Reactions of radicals generated from transition-metal complexes can be divided into two types based on the direction of electron flow. In some of these reactions the transition metal accepts an electron during radical formation (oxidative electron transfer) and in others it donates an electron during this process (reductive electron transfer). The compounds that most often participate in oxidative electron transfer are manganese(III) acetate \([\text{Mn(OAc)}_3]\) and ammonium cerium(IV) nitrate \([\text{(NH}_4)_2\text{Ce(NO}_3)_6]\), while those frequently involved in reductive electron transfer are bis(cyclopentadienyl)titanium(III) chloride \((\text{Cp}_2\text{TiCl})\), and samarium(II) iodide \((\text{SmI}_2)\). Carbohydrates that are bonded to a cobalt-containing complex by a C–Co bond form radicals by oxidative electron transfer and then frequently reform a C–Co bond by reductive electron transfer.

A. Inner-Sphere and Outer-Sphere Electron Transfer

"Inner-sphere" and "outer-sphere" are terms that describe the way in which an electron is transferred between an organic molecule and a coordination compound (typically one that consists of a transition metal surrounded by coordinating ligands).¹ This terminology is borrowed from inorganic chemistry where it describes the basic types of electron transfer between two coordination compounds.² For inner-sphere electron transfer the metal ion either comes into direct contact with the participating molecule (Scheme 1), or the participants are in contact through a bridging ligand (Scheme 2). Outer-sphere electron transfer occurs when no ligand present is capable of serving as a bridge and the ligands coordinated with the transition metal are held so tightly that no direct contact can occur between the metal ion and the molecule involved in electron transfer (Scheme 3).³
B. Oxidative Electron Transfer

When a transition-metal ion changes from a higher to a lower oxidation state during radical formation, oxidative electron transfer is occurring in the substrate molecule. Changes in oxidation states for transition-metal ions in this type of reaction include: Co(III) to Co(II), Hg(II) to Hg(I), Mn(III) to Mn(II), and Ce(IV) to Ce(III).

1. Carbon–Cobalt Bond Homolysis

Carbon–cobalt bonds have bond dissociation energies in the range of 20 to 37 kcal/mol.\(^4\),\(^5\) This means that organocobalt complexes are attractive radical precursors because their C–Co bonds are strong enough to be part of stable structures but weak enough to cleave homolytically upon mild heating or photolysis (or, in biological systems, upon enzymatic reaction). A reaction that illustrates the ease with which a carbon–cobalt bond is broken is the interconversion of the cobaloxime epimers 1 and 2, compounds that equilibrate upon heating at 78 °C or upon photolysis at 20 °C (Scheme 4).\(^6\) The equilibration of these epimers involves the intermediate carbohydrate radical 3 and cobalt-centered radical 4. (In this reaction cleavage of the C–Co bond represents an oxidative electron transfer, while reforming the C–Co bond is a reductive electron transfer.)

Even though carbon–cobalt bonds cleave homolytically at relatively low temperatures, nearly all nonenzymatic reactions involving these bond cleavages are photochemical. Photolysis is the method of choice because fragmentation takes place with visible light under conditions (e.g., room temperature) that avoid the side reactions possible from even mild heating of complex, cobalt-containing compounds.
a. Coenzyme B<sub>12</sub>

Coenzyme B<sub>12</sub> (5, Figure 1) is one of a group of biologically active molecules that have similar structures. Each member of this group has a cobalt atom surrounded by a macrocyclic ligand (a corrin ring) that bears various substituents. In addition to the corrin ring the cobalt atom in each of these compounds also is coordinated with a ligand that contains a phosphate group, a sugar moiety, and a nitrogenous base. Compounds related to 5 differ from each other in the structure of the R group attached to cobalt. R represents the 5′-deoxyadenosyl group in coenzyme B<sub>12</sub> (5), but for related compounds R can be as structurally simple as a methyl or hydroxyl group.

