

**Chemistry of Functionalized Organic Intermediates in the Earth's Atmosphere:
Impact, Challenges, and Progress**

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Abstract

The gas-phase oxidation of organic compounds is a key chemical process in the Earth's atmosphere, governing oxidant levels and controlling the production of key secondary pollutants, and hence has major implications for air quality and climate. Organic oxidation is largely controlled by the chemistry of a few key reactive intermediates, namely alkyl (R) radicals, alkoxy (RO) radicals, peroxy (RO₂) radicals, and carbonyl oxides, which may undergo a number of unimolecular and bimolecular reactions. Our understanding of these intermediates, and the reaction pathways available to them, is based largely on studies of unfunctionalized intermediates, formed in the first steps of hydrocarbon oxidation. However, it has become increasingly clear that intermediates with functional groups, which are generally formed later in the oxidation process, can exhibit fundamentally different reactivity than unfunctionalized ones. In this perspective, we explore the unique chemistry available to functionalized organic intermediates in the Earth's atmosphere. After a brief review of the canonical chemistry available to unfunctionalized intermediates, we discuss how the addition of functional groups can introduce new reactions, either by changing the energetics or kinetics of a given reaction, or by opening up new chemical pathways. We then provide examples of atmospheric reaction classes that are available only to functionalized intermediates. Some of these, such as unimolecular H-shift reactions of RO₂ radicals, have been elucidated only relatively recently, and have can have important impacts on atmospheric chemistry (e.g., on radical cycling or organic aerosol formation); it seems likely that other, as-yet undiscovered reaction of (multi)functional intermediates may also exist. We discuss the challenges associated with the study of the chemistry of such intermediates, and review novel experimental and theoretical approaches that have recently provided (or hold promise for providing) new insights into their atmospheric chemistry. The continued use and development of such techniques, and the close collaboration between experimentalists and theoreticians, is necessary for a complete, detailed understanding of the chemistry of functionalized intermediates, and their impact on major atmospheric chemical processes.

I. Introduction

The gas-phase oxidation of non-methane volatile organic compounds (VOCs) is a central to the chemistry of Earth's atmosphere, playing an important role in air quality, human health, and global climate.¹ VOCs are emitted into the atmosphere from a variety of sources, including anthropogenic sources such as fossil fuel use, natural sources like terrestrial vegetation, and biomass burning.²⁻⁴ VOCs emitted into the atmosphere (primary VOCs) are dominated by hydrocarbons, such as biogenic terpenoids (e.g., isoprene and monoterpenes), and anthropogenic species (e.g., alkanes and aromatics); some oxygenated organic species are emitted directly as well. Once emitted, most of these species undergo oxidation by strong oxidants (most importantly OH but also O₃, NO₃, and others), leading to the formation of a wide variety of reaction products (secondary species), which can be both inorganic (CO and CO₂) or organic. Many oxidation pathways are typically available, and so secondary organic species formed from the oxidation of even a single organic precursor can number in the thousands.⁵ These secondary species are highly varied in structure, and may be smaller and/or more oxidized than their primary counterparts, due to reactions that break C-C bonds and/or add functional groups (including hydroxy, peroxy, carbonyl, acid, and nitrate groups) to the carbon skeleton.⁶ Thus, their key properties, such as volatility, solubility, and reactivity, can be fundamentally different from those of the parent species (and each other). Oxidation chemistry can occur over multiple generations, with secondary organic compounds undergoing further reactions to form an even more oxidized and complex mixture of products. The chemical evolution of this ensemble of organic species governs oxidant levels in the atmosphere, and controls the production of key secondary pollutants. These include tropospheric ozone and secondary organic aerosol (SOA) (a major component of atmospheric particulate matter),⁷ both of which have major impacts on air quality and radiative forcing.^{8,9}

Historically, much of our understanding of these oxidation processes is from efforts to understand the production of ground-level ozone (a key component of urban smog). This process which

is now reasonably well-captured by concise descriptions of oxidation mechanisms: air quality models can now reasonably accurately estimate measured ozone levels, using condensed chemical mechanisms that include a very limited number of reactions and leave out many details regarding how organic molecules evolve in the atmosphere.¹⁰

