Chapter 8
Carboxylic Acids and Esters

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I. Introduction

Carbohydrates containing typical O-acyl groups are unreactive under the reduction conditions (AIBN initiation, Bu3SnH, 80-110 °C) normally used for radical reactions. This lack of reactivity changes when O-acyl groups become part of the more complex structures found in α-acyloxy ketones, methyl oxalyl esters, and p-cyanobenzoates. For such compounds radical reaction with Bu3SnH under normal reaction conditions replaces the acyloxy group with a hydrogen atom.
There are conditions under which a less complex \( O \)-acyl group (e.g., an \( O \)-acetyl or \( O \)-benzoyl group) is replaced with a hydrogen atom. One set of conditions includes raising the reaction temperature dramatically, a change with potentially destructive consequences for the compounds involved. A more attractive approach depends upon photochemically promoted electron transfer to an esterified carbohydrate. Electron transfer (both photochemical and nonphotochemical) permeates the radical reactions of carboxylic acid esters; that is, many of these reactions either involve (or may involve) electron transfer.

Another way in which \( O \)-acyl groups participate in radical reactions is by group migration. When a radical centered at C-1 in a pyranoid or furanoid ring has an \( O \)-acyl group attached to C-2, this group will migrate to C-1 when the conditions are properly selected. Such migration provides an effective method for producing 2-deoxy sugars.

Although esters of carboxylic acids are rich sources for substrates in radical-forming reactions, the acids themselves also can produce radicals. Under the proper conditions carboxylic acids generate carboxyl radicals, intermediates that lose carbon dioxide to form carbon-centered radicals. Carboxyl radicals are generated by electrolysis of carboxylate anions and by the reaction of carboxylic acids with hypervalent iodine compounds.

II. Replacement of an Acyloxy Group with a Hydrogen Atom

A. \( \alpha \)-Acyloxy Ketones

\( \alpha \)-Acyloxy ketones react with tri-\textit{n}-butyltin hydride by replacing the acyloxy group with a hydrogen atom (eq 1).\(^1\) The importance of the carbonyl group to this replacement process is
evident in the two reactions shown in eq 2. In the first of these a benzoate (1) containing a keto group forms a deoxy sugar in good yield, but in the second a benzoate (2) lacking such a group is unreactive.\textsuperscript{1} Even though reactions of α-acyloxy ketones lead to formation of deoxy sugars, the usefulness of such reactions is limited by the relatively small number of carbohydrates that either have the necessary substituents or easily can be converted into compounds that do.\textsuperscript{1,2}

A proposed mechanism for group replacement in α-acyloxy ketones is pictured in Scheme 1. Both addition-elimination and electron-transfer-elimination sequences are presented as possibilities for acyloxy group loss. The addition-elimination possibility was proposed at the time of the discovery of this reaction,\textsuperscript{1} but the electron-transfer option was recognized as a viable alternative later when loss of the benzoyloxy group from α-(benzoyloxy)acetophenone was shown to involve electron transfer from \(\text{Bu}_3\text{Sn}^-\) to this α-acyloxy ketone.\textsuperscript{3} There is no decisive evidence favoring either mechanism.

![Scheme 1](image)

**B. Methyl Oxalyl Esters**

Methyl oxalyl esters can be prepared easily by esterification of partially protected carbohydrates with methyl oxalyl chloride (Scheme 2).\textsuperscript{4} These esters react with tri-\(n\)-butyltin hydride to replace the methyl oxalyl group with a hydrogen atom.\textsuperscript{4–19} Studies of noncarbohydrate esters show that those derived from secondary and tertiary alcohols are suitable starting materials in this
deoxygenation process, but esters of primary alcohols are not because they regenerate the alcohols from which they were synthesized.\textsuperscript{20} Most of the reactions of methyl oxalyl esters of carbohydrates are of compounds in which a tertiary hydroxyl group has been esterified. Many of these compounds are nucleosides.\textsuperscript{4,7–16} One reason that most methyl oxalyl esters are formed from tertiary alcohols is that the $O$-thiocarbonyl compounds commonly used for deoxygenation in the Barton-McCombie reaction (Section II in Chapter 12) sometimes have difficulty forming when an alcohol is tertiary.\textsuperscript{5} Methyl oxalyl chloride typically esterifies tertiary alcohols without difficulty.\textsuperscript{4,6–19} Another reason for selecting methyl oxalyl esters is that they are less likely to experience the thermal elimination (Chugaev reaction) that is common for tertiary $O$-thiocarbonyl compounds. In molecules with the proper structure cyclization can precede hydrogen-atom abstraction.\textsuperscript{13}

![Scheme 2](image)

A proposed mechanism for reaction of methyl oxalyl esters with tri-$n$-butyltin hydride is shown in Scheme 3. According to this mechanism the tri-$n$-butyltin radical transfers an electron to the $\pi$ system of the ester to produce a highly stabilized radical anion (a semidione).\textsuperscript{20} (Supporting the idea that such a transfer takes place is the observation that $Bu_3Sn^-$ reacts with oxalate esters to produce intermediates with ESR spectra characteristic of radical anions.\textsuperscript{21}) Fragmentation of such
a radical anion then generates a carbon-centered radical that abstracts a hydrogen atom from Bu$_3$SnH (Scheme 3).

