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Nickel-Catalyzed Oxidations: from Hydrocarbons to DNA*

Cynthia J. Burrows,[a,†] James G. Muller,[a] Gregory T. Poulter[a] and Steven E. Rokita[b]

[a]Department of Chemistry, University of Utah, Salt Lake City, UT 84112, USA and [b]Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742, USA

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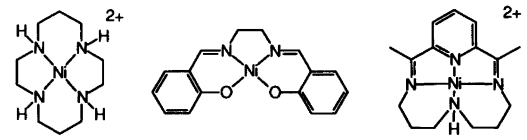
Nickel(II) complexes of tetradentate ligands such as cyclam and salen are catalysts for olefin epoxidation using PhIO and NaOCl, respectively. In order to understand the lack of enantioselectivity observed with chiral cyclam and salen complexes, studies of DNA and RNA oxidation were carried out in which evidence for diffusible oxidants might be found. A variety of square-planar, tetradentate nickel(II) complexes were observed to mediate guanine-specific modification in the presence of $KHSO_5$ or magnesium monoperphthalate. In particular, the cationic complex, [(2,12-dimethyl-3,7,11,17-tetraazabicyclo [11.3.1]heptadeca-1(17),2,11,13,15-pentaenato)nickel]$^{2+}$, $[NiCR]^{2+}$, has been studied as a probe of nucleic acid folding. The extent of guanine reaction depends upon the exposure of N7, a good transition metal binding site, thus implicating nickel–guanine binding during DNA oxidation. If this is the case, related systems should be able to confer enantioselectivity during the use of chiral nickel complexes and achiral substrates for oxidation. Mechanistic studies, including radical quenching and DNA enantioselectivity, are described and their mechanistic implications discussed.

Curiosity about the mechanisms of biological oxidations and the search for new catalysts for industrial applications have led to exciting discoveries in transition metal-mediated oxidation of organic and biological substrates. Our interests began with the study of macrocyclic nickel(II) complexes where the inorganic coordination chemistry was known, but applications to catalysis were not. Nickel coordination compounds are well suited to catalytic oxidation chemistry; complexation within a polyazamacrocyclic cavity allows the metal ion to oscillate between various coordination numbers (4, 5 or 6), coordination geometries (square planar, tetrahedral, square pyramidal or octahedral) and oxidation states (I, II, III, or IV).[1] Each of these features is tunable and highly sensitive to the structure of the ligand.



1 2 3

ligand = cyclam salen CR

In 1987, we found that simple tetradentate ligands such as cyclam, **1**, and salen, **2**, render nickel(II) active as a catalyst for olefin epoxidation.[2] A particularly exciting discovery was the observation that nickel salen complexes utilize a practical oxidant, sodium hypochlorite, and show very high catalytic turnover in epoxidation reactions, over 600 min^{-1} in some cases.[3]

The use of bleach under phase transfer conditions was described for manganese porphyrin-catalyzed epoxidations by Meunier *et al.* [4] and can be adapted to nickel catalysis as well. In the case of nickel salen, the reactivity is dramatically influenced by pH, and conversion of styrenes into epoxides was quantitative under optimized conditions at pH 9.3 [eqn. (1)].

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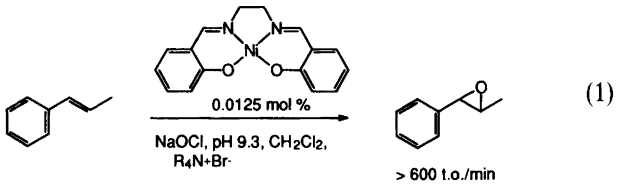
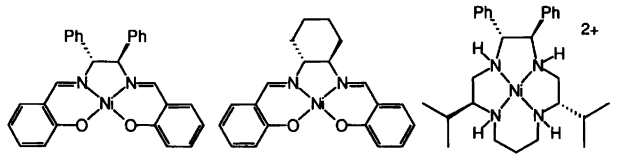
† To whom correspondence should be addressed.



(1)

Having discovered an efficient epoxidation catalyst, one is eager to enter the chiral manifold. A series of chiral C_2-symmetric ligands was prepared incorporating 2–4 stereogenic centers in the ligand. Unfortunately, the nickel(II) complexes **4–6** failed to give any measurable enantiomeric excess in the epoxide products.[5]



4 5 6

There were two possible explanations for this failure: (1) the three-dimensional structures of the ligands do not present a sufficient steric bias in selecting one face of the alkene with which to react, or (2) the mechanism of the reaction does not involve a metal-bound oxidant during the oxygen atom transfer step. The first possibility was soon ruled out when Jacobsen and coworkers reported that the Mn^{III} complex of **4** was competent to carry out asymmetric epoxidation of *cis*-alkenes,[6] although better results were obtained with more sterically demanding ligands bearing *o-tert*-butyl groups. We were then led to examine further the mechanism of the nickel-catalyzed reaction. In the case of salen complexes, we postulated that the metal might serve as a site of electron transfer, in which nickel(II) is oxidized by reaction with either HOCl, Cl_2O, or $Cl^{\cdot}$ generating an Ni^{III}–OCl species. Homolytic cleavage of the nickel–oxygen bond would regenerate the nickel(II) catalyst and produce $ClO^{\cdot}$, a freely diffusible and achiral radical that could be ultimately responsible for olefin epoxidation (Fig. 1).