However, such details matter in determining other impacts of atmospheric organic oxidation. A key example is the production of SOA, which occurs via reactions that lower the volatility of the organic species. The kinetics, products, and branching ratios of these reactions govern the amounts, properties, and ultimate impacts of the SOA. For example, the amount of SOA formed (both mass and number concentration) is a strong function of the changes to volatility of organic species upon oxidation. Further, the identities (molecular structures) of the particle-phase species formed in these reactions may influence particles' interactions with light and water,¹¹ as well as their toxicities, and hence their impacts on climate and human health.¹²

Radical cycling and the oxidation capacity of the atmosphere also depend critically on the detailed mechanisms of atmospheric VOC oxidation. In the absence of any radical recycling or regeneration, the oxidation of VOCs by radicals such as OH might be expected to drive down the radical concentrations.¹³ However, when radicals or oxidants are regenerated as part of the VOC oxidation process (via photolysis reactions or radical propagation reactions),^{14,15} this effect will be buffered considerably. This balance between oxidant loss and regeneration means that organic oxidation mechanisms can have a controlling influence on atmospheric oxidant levels, which in turn control the lifetimes of a wide range of both organic and inorganic atmospheric constituents.

A detailed and complete understanding of the atmospheric oxidation of organic species is thus critical to accurately predicting the extent of impacts of key atmospheric processes (such as SOA formation and radical cycling). Such predictions are typically carried out using chemical transport models

or earth system models; which generally employ reduced mechanisms based on our current understanding of oxidation processes and the formation of secondary organic species. However, there are often major incongruities between the predictions from such models and atmospheric observations. For example, there are longstanding discrepancies between measured and modeled SOA concentrations,¹⁶ OH levels (particularly in remote regions),¹⁷ and OH reactivity.¹⁸ These suggest gaps in our understanding of detailed organic oxidation processes, particularly related to the formation of low-volatility organic species and the cycling of radicals.

The chemistry of atmospheric organic oxidation processes is largely determined by the behavior of a few key reactive intermediates, namely alkyl (R) radicals, alkoxy (RO) radicals, peroxy (RO₂) radicals, and carbonyl oxides (R₁R₂COO)^{6,19} (we restrict our discussion of these intermediates to the gas phase, though they can also be involved in condensed-phase and heterogeneous oxidation). Such reactive intermediates serve as branch points in the complex web of unimolecular and bimolecular reactions that make up atmospheric organic oxidation chemistry. There are typically a number of pathways available to each intermediate, with branching ratios that depend on factors such as the chemical structure of the intermediate, the energy with which it is formed, the local concentrations of bimolecular reaction partners, and environmental parameters (most importantly temperature and pressure). Understanding the relative importance of these competing pathways is a central challenge in atmospheric organic chemistry.

Decades of theoretical and experimental work have built a canonical picture of organic oxidation mechanisms, and specifically the reaction pathways available to key organic intermediates.^{6,20,21} Because of the longstanding focus on the oxidation of emitted hydrocarbons, this picture is primarily based on the chemistry of unfunctionalized (alkyl-substituted) intermediates. The chemistry of functionalized intermediates, such as those formed in the oxidation of oxygenated VOC or in later steps of hydrocarbon oxidation, have also received considerable study,²¹ though substantially less than their alkyl-substituted

counterparts, and descriptions of their chemistry are typically based on hydrocarbon oxidation mechanisms. Functional groups can affect the potential energy landscape of a reaction system, so functional-group based differences in reaction rates are often considered and predicted using structure-activity relationships (SARs);²² but broadly speaking the reactions themselves are assumed to be the same or similar to those of unfunctionalized species.

