

Transition Metal Complexes as DNA Cleaving Agents

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Restriction enzymes are commonly used both *in vivo* and *in vitro* to bind and cleave DNA selectively, but they suffer from limitations such as pH and temperature dependence, and fragility. Metal complexes with comparable selectivity would be good alternatives because in addition to higher stability, they have useful redox properties and controllable shape selectivity.

In 1979, the first study of DNA cleavage by a simple transition metal coordination compound, $\text{Cu}(\text{phen})_2^+$ where phen is 1,10-phenanthroline, was published.² Since then, DNA-cleaving abilities of many transition metal derivatives have been studied.^{1,2} Metal complexes with flat aromatic ligands such as phenanthroline (Figure 1) have been shown to intercalate between the base pairs of DNA.¹ Once a molecule binds to DNA, its ability to cleave DNA selectively can be monitored by gel electrophoresis.

Cationic metalloporphyrins have been studied for their DNA binding and cleaving ability. FeTMPyP and ZnTMPyP (TMPyP = tetrakis(4-N-methylpyridiniumyl)porphyrin) bind to regions rich in adenine-thymine pairs and cleave DNA in those locations.³ MnTMPyP binds to the minor groove and cleaves regions with three consecutive adenine-thymine base pairs. Additional approaches to alter the cleavage selectivity of the manganese system include linking oligonucleotide and nuclease units to the parent metalloporphyrin.^{3,4}

To determine how the nature of the metal affects DNA cleavage, Mn(III) and Ni(II) salen derivatives were compared (salen = bis(salicylidene)ethylenediamine).⁵ Quaternary ammonium chains were attached to the salen ligand to aid in water solubility (Figure 2).

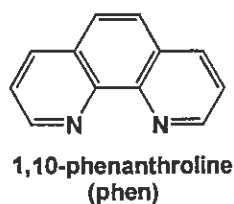


Figure 1. DNA-intercalating ligand.

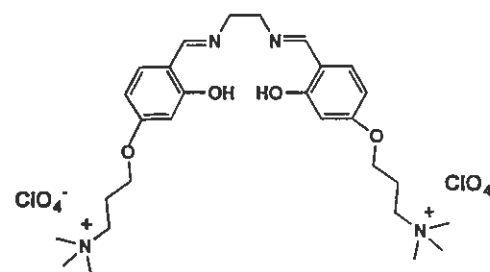


Figure 2. Water-soluble, bis-cationic salen-based ligand.⁵

Bhattacharya and coworkers observed that the Mn(III) derivative was a more active DNA cleavage agent than the square planar Ni(II) species.⁵ Ligand effects of substituted Mn(III) salen derivatives were studied by Griffin and coworkers, who found that cleavage efficiency decreased as the size of substituents increased.⁶

Ruthenium(IV)-oxo species have been shown to bind non-covalently and cleave DNA.⁷ When comparing $[\text{Ru(O)}(\text{tpy})(\text{bpy})]^{2+}$, $[\text{Ru(O)}(\text{tpy})(\text{phen})]^{2+}$, and $[\text{Ru(O)}(\text{tpy})(\text{tmen})]^{2+}$ (tpy = 2,2',2''-terpyridine, bpy = 2,2'-bipyridine, phen = 1,10-phenanthroline, tmen = N,N,N',N'-tetramethylethylenediamine), Thorp and coworkers found that the phen derivative cleaved DNA

to a lesser extent than either the bipy or tmen derivatives. This difference was attributed to the strong intercalating ability of phen.^{7,8} The osmium complex $[\text{Os}(\text{O})(\text{tpy})(\text{bpy})]^{2+}$ was synthesized and its cleaving efficiency was lower than that of the analogous ruthenium complex, perhaps because it is a less potent oxidant.¹⁰

The complex $[\Delta\text{-Rh}(\text{phen})_2(\text{phi})]^{3+}$ has been shown by 2D ^1H NOESY NMR spectroscopy to intercalate between adjacent guanine-cytosine residues in the major groove of DNA.¹¹ Barton and coworkers have also shown that $[\text{Rh}(\text{phen})_2(\text{phi})]^{3+}$ and $[\text{Rh}(\text{phi})_2(\text{bpy})]^{3+}$ photocleave DNA in a sequence-specific and sequence-neutral manner, respectively.^{12,13} This difference in selectivities has been ascribed to steric interactions between protons in the ancillary phen ligands of $[\text{Rh}(\text{phen})_2(\text{phi})]^{3+}$ and the base pairs of DNA, which limit intercalation to "open" sites of the DNA helix (Figure 3).¹³

