Regioselectively replacing a particular hydrogen atom in a carbohydrate with a halogen atom depends upon a radical abstracting one hydrogen atom from among the many present in a typical molecule. When this type of selectivity occurs, it sometimes is linked to radical philicity; that is, a hydrogen atom that is more electron rich than others in a molecule can be abstracted preferentially by a highly electrophilic radical. This regioselectivity caused by radical philicity only occurs when the transition state is early in a reaction. When the transition state is late, selective reaction also can take place, but in this case selectivity exists because abstraction of a particular hydrogen atom produces a carbon-centered radical that is much more stable than radicals formed by abstraction of other hydrogen atoms. Since there are relatively few carbohydrates where highly selective hydrogen-atom abstraction occurs and since hydrogen-atom abstraction typically is the first step in halogenation, regioselective, free-radical halogenation reactions are limited in number.

A. Benzylidene Acetals

Radical reaction of a benzylidene acetal with bromine (the Hanessian-Hullar reaction\(^{178-180}\)) produces a bromodeoxy benzoate (Scheme 25).\(^{180}\) This reaction begins with regioselective hydrogen-atom abstraction by a bromine atom to give a resonance-stabilized radical (15) that then reacts with molecular bromine (generated from N-bromosuccinimide) to produce an easily ionized bromide (16). Hydrogen-atom abstraction from the phenyl substituted carbon atom in a benzylidene acetal is heavily favored over other possible abstraction reactions; consequently, there is little or no competing hydrogen-atom abstraction from other protecting groups or from carbon atoms in the carbohydrate framework.\(^{2,178–180}\) The stability of the radical 15, therefore, is the primary factor in determining which hydrogen atom will be abstracted and, consequently, where bromine will be introduced. Later in the reaction sequence, stability again is the driving force in the formation of the resonance-stabilized cation 17, an intermediate that undergoes regioselective reaction with bromide ion at the less hindered 6-position to give the bromodeoxy benzoate 18.
As long as ring opening involves a choice between bromide ion bonding with a primary (C-6), as opposed to a secondary (C-4), carbon atom, reaction usually will occur at the less-hindered primary center (Scheme 25). This means that 4,6-O-benzylidene acetals, common intermediates in carbohydrate synthesis, can be expected to undergo highly regioselective reaction with bromine. If, however, the choice is between reaction at two secondary carbon atoms, a mixture of products involving substantial amounts of two structural isomers is a distinct possibility (eq 36). 179

Several variations on the Hanessian-Hullar reaction are known. In one of these bromotrichloromethane replaces N-bromosuccinimide as the bromine source. 181–185 Reaction of the benzylidene acetal 19 under these modified conditions (X = CCl₃) is more regioselective than reaction under typical Hanessian-Hullar reaction conditions (eq 37, X = Br). 181 An explanation for this difference in regioselectivity is that although the primary product (20) in both of these reactions (eq 37) is the same, under normal Hanessian-Hullar conditions this product is converted into the rearranged bromide 21.
through the series of steps outlined in Scheme 26.\textsuperscript{179} When reaction is conducted without deliberate heating and with BrCCl\textsubscript{3} as the bromine source, the isomerization pictured in Scheme 26 is too slow to be observed.

B. Benzylidene Acetals in the Presence of Water

The Hanessian-Hullar reaction can be diverted from its normal course if a nucleophile other than bromide ion is present in the reaction mixture. When reaction is conducted in the presence of water, as is the case in the reaction shown in Scheme 27,\textsuperscript{186} the intermediate carbocation captures a molecule of H\textsubscript{2}O leading to formation of a hydroxybenzoate.\textsuperscript{186–189}
C. Benzyl Ethers

Bromination of a benzyl ether has much in common with bromination of a benzylidene acetal. Although the compounds resulting from benzyl ether bromination are stable enough that they can be detected in some reaction mixtures,\textsuperscript{190} they react so rapidly with water that any moisture present causes bromide displacement leading to debenzylation (Scheme 28).\textsuperscript{191} Removing O-benzyl groups in this way is more synthetically useful if a carbonate is added to the reaction mixture to consume the HBr as it is produced (eq 38).\textsuperscript{192–195} Structurally related sugars that are not benzyl ethers but form comparably stable radicals exhibit similar reactivity.\textsuperscript{196}

\begin{center}
\textbf{Scheme 28}
\end{center}

\begin{center}
\begin{align*}
\text{ROCH}_2\text{Ar} + \text{Br}_2 &\xrightarrow{\text{hv}} \text{ROCH}_2\text{Br} + \text{HBr} \\
\text{ROCH}_2\text{Ar} + \text{H}_2\text{O} &\rightarrow \text{ROCH}_2\text{OH} + \text{HBr}
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\text{Ar} = \text{C}_6\text{H}_5
\end{align*}
\end{center}

D. Acylated Sugars

In the absence of an O-benzylidene or O-benzyl group, bromination can occur at a carbon atom that is part of the carbohydrate framework.\textsuperscript{197} Reaction is usually regioselective because the most reactive hydrogen atoms are those that produce an intermediate radical stabilized by a ring oxygen atom. Further affecting this regioselectivity are any substituents that stabilize the developing radical; for example, hydrogen replacement in compound 22 occurs exclusively at the carbon atom that is adjacent to the ring oxygen atom and bears the cyano group (eq 39).\textsuperscript{198} Similar selectivity occurs in other compounds that form radicals stabilized by a ring oxygen atom and by a cyano\textsuperscript{198–201} or carbonyl\textsuperscript{202,203} group. For compounds with less effective radical stabilization at C-1 (e.g., 23), site selectivity can change and a bromine atom will replace H-5 in a pyranoid ring (eq 40)\textsuperscript{204–210} or H-4 in a furanoid ring (eq 41).\textsuperscript{211}

\begin{center}
\begin{align*}
\text{CH}_2\text{OAc} &\xrightarrow{\text{hv}} \text{AcOCH}_2\text{Br} \\
\text{AcO} &\xrightarrow{\text{hv}} \text{AcOCH}_2\text{Br}
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\text{NBS} &\xrightarrow{\text{hv}} \text{AcOCH}_2\text{Br}
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\text{Ar} = \text{C}_6\text{H}_5
\end{align*}
\end{center}
E. Anhydro Sugars

As described in the previous paragraph, halogenation of a carbon atom flanked by a ring oxygen atom normally is more rapid than reaction at other carbon atoms in a ring. For 1,6-anhydro sugars C-6 is one of the activated carbon atoms (Scheme 29). The reason for reaction taking place regioselectively at C-6 is that the rigidity of the molecular framework allows only poor overlap between orbitals on the ring oxygen atoms and the sp\(^3\) hybrid orbital on C-1 that would form by abstraction of H-1 (24) or the sp\(^3\) hybrid orbital on C-5 by abstraction of H-5; in contrast, effective overlap between carbon and oxygen p-type orbitals exists for the radical centered on C-6 (25). The bicyclic nature of the intermediate radical, for which 25 represents the basic structure, affects reaction stereoselectivity by directing the approach of bromine to the convex face of the bicyclic system. This face also is preferred because it is not blocked by the O-benzoyl group at C-3 (Scheme 29). Similar, preferential bromination occurs during reaction of other bicyclic and related sugars.

![Scheme 29](image)
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