Chapter 3
Compounds with Carbon–Sulfur Single Bonds

I. Introduction

A carbohydrate derivative that contains a sulfur atom bonded to two carbon atoms is capable of forming carbon-centered radicals. A common pathway for radical formation in compounds of this type is homolytic cleavage of a carbon–sulfur bond brought about by group abstraction (eq 1). When the sulfur atom in a C–S bond is part of an electronegative group, as is the case in a glycosyl phenyl sulfone, electron transfer of the type shown in Scheme 1 represents another pathway to carbon-centered radical formation. A beginning point for discussing these reactions is examining their possible mechanisms.

\[ \text{R = an alkyl or aryl group} \]
II. Reaction Mechanisms

A. Group Abstraction

Two mechanisms are considered to be reasonable possibilities for the carbon–sulfur bond cleavage described by the reaction shown in eq 1.\(^1\) The first is the bimolecular, homolytic, substitution (S\(_\text{H2}\)) reaction pictured in Scheme 2, and the second is a stepwise process that involves formation of an intermediate (1) with a hypervalent sulfur atom (Scheme 3). The choice between these two hinges on the existence of 1.

There is little experimental evidence upon which to base a decision about formation of a compound with a hypervalent sulfur atom during carbon–sulfur bond cleavage, but reaction of the thioacetal 2 with the tri-\(n\)-butyltin radical provides some suggestive information (Scheme 4).\(^2\) Although this reaction produces BuOCH\(_2\)· (3), the effect of temperature on the ESR signal for this radical is unexpected because the intensity of the signal increases as the temperature in the ESR cavity rises. (Signals due to radicals arising from reaction of bromides with Bu\(_3\)Sn· decrease with rising temperature due to leveling of the Boltzmann distribution of spin states.\(^2\)) A possible explanation for this behavior is that a slow, temperature-dependent reaction between the thioacetal 2 and Bu\(_3\)Sn· produces the hypervalent, sulfur-centered radical 4 (not observable by ESR), an intermediate that then fragments rapidly to give the ESR observable radical 3 (Scheme 4).\(^2\)
Molecular orbital calculations also have been used to study the possibility of formation of intermediates with hypervalent sulfur atoms. When these calculations focus on the reactions of sulfides, they do not support the existence of such intermediates.\(^1,3^{-6}\)

**Scheme 4**

\[
\begin{align*}
\text{BuOCH}_2\text{SC}_6\text{H}_5 & \xrightarrow{\text{Bu}_3\text{Sn}^+} \text{BuOCH}_2^+ + \text{Bu}_3\text{SnSC}_6\text{H}_5 \\
\text{BuOCH}_2^+ & \xrightarrow{\text{Bu}_3\text{Sn}^+} \text{BuOCH}_2^+ + \text{Bu}_3\text{SnSC}_6\text{H}_5 \\
\text{possible intermediate}
\end{align*}
\]

B. Electron-Transfer

Electron transfer to a sulfur-containing carbohydrate naturally depends upon such a compound having a group that readily accepts electrons. Sulfones meet this requirement and, thus, are prime candidates for electron-transfer reaction.\(^7\) Two proposed mechanisms showing how such transfer could lead to cleavage of a carbon–sulfur bond are shown in Scheme 5. In one of these a sulfone reacts with an electron donor (e.g., SmI\(_2\)) to produce a radical anion (5) that then fragments

**Scheme 5**

\[
\begin{align*}
\text{R} \cdot \text{X}^\ominus + \text{Sm}^{\text{III}}\text{I}_2 & \rightarrow \left[ \text{R} \cdot \text{X} \right]^\ominus + \text{Sm}^{\text{III}}\text{I}_2 \\
\cdot \text{Sm}^{\text{III}}\text{I}_2 & \rightarrow \cdot \text{X}^\ominus \\
\text{radical reactions} & \rightarrow \text{R} \cdot \text{Sm}^{\text{III}}\text{I}_2 \\
\text{X} = \text{SO}_2\text{Ar} & \quad \text{R} \cdot = \text{a carbohydrate radical}
\end{align*}
\]