There are two significant problems associated with the synthesis and reaction of methyl oxalyl esters. One of these is the difficulty in starting-material purification that arises because these esters hydrolyze readily, in particular, during chromatography on silica gel.$^4,22$ A second problem has to do with alcohol regeneration, a significant side reaction from treatment of some methyl oxalyl esters with tri-$n$-butyltin hydride.$^5,20$

![Scheme 3](image)

C. Acetates and Trifluoroacetates

Acetylated carbohydrates do not react with tri-$n$-butyltin hydride under normal conditions ($80-110$ °C, 2 h, AIBN initiation), but under different, more vigorous conditions (triphenylsilane, $140$ °C, 12 h, two equivalents of benzoyl peroxide) these compounds produce the corresponding deoxy sugars (eq 3).$^{23}$ These more vigorous conditions cause similar reaction in $O$-trifluoroacetyl substituted carbohydrates.$^{24}$ The need for two equivalents of benzoyl peroxide in the reaction shown in eq 3 indicates that a nonchain process is taking place.

![Scheme 4](image)

D. $p$-Cyanobenzoates

Replacement of the benzoyl group in compound 2 with a $p$-cyanobenzoyl group converts an unreactive compound (2) into a reactive one (3) (eq 4).$^{25}$ One explanation for this difference in reactivity is that because a cyano group is quite effective at stabilizing a radical anion, electron transfer to compound 3 is taking place where analogous transfer to the unsubstituted benzoate 2 does not occur. Since radical anions can form by electron transfer from the tri-$n$-butyltin radical to easily reduced organic compounds,$^{21,26}$ the electron-transfer mechanism pictured in Scheme 4
represents a possible pathway for replacement of a \( p \)-cyanobenzoyloxy group with a hydrogen atom.

\[
\text{Scheme 5}
\]

\[\begin{align*}
\text{HMPA} & \xrightarrow{\text{hv}} (\text{Me}_2\text{N})_3\text{PO}^+ \quad \left(\text{Me}_2\text{N}\right)_3\text{PO}^+ \quad \left(\text{Me}_2\text{N}\right)_3\text{PO}^+ \quad + \ \text{esol}^+ \\
\text{R}_1\text{OCR}_2 & \quad + \quad \text{esol} \quad \rightarrow \quad \text{R}_1\text{OCR}_2 \quad \rightarrow \quad \text{R}_1^+ \quad + \quad \text{R}_1^+ \quad \text{R}_1\text{H}
\end{align*}\]

\( R_1^+ = \text{carbohydrate radical} \quad R_2 = \text{CH}_3 \text{ or C(CH}_3)_3 \)

III. Photochemical Electron Transfer to Carboxylic Acid Esters

A. Acetates and Pivalates

Photochemical electron transfer from excited hexamethylphosphoramide (HMPA) to an \( O \)-acyl group in a carbohydrate begins a series of events that result in replacing each \( O \)-acyl group with a hydrogen atom. An example of a typical reaction is shown in eq 5.\textsuperscript{27} The temperature at which this reaction can be conducted (~25 °C) is synthetically far more attractive than the 140 °C needed for the corresponding thermal reaction of an acetylated carbohydrate (eq 3).\textsuperscript{23} Photochemical electron transfer to acetates has been used for the synthesis of a number of deoxy sugars.\textsuperscript{27–34} Esters of pivalic acid, which also can serve as substrates in this type of reaction,\textsuperscript{28,35–41} sometimes give better yields than the corresponding acetates.\textsuperscript{28,35,36}

1. Reaction Mechanism

Photochemical electron transfer begins with absorption of light by HMPA to produce a highly reactive, electronically excited molecule that ejects an electron into the solution (Scheme 5).\textsuperscript{42,43} The ejected electron is captured by the acylated carbohydrate to produce a radical anion that cleaves to give a carboxylate anion and a carbohydrate radical (\( R^- \)).\textsuperscript{43} Hydrogen-atom abstraction by the carbohydrate radical then completes the replacement process (Scheme 5). The water present...
in the reaction mixture extends the lifetime of the solvated electron and, in so doing, increases the probability that this electron will be captured by a molecule of ester.\textsuperscript{43} (The importance of water to the success of this process is demonstrated by the yields of the reactions shown in eq 6.\textsuperscript{44,45})

