

Review

The Ruff degradation: a review of previously proposed mechanisms with evidence that the reaction proceeds by a Hofer–Moest-type reaction

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Dedicated to the memory of Professor Nikolay K. Kochetkov

Abstract—The Ruff degradation reaction is critically reviewed. Based on available information, the Hofer–Moest decarboxylation mechanism is presented as the mechanism for it. Cu(III) is proposed as the active species of the copper variant of the Ruff degradation, which is the most efficient form of the reaction.

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1. Introduction

1.1. Electrochemical decarboxylation

Because we believe that the Hofer–Moest mechanism is the likely mechanism of the Ruff degradation reaction, that mechanism is described first, with an emphasis on

Hofer–Moest reactions of carbohydrates. The electrolytic decarboxylation of organic acids was first explored by Kolbe¹ in the mid-19th century. The Kolbe reaction entails a one-electron oxidation of an organic acid, ensuing decarboxylation yielding a radical, and subsequent dimerization of the degradation product (in early work an alkyl radical). Reichenbacher et al.² observed that the stability of the ensuing radical did not affect reaction kinetics, but that the solubility of the starting acid within the electrolytic system had a great effect on the kinetics. However, May and Skell³ showed, with more precise experiments, that structure did have an

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effect on the rate of decarboxylation once the acyloxy radical was formed, the decarboxylation being rapid in all cases. Chart 1 depicts the decarboxylation of acetate ions via the Kolbe reaction with the formation of carbon dioxide and ethane.

It was determined by Hofer and Moest⁴ that, if the reaction occurred in an alkaline medium or if there was a significant electron-withdrawing group alpha to the carboxylate group, the reaction became a two-electron oxidation (i.e., two successive one-electron oxidations) with a carbocation being formed as an intermediate before nucleophilic addition of the solvent (Chart 2). Further work on the Hofer–Moest reaction (also called the non-Kolbe reaction) showed that the use of a graphite anode and small current densities favored the two-electron oxidation to such an extent that the reaction could be stoichiometric. These reactions have been extensively reviewed.^{5–9}

Some early research explored electrolyses of sugars¹⁰ and electrolytic decarboxylation of α -hydroxy acids to aldehydes,¹¹ but it was not until early in the 20th century that a systematic study of sugar degradation at anodes was conducted. Both Neuberg and co-workers^{12–14} and Loeb^{15,16} explored the anodic oxidation of sugars. Neuberg used a platinum anode, while Loeb used a lead anode. In particular, Neuberg¹² demonstrated that the anodic decarboxylation of sugar acids to aldehydes was facile and widely applicable.

Hay and Smith¹⁷ explored the electrolysis of anhydrous neutral monosaccharides, but it was not until the latter portion of the 20th century that researchers explored decarboxylations of sugar acids in detail (finding that decarboxylations of aldonic acids could be economically important) and implemented several continuous-flow reactors.^{18–20} D-Gluconic acid was decarboxylated electrochemically to yield D-arabinose with a specificity of up to 98%,^{21–23} but we conclude that the mechanism proposed in these reports is inconsistent with observation and theory. Chou and Chou²⁴ explored the coupled,

split-cell oxidation of D-gluconic acid to yield D-arabinose at both the anode and cathode, the cathodic oxidation being mediated by molecular oxygen and iron ions.

Renaud et al.²⁵ found that the electrolytic decarboxylation of α -hydroxy acids in methanol yields aldehydes.

1.2. Photochemical Hofer–Moest reactions

Daniels²⁶ found that visible light enhances the Ruff degradation reaction, so photochemical forms of the Hofer–Moest reaction must also be reviewed. Many photochemical transition metal ion-catalyzed reactions of carboxylate groups are of the Kolbe/Hofer–Moest type and are characterized by transfer of an electron from the carboxylate group to the metal ion. The metal ion is consequently reduced, and the acyloxy radical decomposes, releasing carbon dioxide.²⁷

Titanium dioxide has been employed in concert with ultraviolet radiation for a complete oxidation of organic substances. The ultraviolet radiation excites electrons on the semiconductor surface and results in positively charged regions, otherwise referred to as electron holes. These holes act as anodes, that is, locations at which acids and other organic molecules adsorbed to the particle surface are oxidized. This chemistry is similar to that of electrochemical Kolbe/Hofer–Moest decarboxylations, but the system has a much higher oxidizing potential. The adsorbed molecules remain adsorbed after decarboxylation and are swiftly oxidized further to carbon dioxide.^{28–32}

Benrath³³ first reported that Fe(III) would decarboxylate α -hydroxy acids in the presence of light. The reaction was reported to be stoichiometric. Two Fe(III) atoms are presumably reduced to Fe(II). Abrahamson et al.³⁴ described the Fe(III) photo-decarboxylation of many biologically relevant carboxylic acids, with an emphasis on citric acid. Araki et al.^{35–37} reported the photodegradation of neutral monosaccharides by Fe(III). Under acidic conditions, the monosaccharides

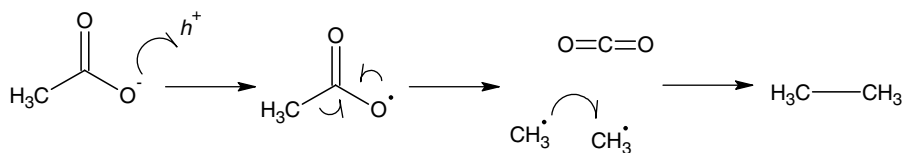


Chart 1. The Kolbe reaction; h^+ symbolizes an anode.