**Scheme 6**

\[
\begin{align*}
\text{R} \cdot & \xrightarrow{\text{Bu}_3\text{Sn}^+} \text{Bu}_3\text{SnS-CAR}B \quad \text{CAR}B \rightarrow \text{ CAR}B \rightarrow \text{ CAR}B \cdot \\
\text{CAR}B \cdot & = \text{a carbon-centered carbohydrate radical} \\
\text{R} & = \text{CH}_3, \text{CH}_3\text{CH}_2, \text{C}_6\text{H}_5
\end{align*}
\]
to give an anion and a carbon-centered radical. In the other, dissociative electron transfer forms an anion and a carbon-centered radical directly from reaction of a sulfone with SmI$_2$.

III. Alkylthio and Arylthio Substituted Carbohydrates and Related Compounds

The identity of the carbon–sulfur single bond broken during reaction of a carbohydrate that has two such bonds depends upon the stability of the carbon-centered radical being formed. If the sulfur atom is part of a methylthio, $^8$–$^{11}$ ethylthio, $^{12}$–$^{15}$ or arylthio $^{15}$–$^{24}$ group, radical stability favors producing a carbohydrate radical rather than a methyl, ethyl, phenyl, or $p$-tolyl radical (Scheme 6).

A. Simple Reduction

Since the ease of alkylthio and arylthio group abstraction correlates with the stability of the carbon-centered radical produced, a radical stabilized by one or more oxygen atoms attached to the radical center can be generated under relatively mild reaction conditions.$^{8}$–$^{11}$ The reaction pictured in Scheme 7 provides an example of the relation between radical stability and ease of radical formation because the intermediate radical 6, with a stabilizing oxygen atom attached to the radical center, forms upon heating of the corresponding methylthio glycoside with Bu$_3$SnH for only 30 min at 110 °C.$^{11}$ A noticeable feature of this reaction is the highly stereoselective hydrogen-atom transfer to 6 attributable to the kinetic anomeric effect. (For a discussion of the kinetic anomeric effect see Section III.B (page 255) of Chapter 13 in Volume I.)

It is reasonable to expect that if group abstraction cannot produce an oxygen-stabilized radical, carbon–sulfur bond cleavage will require more vigorous reaction conditions. Experimental findings support this expectation. The reaction shown in eq 2, which does not produce a stabilized radical, requires heating at 100 °C over a period of 8-12 h to reach completion.$^{18}$ Other transfor-
mations of this type need similar\textsuperscript{14} or even longer reaction times\textsuperscript{19,21} or higher temperatures\textsuperscript{20} and some do not occur at all.\textsuperscript{22} The shorter time (3 h) for the reaction shown in eq 3\textsuperscript{23,24} may reflect a relief of steric strain caused by the heavily substituted carbon atom adjacent to the reactive center.

\begin{equation}
\text{R} = \text{Me}_2\text{C}
\end{equation}

\[ \text{Ar} = \text{C}_6\text{H}_5 \]

B. Radical Cyclization

When alkylthio or arylthio group abstraction takes place from an unsaturated carbohydrate, ring formation becomes a possibility; thus, cyclization follows loss of the phenylthio group from compound 7 (Scheme 8).\textsuperscript{25} As with most cyclization reactions, ring formation is forced to compete with hydrogen-atom abstraction. Favoring cyclization in the reaction shown in Scheme 8 is the generally rapid formation of five-membered rings, but opposing it is the difficulty inherent in a
nucleophilic radical, such as 8, adding to a double bond that is not decidedly electron-deficient. Successful cyclization in this situation requires suppressing hydrogen-atom abstraction by maintaining the concentration of the hydrogen-atom donor (Bu$_3$SnH) at a low level during reaction.

