

Chapter 3

Nonchain Reactions

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I. Introduction

Although many radical reactions in carbohydrate chemistry are chain processes, nonchain reactions also play a significant role in the chemistry of these compounds. As mentioned at the beginning of Chapter 2, chain and nonchain reactions each involve radical formation, transformation, and disappearance. The difference is that for chain reactions the transformation cycle typically is repeated many times for each initiating radical, but for nonchain reactions each radical formed causes transformation to take place only once.

The radicals that participate in nonchain reactions sometimes are formed by bond homolysis but more often are produced by electron transfer. Bond homolysis is usually a photochemical reaction. Electron transfer typically involves transition-metal-generated radicals.

II. Transition-Metal-Generated Radicals

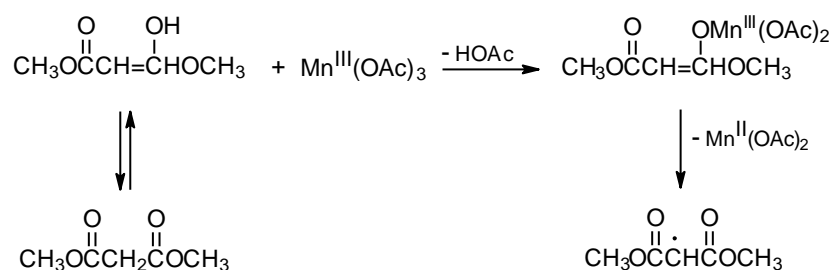
Reactions of radicals generated from transition-metal complexes can be divided into two types based on the direction of electron flow. In some of these reactions the transition metal accepts an electron during radical formation (oxidative electron transfer) and in others it donates an electron during this process (reductive electron transfer). The compounds that most often participate in oxidative electron transfer are manganese(III) acetate $[\text{Mn}(\text{OAc})_3]$ and ammonium cerium(IV) nitrate $[(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6]$, while those frequently involved in reductive electron transfer are bis(cyclopentadienyl)titanium(III) chloride (Cp_2TiCl), and samarium(II) iodide (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

Scheme 1

inner-sphere electron transfer

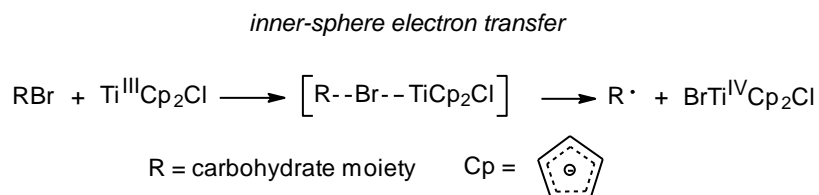


B. Oxidative Electron Transfer

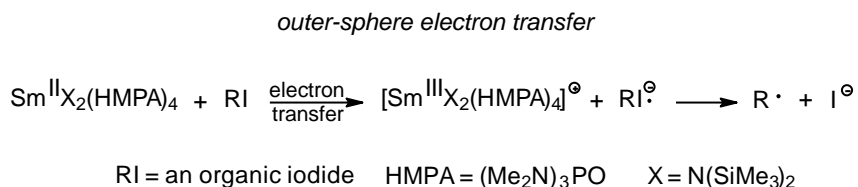
When a transition-metal ion changes from a higher to a lower oxidation state during radical formation, oxidative electron transfer is occurring in the substrate molecule. Changes in oxidation

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).

Scheme 2



Scheme 3



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 B₁₂

Coenzyme B₁₂ (**5**, Figure 1) is one of a group of biologically active molecules that have similar structures.⁷ 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 struc-

ture of the R group attached to cobalt. R represents the 5'-deoxyadenosyl group in coenzyme B₁₂ (5), but for related compounds R can be as structurally simple as a methyl or hydroxyl group.⁷

Scheme 4

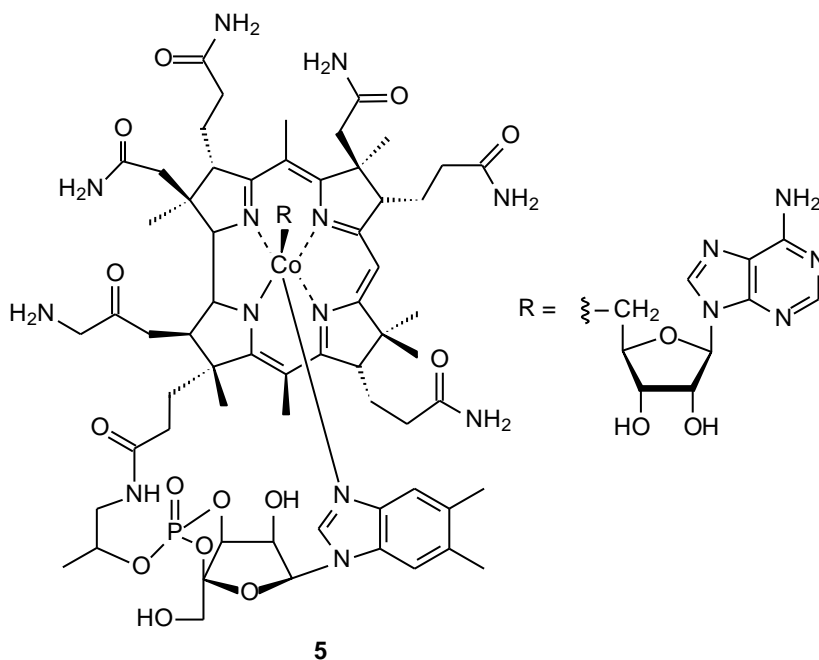
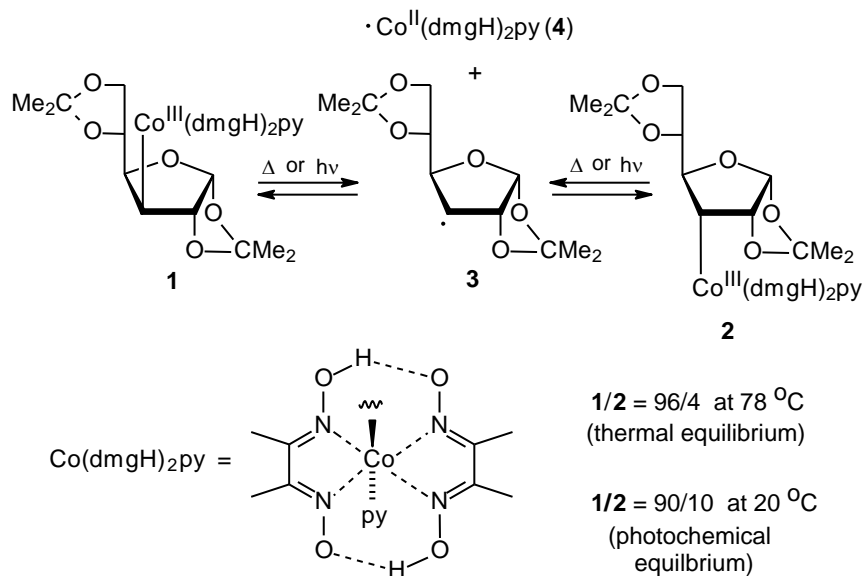
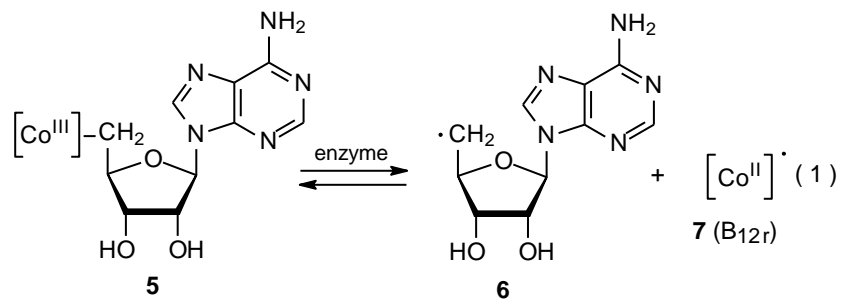
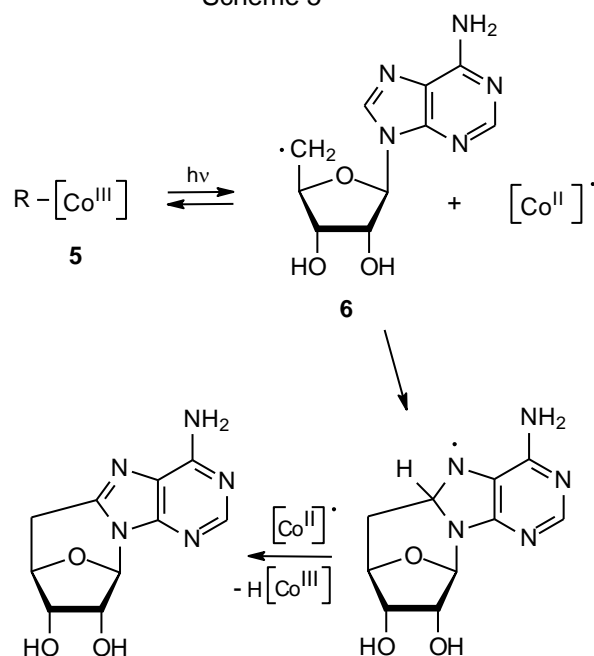