However, functional groups can also dramatically alter the reactivity of the intermediates, opening up new reaction pathways and forming products that are fundamentally different from those of the unfunctionalized intermediates. Some of these channels have long been known and are already incorporated into atmospheric reaction schemes. But as described below, many channels have been elucidated only in recent years, and it is likely that additional reaction pathways for functionalized intermediates may be important, but have yet to be discovered.

The aim of this Perspective is to illustrate the importance of, and discuss the challenges associated with, describing the unique chemistry available to functionalized organic intermediates (R , RO , RO_2 , and R_1R_2COO) in the atmosphere. We begin by briefly reviewing the canonical chemistry available to unfunctionalized intermediates, before delving into known examples of reactions available only to functionalized ones. We discuss recent experimental and theoretical advances that have enabled the discovery and exploration of these pathways, and outline challenges associated with making progress in our understanding of such chemistry. Finally, we discuss broad approaches that hold promise for continued progress in unraveling the chemistry of functionalized species in the atmosphere.

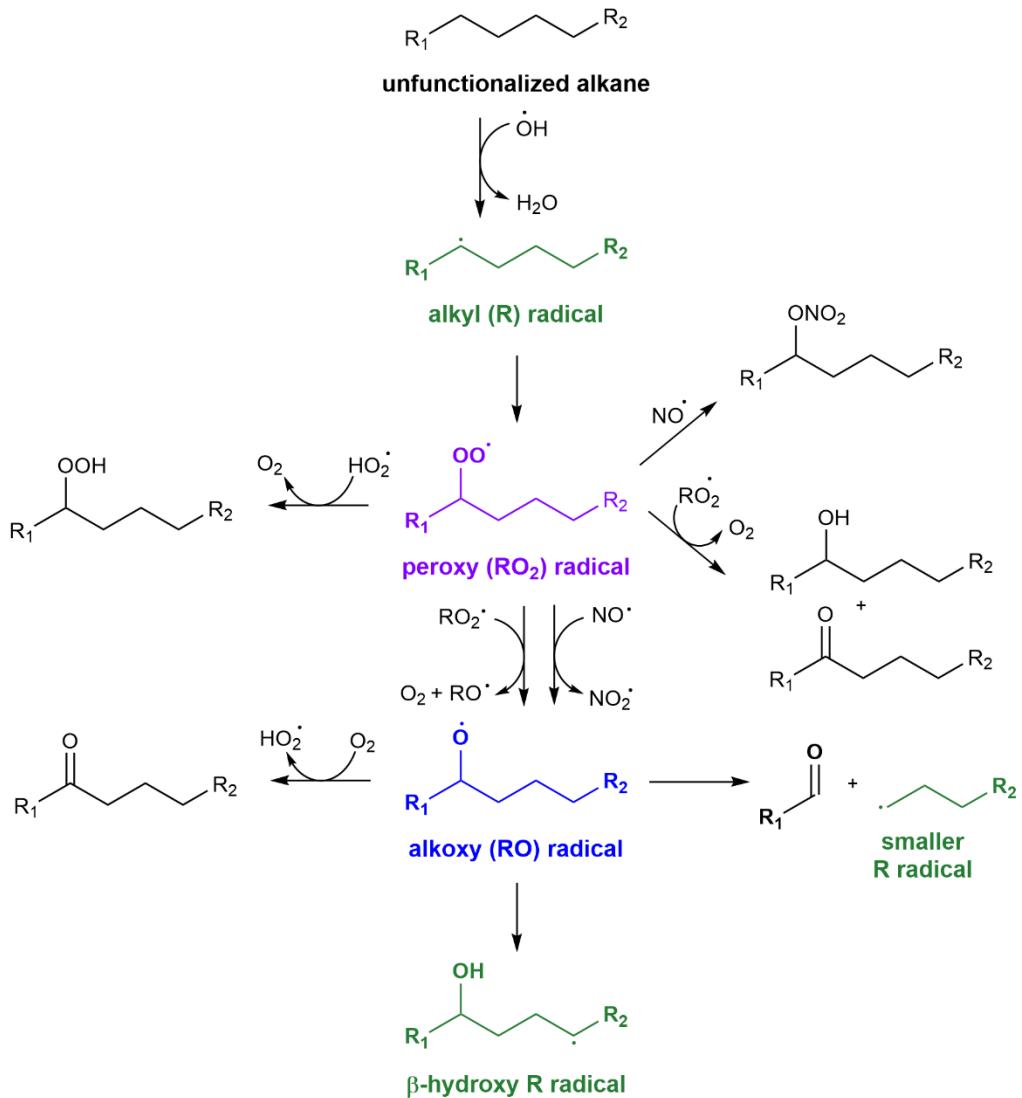


Figure 1: Chemistry available to unfunctionalized (alkyl-substituted) alkyl radicals (R , green), alkoxy radicals (RO , blue), and peroxy radicals (RO_2 , purple).

II. Reactions of Unfunctionalized Intermediates

We begin by briefly outlining the standard (“canonical”) pathways available to unfunctionalized R , RO , RO_2 , and carbonyl oxide intermediates. These reactions, shown in Figure 1 (for R , RO , and RO_2), and Figure 2 (for carbonyl oxides), represent the chemistry that any new pathways available only to

functionalized intermediates will compete with. Reactions unique to functionalized species are not included here, and instead are discussed in the following section.

a. Unfunctionalized Alkyl (R) Radicals

