Chapter 7
Unprotected Carbohydrates

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I. Introduction

Radical reactions of unprotected carbohydrates begin with hydrogen-atom abstraction from a carbon–hydrogen bond in the carbohydrate structure. Such reaction requires a radical more reactive than the tin- or silicon-centered ones that are common in reactions of carbohydrate derivatives. A hydrogen atom usually is abstracted from an unprotected carbohydrate by a hydroxyl radical (HO·), but sometimes the sulfate radical anion (SO_4^{2-}) is the abstracting agent. A beginning point for discussing radical reactions of unprotected carbohydrates is to examine how the abstracting radicals HO· and SO_4^{2-} are formed.
II. Radicals That Abstract Hydrogen Atoms from Unprotected Carbohydrates

A. Hydroxyl Radicals

1. Ionizing Radiation and Ultraviolet Light

γ-Radiolysis of water produces hydroxyl radicals along with the compounds, ions, and other radicals shown in eq 1. The yield of hydroxyl radicals in this reaction can be increased by adding N₂O to the reaction mixture because hydrated electrons react with N₂O to form hydroxyl radicals (eq 2). In N₂O-containing solutions 85% of the radicals are HO· and 15% are H·. Both HO· and H· abstract hydrogen atoms from carbon–hydrogen bonds. Hydroxyl radicals (and hydrogen atoms) also can be produced by photolysis of water with ultraviolet light of wavelength less than 185 nm (eq 3).

\[ \text{H}_2\text{O} \xrightarrow{\text{ionizing radiation}} \text{e}_{\text{aq}}^0 + \text{HO}^\cdot + \text{H}^\cdot + \text{H}_2\text{O}_2 + \text{H}_2 + \text{H}^0 + \text{HO}^0 \quad (1) \]

\[ \text{e}_{\text{aq}}^0 + \text{N}_2\text{O} + \text{H}_2\text{O} \rightarrow \text{N}_2 + \text{HO}^\cdot + \text{HO}^0 \quad (2) \]

\[ \text{H}_2\text{O} \xrightarrow{\text{hv}} \text{H}^\cdot + \text{HO}^\cdot \quad (3) \]

2. Reaction of H₂O₂ with Fe²⁺ and Ti³⁺

Reaction of H₂O₂ with Fe²⁺ (eq 4) or Ti³⁺ (eq 5) produces hydroxyl radicals. (These reagent combinations are sometimes described as radiomimetic, that is, imitating radiation.) Each hydroxyl radical produced is capable of abstracting a hydrogen atom from a carbon–hydrogen bond present in a molecule of substrate (eq 6). The Ti⁴⁺ generated by the reaction shown in eq 5 does not react further with the carbon-centered radical produced, but the Fe³⁺ formed in the reaction shown in eq 4 does; Fe³⁺ oxidizes an α-hydroxy radical to a carbonyl group while itself being reduced to Fe²⁺. Regeneration of Fe²⁺ from Fe³⁺ by the reaction shown in eq 7 means that when this reaction occurs, only a catalytic amount of Fe²⁺ may be necessary for complete decomposition of H₂O₂ (eq 4). (The combination of H₂O₂ and Fe²⁺ is known as Fenton’s reagent, and that of H₂O₂ and Te³⁺ as a Fenton-type reagent.)

\[ \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{HO}^\cdot + \text{HO}^0 \quad (4) \]

\[ \text{Ti}^{3+} + \text{H}_2\text{O}_2 \rightarrow \text{Ti}^{4+} + \text{HO}^\cdot + \text{HO}^0 \quad (5) \]

\[ \text{HO}^\cdot + \text{H} \rightarrow \text{H}_2\text{O} + \text{HO}^\cdot \quad (6) \]
B. Sulfate Radical Anions

The sulfate radical anion (SO$_4$·$^-$) forms when the peroxydisulfate dianion (S$_2$O$_8^{2-}$) reacts with Ti$^{3+}$ (eq 8).$^{10}$ A low concentration of Cu$^{2+}$ present in the reaction mixture enhances the rate of generation of SO$_4$·$^-$ via the reactions shown in equations 9 and 10. The sulfate radical anion also forms from direct photolysis of S$_2$O$_8^{2-}$ (eq 11).$^{10}$

\[
\text{Ti}^{3+} + \text{S}_2\text{O}_8^{2-} \rightarrow \text{Ti}^{4+} + \text{SO}_4^{2-} + \text{SO}_4^{2-} \quad (8)
\]

\[
\text{Ti}^{3+} + \text{Cu}^{2+} \rightarrow \text{Ti}^{4+} + \text{Cu}^{+} \quad (9)
\]

\[
\text{Cu}^{+} + \text{S}_2\text{O}_8^{2-} \rightarrow \text{Cu}^{2+} + \text{SO}_4^{2-} + \text{SO}_4^{2-} \quad (10)
\]

\[
\text{S}_2\text{O}_8^{2-} \xrightarrow{\text{hv}} 2 \text{SO}_4^{2-} \quad (11)
\]