Figure 1. The structure of coenzyme B₁₂ (5'-adenosylcobalamin)



$[\text{Co}^{\text{III}}]$ or $[\text{Co}^{\text{II}}]$ = coenzyme B₁₂ (Figure 1) without the adenosyl group but with cobalt in different oxidation states

Scheme 5



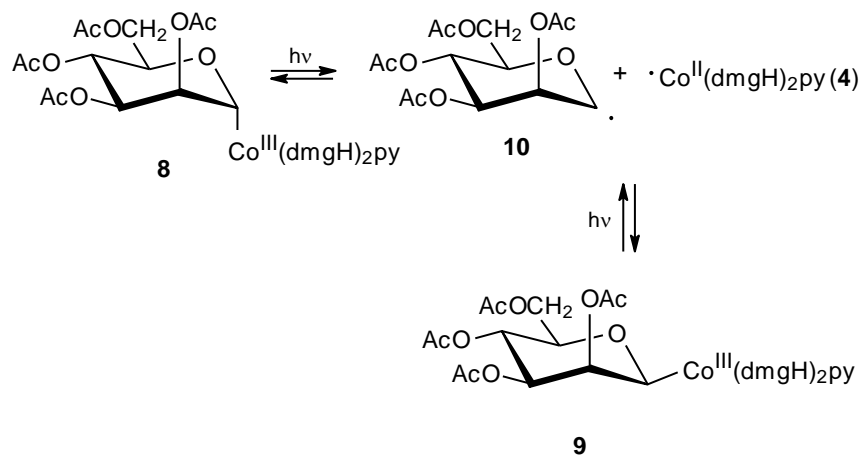
$\text{R-[Co}^{\text{III}}\text{]}$ = coenzyme B₁₂ (see Figure 1)

$[\text{Co}^{\text{II}}]^{\cdot}$ = coenzyme B₁₂ without the adenosyl group

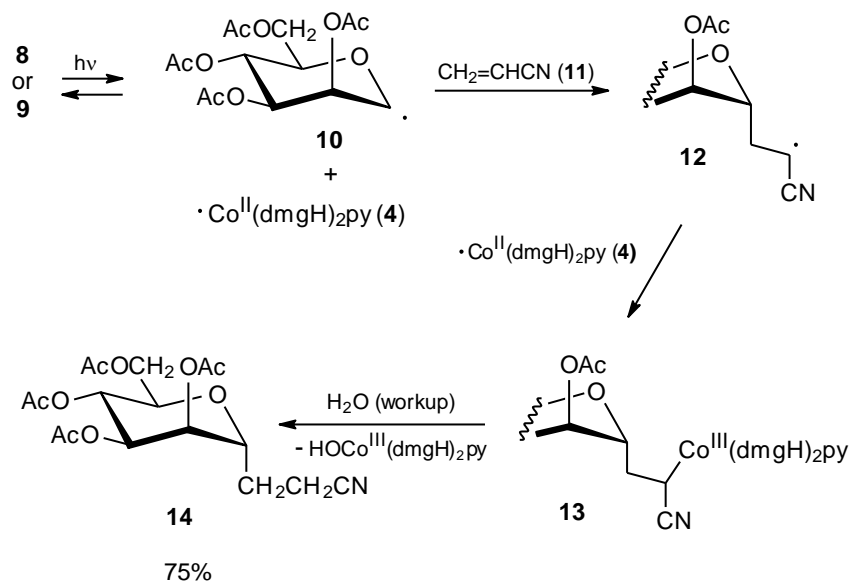
The original stimulus for study of carbon–cobalt bond homolysis as a pathway for forming carbon-centered radicals came from investigation of the reactions of coenzyme B₁₂ (**5**).^{8–10} In biological systems enzyme-induced homolysis of the carbon–cobalt bond in **5** produces the 5'-deoxyadenosyl radical **6** and the cobalt-centered radical **7** (B_{12r}, eq 1).^{8–10} In experiments outside biological settings the 5'-deoxyadenosyl radical (**6**) is produced from coenzyme B₁₂ (**5**) by photolysis with visible light.¹¹ 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).^{8-10,12}

Scheme 6



Scheme 7



b. Cobaloxime Complexes

The discovery that carbon–cobalt bond homolysis in coenzyme B₁₂ (**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.¹³⁻¹⁶ Carbohydrate cobaloximes **8** and **9** produce radicals **10** and **4**, which recombine in the absence of radical traps (Scheme 6).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 $\cdot\text{Co}(\text{dmgH})_2\text{py}$ (**4**) to form the addition product **13** (Scheme 7).¹³