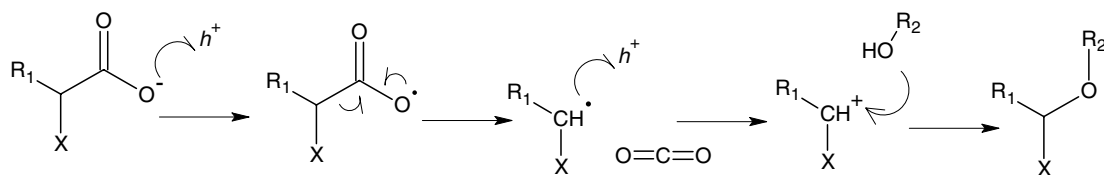


Chart 2. Hofer–Moest decarboxylation.

complexed with Fe(III) (in a roughly 2:1 molar ratio). Upon irradiation with near-UV–vis light, an almost complete degradation ensued, yielding aldoses of mostly one carbon atom less (in the case of most aldoses) or two carbon atoms less (in the case of fructose).

α -Aryl carboxylic acids have been decarboxylated in organic solvents with both iron(III) porphyrin + periodate and manganese(III) porphyrin + periodate at room temperature.^{38–40} Investigations of the photoreduction of iron(III) porphyrins to iron(II) porphyrins have shown that a one-electron transfer from an axial ligand is involved. This mode of reaction efficiently decarboxylates amino acids⁴¹ and alkyl- and aryl-methyl carboxylates.⁴² By this method, a carboxylic acid associates with the iron–porphyrin complex and visible light induces a one-electron transfer as in a Kolbe/Hofer–Moest-type oxidation.⁴³ It has been reported that the presence of an oxidant, such as (but not limited to) oxygen, can generate a catalytic system by regenerating Fe(III).^{44,45} Under some conditions, Fe(III) porphyrins are hypothesized to shuttle between hyper-valence states.⁴⁶ Fe(IV) porphyrins have been catalytically regenerated with peroxy acids.⁴⁷

Matsushima et al.⁴⁸ reported that the photolytic decarboxylation of Cu(II) lactate yielded acetaldehyde and pyruvate. They also showed that pyruvate resulted from the formation of radical species, and that the addition of radical traps reduced the formation of pyruvate to almost zero. The reaction is pH dependent and is analogous to the photochemical decarboxylation of Ur(IV)–lactate complexes described by Sakuraba and Matsushima.⁴⁹ The formation of acetaldehyde is consistent with a Hofer–Moest-type decarboxylation.

Habibi and Farhadi⁵⁰ reported that irradiation of carboxylates over mercury(II) oxide resulted in a photo-Kolbe decarboxylation.

2. Ruff degradation

The Ruff degradation,⁵¹ which involves the decarboxylation of aldonic acids by Fe(III) and hydrogen peroxide (also called ‘Fenton’s-like reagent’) to yield aldoses with one less carbon atom than the original aldonic acid has been extensively applied.[‡] Only slight modifications of the Ruff degradation reaction have been made during its more than 100 years of implementation,^{52,53} and yields have remained less than quantitative (below 50% in most cases). The reaction mechanism has long been debated. As already stated, we propose that the Ruff degradation, a chemical reaction, occurs by a Hofer–

[‡]It is not the intent of this article to review all applications of the Ruff degradation or related reactions in various syntheses. Rather this article focuses on those reports in which mechanisms are proposed or which are pertinent to the mechanisms proposed here.

Moest-type mechanism (as depicted in Chart 2, with a transition metal ion taking the place of the anode), so we call the reaction a Hofer–Moest-type reaction. Below we discuss most mechanisms that have been proposed, pointing out their deficiencies. Even some contemporary papers cite mechanisms that are contradictory or ill-conceived.^{54,55}

Isbell and Salam⁵⁶ studied the decarboxylation of D-gluconate-2-*d* in a Fe(II) + H₂O₂ system in an experiment designed to probe the role of the α -hydrogen atom in the Ruff degradation. [Reference to the Ruff degradation of saccharinic acids^{57–59} (Chart 3) would have obviated the need for the experiment.] Despite the use of Fenton’s reagent, which has been shown to yield products different than those of the Ruff system,⁵² Isbell and Salam obtained D-arabinose-1-*d* in small yields. While Isbell and Salam were correct that the retention of deuterium in the isolated D-arabinose disallows a pathway that proceeds via an α -carbonyl intermediate, they failed to recognize evidence against their proposed mechanism (Chart 4). While abstraction of the hydroxyl hydrogen atom is possible, the α -proton is abstracted preferentially in a free-radical system.^{60,61} Either of the ensuing radical species are terminated by the formation of an α -carbonyl compound,^{52,62} which is precluded by the isolation of D-arabinose-1-*d*. Indeed, the subjection of D-gluconate to hydroxyl radicals (formed either by radiolysis or sonication) results in the formation of the α -keto acid.⁶³ Moreover, Fenton and Jones⁶⁴ showed that Fenton’s reagent oxidizes the α -hydroxyl groups of many acids to carbonyl groups. Furthermore, Isbell and Salam’s reported yields are far less than those reported using an Fe(III) + H₂O₂ system.^{65,66} If Isbell and Salam’s mechanism were correct, starting with Fe(II) would favor production of D-arabinose from D-gluconic acid, and thus enhance yields.