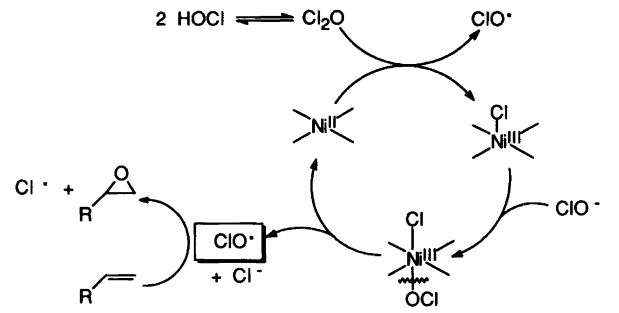


Fig. 1. Proposed mechanism of olefin epoxidation in nickel salen-catalyzed reaction of hypochlorite. An achiral intermediate, $ClO^{\cdot}$, is proposed.

A general question then arises: *Is it possible for nickel(II) coordination compounds to form metal- or ligand-bound oxygen atom transfer agents?* To address this question we sought methods to detect the generation of diffusible, and likely achiral, intermediates in oxidation. One such mechanistic tool involves the attachment of two reactants to solid supports in the 'three-phase test' reviewed by Rebek.[7] Alternatively, one can envisage the use of DNA as a substrate for site-specific oxidation.

Nickel-mediated cleavage of DNA. Extensive research by Dervan and others has shown that Fe–EDTA tethered to sequence-specific DNA-binding agents in the presence of oxidants leads to formation of freely diffusible hydroxyl radicals ($HO^{\cdot}$) that oxidize sugar and base residues in the general region in which Fe–EDTA is bound.[8] Indeed, the use of $HO^{\cdot}$ as a probe of solvent exposure of sugar moieties in folded nucleic acids has enjoyed widespread application in both DNA[9] and RNA[10] structural studies. On this basis, one would predict that metal chelates bound to specific sites in DNA would effect single-site modification if the oxidation involves a complex-bound oxidant (bound either to the metal ion or its ligand), but that a cluster of sites would be modified if a diffusible oxidant is generated. (See Fig. 2.)

With this idea in mind, we investigated oxidative chemistry mediated by a series of square-planar nickel(II) complexes initially in the absence of appended DNA binding agents. Several exciting features of the reaction emerged, including site-specificity and a strong dependence on the choice of metal, ligand and oxidant. Typical reaction conditions involve the use of Busch's

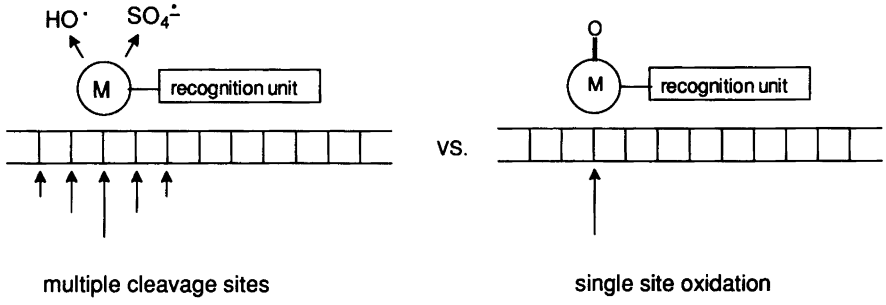


Fig. 2. Using DNA as a substrate, one might be able to distinguish between diffusible vs. metal-bound oxidants.

macrocyclic nickel complex,[11] $[NiCR]^{2+}$, (**3**), in about 3 μM concentration, either monopersulfate (HSO_5^-) or magnesium monoperoxyphthalate (MMPP) as the oxidant, and a subsequent treatment with hot piperidine to effect strand scission at sites of nucleobase modification.

Single-stranded oligonucleotides are oxidized only at guanine residues, and the products suggest that oxidation occurs exclusively at the base, not at the sugar.[12] Strand scission was obtained after oxidative depurination, and the DNA fragments were essentially those of phosphodiester hydrolysis, i.e. phosphate termini.[13] A surprising result came when the corresponding duplex DNA was studied—now reactivity was seen only at those guanine residues that were not part of a standard Watson–Crick B helix (Fig. 3). For example, nickel complexes recognized Gs located at strand termini, in certain G–G mismatches, G-bulges, and as part of hairpin loops.[14] Guanine residues that were paired to cytosines in a normal B helix were unreactive.