The original stimulus for study of carbon–cobalt bond homolysis as a pathway for forming carbon-centered radicals came from investigation of the reactions of coenzyme B<sub>12</sub> (5). In biological systems enzyme-induced homolysis of the carbon–cobalt bond in 5 produces the 5′-deoxyadenosyl radical 6 and the cobalt-centered radical 7 (B<sub>12r</sub>, eq 1). In experiments outside biological settings the 5′-deoxyadenosyl radical (6) is produced from coenzyme B<sub>12</sub> (5) by photolysis with visible light. When photolysis is conducted in the absence of an effective hydrogen-atom donor or other radical trap, cyclization follows homolysis of the carbon–cobalt bond (Scheme 5).
b. Cobaloxime Complexes

The discovery that carbon–cobalt bond homolysis in coenzyme B$_{12}$ (5) produced the carbon-centered radical 6 (eq 1), led to investigation of simpler molecules that could model this behavior. Cobaloximes are one of several types of compounds found to be effective choices for this role.\textsuperscript{13–16} Carbohydrate cobaloximes 8 and 9 produce radicals 10 and 4, which recombine in the absence of radical traps (Scheme 6).\textsuperscript{13} In the presence of compounds that react with radicals, 10 and 4 undergo characteristic radical reactions; thus, the D-mannopyranos-1-yl radical 10 adds to acrylonitrile (11) to give the adduct radical 12, which then combines with \( \cdot \text{Co(dmgH)}_2\text{py} \) (4) to form the addition product 13 (Scheme 7).\textsuperscript{13}
A necessary condition for the reaction shown in Scheme 7 is that \([\text{Co(dmgH)}_2\text{py}]\) be stable enough to remain unchanged while the addition of \(10\) to \(11\) is taking place. The needed stability of \(4\) derives from protection of its radical center by the attached ligands; thus, \(4\) can be viewed as a persistent radical.

c. The Persistent-Radical Effect

Persistent radicals, such as \(\cdot\text{Co(dmgH)}_2\text{py}\) (4), are responsible for a type of reactivity known as the persistent-radical effect.\(^{17-19}\) This effect causes a reaction that generates a persistent radical (\(R_1\cdot\)) and a transient radical (\(R_2\cdot\)) in equal amounts to give a higher yield of the cross-coupling product \((R_1R_2)\) than would be expected from random radical coupling. The explanation for greater cross-coupling product formation begins with the recognition that although persistent and transient radicals are formed in equal amounts, this equality is short lived. Due to the reactive nature of transient radicals, their concentration decreases more rapidly in the early stages of a reaction than does the concentration of persistent radicals. (Transient radicals combine, disproportionate, and undergo other reactions much more rapidly than persistent radicals.) The rapidly developed, higher concentration of persistent radicals in the early stages of reaction means that any newly formed, transient radical is more likely to encounter and combine with a persistent radical than with another transient one; in other words, the cross-coupling product \(R_1R_2\) becomes the major coupling product.

An example of the persistent radical effect is shown in the reaction given in Scheme 4, where carbon–cobalt bond homolysis in 1 or 2 produces the persistent radical 4 and the transient radical 3. Even with the extended heating or photolysis needed to reach equilibrium, there was no evidence of formation of a coupling product other than the cross-coupling products 1 and 2. The persistent radical effect also is operative in the addition reaction shown in Scheme 7. In this case the transient radical 12, produced by addition of 10 to acrylonitrile (11), and the persistent radical 4 combine to form the only radical-coupling product isolated.

2. Carbon-Mercury Bond Homolysis

There are similarities in reactivity among compounds with C–Co and C–Hg bonds. Both bonds are strong enough to exist in stable structures at room temperature but both readily cleave upon photolysis. The result in each case is formation of a metal-centered and a carbon-centered radical. Carbon-centered radicals produced by carbon–mercury bond homolysis
undergo typical radical reactions, such as the hydrogen-atom abstraction shown in Scheme 8.\(^{20}\)

![Scheme 8](image)

### 3. Manganese(III) Acetate [Mn(OAc)\(_3\)] Reactions

Carbon-centered radicals can be generated by reaction of manganese(III) acetate with CH-acidic compounds such as the β-diketone shown in Scheme 9.\(^{21–24}\) The first step in this process is formation of the enolate \(^15\).\(^{23}\) In the presence of an unsaturated compound two mechanisms for reaction of \(^15\) are considered to be possible. In the first of these electron transfer forms manganese(II) acetate and the resonance-stabilized radical \(^16\), which then adds to an unsaturated compound. A second possible pathway for addition is a concerted process in which the enolate \(^15\) reacts directly with the unsaturated compound to produce the adduct radical \(^17\) (Scheme 9).\(^{23}\) Reaction by either of these pathways is believed to take place by inner-sphere electron transfer.