Hough and Richardson⁶⁷ described the Ruff degradation in their review of monosaccharide synthesis. Their proposed mechanism involves oxidation of the carbon atom adjacent to the carboxylate group to a keto group (Chart 5). While α -keto acids are known to decarboxylate in the presence of hydrogen peroxide,^{68,69} Isbell’s proof that the aldehydic product of the degradation

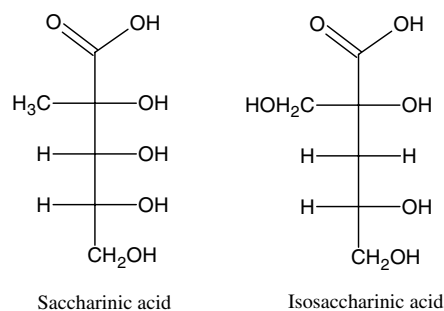


Chart 3. Saccharinic acids.

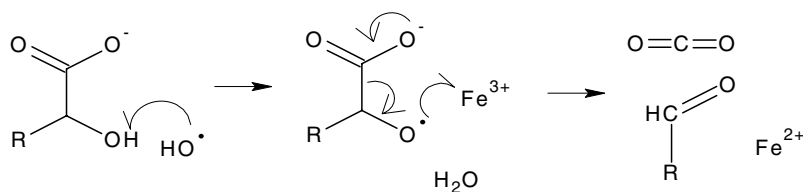


Chart 4. Isbell and Salam's proposed mechanism of the Ruff degradation.⁵⁶

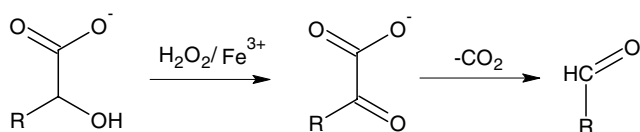


Chart 5. Hough and Richardson's proposed mechanism of the Ruff degradation.⁶⁷

retains its α -proton and the successful degradations of saccharinic acids rule out an α -keto acid pathway. Vázquez-Vivar et al.⁷⁰ concluded that decarboxylation of α -keto acids in a Fe(II) + H₂O₂ system follows two pathways (Chart 6), both of which produce acids rather than aldehydes.

Sosnovsky⁷¹ proposed a mechanism which is similar to and retains the major flaws of the Hough and Richardson proposal. Sosnovsky also conjectures that the specificity of the reaction is somehow affected by the occurrence of hydroperoxy radicals. Green⁷² and Varela,⁷³ agreeing with Moody,⁵² attributed the formation of a carboxyl radical to hydrogen atom abstraction and proceeded to suggest that the carboxyl radical undergoes degradation to liberate CO₂. We agree that

the formation of a carboxyl radical is one step in the mechanism, but disagree with the proposed mechanism of its formation on the following grounds. The Ruff degradation reaction only occurs when the carboxylic acid group is ionized (see Section 2.2) and there is no evidence that hydroperoxy radicals are formed in the copper variant of the reaction, the most efficient form of the reaction (see Section 2.3).

Buchanan et al.⁷⁴ proposed a mechanism (Chart 7) that also presents several problems. Primarily, the mechanism requires two Fe(II) atoms, while offering no scheme for their regeneration (another confusion with Fenton's reagent). Beyond the limitations set by the requirement of the initial reagents, the premise that a hydroxyl radical abstracts the beta proton is doubtful. Moreover, it has been shown that 3-deoxyaldoses are decarboxylated effectively in the Ruff degradation.^{75,76} Another compelling argument against the Buchanan mechanism is that there is no precedent or evidence for the isomerization between ketoses and aldoses under the conditions of the Ruff degradation. Indeed, isomerization would result in the production of both D-arabinose and D-ribose from D-gluconate, but D-ribose has not been observed.

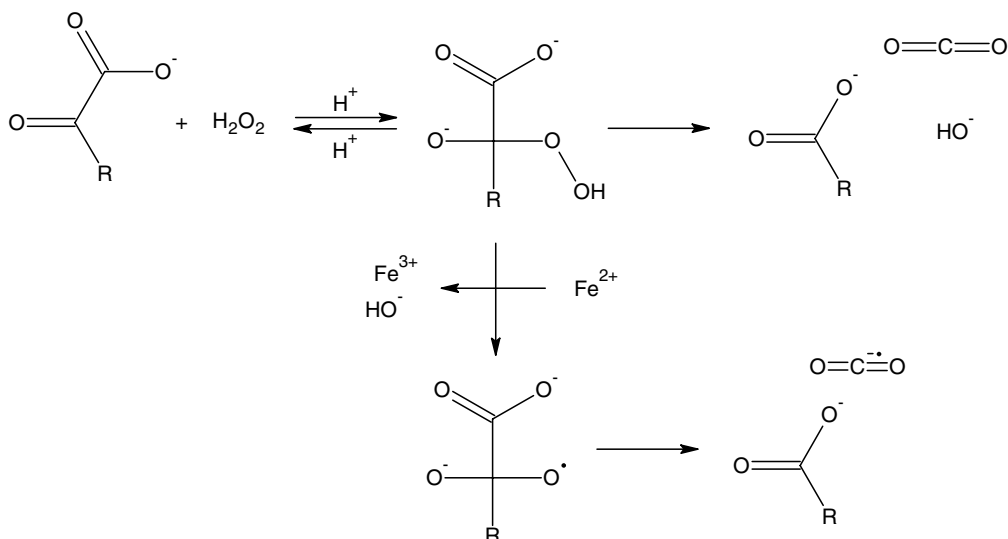


Chart 6. Decarboxylation of α -keto acids by Fenton's reagent according to Vázquez-Vivar et al.⁷⁰