Molecular recognition of such structures suggested that nickel complexes would be powerful tools for detecting aberrant DNA sites and for probing the folding patterns of RNA.

Probes of RNA Structure. RNA even more than DNA adopts a wide variety of conformations that significantly depart from the canonical double helix. Since the biological activity of RNA is intimately related to the molecule's tertiary structure (in addition to its primary sequence), the determination of RNA structure is of

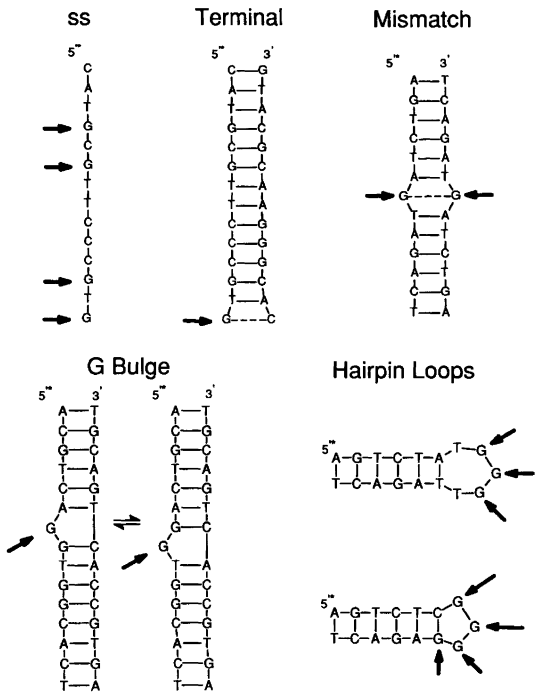


Fig. 3. Oligodeoxynucleotides used in a study of guanine-recognition by $[NiCR]^{2+}$ and HSO_5^-. Arrows indicate sites of reaction, and * indicates strands labeled with ^{32}P and analyzed by autoradiography.

paramount importance. Both physical (X-ray crystallography and NMR spectroscopy) and chemical methods are used.[15,16] The chemical reagents for RNA structural analysis include enzymes, organic reagents and metal complexes, and each has its strengths and limitations. Of the metal complexes, only Fe–EDTA has found substantial use in mapping the solvent-accessible regions of the sugar–phosphate backbone of RNAs since it reacts in a highly predictable fashion.

In order to assess the applicability of nickel-catalyzed oxidation to RNA structure determination, a well characterized structure, $tRNA^{Phe}$, was first examined. Both the molecule itself and its crystal structure are readily available.[16]

Reaction of $tRNA^{Phe}$ with $[NiCR]^{2+}$ and either $KHSO_5$ or MMPP led to scission of the RNA strand at four principal sites in the presence of Mg^{2+} and at 12 sites in the absence of Mg^{2+} in which case the biopolymer is partially unfolded [Fig. 4(a)]. The four most reactive sites are: G19 > > G18 > G34 = G20.[17]

Interestingly, this order of reactivity had been predicted in calculations of the surface accessibility and local electrostatics in an analysis of guanine N7 reactivity with electrophiles.[18]

Examination of the crystal structure of $tRNA^{Phe}$ further supports a proposal that nickel complexes recognize the surface accessibility of N7 of guanine. G19 in $tRNA^{Phe}$ is oriented such that N7 lies on the surface of the molecule, and its lone pair of electrons is directed outward. In contrast, the adjacent G20 is a less reactive site, and in this case the purine ring lies parallel to the surface of the folded molecule. The higher reactivity of G19 argues in favor of Ni–N7 coordination as the recognition determinant since G20 would be expected to be more reactive if exposure to radical attack at the purine ring had been dominant. This correlation of structure and reactivity led to both a mechanistic proposal (below) and the projection that $[NiCR]^{2+}$ can be used reliably and predictably to determine the folding pattern of guanines in RNAs whose tertiary structures are unknown. To date, $[NiCR]^{2+}$ has been used in our laboratories and others to examine guanine sites in the *Tetrahymena* group I intron [Fig. 4(b)],[17] a hairpin ribozyme,[19] viral pseudoknots,[20] the *micF/ompF* mRNA anti-sense duplex,[21] and the pre-mRNA binding site for yeast ribosomal protein L32.[22]

In all cases, the distribution of reaction sites correlated well with the predicted exposure of guanine in the folded RNA.