### Scheme 5

\[
\begin{align*}
\text{(Me}_2\text{N)}_3\text{PO} & \xrightarrow{h\nu} \text{(Me}_2\text{N)}_3\text{PO}^+ + e^o_{\text{sol}} \\
\text{R}_1\text{OCR}_2 + e^o_{\text{sol}} & \rightarrow \text{R}_1\text{OCR}_2^+ \rightarrow \text{R}_1^+ + \text{OCR}_2^o
\end{align*}
\]

- $R_1^+$ = carbohydrate radical
- $R_2 = \text{CH}_3$ or $\text{C(CH}_3)_3$

2. Alcohol Regeneration

Ester photolysis in aqueous HMPA sometimes regenerates the alcohol from which the ester was synthesized (eq 7).\textsuperscript{34} In some instances, alcohol formation may be due to nonphotochemical ester hydrolysis. Nonphotochemical reaction provides a reasonable explanation for the easily hydrolyzed, anomeric acetate shown in eq 8 undergoing only hydrolysis (no deoxygenation) when
photolyzed in aqueous HMPA. Even though simple hydrolysis may be significant for some compounds, as described below, alcohol regeneration during photolysis of other, probably most, esters must occur in a different way.

Alcohol formation during ester photolysis cannot be explained, in general, by simple hydrolysis because, as is shown by the reaction pictured in Scheme 6, the yield of the alcohol can depend on the concentration of the starting ester. One explanation for this dependence begins with the ester capturing a solvated electron to form the radical anion. This radical anion then abstracts a hydrogen atom from a second molecule of to produce the anion, which then forms an alkoxide ion that protonates to give the observed alcohol. Since, according to this explanation, raising ester concentration should increase the rate of hydrogen-atom abstraction to give but not
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the rate of the competing β-cleavage that forms R⁻, greater ester concentration should increase the amount of alcohol (ROH) produced at the expense of the deoxygenated product (RH).

A critical question about the mechanism for alcohol formation presented in Scheme 6 concerns whether the radical anion 6 can abstract a hydrogen atom from the ester 5. The evidence found in eq 9 supports the idea that 5 can function as a hydrogen-atom donor. Irradiation of 5 in HMPA-d_{18}/D_{2}O gives a 27% yield of 8, a reduction product that contains no deuterium. Since the only source for the second hydrogen atom at C-3 in 8 is one of the carbohydrates in the reaction mixture and since the ester 5 is the only carbohydrate present at the beginning of the reaction, abstraction from 5, at least in the early stages of reaction, seems unavoidable. If 5 can act as a hydrogen-atom donor in the formation of 8, it becomes a strong candidate for the same role in the conversion of the radical anion 6 into the alkoxide ion 7 (Scheme 6).

\[ \text{Scheme 6} \]

3. Competition from Light-Absorbing Chromophores

If an ester contains a strongly absorbing chromophore, HMPA excitation will be effectively precluded because most of the incident light will be absorbed by the ester. Failure to excite HMPA
will forestall replacement of the acyloxy group with a hydrogen atom by preventing electron transfer. The light absorbing properties of the benzyloxy group, for example, render benzoates much less desirable participants in these electron-transfer reactions because far less incident light reaches the HMPA. This means that an important factor in reaction of simple acetates and pivalates is that these compounds contain no strongly absorbing chromophore. An example of an ester that fails to undergo replacement of the acyloxy group due to the presence of a light-absorbing substituent (i.e., the 4,6-\textit{O}-benzylidene group) is shown in eq 10. Even though the benzylidene group is removed during photolysis, the aromatic chromophore remains in the solution and continues to absorb the incident light. Changing 4,6-\textit{O}-benzylidene to 4,6-\textit{O}-isopropylidene protection allows reaction to proceed in the normal fashion (eq 11).

**B. \textit{m}-(Trifluoromethyl)benzoates**

\textit{m}-(trifluoromethyl)benzoate will accept an electron from excited \textit{N}-methylcarbazole (11) in a reaction that leads to replacement of the acyloxy group with a hydrogen atom; for example,

\begin{align*}
\text{R} = -\text{CC}_6\text{H}_4\text{CF}_3(\text{m}) & \quad \text{C}_{13}\text{H}_{11}\text{N} = \begin{array}{c}
\text{N}
\end{array} \\
\text{R} = -\text{CC}_6\text{H}_4\text{CF}_3(\text{m}) & \quad \text{C}_{13}\text{H}_{11}\text{N} = \begin{array}{c}
\text{N}
\end{array} \\
\text{BzOCH}_2 & \quad \text{BzO}
\end{align*}
photolysis of 2',3',5'-tri-\textit{O}-[\textit{m}-(trifluoromethyl)benzoyl]-adenosine (9) produces the 2',3'-dideoxyadenosine derivative 10 (eq 12).\textsuperscript{46} (Most,\textsuperscript{46-52} but not all,\textsuperscript{48} compounds reported to undergo this type of reaction are nucleosides.) Reactions, such as the one shown in eq 12, are regioselective because the radical anion generated from a \textit{m}-(trifluoromethyl)benzoyl group does not fragment to give a primary radical.