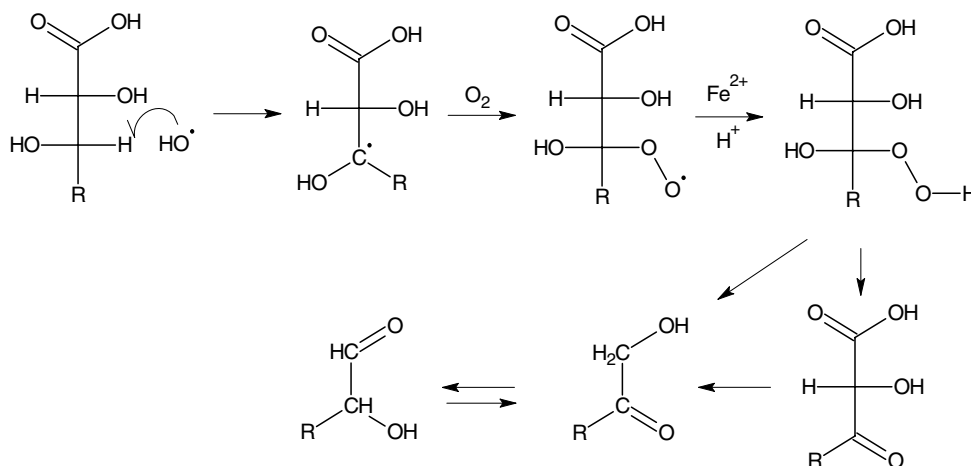


Chart 7. Proposed mechanism of the Ruff degradation by Buchanan et al.⁷⁴

While the discussed mechanisms are incompatible with the products of the Ruff degradation, it is likely that parts of them are involved to some extent and lead to reaction byproducts. As previously stated, the yields of product are less than 50% in the majority of cases, and the side reactions result in acidic compounds, potentially via the oxidative decarboxylation of α -keto acids.²⁶

Daniels²⁶ studied the Ruff degradation of several model compounds (α -hydroxy acids) and, in our opinion, provided the most convincing argument for the mechanism to date. Based on the results of experiments designed to investigate the effects of visible light, H_2O_2 , and pH on the reaction, he concluded that there are two basic classes of reactions occurring in the Ruff degradation. Foremost is the reaction yielding the aldehyde, which reaction proceeds via a Hofer–Moest-type decarboxylation (Chart 8). The other pathway involves abstraction of either α -protons or α -hydroxyl protons to yield free radicals and subsequent decarboxylation to acidic products. As sugars are chains of hydroxylated carbon atoms, the acidic products would continue to react. Daniels also observed a dependence of the Ruff degradation on light. In the dark, the radical abstraction pathways were the only reactions that occurred. In summary, Daniels describes the Ruff degradation as a decarboxylation by photo-induced decarboxylation of Fe(III) salts of aldonic acids, which results in the reduction of

iron to Fe(II), with Fe(III) being regenerated by hydrogen peroxide.

Major drawbacks of the Daniels mechanism are that Fe(III)–gluconate complexes are known to be stable⁷⁷ and that the Ruff degradation is exothermic and relatively rapid. It is obvious that the addition of hydrogen peroxide activates the reaction in some way that is not accounted for in the Daniels mechanism.

2.1. Metal ion regeneration

The mechanism by which iron and other transition metal ions decompose peroxides catalytically is also controversial and has been debated for more than 70 years. There are basically two camps involved in the debate: those who argue that the decomposition follows a free-radical chain process^{78,79} and those who support an ionic mechanism.^{80–82} While the arguments set forth in each case are persuasive, it is evident that the manner by which hydrogen peroxide decomposes in either a Fenton or a Fenton-like system varies with reaction conditions. The complexity of such systems requires empirical evidence to elucidate the mechanism of each system. The likely competition of mechanisms and the transience of intermediate species further complicate the determination of what occurs.

Buda et al.⁸³ and Ensing et al.⁸⁴ offer strong evidence that Fenton chemistry is essentially ionic in vacuo.

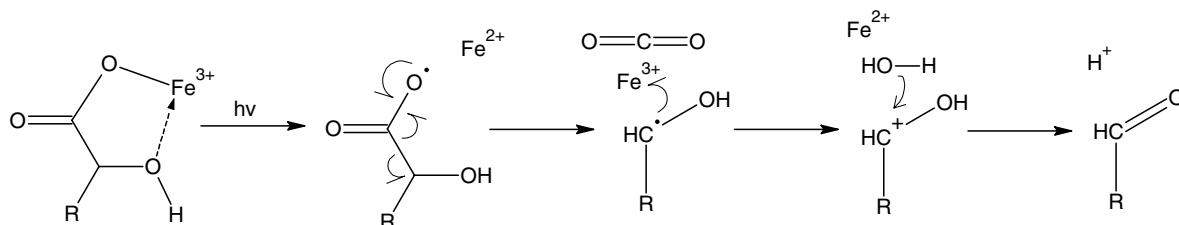


Chart 8. Proposed mechanism of the Ruff degradation, derived from Daniels.²⁶

However, there is a substantial evidence that, in aqueous systems like those pursued in this work, the degradation follows a radical pathway (Chart 9).^{85,86} (The scheme in Chart 9 has been simplified by the removal of the iron peroxide complex formation steps and is identical to the scheme originally proposed by Barb et al.^{87–89} and championed by Walling and Goosen.⁹⁰) Daniels²⁶ found that, when radical traps were present in the Ruff system, there were no acidic products formed; however, Sawyer et al.⁸⁰ state that radical traps will react with non-radical species. It is likely that there is some ionic degradation of hydrogen peroxide to yield Fe(IV) and Fe(V) species that react in a Hofer–Moest style mechanism; however, the large amount of byproduct formed in a standard Ruff system, and its exclusion by radical traps, suggests that much of the oxidation of iron ions may occur via radical pathways.