A necessary condition for the reaction shown in Scheme 7 is that **4** [$\text{Co}(\text{dmgH})_2\text{py}$] 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

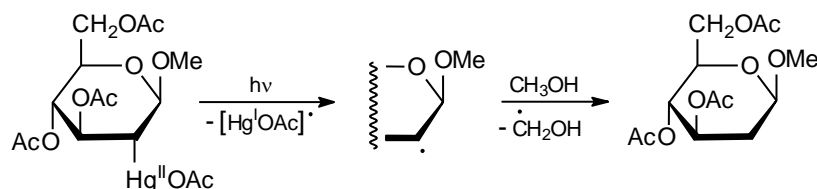
Persistent radicals, such as $\cdot\text{Co}(\text{dmgH})_2\text{py}$ (**4**), are responsible for a type of reactivity known as the persistent-radical effect.¹⁷⁻¹⁹ This effect causes a reaction that generates a persistent radical ($\text{R}_1\cdot$) and a transient radical ($\text{R}_2\cdot$) in equal 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

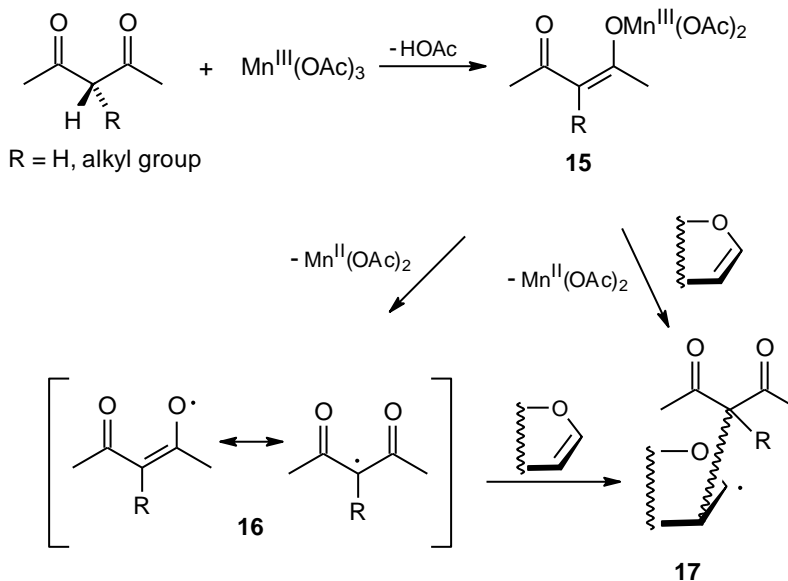
Scheme 8



3. Manganese(III) Acetate $[\text{Mn}(\text{OAc})_3]$ Reactions

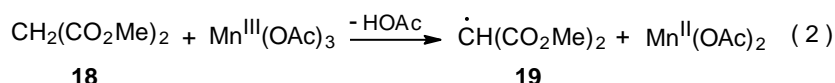
Carbon-centered radicals can be generated by reaction of manganese(III) acetate with CH-acidic compounds such as the β -diketone shown in Scheme 9.²¹⁻²⁴ The first step in this process is formation of the enolate **15**.²³ In the presence of an unsaturated compound two mechanisms for reaction of **15** 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

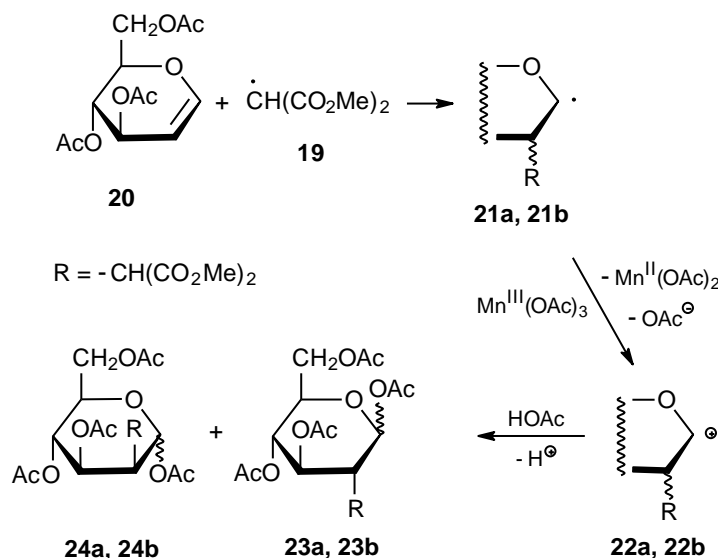


Since radical centers with two, attached carbonyl groups are electrophilic, radicals such as **16** (Scheme 9) add most easily to unsaturated compounds with electron-rich multiple bonds.²² This is the point at which carbohydrates typically become involved in reactions begun by manganese(III) acetate 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.)



Scheme 10



Manganese(III) acetate has a more complicated structure than the formula $\text{Mn}(\text{OAc})_3$ 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 $\text{Mn}(\text{OAc})_3$.

4. Ammonium Cerium(IV) Nitrate $[(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6]$ 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).³⁰ 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 tempera-

ture. [The reactions of manganese(III) acetate and ammonium cerium(IV) nitrate are discussed further in Chapter 21 of Volume II.]

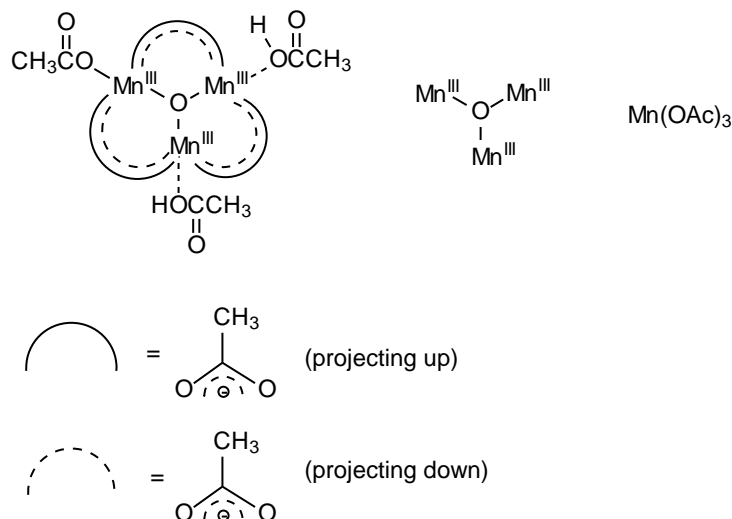
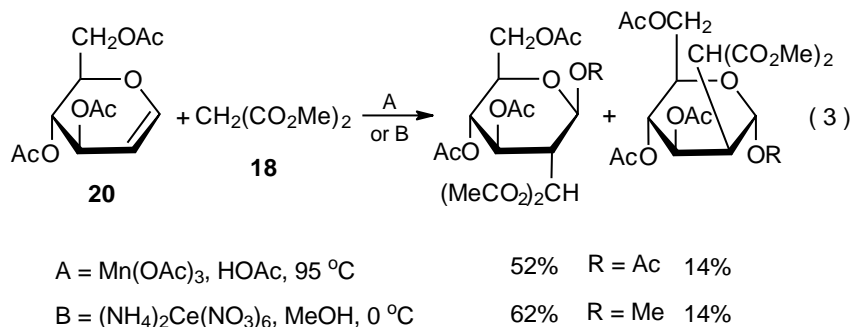