C. Ring-Opening Reactions

Some reactive carbohydrates have a thioether linkage that is not part of an alkylthio or arylthio group. Reactions of these compounds usually, but not always, involve opening of a ring that contains a sulfur atom. Some ring-opening reactions stop with formation of a thiol (eq 4), but others continue with the cleavage of the second carbon–sulfur bond (Scheme 9). The reaction shown in eq 4 provides yet another example of the frequent competition between simple
reduction and other radical reactions. In this case ring opening is minor when compared to simple reduction.

IV. Dithioacetals

Dithioacetals react with tri-\(n\)-butyltin hydride to replace first one, and then the second, alkylthio group with a hydrogen atom (Scheme 10).\(^{30}\) Because the first group is replaced more rapidly than the second, good yields of compounds with a single sulfur atom are obtained under the proper reaction conditions.\(^{31-35}\) The greater reactivity of the first ethylthio group in these compounds is due to formation of an intermediate, carbon-centered radical that is stabilized by the sulfur atom in the remaining ethylthio group.

An unsaturated dithioacetal in which the double bond is properly positioned undergoes intramolecular radical addition.\(^{31-34}\) Reaction typically involves capture of the first-formed, carbon-centered radical by the multiple bond; thus, in the reaction shown in Scheme 11, the major
product has a new ring system with an ethylthio substituent. Here again the greater reactivity of the first ethylthio group allows reaction to occur with no detectable loss of the second.

![Chemical reactions and structures](image)

V. Thiocarbonates and Dithiocarbonates

Thiocarbonates and dithiocarbonates are compounds in which at least one sulfur atom is bonded to the carbon atom of a carbonyl group. The reactivity of these compounds is similar to that of the sulfur-containing compounds already discussed in that reaction begins with carbon–sulfur bond cleavage producing the more stable of the possible carbon-centered radicals; thus, in the reaction shown in eq 5, product identity is consistent with forming an intermediate allylic radical from reaction of a thio carbonate.

Addition of Bu₃Sn· to the dithiocarbonate 9 is the first step in an addition-elimination reaction that produces the tin-containing compound 11 (Scheme 12). The stability of CH₃SC(=O)S·
is critical to this type of reaction because it, rather than Bu$_3$Sn\textsuperscript{−}, is expelled when a radical such as 10 forms a tin-containing product\textsuperscript{37,38} Since Bu$_3$Sn\textsuperscript{−} addition to a double bond often is reversible, 10 sometimes may break a carbon–tin bond causing an undetectable regeneration of Bu$_3$Sn\textsuperscript{−} and the substrate 9.

VI. \textit{O}-Thiocarbonyl Compounds

Compounds with carbon–sulfur single bonds are substantially less reactive with tin- and silicon-centered radicals than are compounds with C–S double bonds. Among carbohydrates these double bonds are almost always part of \textit{O}-thiocarbonyl groups. (The reactions of \textit{O}-thiocarbonyl carbohydrate derivatives are discussed in Chapter 12.) The reaction shown in eq 6 illustrates the greater reactivity of a C–S double bond when compared to a C–S single bond because only the \textit{O}-thiocarbonyl group in the 1-thioglycoside 12 reacts even though an ethylthio group is present in the molecule\textsuperscript{39} Greater reactivity of a carbon–sulfur double bond also can be seen in the reaction shown in Scheme 13, where Bu$_3$Sn\textsuperscript{−} reacts only with the \textit{O}-thiocarbonyl group\textsuperscript{26} A quantitative measure of the reactivity of C–S single and double bonds comes from comparing absolute rate constants for their reactions; thus, rate constants for reaction of (Me$_3$Si)$_3$Si\textsuperscript{−} with C$_{10}$H$_{21}$SC$_6$H$_5$ and
C₆H₁₁OC(=S)SMe are less than 5 x 10⁶ and 1.1 x 10⁹ M⁻¹s⁻¹, respectively, at 21 °C.⁴⁰ The reactions in Schemes 12 and 13 also illustrate the ease of fragmentation of a carbon–sulfur single bond when a radical is centered on an adjacent carbon atom.

