Pure & Appl. Chem., Vol. 61, No. 3, pp. 563–564, 1989.
Printed in Great Britain.

Targeting DNA sites with chiral metal complexes

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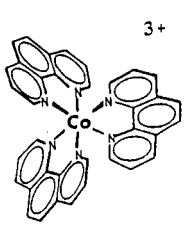
Abstract - Complexes derived from tris(phenanthroline) metal cations possess several features in common which are critical to their application as site-specific DNA binding molecules.

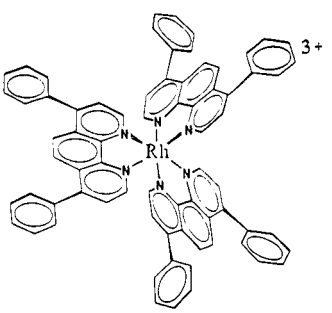
Transition metal complexes have been designed which recognize and react at specific conformations along the DNA strand. The complexes, derivatives of tris(phenanthroline) metal cations, possess several features in common which are critical to their application as site-specific DNA binding molecules. The complexes all are rigid, chiral, and contain a coordinatively saturated metal ion at their core.

The complexes bind to DNA in a non-covalent fashion. Spectroscopic studies have been useful in characterizing both intercalative and groove-bound interactions of the complexes with the DNA helix (ref 1). Because the complexes are rigid, once aspects of the binding interaction with DNA are determined, the orientation of the molecule as a whole with respect to the DNA helix can be considered. The chirality of the complexes is furthermore useful in specifying conformation-selective recognition along the strand (ref 2). The two binding modes to DNA show differing enantiomeric selectivity. In addition, simply, the diastereomeric interaction of the transition metal complexes with the dissymmetric DNA helical structure in itself provides a level of specificity that is usefully exploited. Lastly, the importance of the central metal ion at the core of the structure of the DNA binding molecule is noteworthy. Besides serving as a spectroscopic and photoreactive handle to monitor sensitively the binding of the complex to DNA, the central metal ion provides the core to hold together the ligand scaffolding around it. The metal, though not directly coordinating to the DNA helix, instead defines the shape of the rigid asymmetric structure which may be matched to that of the DNA.

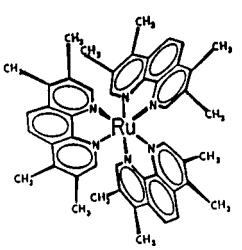
Some of the complexes which recognize and react at sites along the DNA are shown below:



$Co(phen)_3^{3+}$



$Rh(DIP)_3^{3+}$



$Ru(TMP)_3^{2+}$

DNA-binding molecules may be converted into DNA cleaving molecules by substitution of a redox active metal ion into the core of the complex structure. Photoreduction of a tris(phenanthroline) complex of cobalt(III), for example, bound along the DNA strand may be used to oxidatively cleave the sugar-phosphate backbone (ref 3). If the photoredox reaction is tightly coupled to the binding, the reaction provides a sensitive scheme to

TABLE 1. Metal Complexes which Target Different DNA Sites and Structures

	Binding Mode	Cleavage	Sites
$Rh(phen)_3^{3+}$	Intercalation Surface Binding	Photoredox	B-DNA
$Co(phen)_3^{3+}$	Intercalation Surface Binding	Photoredox	B-DNA
$Ru(phen)_3^{2+}$	Intercalation Surface Binding	$^1O_2$	guanines
Λ-$Co(DIP)_3^{3+}$	Intercalation Surface Binding	Photoredox	Z-DNA- (non-B-DNA)
$Ru(TMP)_3^{2+}$	Surface Binding	$^1O_2$	A-DNA + guanines
$Rh(DIP)_3^{3+}$	Intercalation Surface Binding	Photoredox	cruciforms

mark chemically the site of binding. By coupling different photoreactions to the DNA binding modes, a variety of site-specific DNA cleavage reactions have been obtained. Table 1 summarizes the differing metal complexes and reactions that have been used to target sites along the strand (ref 3-6).

Using these shape-selective molecules, we may examine distinctive conformations along the DNA helix. An intriguing correspondence between sites of altered conformation and the borders of gene coding regions, where binding sites for DNA regulatory proteins are found, have become evident (ref 2,4). In addition, the sites of binding and reaction of our simple transition metal complexes have been found to be remarkably specific. The targeting of altered conformations provides, therefore, a useful strategy to effect site-specific reactions along a DNA strand. Perhaps this also is a strategy employed by Nature, in the design of shape-specific proteins which bind to conformationally distinct sites along the strand.

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