Figure 2. Three representations for manganese(III) acetate



C. Reductive Electron Transfer

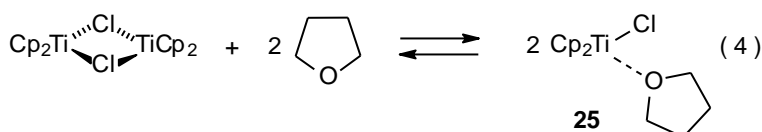
Reductive electron transfer occurs when an electron is donated to a carbohydrate from a transition metal ion such as Ti(III), Sm(II), or Cr(II). This transfer raises the oxidation state of the transition metal and leads to formation of a carbon-centered radical.

1. Bis(cyclopentadienyl)titanium(III) Chloride [Cp_2TiCl] Reactions

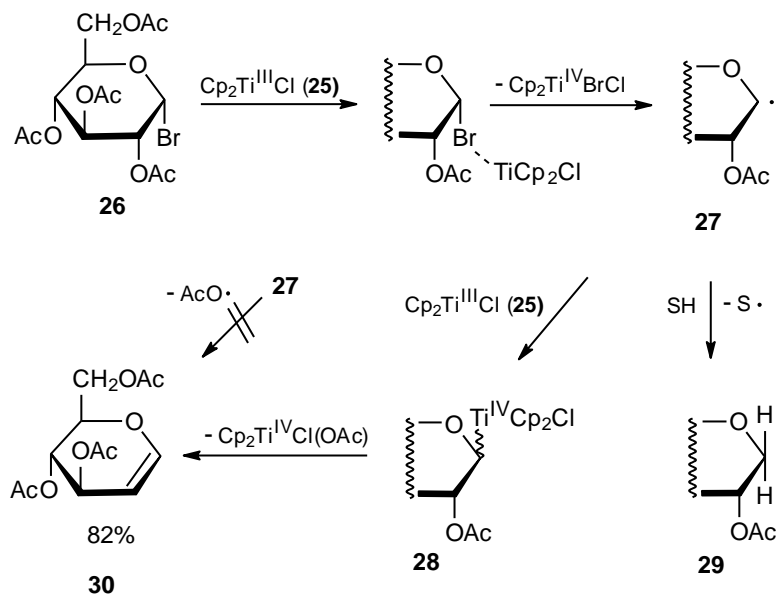
a. Halogen-Atom Abstraction

Bis(cyclopentadienyl)titanium(III) chloride [titanocene(III) chloride, Cp_2TiCl (**25**)] exists in the solid state as a dimer, but coordinating solvents, such as tetrahydrofuran, dissociate the dimer into a reactive monomer (eq 4).³² [Although the monomer is coordinated with the solvent, its

structure usually is represented simply as Cp_2TiCl .] Glycosyl halides react with Cp_2TiCl (**25**) to produce the corresponding glycols.^{33–37} An example of this type of reaction is shown in Scheme 11. Reaction begins with bromine-atom abstraction by **25** from the glycosyl bromide **26** to give the pyranos-1-yl radical **27** and Cp_2TiBrCl . 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).³³ The carbohydrate radical **27** combines with a second molecule of Cp_2TiCl (**25**) to give a pair of organotitanium anomers (**28**), compounds that form the glycol **30** by a β -elimination reaction.^{33,34}

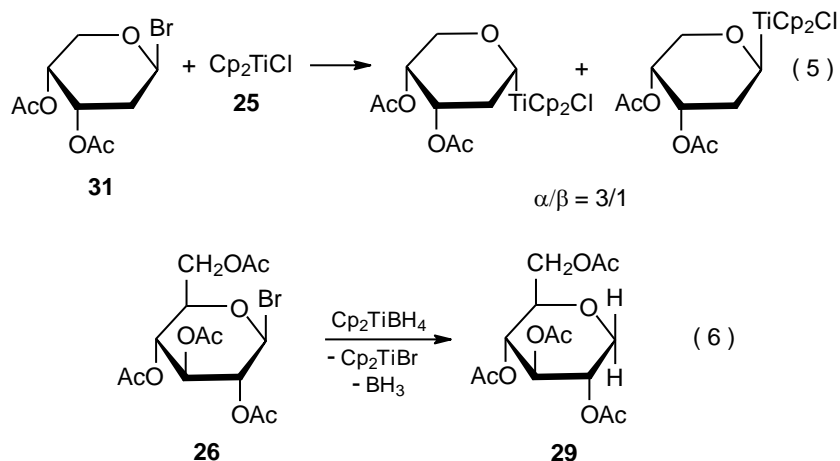


Scheme 11



Elimination reactions leading to glycols 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 glycol 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 glycol but rather forms a pair of anomeric titanium compounds upon reaction with Cp_2TiCl (**25**, eq 5).³⁵

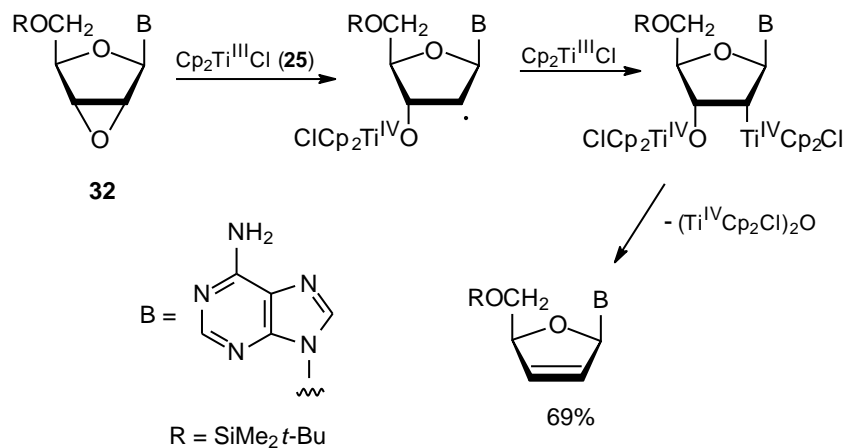
Competing with glycal formation by the pyranos-1-yl radical **27** is abstraction of a hydrogen atom from the solvent before reaction with a second molecule of Cp_2TiCl (**25**) can take place (Scheme 11).³³ When hydrogen-atom abstraction is the desired reaction, replacing **25** with Cp_2TiBH_4 is recommended because Cp_2TiBH_4 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

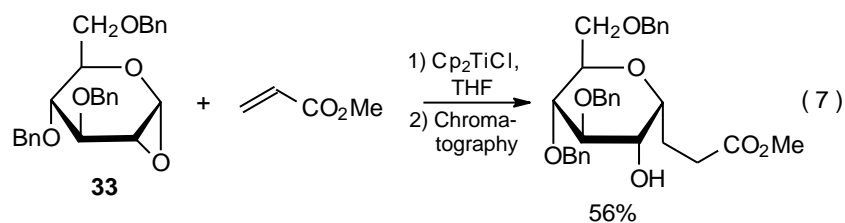


b. Reductive Ring Opening

Reductive ring opening of epoxides by Cp_2TiCl (**25**) produces intermediates that undergo characteristic radical reactions.^{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).³² A second example of reaction of an epoxide with Cp_2TiCl 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 α,β -unsaturated ester.⁴⁰ (Further discussion of the reactions of carbohydrates with Cp_2TiCl and related compounds is found in Chapter 22 of Volume II.)