![Scheme 9](image)

Since radical centers with two, attached carbonyl groups are electrophilic, radicals such as \(^16\) (Scheme 9) add most easily to unsaturated compounds with electron-rich multiple bonds.\(^{22}\) This is the point at which carbohydrates typically become involved in reactions begun by manganese(III) acetate because glycals have electron-rich π systems that are attractive targets for addition of electrophilic radicals; for example, the radical \(^19\), formed by reaction of dimethylmalonate (18) with manganese(III) acetate (eq 2), adds to the tri-O-acetyl-D-glucal 20 to produce the stereoisomeric radicals 21a and 21b (Scheme 10).\(^{25,26}\) This addition, which occurs regioselectively at C-2, is followed by oxidation of the resulting radicals with a second molecule of manganese(III) acetate to give the corresponding cations 22a and 22b. These cations react with the solvent (acetic acid) to yield the final products (23a, 23b, 24a, and 24b). Manganese(III) acetate, therefore, is involved in both the formation and disappearance of the radicals in this reaction. (Electrophilic radicals and other aspects of radical philicity are discussed in Chapter 7.)
Manganese(III) acetate has a more complicated structure than the formula Mn(OAc)$_3$ indicates. It is an oxo-centered trimer of three manganese ions held together by six bridging acetates.$^{27-29}$ Three representations for this structure are shown in Figure 2. It is often convenient in discussing reactions of this compound to use the abbreviated formula Mn(OAc)$_3$.

4. Ammonium Cerium(IV) Nitrate [(NH$_4$)$_2$Ce(NO$_3$)$_6$] Reactions

Reaction of CH-acidic compounds with ammonium cerium(IV) nitrate generates electrophilic, resonance-stabilized radicals in a manner similar to reaction with manganese(III) acetate.$^{30,31}$ As mentioned in the previous section, these
radicals add readily to the electron-rich double bonds such those found in glycals (eq 3). Oxidation of CH-acidic compounds with ammonium cerium(IV) nitrate to produce electrophilic radicals has the advantage, when compared to reactions with manganese(III) acetate, of being able to be conducted at or below room temperature. [The reactions of manganese(III) acetate and ammonium cerium(IV) nitrate are discussed further in Chapter 21 of Volume II.]

C. Reductive Electron Transfer

Reductive electron transfer occurs when an electron is donated to a carbohydrate from a transition metal ion such as Ti(III), Sm(II), or Cr(II). This transfer raises the oxidation state of the transition metal and leads to formation of a carbon-centered radical.

1. Bis(cyclopentadienyl)titanium(III) Chloride [Cp₂TiCl] Reactions

a. Halogen-Atom Abstraction

Bis(cyclopentadienyl)titanium(III) chloride [titanocene(III) chloride, Cp₂TiCl (25)] exists in the solid state as a dimer, but coordinating solvents, such as tetrahydrofuran, dissociate the dimer into a reactive monomer (eq 4). [Although the monomer is coordinated with the solvent, its structure usually is represented simply as Cp₂TiCl.] Glycosyl halides react with Cp₂TiCl (25) to produce the corresponding glycals. An example of this type of reaction is shown in Scheme 11. Reaction begins with halogen-atom abstraction by 25 from the glycosyl bromide to give the pyranos-1-yl radical and Cp₂TiBrCl. This reaction is described as an inner-sphere electron transfer because the bromine atom in the carbohydrate is believed to coordinate with titanium during the transfer process (Scheme 11). The carbohydrate radical combines with a second molecule of Cp₂TiCl (25) to give a pair of organotitanium anomers (28), compounds that form the glycal by a β-elimination reaction.
Elimination reactions leading to glycals depend upon a leaving group (typically an acyloxy group) being attached to C-2. Direct acetoxy-radical elimination from the pyranos-1-yl radical 27 is unlikely because generating radicals similar to 27 in other ways does not lead to glycal formation. Elimination from the organotitanium compound 28 is a better choice (Scheme 11). Indirectly supporting the intermediacy of 28 is the finding that the 2-deoxyglycosyl halide 31, which has no C-2 substituent, does not produce a glycal but rather forms a pair of anomeric titanium compounds upon reaction with Cp₂TiCl (25, eq 5). 35