2.2. pH Dependency

Larsen and Smidsrød⁹¹ studied Fe(II)- and Fe(III)-catalyzed degradations of carbohydrates in the presence of hydrogen peroxide and found, as Daniels²⁶ later confirmed, that there are three pH ranges for the reactivity of aldonic acids in the Ruff system: (i) Below pH 1, where the aldose is produced in high yields by a non-metal ion-catalyzed, non-radical mechanism; (ii) pH 1–4, where the reaction conditions favor free-radical attack on the carbon chain; (iii) pH > 4, where aldose production increases with increasing pH. Larsen and Smidsrød⁹¹ suggest that this is due to the formation of a Fe(III)–H₂O₂–sugar acid complex which starts to form at pH 4 and predominates at pH 7, though little evidence is offered to support this hypothesis. Recent investigations found that purple EDTA–Fe(III)–peroxide complexes are common and become more stable as the pH is raised.^{92–95}

2.3. Other transition metal ion catalysts

Sala et al.⁹⁶ used Ce(IV) in stoichiometric amounts to decarboxylate calcium D-gluconate and obtained 94% yields of D-arabinose. Ce(IV) has also been used in catalytic amounts to decarboxylate D-gluconic acid effectively to yield D-arabinose. In these applications, Ce(IV) was regenerated electrochemically from

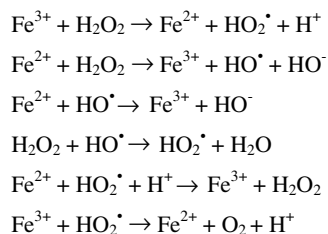


Chart 9. Fe(III), Fe(II)/H₂O₂ equilibrium.

Ce(III).^{97–101} The selectivity of the reaction was greater than 90%. The high selectivity, compared to the traditional Ruff degradation, is most likely due to the absence of hydroxyl radicals, which are not formed during the regeneration of Ce(IV).

Pare et al.¹⁰² found that aliphatic acids are decarboxylated slowly by permanganate ions, but that, when sufficient Mn(II) is formed or added, the decarboxylation proceeds much more rapidly, likely by the formation of Mn(III) species.



Mn(III) has been used to decarboxylate aliphatic acids oxidatively in organic solvents.¹⁰³ Mohri et al.¹⁰⁴ similarly found that α -aryl (benzylic) carboxylic acids were decarboxylated by Mn(III), with higher electron-withdrawing groups on the aromatic groups resulting in an increased efficiency. Mn(III), however, does not decarboxylate uronic acids at low pH values.¹⁰⁵

Alkaline manganese(IV)–gluconate complexes have been reported,^{106,107} which complexes when neutralized undergo a highly exothermic reaction accompanied by gas evolution. While the products of the reaction were not determined, the reaction is reminiscent of the Ruff degradation. Additionally, the results of these studies showed that Mn(II) was preferably oxidized to Mn(III) by oxygen rather than hydrogen peroxide, indicating the possibility of a Ruff degradation using oxygen as the primary oxidant.

Co(II) has been employed as a catalyst in a variant of the Ruff degradation, although at reduced efficiency compared to Fe(III).^{59,108}

Lead(IV) acetate has been employed in decarboxylation reactions¹⁰⁹ and in the selective cleavage of glycuronosidic linkages.^{110–113} The mechanism of this process must be similar to the Hofer–Moest electrolysis, with the formation of a carboxonium ion and, upon hydrolysis, the pentodialdose. The drawback of this process is that that Pb(IV) also effects 1,2-diol cleavage, so the carbohydrates must be completely protected.

Bi(III) has been used as an oxidant in organic synthesis. A novel system that employs atomic bismuth and O₂ in Me₂SO has been shown to decarboxylate mandelic acid derivatives.^{114,115} In this reaction, diatomic oxygen oxidizes metallic bismuth to Bi(III), which acts as the oxidant. While this system is outwardly similar to those discussed elsewhere in this section and is efficient, the mechanisms proposed by both Coin et al.¹¹⁴ and Favier and Duñach¹¹⁵ involve an α -keto acid pathway.

Ferraz et al.¹¹⁶ studied the reactions of β,γ -unsaturated carboxylic acids as thallium(III) diacetate salts in an organic solvent and found that unsaturated aliphatic acids primarily produced lactones, while acids containing an aromatic ring were decarboxylated to some extent. They proposed that the products of decarboxylation were formed by the formation of a rad-

ical on the carbon atom from which the carboxyl group was removed, followed by oxidation to produce a carbocation. This aspect is congruent with our proposed mechanism.