Mechanistic questions. Based on the observation that nucleic acid oxidation occurs exclusively at non-Watson–Crick G sites, it is tempting to suggest that the reaction involves direct binding of the metal ion to guanine N7 and that a non-diffusible oxidant reacts with the guanine base. The precise identity of the reactive nickel intermediate responsible for oxidation is under investigation, but several mechanistic features are now known. A

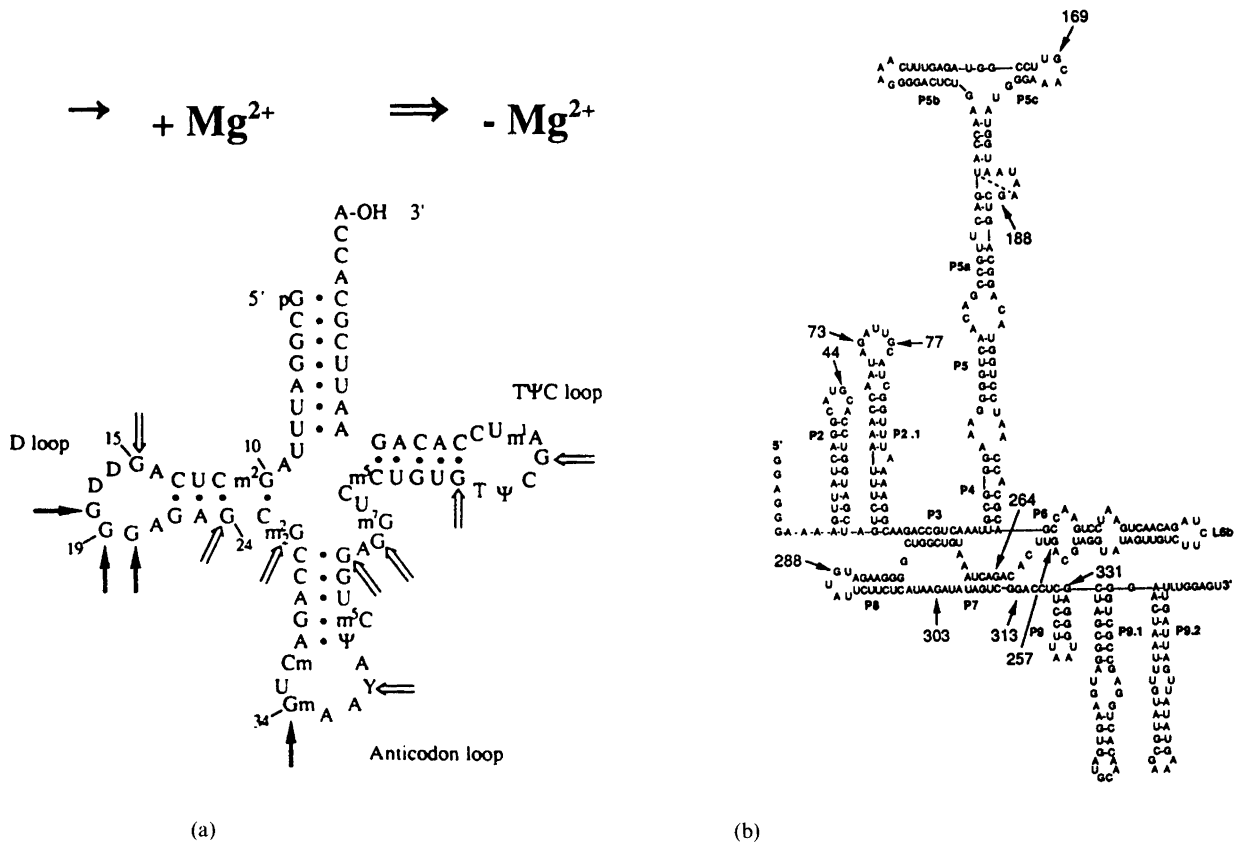


Fig. 4. Secondary structures of (a) $tRNA^{Phe}$ and (b) *Tetrahymena* Group I intron. Arrows indicate sites of reaction with $[NiCR]^{2+}$ and oxidant.

number of crystal structures of simple nickel–guanosine or GMP complexes help establish that N7 is a good binding site for nickel ions.[23] For duplex DNA and folded RNA structures, binding occurs only when the guanine residue is highly exposed to solvent rather than part of a regular B helix. The reason for this may be seen by visualization of the B helix along its axis (Fig. 5). For a G–C pair in a B helix of DNA, binding to N7 (arrow) can only occur if the metal is able to penetrate to the center of the helix since N7 lies deep in the major groove. Steric interactions of the macrocyclic ligand with the neighboring bases, especially in the 5′ direction, are likely responsible for excluding nickel complexes from recognition of G–C pairs in the B helix.[24]