Photochemical electron transfer involving \textit{m}-(trifluoromethyl)benzoates and \textit{N}-methylcarbazole (11) has several advantages over electron transfer between HMPA and acetates or pivalates. One of these is that \textit{N}-methylcarbazole has greater molar absorptivity than HMPA, a fact that renders the carbohydrate reactant less likely to stop the reaction by absorbing the incident light.\textsuperscript{52}
From a safety point of view, eliminating HMPA from the reaction mixture avoids handling a highly toxic, cancer-suspect agent. Because the \( m \)-(trifluoromethyl)benzoyl group is an effective electron acceptor (better than an acetyl or pivaloyl group) few substituents in the carbohydrate will compete with this group for an electron donated by excited \( N \)-methylcarbazole (11); consequently, reactions of \( m \)-(trifluoromethyl)benzoates usually are highly chemoselective. An example of this selectivity is shown in eq 13, where the benzoyl group remains bonded to C-3' while the \( m \)-(trifluoromethyl)benzoyl group at C-2' is replaced by a hydrogen atom.\(^{49}\)

When reaction is conducted in the presence of \( \text{Mg(ClO}_4\text{)}_2 \), it is possible to replace even an unsubstituted benzoyloxy group with a hydrogen atom (eq 14\(^{50}\)).\(^{50-52}\) Magnesium perchlorate affects this reaction by hindering back electron transfer, a process that competes with the fragmentation of the radical anion 13 (Scheme 7). Another factor that affects the reaction of a benzoyloxy group is the choice of the electron donor; thus, replacing \( N \)-methylcarbazole (11) with 3,6-dimethyl-9-ethylcarbazole (12) causes deoxygenation to take place more rapidly.\(^{50}\) Compound 12 is superior to 11 because it forms a more stable radical cation upon electron transfer.\(^{50,53,54}\)

IV. Nonphotochemical Electron Transfer to Carboxylic Acid Esters

Electron transfer to carboxylic acid esters also can occur via nonphotochemical reaction. Transfer of an electron from \( \text{SmI}_2 \) to a carbohydrate \( p \)-methylbenzoate produces a radical anion that fragments to give a carbon-centered, carbohydrate radical and a \( p \)-methylbenzoate anion (Scheme 8).\(^{54,55}\) The carbohydrate radical abstracts a hydrogen atom from a donor present in the solution to form a deoxy sugar. An example of such a reaction is shown in eq 15.
V. Acyloxy Group Migration

Group migration in radical reactions follows one of two basic pathways. For aldehydo, cyano, and aryl groups, migration takes place by a sequence of elementary reactions consisting of cyclization and β-fragmentation steps. (An example of this type of reaction is shown in Scheme 8 of Chapter 10). Group migration in esters is governed by a different mechanism, one that has been the subject of considerable investigation. To follow the progress in understanding this reaction, it is useful to view the advances in mechanistic discovery in a chronological order.
A. Evolution of a Reaction Mechanism

In the late 1960’s reports first appeared of a reaction in which an acyloxy group migrated to a radical center located on a neighboring carbon atom (eq 16). Curiosity about this process gradually increased as its complexity began to unfold. Interest intensified as the synthetic potential of this reaction began to be recognized. An early indication of the synthetic possibilities came from the study of carbohydrates, where acyloxy group migration provided the basis for a new synthesis of 2-deoxy sugars (Scheme 9).58–62

1. Possible Formation of a Cyclic Radical Intermediate

The first proposed mechanism for acyloxy group migration involved the intermediate formation of a 1,3-dioxolan-2-yl radical. Although formation of this cyclic intermediate represented a reasonable possibility, subsequent studies showed that such a radical could not be involved in this reaction. The line of investigation that first pointed to this conclusion was based on the finding that the radical was converted to 15 under conditions where the proposed, intermediate 1,3-dioxolan-2-yl radical did not undergo ring opening fast enough to account for group migration (Scheme 10).63–65

The evidence that a cyclic intermediate was not involved in acyloxy group migration was reinforced by the reactions shown in Schemes 11 and 12. In the first of these reactions the radical was converted into a new radical by group migration (Scheme 11). The question at this point concerned whether the cyclic radical was involved in the process. The answer came in the second reaction where was generated independently under conditions that would allow acyloxy group migration, but opening of the cyclopropane ring took place rather than dioxolane ring opening (Scheme 12). These results eliminated as a possible intermediate in the migration reac-
tion and supported the idea that 1,3-dioxolan-2-yl radicals are not involved in acyloxy group migration.