Scheme 12



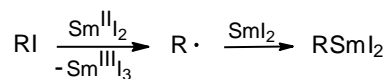


2. Samarium(II) Iodide (SmI_2) Reactions

a. Reaction Mechanism

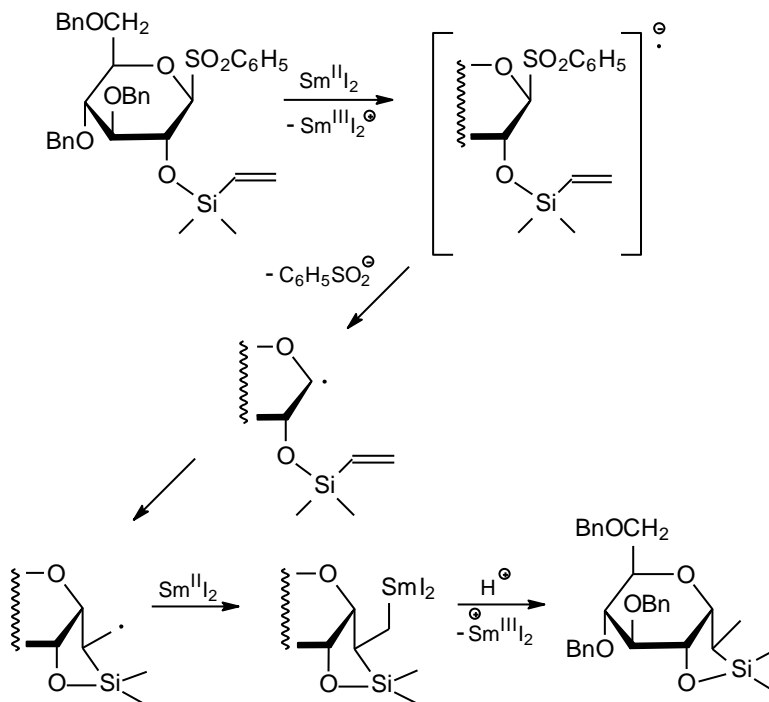
Samarium(II) iodide (SmI_2) reacts with various carbohydrate derivatives (e.g., halides,⁴¹ epoxides,⁴² sulfones,⁴³ and aldehydes⁴⁴) to generate carbon-centered radicals. A radical formed in this way reacts quickly with a second molecule of SmI_2 to produce an organosamarium-compound (Scheme 13). To compete successfully with organosamarium compound formation a reaction must take place rapidly. An example of such a reaction is the radical cyclization shown in Scheme 14.⁴³

Scheme 13



R = carbohydrate moiety

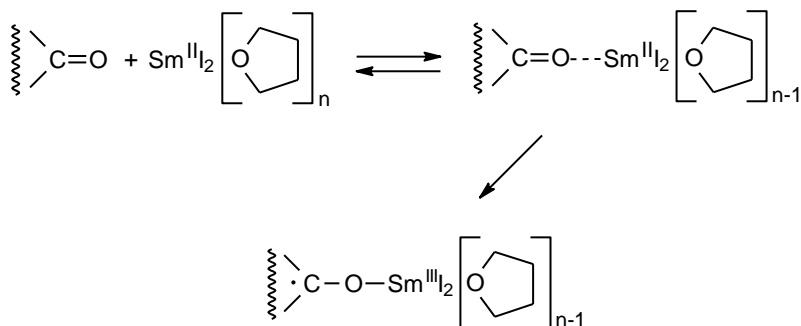
Scheme 14



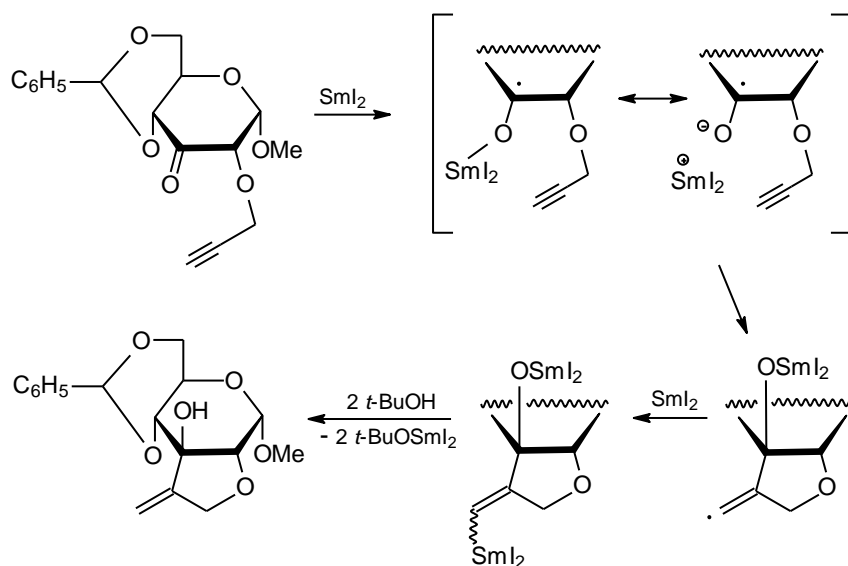
b. Reaction in the Absence of HMPA

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).^{45,46} An example of this type of reaction is shown in Scheme 16.⁴⁷ (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.)