Alkyl (R) radicals in the atmosphere are primarily formed in the initial steps of oxidation of a closed-shell species, in which a radical (OH, NO₃, etc.) abstracts an H atom or adds to a double bond. They may also be formed by photolysis.⁶ Unfunctionalized R radicals mainly react with O₂, forming an RO₂ radical. The typical pseudo-first order rate coefficient (at 298K and 21% O₂) for the reaction of an R radical with O₂ is on the order of 10⁷-10⁸ s⁻¹,²³ considerably faster than any other possible competing pathway at atmospheric temperatures, and is typically the only fate considered for these radicals in oxidation mechanisms.

b. Unfunctionalized Peroxy (RO₂) Radicals

Peroxy (RO₂) radicals, formed from the R+O₂ reaction described above, have traditionally been assumed to react mostly via bimolecular processes with a variety of partners, primarily NO and HO₂.^{6,24} (For most unfunctionalized RO₂, unimolecular reactions, such as isomerization to form QOOH, are too slow to compete with these bimolecular reactions under atmospheric conditions;²⁵ these reactions are discussed in the following section.) The rate coefficients for the RO₂ + NO reaction do not vary substantially with the structure of the peroxy radical, with a typical value of $\sim 8.5 \times 10^{-12}$ cm³ molecule⁻¹ s⁻¹ at 298 K.²⁴ This reaction primarily yields an RO radical and NO₂, and thus is central to the chemistry of the atmosphere because the resulting NO₂ can photolyze to form ozone. Alternatively, a minor channel available to RO₂+NO is the formation of an organic nitrate (RONO₂); the branching between the two RO₂ + NO pathways is a complex function of the size and structure of the RO₂ radical itself, as well as the temperature and pressure. The RO₂ + HO₂ reaction rate constant is weakly dependent on the size of the RO₂ radical, but in general has a value on the order of 10⁻¹¹ cm³ molecule⁻¹ s⁻¹ at 298 K.²⁴ This reaction of

unfunctionalized RO₂ with HO₂ produces a hydroperoxide (ROOH) plus O₂, and is thus a chain-terminating reaction step. Local concentrations of these co-reactants vary considerably according to the environment, so that RO₂ radicals can have lifetimes with respect to their reaction with NO and HO₂ that range from less than a second to several minutes.²⁶