Kochi^{117,118} reviewed Kolbe/Hofer–Moest style decarboxylations by Pb(IV), Ag(II), Mn(III), Co(III), Ce(IV), and Th(III). Some of these ions and several others have been employed in Fenton systems [e.g., Fe(II), Cu(I), Ti(III), Cr(II), and Co(II)], and Fenton-like (Ruff) systems [e.g., Ce(IV), Np(VI), U(IV), Ag(II), Mn(III), and Co(III)].¹¹⁹ Kemp and Waters¹²⁰ concluded, from kinetic data, that several transition metal ions decarboxylate α -hydroxy acids following a Hofer–Moest style mechanism. Sodium molybdate and sodium tungstate have also been employed as catalysts in the decarboxylation of aldonic acids.¹²¹ Cobalt, ruthenium, and nickel, coupled with hydrogen peroxide, are reported to decarboxylate α -hydroxy carboxylic acids by shortening the chain by two carbon atoms instead of one, as is the case in the regular Ruff system.^{108,122,123} Lukáč et al.⁵⁹ successfully employed Ni(II) in the Ruff degradation of saccharinic acids, although at reduced efficiency compared to Fe(III). Daniels²⁶ reported that Ti(IV) may be used in a Ruff-style oxidative decarboxylation and that many metal ions with the oxidation state of +3 (Sc, Y, Al, La, and Ga) are impotent as far as decarboxylation is concerned. Hourdin et al.¹²⁴ reported that titanium-containing zeolites were not effective as catalysts in the Ruff degradation, while copper zeolites were effective.^{55,125} Au(III),¹²⁶ Pt(IV),¹²⁷ and Ir(IV)¹²⁸ have been used to decarboxylate α -hydroxy acids with a proposed Hofer–Moest style mechanism. Ag(II) is the suspected active species in the silver-catalyzed peroxydisulfate decarboxylation of α -hydroxy acids.^{129–131} Guernert¹³² found that boiling a solution of Hg(II) D-gluconate gave D-arabinose. Subsequently, Sayre and Jensen¹³³ described a ‘novel’ decarboxylation employing Hg(II).

Previously reported applications of Ruff’s reagent have been chain-shortening reactions, that is, oxidative decarboxylations of aldonic acids to yield aldoses of one less carbon atom than the original aldonic acid. Much of this research has been related to the production of D-arabinose from D-gluconate (although the reaction has been applied to most aldonic acids). The use of Cu(II) in the Ruff degradation is a recent innovation. The majority of the literature on its use is in the form of patents. Inherent in the nature of such disclosures is a lack of mechanistic or descriptive data on the reaction. Few explorations of these fundamentals have been reported in peer-reviewed literature.

When the products of a Cu(II)-catalyzed Ruff degradation of D-gluconate (Fig. 1) are compared to those of an Fe(III)-catalyzed Ruff degradation (Fig. 2), the difference is dramatic.¹³⁴ (The difference in elution times of identical compounds between these chromatograms is

a result of a change in the procedure. The peaks of interest were verified by comparison against standards.) Several differences are remarkable. First is the specificity of the copper-catalyzed decarboxylation and the purity of the product. There are essentially no products other than arabinose formed. Moreover, the amount of D-gluconate decarboxylated is substantially more when copper ions are present. [The reaction time of the reaction of Fig. 1 is much less than that of the reaction of Fig. 2 and the temperature of the reaction represented by Fig. 2 is higher (15 min, pH 7.0, rt vs 115 min, pH 6.5, 40 °C).] These differences are consistent with reports that the regeneration of Fe(III) by hydrogen peroxide creates radicals, that these radicals are responsible for byproduct formation,²⁶ and that copper ions are more effective than iron ions in the Ruff degradation.^{122,135} The lack of byproducts (Fig. 1) is consistent with the hypothesis of a Cu(III) intermediate that is regenerated ionically.

Bilik¹³⁵ was the first to use copper, rather than iron, ions in the Ruff degradation. While it has been documented that copper ions are more effective than iron

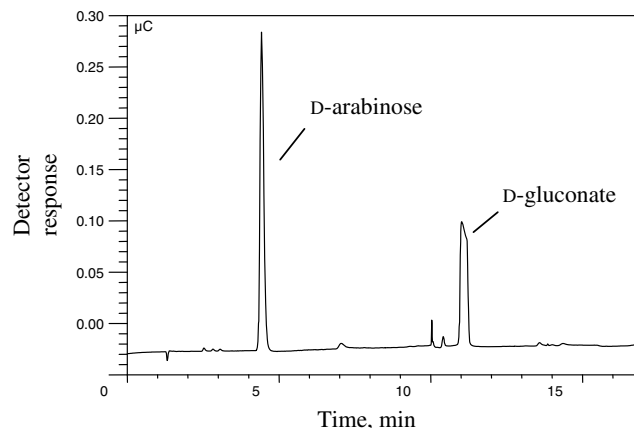


Figure 1. Cu(II) Ruff degradation of D-gluconate.¹³⁴

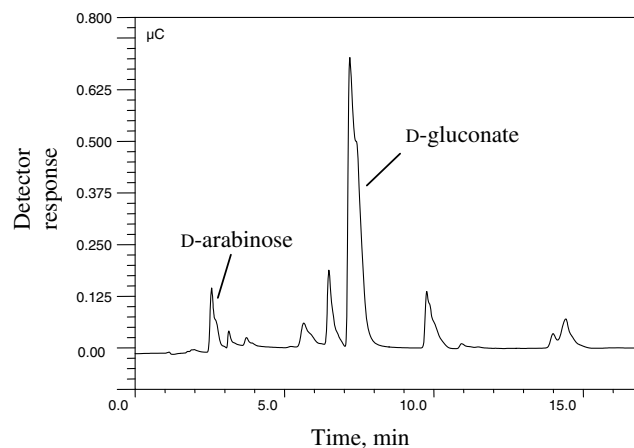


Figure 2. Fe(III) Ruff degradation of D-gluconate.¹³⁴

ions in the Ruff degradation of acidic sugars,^{121,136} comparative and explicative details have not been reported. Copper has been implemented in several contemporary Ruff degradation innovations.^{55,125,137} Undoubtedly, the kinetics and pH sensitivity of a Cu(II) + H₂O₂ system differ greatly from those of the classical Ruff reagent, but these aspects have not been investigated and reported. Cu(II) decarboxylations occur at temperatures above 180 °C.¹³⁸

A review of the literature suggests that the active species in the copper variant of the Ruff system is Cu(III). Toussaint et al.¹³⁹ described the Cu(I) + oxygen decarboxylation of aliphatic and α -hydroxy acids in organic solvents, proposing a Cu(III) intermediate. Cu(III) is an unstable species that exists in few isolatable forms. Cu(III)–peptide complexes^{140–142} are known to decarboxylate α -keto acids oxidatively.¹⁴³ Stable Cu(III) salts of periodate and tellurate have been shown to decarboxylate α -hydroxy acids to yield aldehydes and ketones quite efficiently,^{144–146} as well as convert aliphatic acids to alcohols,¹⁴⁷ but proposed mechanisms are sketchy.