2. A Concerted Reaction with a Cyclic Transition State

Eliminating the 1,3-dioxolan-2-yl radical as a potential reaction intermediate left a mechanistic void that was filled by the proposal of a concerted process in which the transition state had the structure 21 (Scheme 13). Consistent with this proposal was the finding that migration of acyloxy groups containing \(^{18}\)O-labeled carbonyl oxygen atoms yielded products with carbonyl and ether oxygen atoms transposed.

Kinetic studies supported the mechanism shown in Scheme 13. The findings from one of these investigations indicated the existence of a transition state in which C–O bond breaking was virtually complete before the beginning of new bonding between the carbonyl oxygen atom and the radical center. Acceleration of the migration process by an electron-withdrawing R group was consistent with the charge-separated transition state 22 proposed for the reaction shown in Scheme 14. Also supporting charge separation in the transition state was the observation that the
rate of acetoxy group migration was faster in a more polar solvent (water) than in a less polar one (t-butylbenzene).\(^67\)

**Scheme 14**

\[
\begin{align*}
\text{R = CH}_3 & \quad k = 4.5 \times 10^2 \text{ s}^{-1} \text{ at } 75 \degree C \\
\text{R = CF}_3 & \quad k = 7.0 \times 10^4 \text{ s}^{-1} \text{ at } 75 \degree C
\end{align*}
\]

\[k_{rel} = 1 \quad (100\% \text{ oxygen transposition})\]

3. **Competing, Concerted Reactions**

At this point the mechanism shown in Scheme 13 (with the added charge separation shown in Scheme 14) explained the existing information. Subsequent discovery of migration reactions in which transposition of ether and carbonyl oxygen atoms was incomplete forced a reevaluation of this position.\(^68,69\) To be acceptable, any new mechanistic proposal also needed to account for partial oxygen-atom transposition in some reactions and for the fact that migration with complete transposition (eq 17) takes place more slowly than reaction in which transposition is incomplete (eq 18).\(^69\)

One solution to this problem was to add a second, concerted mechanism (Scheme 15) and propose that the two reactions shown in Schemes 13 and 15 were competing.\(^70-74\) A basic differ-
ence between these two was that in one (Scheme 15) the same oxygen atom was bonded to the carbon-atom framework both before and after migration, but in the other (Scheme 13) the framework had a different oxygen atom attached after migration. Proposing migration via a combination of these two reactions made it possible to explain experiments with oxygen-labeled substrates in which only a portion of the labeled oxygen was attached to the carbon-atom framework after migration. The findings at first favored this two-reaction explanation, but results from later investigations required a new proposal because these later studies indicated that ionic intermediates were likely to be involved in the migration process.

Scheme 15

Scheme 16

4. The Ion-Pair Proposal

Formation of a contact ion pair (CIP) consisting of a carboxylate anion and a radical cation (27) was the defining step in the next mechanistic proposal for acyloxy group migration (Scheme 16). This proposal extended the idea of a charge-separated transition state to formation of an intermediate (27) in which there was complete ionization. If the anion and radical cation in 27 were held together sufficiently strongly (i.e., a very “tight” ion pair), no reorientation of the atoms should occur, and recombination should produce a product radical (28) in which there was complete transposition of the carbonyl and ether oxygen atoms (Scheme 16).

If the ions in 27 are sufficiently stable to be held loosely enough for their relative motion to allow the ion pairs 29, 30, and then 31 to form, combination of the ions in 31 will produce a pro-
duct radical (32) with no oxygen-atom transposition (i.e., the oxygen label is still in the carbonyl group), but combination of the ions in 27 will give a product radical (28) in which the label no longer is with the carbonyl group (Scheme 17). Factors that stabilize either component of the ion pair should increase the probability of partial oxygen-atom transposition by reducing the “tightness” of the ion pair. These same factors also should increase the rate of acyloxy group migration by stabilizing the charge-separated transition state leading to the contact ion pair 27; thus, the ion-pair proposal explains the correlation between oxygen-atom transposition and reaction rate (equations 17 and 18).