III. First Formed Radicals: Radicals Produced by Hydrogen-Atom Abstraction from Unprotected Carbohydrates

A hydroxyl radical is sufficiently reactive to abstract a hydrogen atom from any of the carbon atoms in an unprotected carbohydrate.$^3$ The radicals produced by such a reaction often are referred to as “first-formed” radicals, a terminology that correctly implies further transformation is likely. The ESR spectrum produced by the mixture of radicals generated from reaction of even a simple sugar with hydroxyl radicals is understandably complex; nevertheless, in the reaction of D-glucose (the most heavily studied of the simple sugars) signals for all six of the first-formed radicals can be detected.

A. Conditions for Generating First-Formed Radicals

When first-formed radicals arise from hydrogen-atom abstraction by the hydroxyl radicals generated from γ-radiolysis of water (eq 1) [or by its photolysis (eq 3)], sugar molecules and water are the only materials present at the beginning of the reaction. When hydroxyl radicals are formed from reaction of H$_2$O$_2$ with Fe$^{2+}$ or Ti$^{3+}$, not only are these materials present when the reaction begins but the solutions typically are rendered acidic prior to reaction because first-formed radicals produced under acidic conditions are more stable and, consequently, more easily observed.$^6$ Usually the pH is adjusted to 4 because the ESR signals for all first-formed radicals decrease in
intensity with rising pH until the value of 7 is reached, where they effectively disappear.\textsuperscript{7,8,11} First-formed radicals do undergo acid-catalyzed rearrangement (discussed in Section IV.B, p 150), but such reaction only becomes significant at pH values much lower than 4.

**B. Regioselectively Producing First-Formed Radicals from Unprotected Carbohydrates**

1. **Sucrose**

Although hydroxyl radicals exhibit little, if any, regioselectivity in hydrogen-atom abstraction from the carbon atoms in carbohydrates that contain only pyranoid rings, there is selectivity in reaction of compounds containing furanoid rings. Hydrogen-atom abstraction from sucrose (1, Figure 1), for example, occurs primarily from C-5';\textsuperscript{12} thus, not only does abstraction take place regioselectively in the furanoid ring of 1, but within this portion of the molecule reaction is favored at C-5'. Preferential abstraction from C-5' can be attributed to stabilization from interaction of elec-
trons in the \( p \)-type orbital on the oxygen atom in the furanoid ring with the electron in the developing, partially occupied, \( p \)-type orbital on the neighboring carbon atom (Figure 1).\(^{13,14}\) (The two lone pairs of electrons on the ring oxygen atom are not equivalent. One pair is in a high energy, \( p \)-type orbital and the other is in a lower energy, \( s \)-type orbital.\(^{15}\) The \( p \)-type orbital on the furanoid-ring oxygen atom is in a position to overlap immediately and effectively with the developing \( p \)-type orbital on C-5'. This transition-state-stabilizing interaction favors abstraction of H-5' and accounts for its regioselective reaction.

![Figure 3. Possible transition-state structures for hydrogen abstraction from C-1](image)

2. \( \alpha \)- and \( \beta \)-D-Glucopyranose

Even though hydrogen-atom abstraction by hydroxyl radicals from the carbon atoms in a pyranoid ring is not regioselective, selective reaction does take place with a less reactive abstracting agent; thus, the sulfate radical anion preferentially reacts with hydrogen atoms at C-2, C-5, and C-6 in \( \alpha \)-D-glucopyranose (2) and C-1, C-5, and C-6 in \( \beta \)-D-glucopyranose (3) (Figure 2).\(^ {10,16}\) In reactions of the sulfate radical anion the transition state for hydrogen-atom abstraction is late enough that differences in stabilizing effects are able to create significant differences in transition-state stability; for example, abstraction of H-1 occurs more rapidly from \( \beta \)-D-glucopyranose (3) than from its \( \alpha \)-anomer (2) because orbital alignment in the developing radical from reaction of the \( \beta \)-anomer stabilizes the transition state more effectively than does orbital alignment from reaction of the \( \alpha \)-anomer (Figure 3).\(^ {10}\) (Stabilization arising from parallel orbital alignment first was recognized in the study of model compounds.\(^ {17-19}\) ) Abstraction of H-5 from \( \delta \)-glucopyranose anomers 2 and 3 (Figure 4) is stabilized in much the same way as abstraction of H-1 from the \( \beta \)-anomer 3 (Figure 3).

