Chapter 14
Nitro Compounds

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I. Introduction

Carbohydrates contain two types of nitro groups. The first type has the nitrogen atom in this group attached to a carbon atom in the carbohydrate framework (making a deoxynitro or C-nitro carbohydrate) and the second has the nitrogen atom bonded to an oxygen atom in the carbohydrate structure (making an O-nitro carbohydrate or a carbohydrate nitrate). Radical reactions of nitro compounds are highly dependent upon the atom to which the nitro group is bonded.

II. Reaction Mechanisms

A. Addition-Elimination Reaction

The first step in the reaction of the tri-n-butyltin radical with a nitro compound is the addition of the radical to one of the oxygen atoms in the nitro group. The reaction that takes place after this initial addition depends upon whether the reactant is an O-nitro or a C-nitro compound. O-Nitro carbohydrates fragment to give alkoxy radicals (Scheme 1). C-Nitro carbohydrates have more varied possibilities. The adduct radical either breaks the C–N bond to give a carbon-centered
radical, cleaves an O–N bond to form a nitroso compound, or abstracts a hydrogen atom from an available donor, usually Bu₃SnH (Scheme 2).

![Scheme 1](image)

![Scheme 2](image)

![Scheme 3](image)

R• = a carbon-centered, carbohydrate radical

**B. Electron Transfer**

Early investigations raised the possibility that reaction of a C-nitro compound with the tri-\(n\)-butyltin radical could involve electron transfer (Scheme 3).¹⁻³ Later investigation, however, did not support this possibility because the electron transfer between Bu₃Sn· and (CH₃)₂CHNO₂
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(Scheme 3) was found to be endothermic by at least 12 kcal mol\(^{-1}\). This endothermic electron transfer was inconsistent with the large rate constant (\(k = 9.5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}\)) observed for reaction between this pair [Bu\(_3\)Sn· and (CH\(_3\))\(_2\)CHNO\(_2\)]\(^4\). The conclusion from this latter study was that the addition-elimination mechanism (Scheme 2)\(^5\)\(^–\)^\(^8\) provided a better explanation for the reaction between Bu\(_3\)Sn· and a C-nitro compound. The possibility that electron transfer could be involved in reaction of O-nitro compounds (Scheme 4) has not been addressed and, thus, remains open.

\[
\text{Scheme 4}
\]

\[
\begin{align*}
\text{RONO}_2 + & \text{Bu}_3\text{Sn} \rightarrow \text{RO} - \text{N}^\prime \big\lbrack \begin{array}{c} \text{Bu}_3\text{Sn} \end{array} \big\rbrack \rightarrow \text{RO} \cdot + \text{NO}_2^\circ \rightarrow \text{Bu}_3\text{SnH} - \text{Bu}_3\text{Sn} \rightarrow \text{ROH}
\end{align*}
\]

\(\text{RO} \cdot = \text{an oxygen-centered, carbohydrate radical}\)

C. Photochemical Reaction

Photolysis of an O-nitrocarbohydrate fragments the N–O bond in the nitro group to produce nitrogen dioxide and the corresponding alkoxy radical (Scheme 1).

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}_2\text{OMMTr} + \text{Bu}_3\text{SnH} & \xrightarrow{\text{AIBN}, 110^\circ \text{C}} \text{C}_6\text{H}_5\text{R}_1\text{R}_2\text{O} \quad \text{yield not determined}
\end{align*}
\]

\(\text{MMTr} = \text{C}(\text{C}_6\text{H}_3\text{O})_2(\text{C}_6\text{H}_4\text{OMe}(p))\)