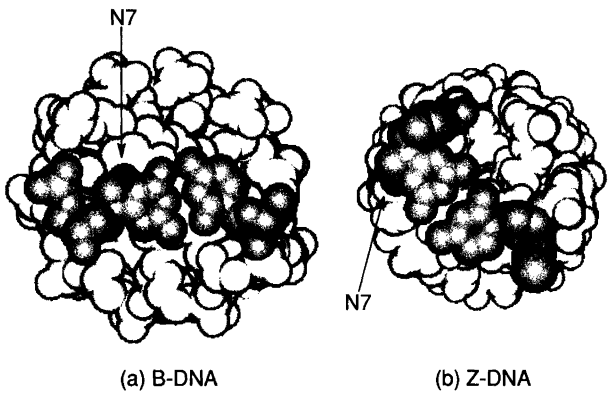


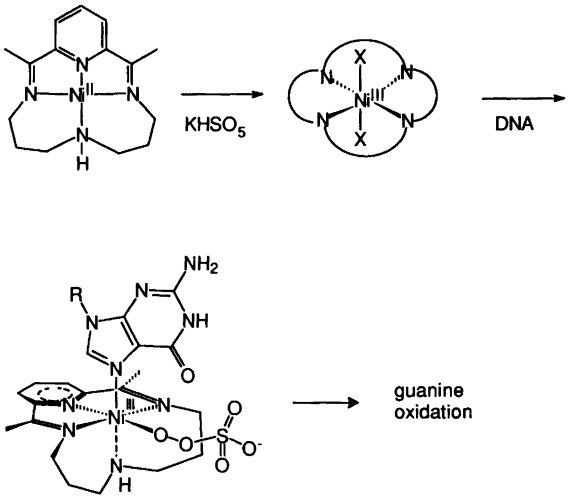
Fig. 5. Axial views of (a) B-DNA^{25c} and (b) Z-DNA^{25d} diastereomers with arrows pointing to the lone pair of electrons on N7 of guanine (darkened atom) in a G–C pair (light gray).

By this same analysis, we would predict that nickel and related metal ions will bind to and catalyze oxidation of Gs found in G–C pairs of left-handed Z-DNA, a diastereomer of B-DNA, since the structure of its helix is such that N7 lies on the surface of the cylindrical molecule. Indeed, crystal structures of Z-DNA with $[Co(H_2O)_5]^{2+}$ and $[Cu(H_2O)_5]^{2+}$ bound to G-N7s have been determined.[25] In contrast, there are no known structures of octahedral metal ions coordinated directly to a site in B-DNA.

Nickel(III) may be the key species that binds to exposed guanines. This is supported by studies using an electrochemical method[26] that show that nickel(III) complexes bind >200 times more strongly to DNA than do nickel(II) complexes.[27] Coupled with the fact that only square-planar nickel complexes, those with vacant axial coordination sites, are active, this suggests that the mode of action is first oxidation of nickel(II) to nickel(III) followed by direct metal ligation to guanine N7. A study of ligand effects further supports this notion.[27] Additional support for G-N7 binding to nickel(III) complexes is found in the ease of B→Z conversion of duplex [poly-d(GC)] in the presence of 51 μM nickel(III) cyclam.[24]

In contrast, the addition of 180 μM nickel(II) cyclam had no effect on the helicity of this polymer as observed by circular dichroism. Such B→Z transitions are thought to occur as a result of direct metal ligation to G-N7.[28]

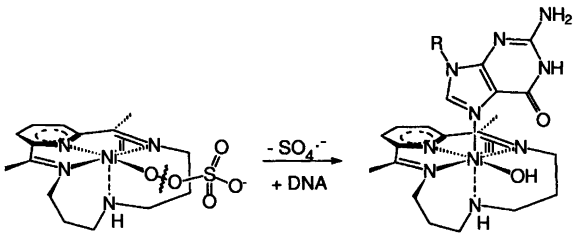
Taken together, these data may be interpreted to mean that a nickel(III) complex with strong in-plane coordination will have exchangeable axial sites so that binding of DNA and, possibly, the oxidant can occur within the lifetime of the reactive nickel(III) complex. A second important feature of the ligand is that it imparts some measure of flexibility to the complex so that DNA binding can be accommodated.[27] An overall mechanistic postulate is shown in eqn. (2).[29]



(2)

In this mechanism, monopersulfate first oxidizes the nickel(II) complex to the corresponding nickel(III) complex. Because of the increased charge, nickel(III) complexes are typically six-coordinate; probably water, phosphate buffer, or monopersulfate would initially bind in the axial positions, X. With a strong in-plane macrocyclic ligand, the X positions are labile allowing DNA binding as well as oxidant binding. Studies of various oxidants support the proposal that monopersulfate also ligates to the metal center.[30] Thus, the nickel(III) ion serves as a template assembling the appropriate guanine and oxidant in proximity for reaction.

