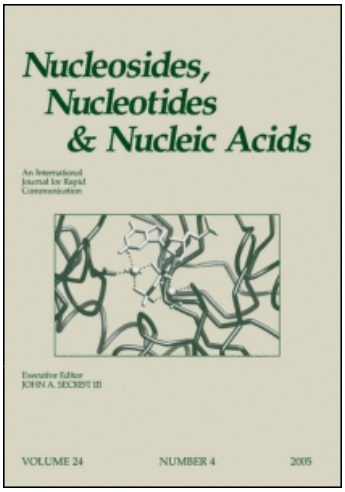


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# $Zn^2$ Promoted Hydrolysis of RNA

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# $Zn^{2+}$ PROMOTED HYDROLYSIS OF RNA

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**Abstract.** The $Zn^{2+}$ promoted hydrolysis of phosphodiester bonds of RNA has been studied by using a series of model compounds from dinucleoside monophosphates to oligo- and polynucleotides. The results will be discussed with respect to complex formation between the metal ion catalysts and substrates.



The basic principles of the mechanism of the $Zn^{2+}$ promoted hydrolysis of RNA phosphodiester bonds were established by studies on dinucleoside monophosphates[1-3] and 2',3'-cyclic monophosphates.[4] It appears that the catalytically active function is a phosphate-bound metal ion bearing a hydroxo ligand. Consistent with this, the hydrolysis is first-order in both hydroxide- and metal ion concentration, yet it shows no catalysis by organic bases added in reaction solutions.[1,4] Furthermore, metal ions that are acidic, are the best catalysts, and among $Zn^{2+}$ complexes, the catalytic activity correlates with the $pK_a$ of an aquo ligand. Base binding does not seem to have any significant effect.[2]

The catalytically relevant findings were very similar with dinucleoside monophosphates and polynucleotides.[5] It was observed, however, that the hydrolysis of phosphodiester bonds of poly-U were up to 100 times as fast as those of 3',5'-UpU. These observations suggest that although the mechanism is the same in both cases, using a polynucleotide as a substrate, provides an additional factor that influences the rate of the reaction.

To study the origin of the reactivity differences, several different chimeric oligonucleotides were synthesised.[6-8] The results of these studies strongly suggest that the clear differences observed between the reactivity of different oligonucleotides can be explained by the strength of the $Zn^{2+}$ ion – substrate complex. $Zn^{2+}$ binds to two phosphate groups of oligonucleotides, whenever possible, which makes the complex

stronger increasing its equilibrium concentration compared to the situation with dinucleoside monophosphates. In molecules which bear a dianionic monophosphate function at one of the termini, this is one of the co-ordination sites, the other being the scissile phosphodiester bond. This is shown by the fact that although an additional phosphodiester bond results in a ten-fold rate enhancement, oligonucleotides bearing a 3'-terminal phosphomonoester group are yet another ten times more reactive. Consistent with these suggestions, the catalysis by a $Zn^{2+}$ chelate where three of the co-ordination sites are already occupied, shows much smaller susceptibility for the structure of the catalyst.

To study the effect of the secondary structure of oligonucleotides on the $Zn^{2+}$ promoted cleavage, a series of RNA chimeric hairpins were synthesised.[9] The most striking result of these studies was that in all the cases studied, a linear oligonucleotide was the most reactive, the phosphodiester bonds within the hairpin loops showing a reduced reactivity in the presence of $Zn^{2+}$ and a $Zn^{2+}$ chelate. Hence it appears that bending alone does not enhance the reactivity of phosphodiester bonds. As the $Zn^{2+}$ complex again shows a less significant sensitivity for the structure of the substrate than $Zn^{2+}$ aquo ion does, it seems likely that the reactivity differences, at least to some extent, are to be attributed to the binding of the catalysts. The most likely explanation is, that a metal is unable to bind to two phosphate groups of a tightly bent molecule.



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