To understand regioselective abstraction of H-6 and H-2 from \( \alpha \)-D-glucopyranose (2) and abstraction of H-6 from \( \beta \)-D-glucopyranose (3), it is useful to recall from Chapter 6 (Section IV.A.2, p 109) that the conformation of a pyranos-1-yl radical depends not just on interaction between \( p_o \) and \( p_c \) orbitals but also on the interaction of these two with the \( \sigma^* \) orbital of a properly oriented C–O bond. Evidence of the importance for this type of interaction is that the D-gluco-
pyranos-1-y1 radical adopts what otherwise would be a high-energy, B2,5-boat conformation in order to benefit from po, pc, σ* orbital stabilization (Figure 5). The parallel orbital alignment responsible for this stabilization can develop during hydrogen-atom abstraction from C-6 in the anomers 2 and 3. Rotation about the C5-C6 bond is all that is needed for interacting po and pc orbitals to become parallel to the σ* orbital of the C5-O ring bond (Figure 6). Further, the axial orientation of the anomeric hydroxyl group in 2 places the σ* orbital of the bond between C-1 and O-1 in the proper orientation to assist abstraction at C-2 (Figure 6). Preferential abstraction of H-6 from 3 and H-2 and H-6 from 2 thus can be explained in terms of po, pc, σ* orbital interaction that causes transition-state stabilization during hydrogen-atom abstraction.

Figure 4. Possible transition-state structure for H-5 abstraction in the anomers 2 and 3

Figure 5. Stabilizing effect of po, pc, σ* orbital interaction.

3. myo-Inositol

Reaction of myo-inositol (4) involves hydrogen-atom abstraction from a six-membered-ring carbohydrate that does not contain an oxygen atom in the ring. The enantiomeric radicals 5 and 6, formed when the sulfate radical anion abstracts a hydrogen atom from myo-inositol, are the ones
expected when \( p_o, p_c, \sigma^* \) orbital stabilization is taken into account (Scheme 1). A third radical (7) produced from reaction of 4 arises from abstraction of the only equatorial hydrogen atom in the molecule. The driving force behind this abstraction is believed to be a combination of the ease of approach of \( \text{SO}_4\cdot^- \) to the equatorial hydrogen atom and the relief of steric strain caused by interaction between the axial hydroxyl group and the 1,3-related, axial hydrogen atoms.\(^{10}\)

Figure 6. \( p_o, p_c, \sigma^* \) orbital interaction.

Scheme 1

4. Sugar Phosphates

Hydrogen-atom abstraction by the hydroxyl radical from a sugar phosphate is similar to abstraction by this radical from simple sugars; thus, the essentially indiscriminate abstraction from the C–H bonds in \( \alpha\)-d-glucose-1-phosphate (8) is reminiscent of the similar lack of selectivity in
hydrogen-atom abstraction from α-d-glucopyranose (2). Fructose-1,6-diphosphate (9) is similar to sucrose (1) in that H-5 abstraction occurs regioselectively in the furanoid ring.

IV. Reactions of First-Formed Radicals

A. Reactions in Neutral Solution

In discussing the various products arising from reaction in neutral solution of first-formed radicals (typically reactions in which the hydroxyl radical is generated by γ-radiolysis), it is convenient to distinguish between products with a molecular weight less than or equal to that of the
substrate and those with a higher molecular weight. Because first-formed radicals can undergo dimerization, disproportionation, elimination, and rearrangement, the number of possible reaction products is staggering; nevertheless, many of them have been identified. Product yields for reactions begun by $\gamma$-radiolysis of water can be expressed in terms of $G$-values; that is, the molecules or radicals formed per 100 eV of energy absorbed. A $G$-value also can be used as a measure of substrate reacted. In the reaction of $D$-glucose shown in Scheme 2 the $G$-value for consumption of starting material is 5.6.$^2$ The values for formation of products 11-13 are 0.95, 0.15, and $<0.08$, respectively. The $G$-values cited for $D$-glucose and compounds 11-13 were determined in the presence of $N_2O$ to maximize the formation of the hydroxyl radical.