An alternative mechanistic proposal would invert the order of certain steps but lead to the same result [eqn. (3)]. Oxidation of $[NiCR]^{2+}$ with $KHSO_5$ could first generate a six-coordinate Ni^{III}–OH complex plus sulfate radical ($SO_4^{\cdot -}$) after homolytic cleavage of the O–O bond of the peracid. Ligand exchange to coordinate G-N7 could then lead to inner-sphere electron transfer giving a guanine radical cation and regenerating the nickel(II) complex. $G^{\cdot +}$ might then be trapped by sulfate radical leading to G oxidation products. The exact products of guanine oxidation are under investigation; both 8-oxoguanine and 5-formamido-2,6-diaminopyrimidine are common products under other reaction conditions. Recent studies by Cadet *et al.*[31] have led to a proposed mechanism of G oxidation by $HO^{\cdot}$, and the reaction of G with reagent generating $SO_4^{\cdot -}$ (or its caged equivalent) may be very similar.



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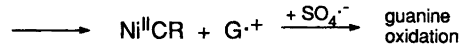


Damage to a guanine heterocycle in oligomeric DNA or RNA may be visualized by various methods: (1) treatment of modified DNA with hot piperidine (or RNA with anilinium acetate) leads to strand scission by an elimination mechanism at an apurinic site generating oligonucleotides with phosphate termini (Fig. 6), or (2) a primer extension method takes advantage of reduced recognition of a modified base by DNA polymerase.[32]

Like all mechanisms, the ones proposed above can never be proved, but they do serve as useful paradigms for discussion and for design of future reagents for site-specific chemistry of nucleic acids. Three features of the proposed mechanisms are unusual in comparison with the reactions of other metal complexes with DNA. (1) Direct metal ligation to a DNA base is proposed. In contrast, most metal complexes previously studied interact with DNA via ligand intercalation, groove binding and/or hydrogen bonding. (2) Intimate contact between the metal complex and accessible guanine sites leads to a high level of predictability of the reaction making $[NiCR]^{2+}$ and its analogues appropriate as tools for RNA and DNA structural studies. (3) Oxidation chemistry occurs, as far as we know, only at the base, not at the sugar, and phosphate termini are generated after alkaline hydrolysis.

Radical quenching. Returning to the question of radical intermediates in olefin epoxidation and DNA modification, we sought additional evidence to rule out freely diffusible radicals such as $SO_4^{\cdot -}$. Sulfate radical is known to be rapidly quenched by ethanol but barely affected by the presence of *tert*-butyl alcohol.[33] Accordingly, we tested the DNA reactivity of $[NiCR]^{2+}$ vs. $[Co(H_2O)_6]^{2+}$, a complex known to generate $SO_4^{\cdot -}$ after reaction with HSO_5^-.[34] While addition of 25 mM EtOH to the DNA reaction medium suppressed 89% of the Co^{II}-mediated reaction, it reduced the $[NiCR]^{2+}$-mediated reaction by only 12%. Addition of 25 mM *t*BuOH had little effect on either the cobalt- or the nickel-mediated reactions. These data support the notion that while a highly diffusible (and quenchable) $SO_4^{\cdot -}$ radical