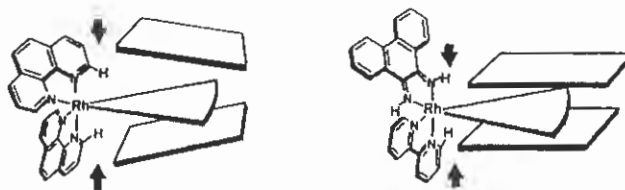


Figure 3. $[\text{Rh}(\text{phen})_2(\text{phi})]^{3+}$ (left) and $[\text{Rh}(\text{phi})_2(\text{bpy})]^{3+}$ (right) binding selectivity.¹³

Because peptide α -helices are known to bind selectively to DNA,¹⁴ a peptide was tethered to the bipyridine ligand of $[\text{Rh}(\text{phi})_2(\text{bpy})]^{3+}$ and a zinc(II) ion was coordinated to two histidine residues to hold the peptide in an α -helical conformation. $\text{Rh}(\text{phi})_2(\text{bpy}'\text{-peptide})$ (Figure 4) binds to the major groove of DNA and subsequent photolysis yields both nicked and linear DNA products. The photocleavage mechanism is thought to be hydrolytic.¹⁵

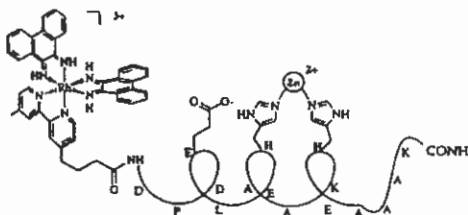


Figure 4. $\text{Rh}(\text{phi})_2(\text{bpy}'\text{-peptide})$ complex.¹⁵

Binuclear complexes have not been extensively explored as DNA cleavage agents. Carrano and coworkers have developed a vanadium(III) oxo-bridged dimer that cleaves DNA without the addition of another agent, but evidence of cleaving ability, and mechanism are lacking and being explored further.¹⁶ Sorlie and coworkers have recently synthesized two organometallic ruthenium DNA cleaving molecules, $[(\eta\text{-C}_5\text{Me}_5)\text{Ru}(\text{NO})(\text{L})]^{2+}$, where L = bpy, dppz (dppz = dipyrldophenazine).¹⁷ Additional studies must be performed to elucidate the DNA binding modes, cleaving sites, and cleavage mechanisms of these molecules.