Scheme 17

If 27, 29, 30, and 31 (Scheme 17) are all contact ion pairs, the radical cation member of each pair should not react with added nucleophiles during the migration process. Testing for this type of reaction by addition of benzoate or azide ions or methanol to the reaction mixture during rearrangement did not generate any products from capture of a radical cation by a nucleophile. Even radicals containing a nucleophile that could react internally with a radical cation did not form any products from such internal trapping during group migration.
In addition to undergoing reaction with partial oxygen-atom transposition (eq 18) the radical 23 also gives a small amount of oxygen-atom mixing in recovered starting material (Scheme 18). The ion-pair mechanism explains this oxygen-atom transposition in the starting material as...
resulting from conversion of 23 into a contact ion pair that usually reacts further to give the group-migrated radicals 24 and 25 but sometimes collapses to the oxygen-atom transposed radical 33. Formation of a small amount of 33 accounts for the distribution of the oxygen-atom label in the products 34 and 35 formed by reduction (without migration) of radicals 23 and 33, respectively (Scheme 18).

5. Direct Observation of an Ion Pair

Phosphatoxy groups undergo migration that is similar to that of acyloxy groups.\textsuperscript{70,78,79} The rate constants for phosphatoxy group migration usually are greater by at least two orders of magnitude than those for acyloxy groups.\textsuperscript{80,81} but basic mechanistic findings support the idea that these two group migration reactions are similar. This similarity takes on added significance in light of the results from flash-photolysis experiments.

Critical support for the ion-pair mechanism for phosphatoxy group migration comes from laser-flash-photolysis (LFP) experiments.\textsuperscript{79,82} Both the solvent-separated ion pair (SSIP) 39 and the diffusively free radical cation 40 can be detected in studies where LFP generates the radical 36 (Scheme 19).\textsuperscript{79} Evidence for the contact ion pair (CIP) 37 in this reaction is indirect because its lifetime, presumably, is too short to permit direct detection. Study of reaction rates in solvents of different polarity supports the idea that the radical 36 is passing through a common intermediate in forming either the rearranged radical 38 or the SSIP 39. A reasonable conclusion is that the common intermediate is the CIP 37 (Scheme 19).\textsuperscript{79} Entropies of activation, which are the same for ion-pair formation in high polarity solvents and group migration in solvents of low polarity, also favor a common intermediate for which 37 is the prime candidate.\textsuperscript{79,83} Generalizing these results leads to the reaction mechanism shown in Scheme 20. (Reactions of radicals containing phosphatoxy groups are described in Chapter 9).

6. Probable Reaction Mechanism

Other studies also show similarities between acyloxy and phosphatoxy group migration.\textsuperscript{83,84} Since the ion-pair mechanism (Scheme 20) is firmly in place for phosphatoxy group migration, such similarities reinforce the idea that migration of an acyloxy group also involves formation of a contact ion pair. Where acyloxy group migration is concerned, however, the failure actually to observe any type of ion pair makes this mechanistic pathway less certain. Not being able to detect ions in these reactions easily could be due to very rapid, ion-pair collapse to the product radical. Without such detection or a similarly definitive observation, however, the possibility remains that acyloxy group migration, at least in some cases, may be a concerted process.

B. Acyloxy Group Migration in Carbohydrates

Because 2-deoxy sugars can be difficult to synthesize, acyloxy group migration represents an attractive route to this important class of compounds (Scheme 9). For group migration to be
effective, it must take place before the initially formed radical reacts with a hydrogen-atom donor. To allow sufficient time for group migration, the concentration of a reactive hydrogen-atom donor, such as tri-\(n\)-butyltin hydride, needs to be maintained at a low level by adding it slowly to the reaction mixture. Under these conditions the yields of 2-deoxy sugars are good.\(^{58-60}\) An alternative to this slow addition is to use a less reactive hydrogen-atom donor; thus, when tris(trimethylsilyl)silane fills this role, slow addition is not necessary in order to observe the migration shown in Scheme 9.\(^{61}\) As might be expected, the very effective hydrogen-atom donors thiophenol\(^{85}\) and benzeneselenol\(^{86}\) dramatically inhibit the migration process by rapidly donating a hydrogen atom to the initially formed carbohydrate radical.

Starting sugars for acyloxy group migration usually are pyranosyl or furanosyl bromides.\(^{58-62,85,87}\) Glycosyl selenides\(^{59,88}\) also are acceptable substrates and, in fact, are better for reaction of furanosyl compounds (eq 19)\(^{59}\) because the corresponding bromides are quite thermolabile.