III. C-Nitro Carbohydrates

A. Group Replacement

Since in the reaction of a C-nitro compound the stability of the developing radical (R·) affects the ease of cleavage of the carbon–nitrogen bond (Scheme 2), group replacement occurs more easily for tertiary nitro compounds\(^9\)\(^–\)^\(^{14}\) than for secondary\(^15\)\(^–\)^\(^{18}\) and, especially, primary ones.\(^20\)\(^–\)^\(^{22}\) Reaction of Bu\(_3\)SnH with a compound containing a tertiary nitro group is given in eq 1.\(^9\) If the nitro group in the substrate is secondary, reaction usually follows the same pathway and replaces this group with a hydrogen atom,\(^15\)\(^–\)^\(^{18}\) but sometimes breaking a C–O bond leading to a nitroso compound (which isomerizes to an oxime) offers significant competition (Schemes 2 and 5).\(^19\) When a nitro group is primary, the elimination phase of the reaction is more likely to produce
only the nitroso compound (eq 2),\textsuperscript{20,21} even though replacement of a primary nitro group with a hydrogen atom has been observed (eq 3).\textsuperscript{22}

\begin{center}

\textbf{Scheme 5}

\end{center}

B. Addition Reactions

A nitro group in a reactant molecule can be involved in radical addition in several ways. First, denitration can produce a carbon-centered radical that undergoes typical addition to an electron-deficient multiple bond (eq 4).\textsuperscript{3} In a different role, nitro groups activate multiple bonds toward addition by nucleophilic radicals and affect the regioselectivity of such reactions (eq 5).\textsuperscript{23}
Deprotonation of a carbon atom bearing a nitro group creates an unsaturated system to which a carbon-centered radical can add to form a new, C–C bond (Scheme 6). Finally, the electron-withdrawing character of a nitro group can contribute to turning a normally nucleophilic radical into one that is electrophilic; thus, the philicity of the radical 1, which has both nitro and ethoxycarbonyl groups attached to the radical center, is reflected in its ability to add to the electron-rich double bond in the glycal 2 (Scheme 7).

\[
\begin{align*}
\text{CH}_2\text{OBn} & \quad \text{OCH}_2\text{OAc} \\
\text{BnO} & \quad \text{OCH}_2\text{OBn} \\
\text{NO}_2 & \quad \text{OBn}
\end{align*}
\]

(4)

\[
\begin{align*}
\text{CH}_2\text{OBn} & \quad \text{OCH}_2\text{OAc} \\
\text{BnO} & \quad \text{OCH}_2\text{OBn} \\
\text{CH}_2\text{CH}_2\text{CN} & \quad \text{OBn}
\end{align*}
\]

45%

\[
\begin{align*}
\text{C}_6\text{H}_5 & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{NO}_2 & \quad \text{OMe}
\end{align*}
\]

(5)

R =

43%

three minor products

C. Cyclization Reactions

A cyclization reaction that begins with a C-nitro carbohydrate is shown in eq 6. The high yield of this reaction, which involves a radical centered on a tertiary carbon atom adding to a multiple bond, illustrates that radical addition can be relatively insensitive to steric congestion at the radical center.

D. Elimination Reactions

A deoxynitro sugar can undergo an elimination reaction, if a radical center develops on a carbon atom adjacent to that bearing the nitro group. In the reaction shown in Scheme 8, such a radical forms and then eliminates nitrogen dioxide to give an unsaturated compound.
Scheme 6

\[
R' + \text{AcOCH}_2\text{OBn} \rightarrow \text{AcOCH}_2\text{OBn} \rightarrow \text{RCHNO}_2
\]

Scheme 7

\[
\text{CH}_2\text{OAc} + \text{Ce}^{IV}(\text{NH}_4)_2(\text{NO}_3)_6 \rightarrow \text{CH}_2\text{OAc} \rightarrow \text{Ce}^{III}(\text{NH}_4)_2(\text{NO}_3)_5
\]

\[
\text{CH}_2\text{OAc} + \text{NO}_2 \rightarrow \text{CH}_2\text{OAc} \rightarrow \text{HNO}_3
\]

\[
\text{CH}_2\text{OAc} + \text{Ce}^{IV} \rightarrow \text{CH}_2\text{OAc} \rightarrow \text{Ce}^{III}
\]
IV. *O*-Nitro Carbohydrates

Reaction of an *O*-nitro carbohydrate with a tri-*n*-butyltin radical or with ultraviolet light produces the corresponding alkoxy radical, an intermediate that is reactive enough to abstract a hydrogen atom from most C–H bonds. Also characterizing the reactivity of alkoxy radicals is rapid carbon–carbon bond cleavage to produce both a compound with a carbonyl group and a carbon-centered radical. Examples of these reactions are discussed in the next several sections.