VII. Sulfones

Radicals are involved in both the synthesis and the reactions of carbohydrate sulfones. Sulfones produce carbon-centered radicals by group abstraction, dissociative electron-transfer, and photochemical bond homolysis. Sulfone synthesis takes place when a sulfonyl radical adds to an unsaturated carbohydrate.

A. Addition-Elimination Reactions

Addition of a carbohydrate radical to an allylic⁴¹ or vinylic⁴² sulfone is the first step in a reaction that forms a new carbon–carbon bond and expels an arylsulfonyl radical. The reaction shown in eq 7 uses this addition-elimination process to attach a six-carbon-atom chain to a pyranoid ring.⁴¹ Addition-elimination reaction also can replace an arylsulfonyl group in an unsaturated sulfone with a tri-n-butyltin group (eq 8⁴³).⁴³⁻⁴⁷ A basic difference in these two reactions is the location of the double bond in the product. When an allylic sulfone reacts (eq 7), the double bond shifts to a new position, but reaction of a vinylic sulfone returns the double bond to its original place (eq 8).
B. Electron-Transfer Reactions

1. Samarium(II) Iodide

Electron transfer from SmI₂ to a glycosyl aryl sulfone generates a pyranos-1-yl radical. The options for reactions of this radical are limited either to combination with a second molecule of SmI₂ or to radical reaction that is fast enough to occur before combination can take place. Combination of pyranos-1-yl radicals with SmI₂ produces organosamarium intermediates that undergo typical reactions of organometallic compounds. These reactions include addition to aldehydes and ketones, proton abstraction, and β-elimination.

a. Reactions of Organosamarium Compounds

1. Addition to Carbonyl Compounds

Addition to an aldehyde or ketone is a common reaction for an organosamarium compound generated from a pyranos-1-yl radical. Formation of the organometallic intermediate takes place during the radical phase of such a reaction while addition of this organosamarium compound to an
aldehyde or ketone occurs during the nonradical portion of the process (Scheme 14). In most such reactions the addition is to a simple carbonyl compound such as cyclohexanone, but sometimes it is to an aldehydo group in a carbohydrate. Addition reactions of the type shown in Scheme 14 are usually accompanied by β elimination to form glycals. At least in some instances, addition of small amounts of nickel(II) iodide to a reaction mixture can decrease glycal formation in favor of an increase in the yield of addition products.

(2). β-Elimination and Proton-Transfer Reactions

Elimination to give a glycal occurs as a side reaction when a glycosyl phenyl sulfone reacts with SmI$_2$ in the presence of an aldehyde or ketone, but elimination can be the major reaction pathway, when carbonyl compounds are absent. The amount of glycal formed in a reaction depends upon how easily a C-2 substituent can depart as an anion. A carbohydrate with an O-acetyl
group at C-2 gives a far higher yield of glycal than does one with an O-benzyl group at this position (Scheme 15).\(^7,\text{49}\) A process competing with elimination is proton abstraction from a donor (presumably water) present in the reaction mixture. The O-acetyl group is so effective as a leaving group that proton transfer from H\(_2\)O to the organosamarium compound is inconsequential, but for the less effective O-benzyl leaving group proton transfer is significant. Proton transfer actually becomes the major reaction pathway when greater than a trace amount of water is present in the reaction mixture. The data given in Scheme 15 show how the balance between \(\beta\)-elimination and proton abstraction changes as reaction conditions and substrate structure change.\(^7,\text{49}\)

### Scheme 16

![Scheme 16 Diagram](image)