Reaction in which a carbon-centered radical stabilized by an attached oxygen atom translocates during acyloxy group migration to become an unstabilized radical (Scheme 9) seems like an
unpromising basis for group migration. The reason this reaction takes place is that migration also creates an acetal linkage involving C-1.\textsuperscript{59,62} Calculations on model systems suggest that forming a second C–O bond at an oxygen-substituted carbon atom stabilizes the system by about 15 kcal/mol,\textsuperscript{89} enough of this stabilization apparently exists at the transition state to allow the reaction shown in Scheme 9 to take place.\textsuperscript{59,62} The calculated stabilization is less that 5 kcal/mol if one of the oxygen atoms in the model system is replaced by a sulfur atom.\textsuperscript{89} This reduced stabilization accounts for the failure of the substrate \textbf{41} to undergo group migration (eq 20).\textsuperscript{62}

An acyloxy group at C-1' in a nucleoside can undergo migration from C-1' to C-2' (eq 21).\textsuperscript{90,91} This type of reaction sometimes is referred to as a “reverse 1,2-shift” because the acyloxy group moves in the opposite direction from that observed in reaction of pyranos-1-yl and furanos-1-yl radicals. The transition state in the reaction shown in eq 21 is believed to be a polar one\textsuperscript{92} and may lead to a contact ion pair (Scheme 21).\textsuperscript{93} Stabilization of the rearranged radical \textbf{42} by a uracil (or adenine) moiety is sufficient to allow the rearranged radical to form.\textsuperscript{91} The stereochemistry at C-1' is determined by approach of the hydrogen-atom donor to the less hindered face of the five-membered ring.\textsuperscript{91} The reaction shown in eq 21 further illustrates the advantage of the
less reactive hydrogen-atom donor $\text{(Me}_3\text{Si)}_3\text{SiH}$ in allowing sufficient opportunity for migration to take place.

VI. Reactions of Carboxylic Acids

Carboxylic acids cannot be converted directly into carboxyl radicals, but they can form these radicals indirectly. One method for indirect formation calls for converting the acid into its anion, which then is subjected to electrolysis (Scheme 22).\(^5\) Other indirect methods require formation of
carboxylic acid derivatives, such as esters of N-hydroxypyrindine-2-thione, compounds that produce carboxyl radicals by photochemically initiated reaction (Scheme 23). Carboxyl radicals expel carbon dioxide to produce carbon-centered radicals (eq 22).

A. Electrolysis

The carbon-centered radicals resulting from electrolysis of carboxylate anions (Scheme 22) either undergo radical reactions (usually radical combination), or they are further oxidized to carbocations. Whether or not oxidation to give a cation takes place depends on the reaction conditions and on the structure of the carbon-centered radical produced. If this radical is capable of forming a stabilized carbocation, it will be further oxidized; for example, in the reaction shown in Scheme 24 oxidation of the radical 44 to the oxygen-stabilized cation 45 is the major, if no exclusive, reaction pathway.
A modest yield of the unsymmetrical radical coupling product 47 forms during electrolysis of the carboxylic acid 43 in the presence of a ten-fold excess of octanoic acid (eq 23). Isolation of orthoester 46 from this reaction indicates that the cation 45 (Scheme 24) still is produced under these new conditions. Formation of the radical coupling product 47 under conditions where the carbocation 45 also is formed, has led to the proposal that simultaneous decarboxylation of coacids may account for radical coupling occurring before further oxidation to 45 can take place.

Oxidation of a radical to a carbocation does not happen if the potential cation is an unsta-bilized one (e.g., a primary cation with no stabilizing groups attached); thus, in the reaction shown in eq 24, radical oxidation to a primary cation does not take place. The only carbohydrate products isolated in this reaction arise either from unsymmetrical radical coupling (48) or disproportionation (49 and 50). Although the carbon-centered radicals produced by electrolysis and loss of carbon dioxide are considered to be “free”, their locally high concentration at the electrode where they are formed would promote radical coupling even if simultaneous decarboxylation of coacids does not occur.

B. Oxidation by Hypervalent Iodine Reagents

Decarboxylation of carboxylic acids by their reaction with hypervalent iodine reagents {(diacetoxyiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene, [bis(trifluoroacetoxy)iodo]pentafluorobenzene, and (diacetoxyiodo)benzene–I₂} is another process that generates carbon-centered, carbohydrate radicals (Scheme 25). When reaction is conducted in the
presence of a heteroaromatic base, the carbohydrate radical adds to the base (eq 25).\textsuperscript{100-102} Base protonation greatly increases its reactivity with carbohydrate radicals (most of which are nucleophilic); thus, product yields are reported to be best when the reaction mixture is decidedly acidic.\textsuperscript{100}

\begin{equation}
\text{Scheme 25}
\begin{align*}
\text{RCO}_2\text{H} + \text{B} & \rightleftharpoons \text{RCO}_2\text{B}^- + \text{BH}^- \\
\text{(CF}_3\text{CO}_2\text{)}_2\text{IC}_6\text{F}_5 + 2 \text{RCO}_2^- & \rightleftharpoons (\text{RCO}_2\text{)}_2\text{IC}_6\text{F}_5 + 2 \text{CF}_3\text{CO}_2^-
\end{align*}
\end{equation}