Cu(III)–biuret complexes have been used to decarboxylate α -aryl (benzylic) carboxylic acids in organic solvents.¹⁴⁸ Johnson et al.^{149,150} argued that Cu(I) forms Cu(III) in the presence of H₂O₂ by an ionic mechanism, but there is a dissenting opinion.¹⁵¹ Ulanski and von Sonntag¹⁵² described the equilibrium between Cu(II), the hydroxyl radical, and Cu(III). Cu(III) salts of periodate and tellurate have been prepared by the treatment of Cu(II) salts with peroxydisulfate.¹⁴⁶ If Cu(III) is the active species, then the reaction with copper is likely to proceed independently of the presence of light.

We hypothesize that Cu(III) is indeed the active species of the copper variant of the Ruff degradation. However, the spectra^{142,153} of potential Cu(III)–carbohydrate complexes could not be obtained, as hydrogen peroxide absorbs across the spectrum of interest and the complexes were too ephemeral to be measured without its presence. We further hypothesize that aldones readily react with Cu(III) to yield aldoses with one less carbon atom via the Hofer–Moest mechanism.

The abilities of and propensities for carbohydrates to form complexes with metal ions have been reviewed.⁷⁶ While many conflicting data have been reported, Gajda et al.¹⁵⁴ offer the most complete and convincing study of the coordination chemistry of hydroxy acids and Cu(II). Using potentiometry, circular dichroism, EPR, and ¹³C NMR, they characterized the Cu(II)–aldonate complexes formed over varying pH values and found that all aldonic acids studied formed analogous complexes under the same conditions.

According to Gyurcsik and Nagy,⁷⁷ carboxylate groups act as ‘anchoring groups’ that, when coordinated to a metal ion, facilitate deprotonation and complexation with the neighboring hydroxyl groups, forming stable species. We believe that it is likely that the formation

of a Cu(II) salt lowers the pK_a of the α -hydroxyl group sufficiently to allow O-2 deprotonation. Gajda et al.¹⁵⁴ found that, at equimolar concentrations of Cu(II) and D-gluconate at pH 7, more than 80% of copper was bound in the binuclear complex Cu₂L₂H₋₃. As the ratio of D-gluconate to copper was increased, the predominant species became Cu₁L₂H₋₂, such that at ratios of greater than 50:1, Cu₁L₂H₋₂ was the only copper species in solution. Chart 10 shows the structure of Cu₁L₂H₋₂ as determined in their investigation. It is evident that the hydroxyl groups at C-2 have been deprotonated and are participating in the ligation.

The complexes of aldonic and uronic acids with iron ions have been studied, but again there is conflicting data⁷⁶ and the exact structures of the complexes have not been determined.

The combined observations that all aldonic acids form M₁L₂H₋₂ complexes, that the Ruff degradation is successful on all aldonic acids, and that D-gluconate–Cu(II) complexes are of a different structure and resistant to decarboxylation¹³⁴ suggest that the M₁L₂H₋₂ complex is necessary for decarboxylation.

Uronic acids are not decarboxylated effectively by the Ruff degradation reaction.¹³⁴ When in the pyranose ring form, the hydroxyl group alpha to the carboxylate group of uronic acids is part of the hemiacetal structure and is, therefore, an –OR group. In order to study a simple but analogous system, lactic acid and 2-methoxypropanoic acid were subjected to the copper variant (the most effective variant) of the Ruff degradation reaction.¹³⁴ While lactic acid was readily decarboxylated, yielding acetaldehyde (HPLC), 2-methoxypropanoic acid remained unaffected by the Cu(II) version of the Ruff reagent, and the time in which hydrogen peroxide was completely decomposed was almost an order of magnitude longer.¹³⁴

Citric acid, which is known for its excellent capacity to chelate metal ions, was also subjected to Ruff degra-

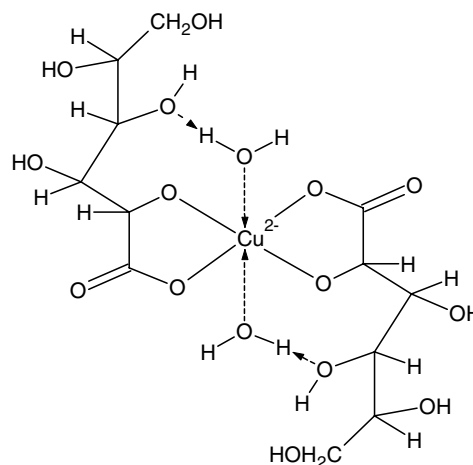


Chart 10. Cu(II)/D-gluconate complex according to Gajda et al.¹⁵⁴

dation conditions.¹³⁴ While citric acid is an α -hydroxy acid, it is thought to form a binuclear complex with metal ions that does not involve the hydroxyl group (Chart 11).³⁴ The color of the reaction mixture did not change with the addition of hydrogen peroxide, nor was the addition accompanied by either effervescence or a drop in pH. Only minor effervescence was observed when the reaction mixture was heated. After 360 min, a large amount of hydrogen peroxide remained and was decomposed by the addition of a small amount of platinum-on-carbon. The chromatogram of the reaction mixture indicated no decomposition of the citrate.¹³⁴ This is a further evidence that an α -alkoxo ligation of the metal ion is required to lower the oxidation potential of the complex to the extent that hypervalent transition metal ion species are formed and effect the one-electron oxidation that initiates decarboxylation.