A. Intermolecular Hydrogen-Atom Abstraction

Hydrogen-atom abstraction by an alkoxy radical generated from an *O*-nitro carbohydrate sometimes occurs internally, but often abstraction is from another molecule present in solu-
In the reaction shown in eq 7, for example, the alkoxy radical produced by photolysis of the carbohydrate nitrate 3 abstracts a hydrogen atom from methanol to give the partially protected sugar 4.  

\[
\begin{align*}
\text{3} & \xrightarrow{\text{hv, CH}_3\text{OH, NaHCO}_3} \text{4} \\
\text{BzO} & \text{CH}_3 \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \\
\text{ONO}_2 & \text{OMe} \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \\
\end{align*}
\]

(7)

\[
\begin{align*}
\text{Me}_2\text{C} & \text{O} \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \\
\text{O}_2\text{NO} & \text{OMe} \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \\
\text{5} & \xrightarrow{\text{AIBN, Bu}_3\text{SnH, C}_6\text{H}_6, 80 \, ^\circ\text{C}} \text{6} \\
\text{H} & \text{O} \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \\
\text{Me}_2\text{C} & \text{O} \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \\
\text{O} & \text{OMe} \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \\
\end{align*}
\]

(8)

Scheme 9

**B. Epimerization at a Chiral Center**

Hydrogen-atom abstraction by an alkoxy radical has such a large rate constant that few other processes successfully compete with this reaction. One that does is β fragmentation. The β fragmentation that takes place in the reaction shown in eq 8 is followed by epimerization at C-3. A proposed mechanism for this fragmentation-epimerization process is shown in Scheme 9. This process depends upon ring opening of the alkoxy radical 5 to give the carbon-centered radical 6.
being faster than hydrogen-atom abstraction from Bu$_3$SnH. Likewise, ring closure of 6 to give the epimerized alkoxy radical 7 also takes place before hydrogen-atom abstraction can intervene (Scheme 9). Ring opening is rapid due to relief of dipole-dipole interactions in the radical 5. The rate of ring closure of the radical 6 also is large due to the close proximity of the radical center to the carbonyl group and the greatly reduced dipole-dipole interaction in the resulting alkoxy radical 7.

Scheme 10

C. Intramolecular Hydrogen-Atom Abstraction

Alkoxy radicals are so effective at hydrogen-atom abstraction from C–H bonds that internal reaction is likely whenever the oxygen atom bearing the radical center closely approaches a hydrogen atom in the radical.\textsuperscript{37-41} (This approach occurs most readily when the interacting atoms are 1,6-related and the molecular structure does not prevent such contact.) Internal reaction leads to a carbon-centered radical that typically will not abstract a hydrogen atom from a carbon–hydrogen bond but will abstract such an atom from tri-$n$-butyltin hydride. Internal hydrogen-atom abstraction by an alkoxy radical often is not detectable unless a donor such as Bu$_3$SnD replaces Bu$_3$SnH as a reactant and a deuterium atom is incorporated in to the product (eq 9).\textsuperscript{37} Other
indications that internal hydrogen-atom abstraction to form a carbon-centered radical has taken place include loss of a group from a neighboring carbon atom (Scheme 10)\textsuperscript{38} and addition of the radical produced by hydrogen-atom abstraction to a compound with a carbon–carbon multiple bond (Scheme 11).\textsuperscript{42,43} [The stereoselectivity of addition of the radical 8 (Scheme 11) is determined by approach of acrylonitrile to the less-hindered face of this radical.]