B = a heteroaromatic base \quad R = a carbohydrate moiety

R\text{CO}_2\text{H} + \begin{array}{c}
\text{5-Cl-2-pyridine} \\
\text{CO}_2\text{Me}
\end{array} \xrightarrow{\text{hv} \ (\text{CH}_2\text{Cl}_2)} \begin{array}{c}
\text{R} \\
\text{CO}_2\text{Me}
\end{array} \quad (25) \quad \begin{array}{c}
\text{42%} \\
\alpha/\beta = 5/1
\end{array}

Oxidative decarboxylation also takes place when a carboxylic acid reacts with (diacetoxyiodo)benzene in the presence of molecular iodine (eq 26).\textsuperscript{103} (No reaction takes place in the absence of iodine.)\textsuperscript{103} One explanation for the role of iodine is that it is necessary for formation of an acyl hypoiodite, an intermediate that then decomposes to give a carboxyl radical and an iodine atom (Scheme 26).\textsuperscript{104} A proposed mechanism for reaction of the carboxyl radical 51 is given in Scheme 27. According to this mechanism 51 expels carbon dioxide to give the carbon-centered radical 52. Iodine capture then produces the iodide 54, which ionizes to give the carbocation 53.
Supporting this pathway is the observation that in compounds where ionization cannot produce a stabilized carbocation, iodides are isolated.\(^{104}\) Formation of the iodide \(\text{54}\) would be expected to occur rapidly because the carbon-centered radical \(\text{52}\) should react with the \(I_2\) present in the reaction mixture at or near the rate of diffusion.\(^{105,106}\) (The rate constant for iodine-atom abstraction from \(I_2\) by the cyclohexyl radical is \(1.2 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}\).)

\begin{align*}
\text{Scheme 26} \\
\text{RCO}_2\text{H} + \text{(AcO)}_2\text{IC}_6\text{H}_5 & \rightleftharpoons \text{(AcO)}_2\text{IC}_6\text{H}_5 + 2 \text{AcOH} \\
\text{(AcO)}_2\text{IC}_6\text{H}_5 + I_2 & \rightleftharpoons 2 \text{RCO}_2I + \text{IC}_6\text{H}_5 \\
\text{RCO}_2I & \rightarrow \text{RCO}_2^- + I^- \\
\end{align*}

\begin{align*}
\text{Scheme 27} \\
\text{CO}_2^- \text{OBn} \rightarrow \text{CO}_2^- \\
\text{51} & \rightarrow \text{52} & \text{52} \rightarrow \text{54} \\
\text{53} & \rightarrow \text{54} \\
\end{align*}

C. Decomposition of Esters of \(N\)-Hydroxypyridine-2-thione

Photochemically initiated reactions of carboxylic acid esters of \(N\)-hydroxypyridine-2-thione represent another route to carboxyl radicals. These reactions are discussed in Chapter 12.

VII. Summary

Carbohydrates with simple acyloxy groups are unreactive under conditions normally used in reduction reactions. Reduction does occur, however, if the reaction temperature is raised to 140 °C and the reaction time is greatly extended. Esters with special structural features undergo reduction
at lower temperatures; thus, both α-acyloxy ketones and methyl oxalyl esters react with tri-\textit{n}-butyltin hydride at or below 110 $^\circ$C.

Photochemical electron transfer provides a way for acyloxy groups to be replaced by hydrogen atoms under mild reaction conditions (at room temperature in neutral solution). Electron transfer occurs when either excited HMPA or \textit{N}-methylcarbazole donates an electron to an ester to form a radical anion. Fragmentation of the radical anion generates a carbon-centered radical that then abstracts a hydrogen atom to produce a deoxygenated compound. Regeneration of the partially protected carbohydrate from which the ester was synthesized sometimes competes with deoxygenation.

Acyloxy group migration to a radical center on an adjacent carbon atom is a reaction that is useful in the synthesis of 2-deoxy sugars. Early proposals for the mechanism of this reaction turned out not to be correct. The considerable investigation that has taken place since then has shown that this reaction is likely to involve the formation of an intimate ion pair consisting of a carboxylate anion and a radical cation. Recombination of this pair produces a new radical, one that has undergone group migration.

Carboxylic acids produce carboxyl radicals by reaction with hypervalent iodine reagents or electrolysis of carboxylate anions. These radicals expel carbon dioxide to form carbon-centered radicals. Electrochemical reaction results in radical coupling, or if the radical is further oxidized, carbocation formation. Reaction of carboxylic acids with hypervalent iodine reagents often is conducted in the presence of heteroaromatic compounds, where radical addition to the aromatic ring takes place.

VIII. References