In addition to these major pathways, RO₂ radicals may also undergo self- or cross-reactions with other RO₂ radicals. This reaction may be either chain terminating, yielding alcohol and carbonyl products (ROH + R'=O + O₂), or chain propagating, yielding 2 alkoxy radicals and an O₂.²⁴ RO₂ radicals may also react with NO₂ to form a peroxy nitrate (ROONO₂); for unfunctionalized RO₂ this product has a short thermal lifetime and so represents an important loss process for RO₂ only at very low (e.g., upper-tropospheric) temperatures.²⁷

c. Unfunctionalized Alkoxy (RO) Radicals

Alkoxy (RO) radicals form from bimolecular reactions of RO₂ radicals, as well as from photolysis of oxygenates such as peroxides, hydroperoxides, and organic nitrates. There are generally three canonical pathways for the reaction of RO radicals in the atmosphere.^{28,29} The first is an α-C-C bond scission, yielding a carbonyl and a new R radical. The second is H-abstraction by O₂, yielding a closed-shell carbonyl product and an HO₂ radical. Finally, alkoxy radicals may undergo an intramolecular 1,4 H-atom shift reaction,²⁵ yielding an OH-substituted R radical. The branching between the pathways described above is determined by a combination of factors including temperature, pressure, and, most critically, the structure of the alkoxy radical itself (This branching is discussed in detail in references ^{30,31}). RO radicals typically have atmospheric lifetimes with respect to these pathways on the order of μs to ms.

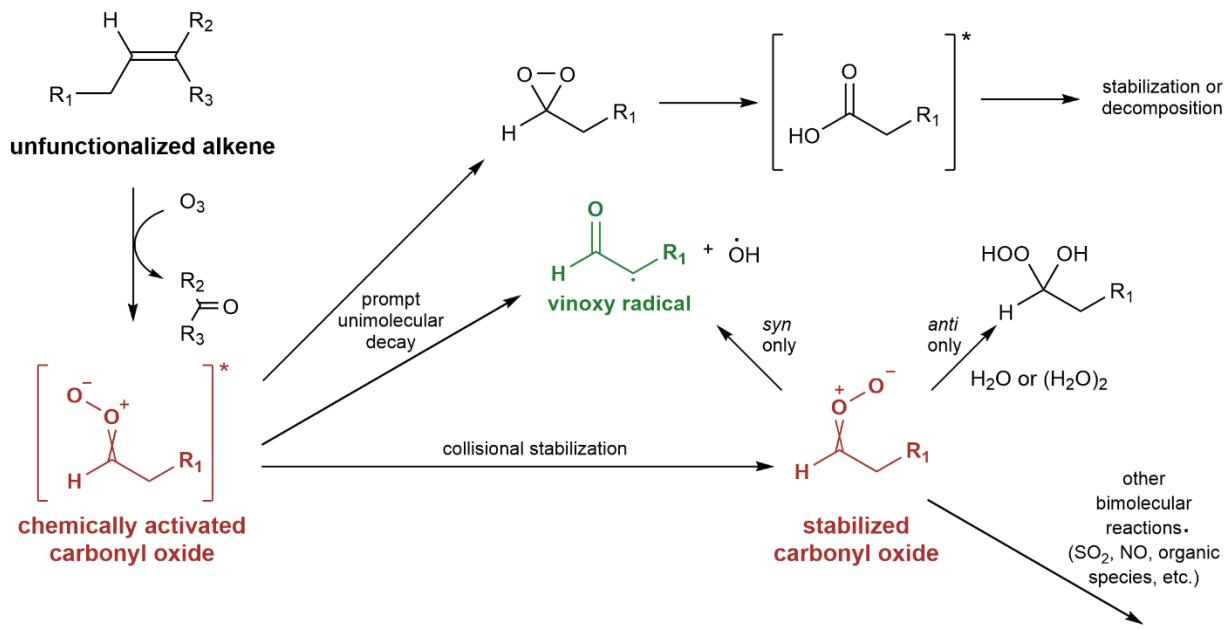


Figure 2: Chemistry available to unfunctionalized (alkyl-substituted) carbonyl oxides (red)

d. Unfunctionalized Carbonyl Oxides

Carbonyl oxides ($\text{R}_1\text{R}_2\text{COO}$) are formed in the ozonolysis of alkenes, as shown in Figure 2.³² Because the ozonolysis reaction is highly exothermic, carbonyl oxides are born with a high degree of internal excitation.³³ The nascent, excited carbonyl oxides have two possible pathways available to them: unimolecular decomposition, or stabilization via collision with a third body. The relative importance of these two pathways depends on pressure and temperature, the size (number of vibrational modes) of the intermediate, and the energetics associated with the unimolecular decomposition pathways. Once stabilized, the carbonyl oxides can undergo thermal unimolecular decomposition or bimolecular reaction.^{34,35}