Scheme 15



Scheme 16

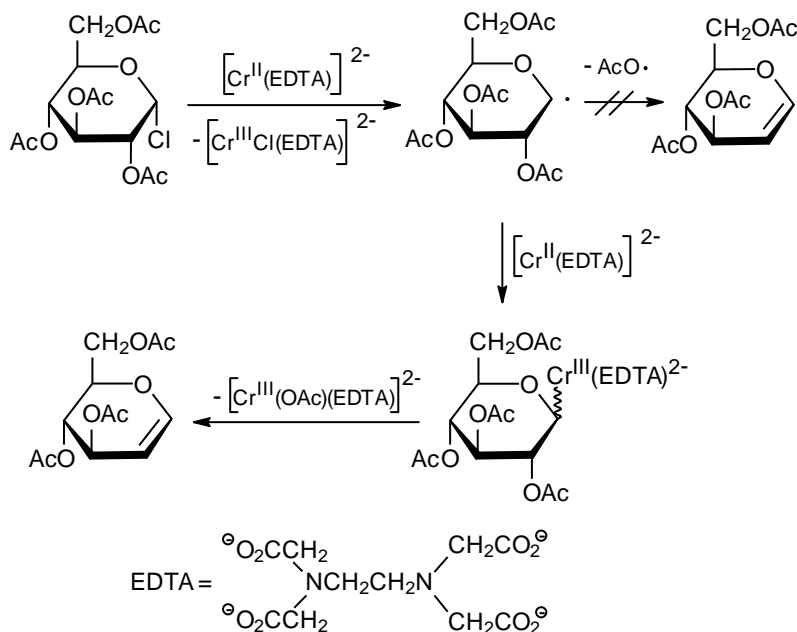


c. Reaction in the Presence of HMPA

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 $\text{Sm}^{2+}/\text{Sm}^{3+}$ 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 $\text{SmI}_2(\text{HMPA})_4$.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 $[\text{Sm}(\text{HMPA})_4(\text{THF})_2]^{2+} 2\text{I}^-$;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.)



Scheme 17



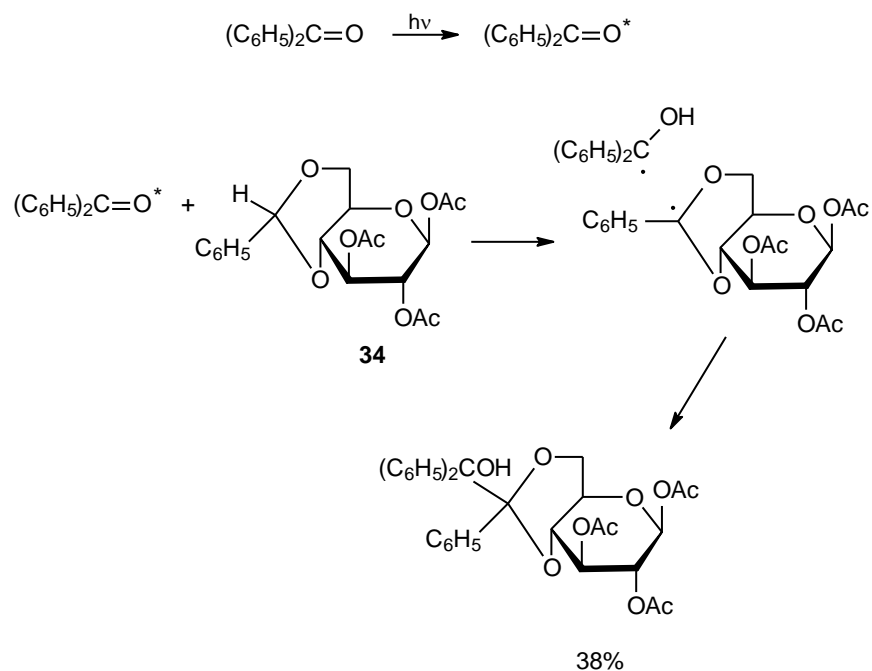
3. Reactions With Chromium(II) Reagents

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 glycols. Glycol formation begins with a chromium(II) complex, such as $[\text{Cr}^{\text{II}}(\text{EDTA})]^{2-}$, reacting with a glycosyl halide to produce a pyranos-1-yl radical. This radical then combines with additional $[\text{Cr}^{\text{II}}(\text{EDTA})]^{2-}$ to generate a glycosylchromium complex that undergoes β elimination to produce a glycol (Scheme 17).^{54,55}

III. Photochemically Generated Radicals

Although, as described in Chapter 2, photolysis sometimes initiates chain reactions, it also can produce radicals that undergo nonchain reactions. In a photochemically initiated chain reaction the number of photons that must be absorbed to cause complete reaction typically is far smaller than the number of molecules reacted. (A radical formed by absorption of one photon can begin a chain that produces many product molecules.) In a nonchain reaction the number of photons absorbed typically must be at least equal to the number of molecules reacted. Actually, it is rare that each, absorbed photon causes a reaction to take place because reaction is only one of the ways an excited molecule dissipates its energy; consequently, for complete reaction to occur in a nonchain process the number of photons absorbed often greatly exceeds the number of molecules reacted.

Scheme 18



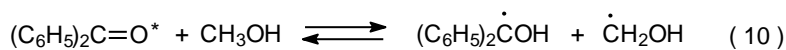
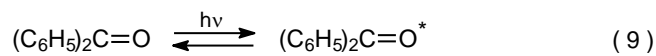
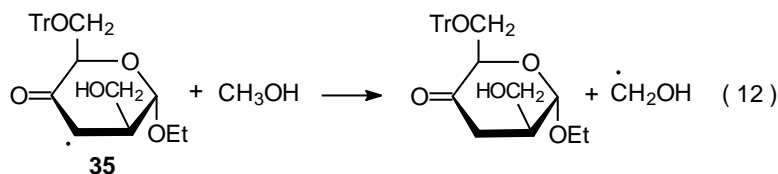
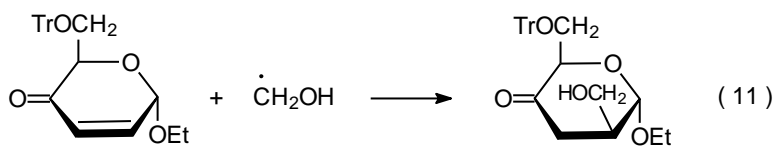
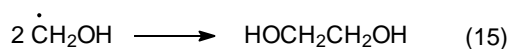
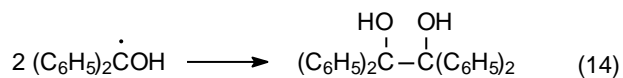
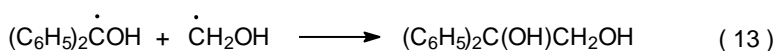
Although cleavage of weak carbon–metal bonds (e.g., carbon–cobalt bonds) tends to occur readily upon photolysis, photochemical processes do not require a reactant to have a weak bond in order for bond homolysis to take place. When ultraviolet light is absorbed by a compound, enough energy is present in the excited system to break even strong bonds.

A. Hydrogen-Atom Abstraction

Since excited carbonyl compounds have reactivity similar to that of alkoxy radicals, they can abstract hydrogen atoms from carbon–hydrogen bonds.⁵⁶ An example of this type of reaction

Scheme 19

chain reaction

initiation*propagation**termination*

is shown in Scheme 18 where excited benzophenone abstracts a hydrogen atom from the benzylidene acetal **34**. The resulting radical pair then combines to give the observed product.⁵⁷

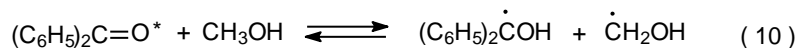
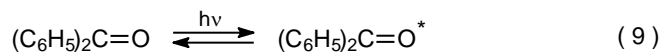
1. Deciding Whether a Photochemical Reaction Has a Chain or Nonchain Mechanism

Formation of a radical combination product leaves little doubt about the nonchain nature of the reaction shown in Scheme 18, but all mechanistic decisions about reactions involving hydrogen-atom abstraction by excited benzophenone are not as clear as this one. Consider the radical addition that is described as a chain reaction in Scheme 19 and a nonchain reaction in Scheme 20.⁵⁸ (Equations 9-16 are found in Schemes 19 and 20). Since the first three steps (equations 9-11) in each mechanism are the same, it is the fourth step that determines the mechanistic pathway. This determination hinges on the fate of the radical **35**. If this radical abstracts a hydrogen atom from methanol (eq 12), a chain reaction is established (Scheme 19). If, on the other hand, the radical **35** undergoes the disproportionation reaction shown in eq 16, the overall reaction becomes a nonchain process (Scheme 20).