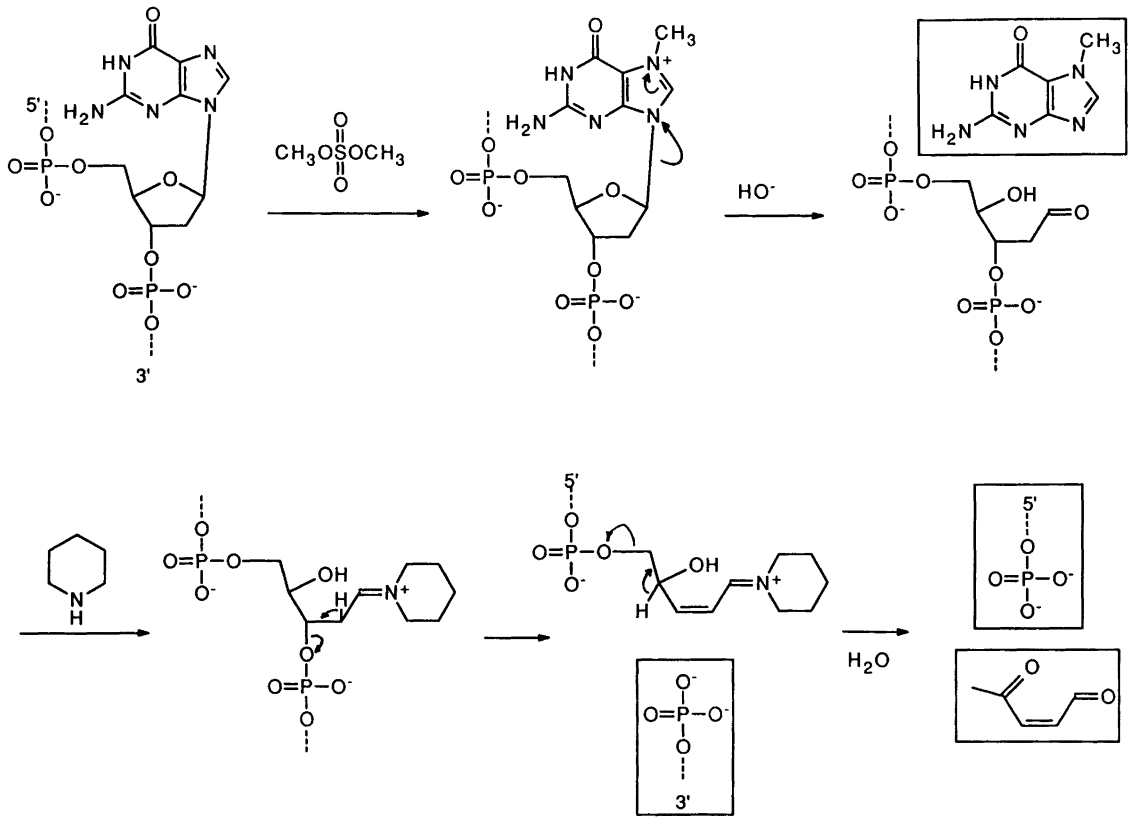


Fig. 6. Products of the Maxam–Gilbert sequencing reaction for guanine. Dimethyl sulfate alkylates guanine N7 making the purine ring labile. Piperidine treatment results in two phosphate eliminations leading to strand scission.

may be formed from cobalt(II) catalysis, the corresponding reaction mediated by nickel(II) involves formation of a caged or partially ligated species in which DNA reaction competes effectively with EtOH trapping (Fig. 7).

Enantioselectivity and DNA. Enantioselectivity is another test of mechanism that can be applied to nickel-mediated oxidation of DNA. If metal ion–DNA binding is a prerequisite for reaction, two enantiomeric nickel complexes should show different reactivities with DNA (a molecule that is, necessarily, enantiopure), reflecting the different stabilities of diastereomeric NiL*–DNA complexes. Salen and picolinamide ligands[35] were prepared from (+)- and (−)-diphenylethylenediamine and from (+)- and (−)-*trans*-1,2-diaminocyclohexane, and their nickel complexes were tested with DNA. The target duplex was chosen such that the accessible Gs were stacked within the helix as much as possible, and thus a thymine bulge structure with flanking guanines (A) was studied in addition to a simple duplex (B) and a hairpin loop (C). Arrows indicate the principle sites of reaction, and the extent of reaction was then analyzed for each enantiomeric nickel complex under identical reaction conditions. The relative reactivities of the *R,R* vs. *S,S* enantiomers as measured by scanning densitometry of the cleavage bands are reported in Table 1. The estimated error in these measurements is about ±15%, and so in most cases it is not clear whether the numbers really differ from a 1:1 ratio. Nevertheless, several interesting

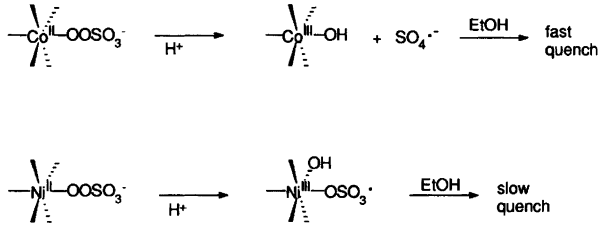
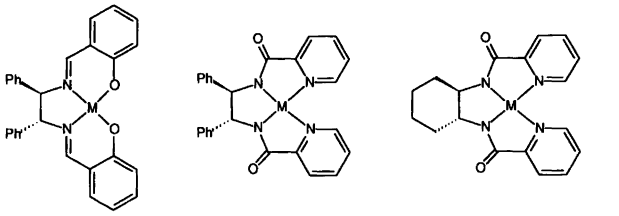


Fig. 7. Proposed intermediates in the reaction of cobalt(II) vs. nickel(II) complexes with HSO_5^-.

Table 1. Enantioselectivity in the reaction of *R,R* vs. *S,S* nickel and manganese complexes with DNA substrates.