\(\text{HX} = \text{a proton donor} \quad \text{Ar} = \text{C}_6\text{H}_5\)

b. **Radical Cyclization**

Cyclization of some radicals is fast enough to prevent combination with SmI\(_2\) from occurring prior to ring formation.\(^59-\text{63}\) The unsaturated glycosyl phenyl sulfone 14, for example, forms a new ring even though combination of the intermediate radical 15 with SmI\(_2\) potentially could suppress this reaction (Scheme 16).\(^62\) HMPA is critical to the reaction shown in Scheme 16 because it promotes electron transfer by reducing the energy required for electron donation from the highest occupied molecular orbital (HOMO) of SmI\(_2\) to the lowest unoccupied molecular orbital (LUMO) of the sulfone (Figure 1).\(^60\) The effect of HMPA is so great that in its absence phenyl sulfones do not react with SmI\(_2\).\(^60\)

HMPA is not required for reaction of 2-pyridyl sulfones due to the effect of the 2-pyridyl group on sulfone MO energy levels. Because the LUMO energy of a 2-pyridyl sulfone is lower than that of a phenyl sulfone, transfer of an electron to the 2-pyridyl derivative occurs more easily than transfer to the corresponding phenyl sulfone (Figure 2); as a result, ring formation from a 2-pyridyl sulfone can take place without HMPA assisting electron transfer (Scheme 17).\(^60\)
Figure 1. Effect of HMPA on the HOMO energy of the SmI₂

Figure 2. Difference in LUMO ($\sigma^*$) energy levels between phenyl and 2-pyridyl sulfones

Scheme 17
c. Radical Dimerization

When the 2-pyridylsulfone 16 reacts with SmI$_2$ (no HMPA present), the glycal 18 forms in high yield (Scheme 18).$^{64}$ Adding HMPA slowly to the reaction mixture over a period of two hours has little effect on the glycal yield, but if the same amount of HMPA is present at the beginning of the reaction, glycal yield decreases and the three possible dimers formed from the pyranos-1-yl radical 17 become (in combination) the major product (Scheme 18). Formation of these dimers indicates that HMPA accelerates the production of 17 but not its reaction with SmI$_2$. When HMPA is present at the beginning of the reaction, the concentration of 17 quickly builds to the point that its dimerization takes place more rapidly than its reaction with SmI$_2$.$^{64}$ {Radical formation from glycosyl bromides [Chapter 2, Section II.G.1 (p 43)] and glycosyl phenyl selenides [Chapter 15, Section II.B.6 (p 95)] under the proper conditions gives dimers similar to those shown in Scheme 18.}

Photolysis of glycosyl phenyl sulfones is another way for producing pyranos-1-yl radicals that dimerize.$^{65}$ The product mixture from such a reaction is more complex and the dimer yield lower than that from the reaction with SmI$_2$ shown in Scheme 18 (HMPA present at the beginning of the reaction). The ratios of the three stereoisomeric dimers in photochemical and SmI$_2$ reactions are quite similar, a fact considered to be a “stereochemical signature” for pyranos-1-yl radical dimerization.$^{64}$
2. Chromium(II) Complexes

Chromium(II) complexes also can function as electron donors in reactions of carbohydrate sulfones, but such reactions are far less common than those in which SmI\(_2\) is the electron donor. The radical produced by electron transfer from [Cr(II)(EDTA)]\(^{2-}\) has the same types of options available as a radical generated by electron transfer from SmI\(_2\); that is, the radical either can combine with another chromium(II) complex or undergo a radical reaction that is fast enough to compete with the combination process (Scheme 19). One reaction that is sufficiently rapid is radical addition to a compound with an electron-deficient double bond (eq 9).
C. Sulfone Synthesis

$p$-Tolylsulfonyl radicals add reversibly to carbon–carbon multiple bonds. If the adduct radical is “captured” before addition is reversed, the resulting product is a sulfone. Radical cyclization, such as that shown in Scheme 20, is rapid enough to trap the intermediate radical 16. As long as the new ring remains intact, loss of the $p$-tolylsulfonyl group will not take place, insuring completion of sulfone formation.