Scheme 11

Scheme 12

\[ R = \text{SiMe}_2t-\text{Bu} \]
D. Carbon–Carbon Bond Cleavage

Alkoxy radicals fragment readily to give carbonyl compounds and carbon-centered radicals. In cyclic structures this fragmentation usually results in ring opening. Such reaction produces open-chain products unless rapid closure reforms the ring system. Ring closure takes place in the reaction pictured in eq 8 and described mechanistically in Scheme 9. In contrast, the product isolated from the reaction shown in Scheme 12 is the ring-open structure 9. One explanation for the difference in ring reformation in these two reactions is that they are reflecting the generally more rapid radical cyclization to give a five-membered ring when compared to that producing a six-membered ring.

![Chemical structure](image)

E. Cyclization of Alkoxy Radicals

An example of a cyclization reaction involving an alkoxy radical adding to a double bond is shown in eq 10. This type of reaction is rare because in most instances alkoxy radicals undergo either hydrogen-atom abstraction or radical fragmentation. A significant factor in the cyclization shown in eq 10 is having the alkoxy radical held in close proximity to the double bond.

![Chemical structure](image)

V. Reactions of Nitro Compounds with Silanes

Concerns with the toxicity of tri-\textit{n}\textendash butyltin hydride and the purification problems that accompany its use have spawned a variety of attempts to replace this reagent with a less troublesome one (see Appendix I). Tris(trimethylsilyl)silane normally is an attractive alternative to Bu$_3$SnH, but it fails completely in this role in group replacement reactions in nitro compounds. The reason
for failure is that the radical formed by addition of (Me₃Si)₃Si· to a nitro group does not break the carbon–nitrogen bond required for group replacement but rather cleaves a nitrogen–oxygen bond to begin a sequence of reactions leading to a complex reaction mixture (Scheme 13).  

\[
\text{RNNO}_2 + \text{Bu}_3\text{SnH} \rightarrow \text{RH} + \text{Bu}_3\text{SnONO} \quad (11)
\]

\[
\text{Bu}_3\text{SnONO} + \text{C}_6\text{H}_5\text{SiH}_3 \rightarrow \text{Bu}_3\text{SnH} + \text{C}_6\text{H}_5\text{SiH}_2\text{ONO} \quad (12)
\]

A more effective procedure for reducing the amount of tri-\(n\)-butyltin hydride needed for nitro-group replacement with a hydrogen atom consists of regenerating \(\text{Bu}_3\text{SnH}\) from the \(\text{Bu}_3\text{SnNO}_2\) formed during the substitution process. A pair of reactions that achieve group replacement and regenerate \(\text{Bu}_3\text{SnH}\) are given in equations 11 and 12. This alternative method requires only 10% of the tri-
\(n\)-butyltin hydride needed in the standard procedure.

VI. Summary

The type of radical produced by reaction of a nitro group in a carbohydrate depends upon whether this group is bonded to a carbon or an oxygen atom. A nitro group bonded to an oxygen atom invariably fragments to produce an alkoxy radical, but a nitro group attached to a carbon atom either fragments to generate a carbon-centered radical, expels an oxygen-centered radical to form a nitroso compound, or abstracts a hydrogen atom. The alkoxy radicals produced from \(O\)-nitro carbohydrates rapidly abstract hydrogen atoms either internally or from molecules present in solution. Competing with or, in some instances, superseding hydrogen-atom abstraction is carbon–carbon bond cleavage to give a carbonyl group and a carbon-centered radical.

The carbon-centered radicals derived from reaction of \(C\)-nitro carbohydrates form most readily if the radical being produced is tertiary. These radicals undergo typical replacement, addition, and cyclization reactions. Primary radicals are much less likely to form from \(C\)-nitro carbohydrates; instead, these carbohydrate derivatives usually produce nitroso compounds.

VII. References