1. Low-Molecular-Weight Products

Although many low-molecular-weight products are formed in detectable amounts from reactions of simple sugars, the yields of most are quite low. Many of these compounds are produced by reactions of the first-formed radicals; for example, the major, low-molecular-weight product (11) from reaction of $D$-glucose is believed to arise by loss of the elements of water from the first-formed radical 10 (Scheme 2, path a).$^2$ Another reaction of 10 that forms a low-molecular-weight product is loss of a hydrogen atom to give $D$-glucono-1,5-lactone (12) (Scheme 2, path b), and a third reaction is opening of the pyranoid ring in 10 by fragmentation of the bond between C-5 and the ring oxygen atom to give, after hydrogen-atom abstraction, a carboxylic acid (13) (Scheme 2, path c).$^2$ All of the reactions of the radical 10 shown in Scheme 2 are driven, at least in part, by the stability gained from forming a C–O double bond.

$$
2 \, \overset{\cdot}{\text{O}} \, -\overset{\cdot}{\text{C}} \, -\overset{\cdot}{\text{C}} \, - \rightarrow \, \overset{\cdot}{\text{O}} \, -\overset{\cdot}{\text{C}} \, -\overset{\cdot}{\text{C}} \, -\overset{\cdot}{\text{C}} \, -\overset{\cdot}{\text{C}} \, - \quad (12)
$$

2. High-Molecular-Weight Products

The products 11-13 (Scheme 2) and the other low molecular-weight products (more than twenty identified) account for less than half of the $D$-glucose consumed during $\gamma$-radiolysis because most products formed have high molecular weights. Little is known about either the structure of the high-molecular-weight materials or the mechanism of their formation. One proposal is that dimerization of radicals that have lost the elements of water may be the first step in formation of some high-molecular-weight products (eq 12).$^2$

B. Acid-Catalyzed Reactions

Under strongly acidic conditions (pH = 1) four of the first-formed radicals generated from $D$-glucose eliminate the elements of water to give in each case a carbonyl-conjugated radical.$^6,26$ A proposed mechanism for this reaction, shown in Scheme 3, involves protonation of the hydroxyl
group adjacent to a radical center in the first-formed radical 1 to produce an intermediate (14) with an excellent leaving group that departs to form a radical cation (15). This radical cation then deprotonates to give the carbonyl-conjugated radical 16. Another mechanistic possibility for forming 16 is a concerted reaction beginning with the protonated radical 14 (Scheme 3). Forming carbonyl-conjugated radicals by acid-catalyzed reaction also has been studied in noncarbohydrate systems.6,27,28

The acid-catalyzed reactions of three first-formed radicals produced from D-glucose deserve further comment. Two of these radicals, 17 (Scheme 4) and 20 (Scheme 5), do not undergo the carbonyl-group-forming reaction characteristic of the other first-formed radicals (Scheme 3).6 Although 17 could start along this pathway by producing the radical cation 18, deprotonation of 18
to give a carbon-centered radical with an adjacent carbonyl group cannot take place. Formation of a carbonyl-conjugated radical from 18 would require opening of the pyranoid ring (Scheme 4). Evidence against such reaction is that 17 is less reactive than other first-formed radicals, and when it does react, no carbonyl-conjugated radical can be detected. The first-formed radical 20 also must undergo ring opening if a carbonyl-conjugated radical is to be produced; in fact, ring opening in this case is necessary to form the radical-cation 21 (Scheme 5). The radical 20, which is the least reactive of the first-formed radicals derived from d-glucose, also gives no indication of forming a carbonyl-conjugated radical.  

Scheme 5

The radical 22 is the third, first-formed radical produced from d-glucose that deserves further comment. This radical is noteworthy because it is the most reactive of the first-formed radicals.
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Protonation of 22 gives the intermediate 23 in which the leaving group has an axial orientation and, therefore, the $p$-type orbitals on C-2 and the ring oxygen atom in 23 begin stabilizing the radical cation 24 as it starts to develop (Scheme 6).

Scheme 7

Scheme 8

30
C. Base-Catalyzed Reaction

Proton abstraction from O-2 in the first-formed radical 25 begins a process that generates the ring-open radical anion 26 (Scheme 7). (Since an α-hydroxy radical is far more acidic than its parent alcohol, the proton attached to O-2 should be removed much more readily than any other proton in 25.) The radical anion 26 rapidly undergoes a proton transfer to produce the semidione 27, one of two semidiones formed from base-catalyzed reaction of a first-formed, D-glucopyranosyl radical. The second of these two (30) is proposed to arise from the radical 28 according to the mechanism outlined in Scheme 8. (Semidiones 27 and 30 are readily detected because for each of them the negative charge slows the rates of dimerization and reduction and thus leads to more prominent ESR spectra.)