Scheme 20

\[
\text{ArSO}_2\text{Br} \xrightarrow{\text{hv}} \text{ArSO}_2^- + \text{Br}^-
\]

\[
\begin{array}{c}
\text{CH}_2\text{OAc} \\
\text{Ar} = \text{C}_6\text{H}_4\text{CH}_3 (p) \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_2\text{OAc} \\
\text{ArSO}_2\text{CH}_2 \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_2\text{OAc} \\
\text{ArSO}_2\text{Br} \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_2\text{OAc} \\
\text{ArSO}_2\text{CH}_2 \\
\end{array}
\]

VIII. Thiols and Thiyl Radicals

In compounds with an H–S bond, hydrogen-atom abstraction to produce a sulfur-centered radical (eq 10) is a significant (sometimes the exclusive) reaction pathway. Such reactivity exists because thiols are among the most effective hydrogen-atom donors in organic chemistry. Rate
constants for hydrogen-atom abstraction by primary, secondary, and tertiary, carbon-centered radicals from thiophenol range from 0.8 x 10^8 to 1.5 x 10^8 M^{-1}s^{-1} at 25°C.\textsuperscript{70}

A characteristic reaction of a thiyl radical is addition to a carbon–carbon multiple bond.\textsuperscript{71–85} In the reaction shown in Scheme 21, for example, addition of the thiyl radical 23 to the unsaturated carbohydrate 21 leads to formation of the S-disaccharide 22.\textsuperscript{77} This reaction is not only regio-specific but hydrogen-atom abstraction from 20 is so much faster than reaction with the molecular oxygen dissolved in the reaction mixture that an inert atmosphere is not required for successful S-disaccharide formation. Similar radical addition takes place between the thiol 20 and various D-glycals, including the D-glucal 24 (eq 11).\textsuperscript{78}
Even though the most common radical reaction of a compound with an H–S bond is hydrogen-atom abstraction, under some conditions the HS group is replaced by a hydrogen atom (eq 12). Although a carbohydrate containing a sulfur-centered radical typically is generated by hydrogen-atom abstraction from a thiol, the reaction shown in eq 13 forms a thiyl radical by the addition-elimination sequence pictured in Scheme 22. Critical to chain propagation in this reaction is the removal of the sulfur atom from 25 by reaction with triphenylphosphine.

IX. Summary

Tin-centered radicals react with carbohydrates that contain methylthio, ethylthio, or phenylthio groups to produce carbon-centered radicals. Two mechanisms have been proposed for such a reaction. The first is a concerted $S_{1,2}$ process, and the second is a stepwise reaction that forms an
Compounds with carbon–sulfur single bonds have an intermediate with a hypervalent sulfur atom. Molecular orbital calculations favor the concerted process.

Compounds with alkylthio or arylthio groups break the C–S bond that produces the more stable, carbon-centered radical. This means that when fragmentation takes place in a carbohydrate containing a methylthio, ethylthio, or phenylthio substituent, a carbohydrate radical forms rather than an alkyl or aryl radical. Reactions that begin with carbon–sulfur bond cleavage often lead to either simple reduction or radical cyclization. Similar reactions occur when the sulfur atom is part of a dithioacetal, thiocarbonate, or dithiocarbonate.

When the carbon–sulfur bonds in a carbohydrate are part of a sulfone and when an electron-donor (usually SmI₂) is present, bond cleavage occurs via an electron-transfer reaction. The resulting radical combines rapidly with a second molecule of SmI₂ to produce an organosamarium intermediate that undergoes reactions typical of an organometallic compound (e.g., proton abstraction, β elimination, or addition to an aldehyde or ketone). Radical cyclization is one of the few reactions fast enough to occur before this combination takes place.

If a compound has a hydrogen–sulfur bond, the major reaction pathway usually is hydrogen-atom abstraction to form a sulfur-centered radical. This radical adds readily to a carbon–carbon double bond.

X. References

![Scheme 22](attachment:image.png)
Compounds With Carbon–Sulfur Single Bonds