Catalyst	Substrate	Oxidant	Reactivity *R,R*:*S,S*
Ni-**7**	A	200 μM HSO_5^-	1.2:1
Mn-**7**	B	1 mM MMPP	1:1.2
Mn-**7**	C	500 μM HSO_5^-	1.2:1
Mn-**7**	C	1 mM MMPP	1:2.0
Mn-**7**	C	500 μM PAA	1:1.3
Ni-**8**	A	250 μM HSO_5^-	1.1:1
Ni-**8**	C	500 μM HSO_5^-	1:1.4
Ni-**8**	C	1 mM MMPP	1.1:1
Ni-**8**	C	500 μM PAA	1:1.1
Ni-**9**	A	250 μM HSO_5^-	1.1:1

points emerge from this study. First, the three oxidants studied, monopersulfate, monoperphthalate and peracetic acid (PAA), all give approximately the same result with Mn–7, suggesting a similar mechanism or intermediate for all three. Secondly, Mn–7 does not give an appreciably higher ee than Ni–7, again implying some similarity of mechanism, although the DNA recognition features are quite different. Third, the enantioselectivities vary only slightly with substrate in the case of Mn–7. However, the general observation in all cases is the same: the level of chiral recognition by these complexes is overall quite low.



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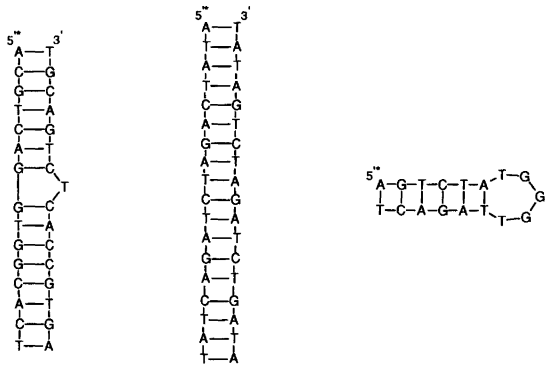
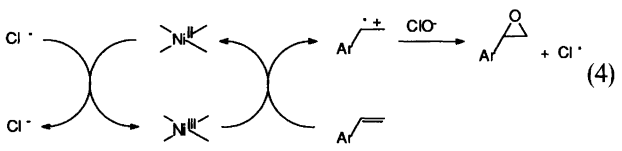


A B C

Mechanistic implications. Several pieces of evidence point to a ternary interaction between the nickel catalyst, oxidant and nucleic acid substrate, including the high specificity for an exposed guanine N7 (and the excellent correlation with well established DNA and RNA structures), the ability of nickel(III) cyclam to induce B→Z transitions which is thought to occur through metal ion binding to G-N7, and the observation that $SO_4^{\cdot -}$ quenching studies show different results with nickel compared with cobalt complexes where $SO_4^{\cdot -}$ is well established as an intermediate. On the other hand, the evidence is not overwhelmingly in favor of such a ternary interaction since DNA showed little, if any, selectivity for enantiopure nickel complexes. However, the structural and geometrical constraints of the proposed intermediate have yet to be defined, and it may be that accessible guanines are poor candidates for chiral recognition with these ligands.

It is likely that the mechanism of nickel-mediated DNA oxidation lies at the border between intra-complex delivery of an oxidant and diffusible radical generation. Whatever the mechanism, the system is remarkably successful as a nucleic acid structural probe; binding of the nickel complex does not appear to perturb the nucleic acid conformation, and therefore must be relatively weak.

In contrast, there is so far no support for formation of a ternary transition state involving NiL*, oxidant and olefin during the course of olefin epoxidation. The ee's of several chiral nickel complexes were indistinguishable from zero, even in cases where the corresponding manganese(III) complexes were enantioselective. In the case of ClO^- as oxidant, the experimental evidence would also support an electron transfer mechanism [eqn. (4)] that in some respects parallels the DNA reaction proposed as eqn. (3). The difference in this case is that olefins are very poor ligands for tetradentate nickel(II) or nickel(III) complexes, and so epoxidation must occur outside the influence of the chiral ligand.



(4)

In conclusion, these studies would suggest that while nickel can be a fast and efficient catalyst for the oxidation of hydrocarbons, it is unlikely to be the metal of choice for asymmetric catalysis unless the substrate contains a ligating functional group to ensure chirality transfer. Thus, guanine oxidations are highly specific owing to nitrogen (G-N7) coordination to nickel while olefin epoxidation is non-selective.

Concluding remarks. Nickel is a remarkably versatile metal in organic and biological chemistry. In addition to its rich organometallic chemistry (not described here), the coordination compounds of nickel(II) show diverse activities in oxidation chemistry. Nickel is a necessary component of certain metalloproteins and is at the same time an environmental carcinogen causing DNA damage and protein–DNA crosslinks. For the organic chemist, its sensitivity to organic ligands and its applicability to catalytic oxidation of small hydrocarbons as well as large biomolecules entreat further exploration.

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