References

1. (a) Barton, J. K.; Pyle, A. M. "Probing Nucleic Acids with Transition Metal Complexes," *Prog. Inorg. Chem.* **1990**, *38*, 413-475. (b) Barton, J. K. "Metal/Nucleic-Acid Interactions," In *Bioinorganic Chemistry*; Bertini, I., et al.; Univ. Science Books: Mill Valley, C. A., 1994, p 455-503.
2. (a) Sigman, D. S. "Chemical Nucleases," *Biochemistry* **1990**, *29*, 9097-9105. (b) Sigman, D. S.; Mazumder, A.; Perrin, D. M. "Chemical Nucleases," *Chem. Rev.* **1993**, *93*, 2295-2316.
3. Meunier, B. "Metalloporphyrins as Versatile Catalysts for Oxidation Reactions and Oxidative DNA Cleavage," *Chem. Rev.* **1992**, *92*, 1411-1456.
4. (a) Bigey, P.; Sonnichsen, S. H.; Meunier, B.; Nielsen, P. E. "DNA Binding and Cleavage by a Cationic Manganese Porphyrin-Peptide Nucleic Acid Conjugate," *Bioconjugate Chem.* **1997**, *8*, 267-270. (b) Mestre, B.; Jakobs, A.; Pratviel, G.; Meunier, B. "Structure/Nuclease Activity Relationships of DNA Cleavers Based on Cationic Metalloporphyrin-Oligonucleotide Conjugates," *Biochemistry* **1996**, *35*, 9140-9149.
5. Mandal, S. S.; Kumar, N. V.; Varshney, U.; Bhattacharya, S. "Metal-Ion-Dependent Oxidative DNA Cleavage by Transition Metal Complexes of a New Water-Soluble Salen Derivative," *J. Inorg. Biochem.* **1996**, *63*, 265-272.
6. Gravert, D. J.; Griffin, J. H. "Steric and Electronic Effects, Enantiospecificity, and Reactive Orientation in DNA Binding/Cleaving by Substituted Derivatives of [SalenMn^{III}]⁺," *Inorg. Chem.* **1996**, *35*, 4837-4847.
7. Grover, N.; Thorp, H. H. "Efficient Electrocatalytic and Stoichiometric Oxidative Cleavage of DNA by Oxoruthenium(IV)," *J. Am. Chem. Soc.* **1991**, *113*, 7030-7031.
8. Grover, N.; Gupta, N.; Singh, P.; Thorp, H. H. "Studies of Electrocatalytic DNA Cleavage by Oxoruthenium(IV)," *Inorg. Chem.* **1992**, *31*, 2014-2020.
9. (a) Neyhart, G. A.; Grover, N.; Smith, S. R.; Kalsbeck, W. A.; Fairley, T. A.; Cory, M.; Thorp, H. H. "Binding and Kinetics Studies of Oxidation of DNA by Oxoruthenium(IV)," *J. Am. Chem. Soc.* **1993**, *115*, 4423-4428. (b) Gupta, N.; Grover, N.; Neyhart, G. A.; Singh, P.; Thorp, H. H. "Synthesis and Properties of New DNA Cleavage Agents Based on Oxoruthenium(IV)," *Inorg. Chem.* **1993**, *32*, 310-316.
10. Cheng, C.; Goll, J. G.; Neyhart, G. A.; Welch, T. W.; Singh, P.; Thorp, H. H. "Relative Rates and Potentials of Competing Redox Processes during DNA Cleavage," *J. Am. Chem. Soc.* **1995**, *117*, 2970-2980.
11. David, S. S.; Barton, J. K. "NMR Evidence for Specific Intercalation of [Δ -Rh(phen)₂(phi)]³⁺ in [d(GTCGAC)₂]," *J. Am. Chem. Soc.* **1993**, *115*, 2984-2985.

12. Pyle, A. M.; Chiang, M. Y.; Barton, J. K. "Synthesis and Characterization of Physical, Electronic, and Photochemical Aspects of 9,10-Phenanthrenequinone Diimine Complexes of Ruthenium(II) and Rhodium(III)," *Inorg. Chem.* **1990**, *29*, 4487-4495.
13. Pyle, A. M.; Long, E. C.; Barton, J. K. "Shape-Selective Targeting of DNA by (Phenanthrenequinone diimine)rhodium(III) Photocleaving Agents," *J. Am. Chem. Soc.* **1989**, *111*, 4520-4522.
14. Sluka, J. P.; Horvath, S. J.; Bruist, M. F.; Simon, M. I.; Dervan, P. B. "Synthesis of Sequence-Specific DNA-Cleaving Peptide," *Science* **1987**, *238*, 1129-1132.
15. Fitzsimons, M. P.; Barton, J. K. "Design of a Synthetic Nuclease: DNA Hydrolysis by a Zinc-Binding Peptide Tethered to a Rhodium Intercalator," *J. Am. Chem. Soc.* **1997**, *119*, 3379-3380.
16. (a) Otieno, T.; Bond, M. R.; Mokry, L. M.; Walter, R. B.; Carrano, C. J. "Plasmid DNA cleavage by oxo-bridged vanadium(III) dimers without added co-oxidants or reductants," *Chem. Commun.* **1996**, 37-38. (b) Czernuszewicz, R. S.; Yan, Q.; Bond, M. R.; Carrano, C. J. "Origin of the Unusual Bending Distortion in the (μ -Oxo)divanadium(III) Complex $[V_2O(l-his)_4]$: A Reinvestigation," *Inorg. Chem.* **1994**, *33*, 6116-6119.
17. Schoch, T. K.; Hubbard, L. L.; Zoch, C. R.; Yi, G.; Sorlie, M. "Synthesis and Structure of the Ruthenium(II) Complexes $[(\eta-C_5Me_5)Ru(NO)(bpy)]^{2+}$ and $[(\eta-C_5Me_5)Ru(NO)(dppz)]^{2+}$," *Inorg. Chem.* **1996**, *35*, 4383-4390.