Competing with glycal formation by the pyranos-1-yl radical 27 is abstraction of a hydrogen atom from the solvent before reaction with a second molecule of Cp₂TiCl (25) can take place (Scheme 11). 33 When hydrogen-atom abstraction is the desired reaction, replacing 25 with Cp₂TiBH₄ is recommended because Cp₂TiBH₄ is able both to create the needed intermediate radical by halogen-atom abstraction and then complete the reaction by acting as a hydrogen-atom donor (eq 6). 38

b. Reductive Ring Opening

Reductive ring opening of epoxides by Cp₂TiCl (25) produces intermediates that undergo characteristic radical
reactions.\textsuperscript{32,39,40} The 2,3-anhydronucleoside 32, for example, reacts with 25 to form a radical that is converted into an unsaturated compound (Scheme 12).\textsuperscript{32} A second example of reaction of an epoxide with Cp\textsubscript{2}TiCl is provided by the addition reaction shown in eq 7, where C-glycoside formation takes place when the pyranos-1-yl radical, produced by ring opening of the 1,2-anhydro sugar 33, is captured by an \(\alpha,\beta\)-unsaturated ester.\textsuperscript{40} (Further discussion of the reactions of carbohydrates with Cp\textsubscript{2}TiCl and related compounds is found in Chapter 22 of Volume II.)

\begin{center}
\begin{align*}
\text{Scheme 12}
\end{align*}
\end{center}

2. Samarium(II) Iodide (SmI\textsubscript{2}) Reactions

\textbf{a. Reaction Mechanism}

Samarium(II) iodide (SmI\textsubscript{2}) reacts with various carbohydrate derivatives (e.g., halides,\textsuperscript{41} epoxides,\textsuperscript{42} sulfones,\textsuperscript{43} and aldehydes\textsuperscript{44}) to generate carbon-centered radicals. A radical formed in this way reacts quickly with a second molecule of SmI\textsubscript{2} to produce an organosamarium-compound (Scheme 13). To compete successfully with organosamarium compound formation a reaction must take place rapidly. An example of such a reaction is the radical cyclization shown in Scheme 14.\textsuperscript{43}

\begin{center}
\begin{align*}
\text{Scheme 13}
\end{align*}
\end{center}
b. Reaction in the Absence of HMPA

Samarium(II) iodide generates radicals by electron transfer in the presence or absence of hexamethylphosphoramide (HMPA). When HMPA is absent, these reactions typically take place under conditions in which tetrahydrofuran (THF), the usual reaction solvent, coordinates with SmI$_2$. In these reactions THF is replaced in the coordination sphere by a reactant molecule, often one that contains a carbonyl group. This replacement allows radical formation to take place by inner-sphere electron transfer (Scheme 15). An example of this type of reaction is shown in Scheme 16. (The intermediate produced by reaction of SmI$_2$ with a compound containing a carbonyl group is sometimes referred to as a samarium ketyl because it has some negative charge on the former carbonyl-oxygen atom and considerable radical character on the former carbonyl-carbon atom.)
c. Reaction in the Presence of HMPA

Samarium(II) iodide is frequently used in conjunction with HMPA to generate carbon-centered radicals. This pair of reagents produces a more powerful reducing agent than SmI$_2$ by itself. (The redox potential of Sm$^{2+}$/Sm$^{3+}$ increases from -1.33 V to -2.05 V when four equivalents of HMPA are added to a THF solution of SmI$_2$.$^{48}$) These two compounds (SmI$_2$ and HMPA) form a crystalline complex that has the structure SmI$_2$(HMPA)$_4$.$^{49}$ If this structure were maintained in solution, the samarium ion would be highly sterically hindered during reaction. Steric congestion and high affinity of HMPA for SmI$_2$ then would make it unlikely that an alkyl halide could “break into” the coordination sphere of the SmI$_2$–HMPA complex. If this were the case, reductions would occur via outer-sphere electron transfer.$^{46,50–52}$ Electrochemical and spectroscopic studies, however, show that the major species present in an HMPA-containing THF solution of SmI$_2$ is [Sm(HMPA)$_4$(THF)$_2^2+ 2I^-$];$^{53}$ thus, it is possible for a carbohydrate reactant (RX) to replace a molecule of THF in the coordination sphere (eq 8). Such a replacement would allow inner-sphere electron transfer to take place.$^{3,53}$ (Further discussion of the reactions of carbohydrates with SmI$_2$ is found in Chapter 20 in Volume II.)

3. Reactions With Chromium(II) Reagents

Reaction of halogenated compounds with chromium(II) reagents is another, but much less common, method for generating carbon-centered radicals from carbohydrates. This reaction, which involves reductive electron transfer, is used primarily to synthesize glycals. Glycal formation begins with a chromium(II) complex, such as [Cr$^{II}$(EDTA)]$^{2-}$, reacting with a glycosyl halide to produce a pyranos-1-yl radical. This radical then combines with additional [Cr$^{II}$(EDTA)]$^{2-}$ to generate a glycosylchromium complex that undergoes β elimination to produce a glycal (Scheme 17).$^{54,55}$
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