Hofer–Moest style decomposition of citrate–Fe(III) complexes has been reported by others,³⁴ however, high-intensity light was required for the reaction to occur. As previously mentioned, Daniels²⁶ reported that the Fe(III) version of the Ruff degradation required light to be effective. The Abrahamson et al.³⁴ research indicates that carboxylates that are resistant to decarboxylation under normal Ruff conditions may be decarboxylated under a high-intensity light source. These data suggest that stable iron carboxylate complexes may form and that such complexes increase the activation energy of electron transfer.

Together, the data gathered suggest that a carboxylic acid requires a hydroxyl group in the α -position in order to be susceptible to the Ruff degradation. The data also suggest a mechanism in which carboxylates with a free α -hydroxyl group form a complex with the metal ion as shown in Chart 12. The metal ion is then ‘activated’

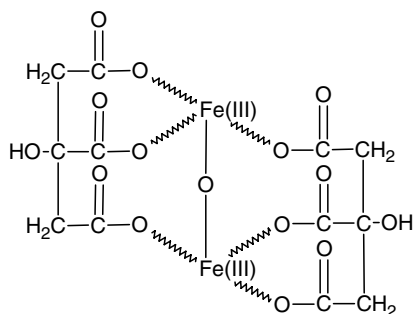


Chart 11. Binuclear complex of Fe(III) and citrate.

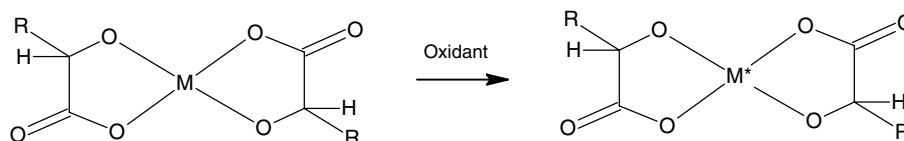


Chart 12. Proposed activation of the metal ion/carboxylate complex of the Ruff degradation.

by the presence of an oxidant. Unlike carboxylate ligands, which are weak, the alkoxo ligand is strong. The oxidation potentials for metal ions are reduced with increasing ligand strength or ‘hardness’.^{140,155} It is, therefore, plausible that, while many metal ion–carboxylate complexes react with hydrogen peroxide, only those with alkoxo ligands (i.e., an α -hydroxyl group) have a low enough oxidation potential to form Cu(III). As Cu(III) will decarboxylate even aliphatic acids, it is reasonable to conclude that it is not being formed in the absence of alkoxo ligands. Additionally, the reduction potential of Cu(III) could be reduced below the oxidation potential of the carboxylic acid (as in the case of many Cu(III)–peptide complexes); however, it is unlikely that this occurs in the Ruff degradation because of ligation. While it is likely that Cu(III) is the active species, it has not been observed directly and the data are, therefore, equivocal. A copper–peroxide complex, such as that proposed by Sutton¹⁵⁶ or Johnson and Nazhat,¹⁵⁷ or a copper–hydroxyl radical complex, such as that proposed by Johnson et al.,¹⁵⁸ may also be the active species.

Upon activation, one of the carboxylate metal bonds undergoes homolytic cleavage, resulting in a reduced metal ion [Cu(II)] and the formation of an acyloxy radical. The radical degrades via a Hofer–Moest-style mechanism, yielding an aldehyde.

In the case of Fe(III), Daniels²⁶ observed that the decarboxylation was light dependant. Knowing that all Fe(III) carboxylate complexes are susceptible to decarboxylation, but knowing that such decarboxylation requires an extensive irradiation, it is likely that the Fe(III)–carboxylate complex is also ‘activated’ by hydrogen peroxide, that is, the iron is oxidized to a higher oxidation state. There is, however, insufficient data to speculate as to the oxidation state of the active iron species.

A two-electron oxidation may also be considered as a potential mechanism (Chart 13). In such a case, the decarboxylation occurs in one step, with neither radical nor cation intermediates and is similar to the mechanism proposed by Toussaint et al.¹³⁹ in their oxygen-induced decarboxylation of anhydrous Cu(I) salts of α -hydroxy acids. Cu(III), Fe(IV), Fe(V), and Fe(VI) could be viable active species as they allow for a two-electron reduction. Kemp and Waters¹²⁰ concluded that Ce(IV) and Mn(III) decarboxylate α -hydroxy acids by a one-electron oxidation. While the oxidation states of these two

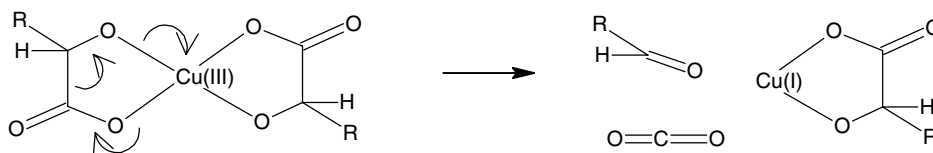


Chart 13. Alternative mechanism for the Ruff degradation.

ionic species do not allow for a two-electron transfer, they behave similarly to the Cu(III) decarboxylations already discussed. The fact that Cu(III) salts decarboxylate even aliphatic acids would suggest that any lack of decarboxylation is a result of Cu(III) not being formed.

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