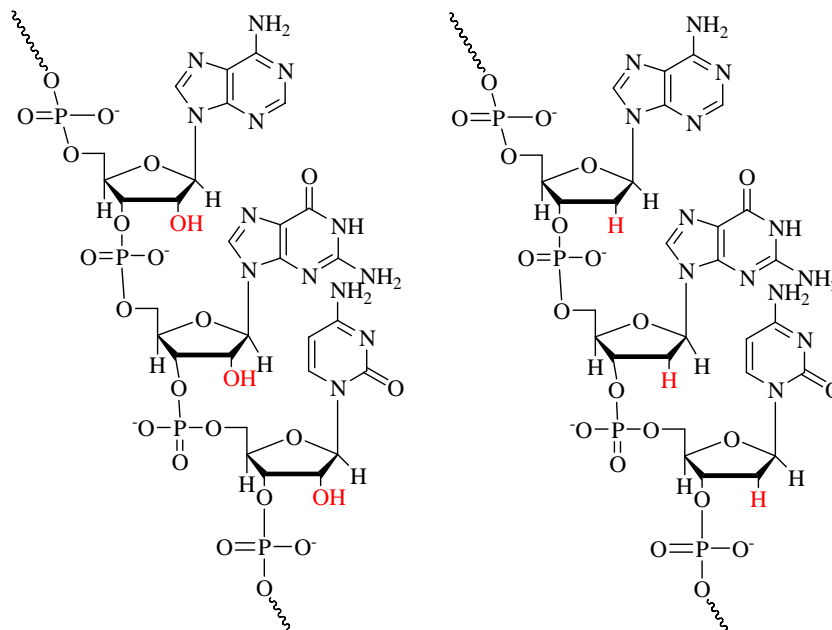


## Modelling the Zn(II)-containing RNase and DNase Enzymes.

Nature preserves its genetic information in RNA and DNA which are information rich polymers held together the extremely stable phosphodiester linkages as in **1** (<http://en.wikipedia.org/wiki/RNA>) and **2** (<http://en.wikipedia.org/wiki/DNA>).

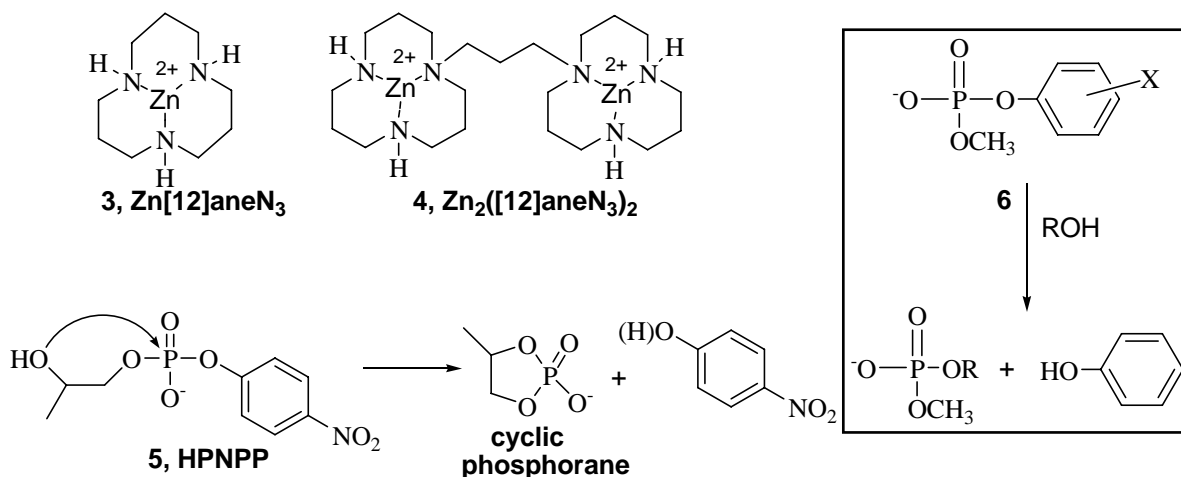


1 a hypothetical piece of RNA

2 a hypothetical piece of DNA

From a reactivity standpoint, the RNA and DNA differ in their rates of cleavage of the sugar-O-P-O-sugar linkage by about 5-10 thousand fold, the cleavage of the RNA being faster due to the presence of the 3'-OH group which is absent on DNA. While the respective half-times for hydrolysis of RNA and DNA at pH 7 and 25 °C are 110 and 10-100 billion years, Nature provides enzymes that promote the hydrolyses by up to a factor of  $10^{15}$ , affording some of the largest rate enhancements known. Many of these enzymes have active sites with two or more metal ions (usually  $\text{Zn}^{2+}$  and in some cases  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$  and  $\text{Fe}^{2+}$ ) as exemplified by phosphodiesterases such as ribonuclease H from HIV reverse transcriptase, 3',5'-exonuclease from DNA polymerase I, the P1 nucleases, and phospholipase C. Intense research was directed at understanding the origins of catalysis provided by metal ion systems in promoting the hydrolysis of phosphate diesters, and while many advances in our understanding of this remarkable catalysis, but as yet none of the simple systems that have been studied in water approach the rates of the enzymes.

In this work we are interested in the synthesis of simple systems that bind two metal ions, notably  $\text{Zn}^{2+}$  ions, in such a way that they can interact cooperatively to cleave some simple phosphate diesters. Two of the systems (**3**, **4**) in which we are interested are being studied for their ability to promote the cleavage of the simple RNA model 2-hydroxypropyl *p*-nitrophenyl phosphate (**5**, **HPNPP**). For our reactions, we are particularly in the cleavage of HPNPP in alcohol media such as methanol and ethanol



where the low dielectric constant more closely approximates that in the active sites of the enzymes. Future studies with these catalysts will include looking at the cleavage of a series of 2-hydroxypropyl aryl phosphates where the aryl group has various substituents that change its electronic properties in predictable ways.

In order to model the DNA cleaving enzymes, we are looking at the ability of various dinuclear  $M^{x+}$ -containing complexes such as **4** to promote the cleavage of methyl aryl phosphates (**6**) that do not contain the hydroxypropyl group. Once again the reactions are studied in the low dielectric constant alcohol media which seems to enhance the interaction of the positively charged metal ion containing catalyst and the negatively charged phosphate diesters.

For a preliminary report on the effect of  $La^{3+}$  to catalyze the methanolysis of HPNPP, see:

Josephine S. W. Tsang, Alexei A. Neverov and R. S. Brown. "La<sup>3+</sup>-Catalyzed Methanolysis of Hydroxypropyl-*p*-nitrophenyl Phosphate as a Model for the RNA Transesterification Reaction." *J. Am. Chem. Soc.* **2003**, *125*, 1559-1566.