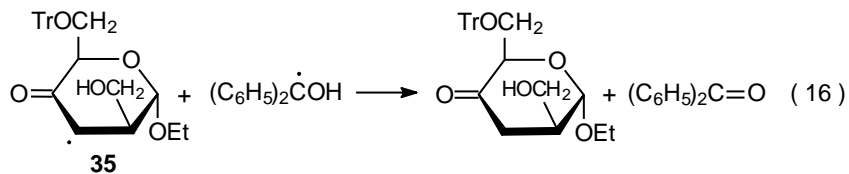
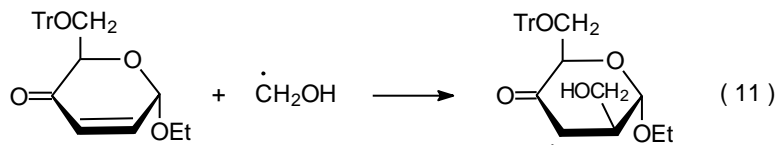
Scheme 20

nonchain reaction

radical formation



radical reaction



2. Interpretation of Quantum Yields

Quantum yields can be helpful in deciding whether a reaction, such as that described in Schemes 19 and 20, is a chain or nonchain process. In making this decision it is valuable to know if

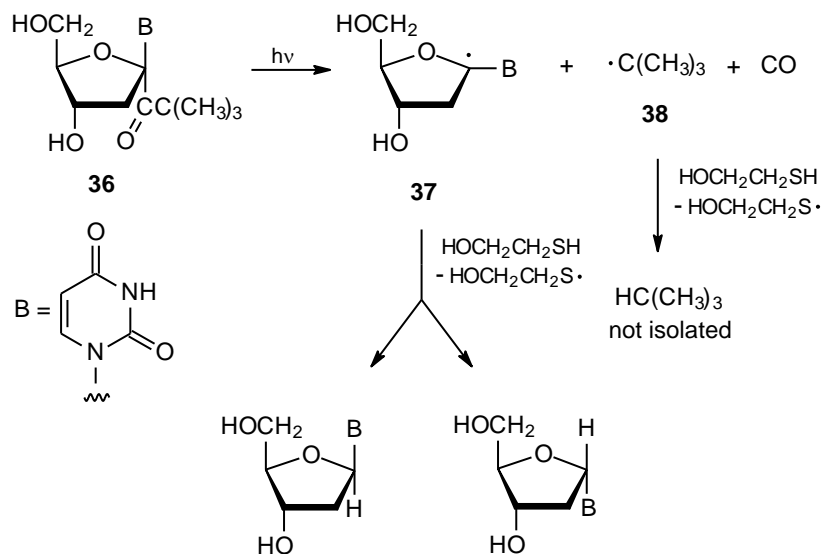
the quantum yield is greater or less than unity. The importance of this dividing line is described in the next two sections.

a. Meaning of a Quantum Yield Less Than Unity

The maximum value for a quantum yield in a typical, nonchain reaction is unity because each photon normally can cause reaction of only one molecule. A quantum yield less than one is characteristic of nonchain reactions because it is the nature of excited molecules to have a variety of possible pathways for dissipating excitation energy before a reaction can occur. Any loss of excitation energy prior to reaction reduces the magnitude of the quantum yield from its normal limiting value of one.

One way for an excited molecule to lose its excitation energy without undergoing a chemical reaction is for the molecule to emit a photon, that is, for it to fluoresce or phosphoresce. A second way is by transformation of an electronically excited molecule into a vibrationally excited, ground-state molecule. Producing a ground-state molecule in this way is described as internal conversion because within a single molecule excitation energy is converted into vibrational energy. Once internal conversion has taken place, a molecule quickly dissipates its excess vibrational energy to its surroundings by colliding with solvent molecules. Since photon emission and internal conversion are two photophysical processes that divert an excited molecule away from chemical reaction, they are events that cause a quantum yield for a reaction to have a value less than one. The quantum yield for the reaction pictured in chain and nonchain forms in Schemes 19 and 20, respectively, is 0.139. This value is consistent with a nonchain mechanism (Scheme 20).

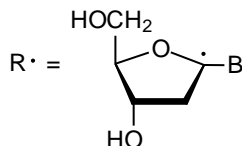
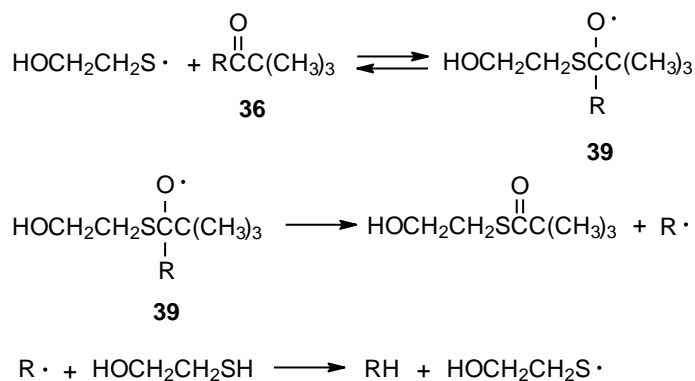
Scheme 21



b. Meaning of a Quantum Yield Greater than Unity

It is also useful to consider the meaning of a quantum yield greater than unity. Imagine a molecule that absorbs a photon and then undergoes a homolytic bond cleavage to give two radicals. If each of these radicals somehow causes the formation of a product molecule, a nonchain reaction with a quantum yield as high as two is possible (but rare). (A quantum yield of this magnitude has been measured for the nonchain, photochemical reduction of benzophenone by 2-propanol.⁵⁹) A chain mechanism must be operative in nearly all reactions with a quantum yield greater than one and certainly in any reaction that has a quantum yield greater than two.