V. Reactions of Carbonyl-Conjugated Radicals

In addition to dimerization (eq 12) carbonyl-conjugated radicals also can be reduced to anions in a pH-dependent reduction by Ti$^{3+}$ (eq 13). At pH 1 the reaction shown in eq 13 is negligible, but at pH 7 this reaction becomes an important pathway for removing carbonyl-conjugated radicals from a reaction mixture.

\[
\begin{align*}
2 \text{RCCH}_2\text{O} &\text{C=O} \rightarrow \text{RCCH}_2\text{O} \text{C=C} \\
\text{Ti}^{3+} + \text{RCCH}_2\text{O} &\text{C=O} \rightarrow \text{RCCH}_2\text{O} \text{C=C} \\
\text{Ti}^{3+} &\rightarrow \text{Ti}^{4+} \\
\text{RCCH}_2\text{O} \text{C=O} &\rightarrow \text{RCCH}_2\text{O} \text{C=C} \\
\end{align*}
\]

VI. Oxidative Degradation of Carbohydrates

The oxidative degradation of carbohydrates in the presence of base is another reaction that involves radical intermediates. Such reaction of D-glucose begins with ring opening and deprotonation to give the enediolate anion 31 (Scheme 9). Oxidation of this anion with O$_2$ produces the resonance stabilized radical 32, which then is converted to the peroxy radical 33 by addition of O$_2$. Subsequent reduction of 33 gives an anion that ultimately fragments the C$_1$–C$_2$ bond to give a five-carbon-atom aldonic acid (Scheme 9). Fragmentation of other carbon–carbon bonds also takes place because base-catalyzed isomerization of the 1,2-enediolate anion 31 produces the 2,3-enediolate anion 34 (Scheme 10). Reaction of 34 with O$_2$ and fragmentation analogous to that shown in Scheme 9 cleaves the D-glucose structure into two-carbon-atom and four-carbon-atom carboxylic acids. Continued isomerization of this type (31 to 34) produces other enediolates that undergo similar fragmentation reactions.
VII. Reactions of Polysaccharides

Study of radical reactions of polymeric carbohydrates is a challenging undertaking. The reactions that occur are documented by changes in physical properties that come from polymer degradation (e.g., reduced solution viscosity, differences in solubility, and gel formation). Changes in physical properties have been recorded in the reactions of the hydroxyl radical with cellulose,\(^8,32\) hemicellulose,\(^32\) starch,\(^16\) and various dextrans.\(^{33}\)

Studies of dextrans [polymers of 1→6 linked α-\(\text{d}-\)glucose with α-(1→3) linked side chains], for example, show essentially indiscriminate attack by hydroxyl radicals produced from reaction of Ti\(^{3+}\) with H\(_2\)O\(_2\).\(^{33}\) (The polymers studied had molecular weights ranging from 10,000 to 500,000 Da) These reactions cause depolymerizations (as evidenced by reduced solution viscosity) and an increase in the number of carbonyl and carboxyl groups in the polymer fragments. Upon lowering or raising the solution pH, the first-formed radicals appear to rearrange in a manner similar to the rearrangement of first-formed radicals derived from \(\text{d}-\)glucose.
VIII. Summary

The hydroxyl radical and the sulfate radical anion both abstract hydrogen atoms from unprotected carbohydrates. In each case first-formed, carbon-centered radicals are produced. The hydroxyl radical is so reactive that it shows little regioselectivity when reacting with d-glucose; that is, spectroscopic evidence indicates that hydrogen-atom abstraction occurs from each of the six carbon atoms in this molecule. The hydroxyl radical remains unselective in reaction with other simple sugars that contain only pyranoid rings, but it does regioselectively abstract H\textsubscript{5}' from the furanoid ring in sucrose. The sulfate radical anion is a more selective abstracting agent. Hydrogen-atom abstraction occurs primarily from C-2, C-5, and C-6 in α-D-glucopyranose and at C-1, C-5, and C-6 in β-D-glucopyranose.

First-formed radicals derived from d-glucose undergo acid-catalyzed rearrangement under strongly acidic conditions to produce carbonyl-conjugated radicals. Under basic conditions first-formed radicals produce radical anions that form semidiones. When molecular oxygen is present in the reaction mixture, first-formed radicals react to give peroxy radicals.
IX. References