Scheme 22



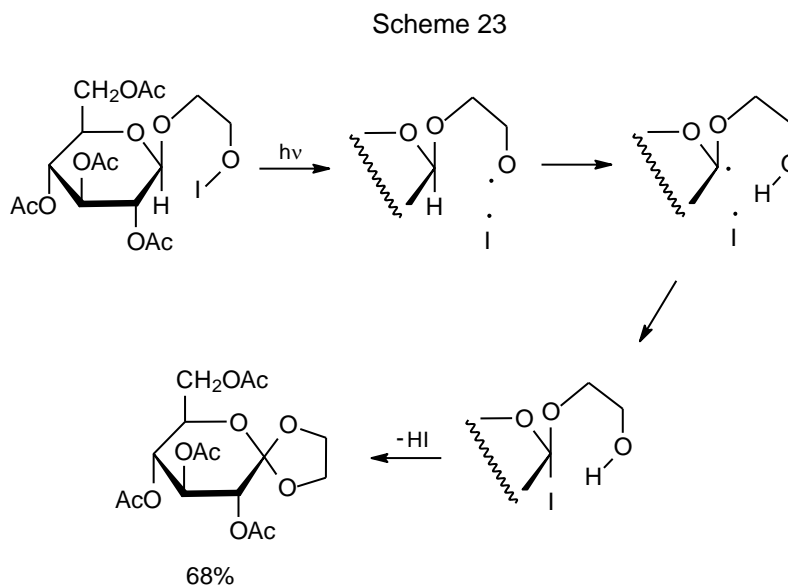
B. Carbon–Carbon Bond Homolysis

If a pair of radicals produced by photolysis is not held in close proximity by a connecting chain of atoms, these radicals are free to diffuse apart in solution and potentially become involved in chain reactions. Having radicals escape the solvent cage in which they were formed does not insure that a chain reaction will transpire because a viable propagation sequence may not exist. If such a sequence is absent, nonchain reaction still can take place; for example, according to the mechanism presented in Scheme 21, the radical **37**, which is formed by photochemical, carbon–carbon homolysis, abstracts a hydrogen atom from $\text{HOCH}_2\text{CH}_2\text{SH}$ to produce the product nucleosides in a nonchain reaction.⁶⁰ It is also possible to propose a chain mechanism for this reaction (propagation steps pictured in Scheme 22), but in order for this chain reaction to be operative, $\text{HOCH}_2\text{CH}_2\text{S}\cdot$ would need to add rapidly to the starting material **36**, a process that would generate the much less stable alkoxy radical **39**. Since this addition would be, at best, a slow process and not

the rapid one needed for chain propagation and since if **39** ever formed, it would be most likely to revert to **36** and $\text{HOCH}_2\text{CH}_2\text{S}\cdot$, the sequence in Scheme 22 is not a viable one. The nonchain mechanism shown in Scheme 21, therefore, offers a much better explanation for this reaction.

C. Oxygen–Iodine Bond Homolysis

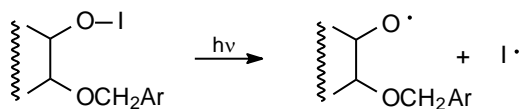
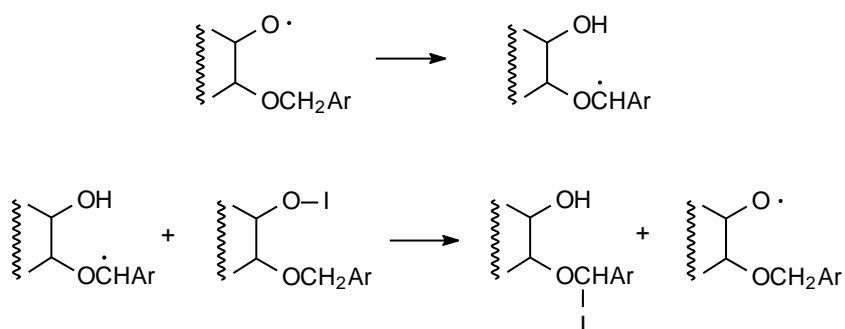
Hypoiodite photolysis is an effective reaction for generating alkoxy radicals. Both chain and nonchain mechanisms are possible. The case for a nonchain process is strongest when the alkoxy radical formed by O–I bond cleavage rapidly abstracts a hydrogen atom internally to produce a carbon-centered radical in the vicinity of the recently formed iodine atom. Under these conditions radical combination easily could produce the observed product in a nonchain reaction (Scheme 23⁶¹).⁶² If the radicals do not remain in close proximity long enough to combine, a chain reaction, such as that proposed in Scheme 24, becomes a possibility.⁶³ (Further discussion of radical formation from hypoiodites and subsequent reaction of the alkoxy radicals formed is found in Chapter 6 of Volume II.)



D. A Comment About Photochemical Reactions

From the discussion in this and the previous chapter it is clear that photolysis can serve as a beginning point for both chain and nonchain reactions. Photochemical reactions, seen just from this point of view, appear to be a subset of radical reactions. Although there is certainly overlap between these two areas, forming an excited state also can lead to photochemical reactions that do not involve free radicals; consequently, radical formation brought about by photolysis represents only one aspect of carbohydrate photochemistry. A comprehensive discussion of the photochemical reactions of carbohydrates can be found in reference 64.

Scheme 24

initiation*propagation*

IV. Thermally Generated Radicals

Heating of carbohydrates has a limited role in causing useful radical reactions. Few carbohydrates or their derivatives have bonds weak enough to generate radicals at temperatures that avoid general structural decomposition. As described earlier in this chapter, a carbohydrate derivative with a carbon–cobalt or oxygen–iodine bond can generate radicals by thermal reaction, but even for such compounds radical formation usually takes place photochemically.

V. Summary

Transition-metal-generated radicals are involved in most nonchain, radical reactions of carbohydrates. In some of these reactions the transition metal accepts an electron, and in others it is an electron donor. The carbohydrate radicals thus produced undergo typical radical reactions, such as addition to a double bond and hydrogen-atom abstraction. Manganese(III) acetate and ammonium cerium(IV) nitrate both react with CH-acidic compounds, such as those with β -dicarbonyl substituents, to produce electrophilic radicals that add readily to electron-rich double bonds (e.g., those present in glycals). Bis(cyclopentadienyl)titanium chloride (Cp_2TiCl) reacts with glycosyl halides to produce pyranos-1-yl radicals. In the absence of a radical trap these radicals generate anomeric mixtures of glycosyl titanium compounds that undergo β -elimination to form glycals.

Radical intermediates also are produced when Cp_2TiCl causes reductive opening of epoxide rings. The samarium(II) iodide–hexamethylphosphoramide ($\text{SmI}_2\text{–HMPA}$) complex often serves as an electron donor in radical-forming reactions where a carbohydrate sulfone or halide is the electron acceptor.

Organocobalt and organomercury compounds generate radicals by carbon–cobalt and carbon–mercury bond homolysis, respectively. These compounds form carbon-centered radicals by both thermal and photochemical reaction. Carbon–cobalt bonds also undergo enzymatic cleavage, but in nonbiological settings photochemical bond homolysis is most common.

Photolysis of a variety of carbohydrates produces radicals that participate in nonchain reactions. Excited carbonyl compounds generate radicals by hydrogen-atom abstraction and by C–C bond fragmentation. Oxygen–iodine bonds cleave homolytically upon photolysis to produce highly reactive, alkoxy radicals.

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