The unimolecular pathways available under both chemically activated and thermal conditions are highly dependent on the structure and conformation of the carbonyl oxide. If an α -H-atom is present, and the carbonyl oxide group is oriented such that the terminal oxygen is on the same side of the C-O

bond as this α -H-atom (typically referred to as the *syn* conformation), it can undergo a 1,4 H-atom transfer reaction, to produce a vinyl hydroperoxide intermediate, which then rapidly decomposes to yield OH and a vinoxy radical.³⁶ The vinoxy radical essentially behaves as a carbonyl-substituted R radical. If an α -H-atom is not available, or if it is *anti* to the terminal oxygen of the carbonyl oxide group, available unimolecular reactions involve the formation of a dioxirane intermediate, leading to an assortment of decomposition products.³⁵

If the excited carbonyl oxides are collisionally stabilized, they are also subject to a number of bimolecular reactions. The most prominent is reaction with water vapor, which yields a hydroxy hydroperoxide species. This reaction is most important for carbonyl oxides that have only an H-atom in the *syn* position of the carbonyl oxide group (for example, *anti*-CH₃CHO). In these cases, where reaction with water can be quite fast (lifetimes with respect to reaction with water on the order of 10⁻³ s)³⁴, and the unimolecular reaction pathways are quite slow, reaction with water is likely to dominate the fate of the carbonyl oxide. There have been a number of investigations of bimolecular reactions of carbonyl oxides with other partners including other SO₂ (as a possible source of H₂SO₄),³⁷ carbonyl oxides, organic and inorganic acids, alkenes, amines, peroxy radicals, NO, and more.³⁴ In many cases, these reactions are quite fast. Though low concentrations of reaction partners prevent these reactions from being major sinks for carbonyl oxides, they may serve as sources of product species.

III. Reactions of functionalized intermediates

Our understanding of the pathways described above are a result of a large number of experimental and theoretical studies carried out over many years.^{6,20,21} The focus on unfunctionalized species was a result both of the need to understand the oxidation of atmospherically abundant hydrocarbons and of the relative simplicity afforded by unfunctionalized intermediates. However, the chemistry of functionalized intermediates (those formed in later steps of hydrocarbon oxidation, and in

the oxidation of atmospheric oxygenates), may exhibit entirely different reactivity than their unfunctionalized counterparts. Thus, the reactions described above (and shown in Figures 1 and 2) may not accurately describe their reactivity, or their ultimate impacts. Instead, there may be pathways that are wholly different from traditional oxidation mechanisms, and are available only to intermediates with particular functional groups present. Here, we discuss examples of chemistry available only to particular functionalized intermediates. While some of these have been known for some time, many of them have been elucidated only recently. We group these reactions into two broad categories, based on the effect of the functional group(s): those whose functional groups affect the reaction energetics and kinetics to change the relative importance of a given reaction, and those whose functional groups are directly involved in the chemical transformations, thereby opening up fundamentally new reactions.

a. Reactions enabled by changes in energetics/kinetics by the functional group

Typically, it is assumed that the effects of functional groups are to simply alter the kinetics, energetics, and branching ratios associated with known pathways, due to differences in barrier heights and/or reaction energies (i.e., by stabilization or destabilization of a reactant, transition state, or product). For singly functionalized intermediates at least, these effects are often described using SARs. But in some cases, such changes to the kinetics or thermodynamics can be so great that they enable transformations that essentially would not occur for unfunctionalized (or less-functionalized) species; these alterations can have important atmospheric consequences. Major known examples of such reactions, shown in Figure 3, are discussed below.

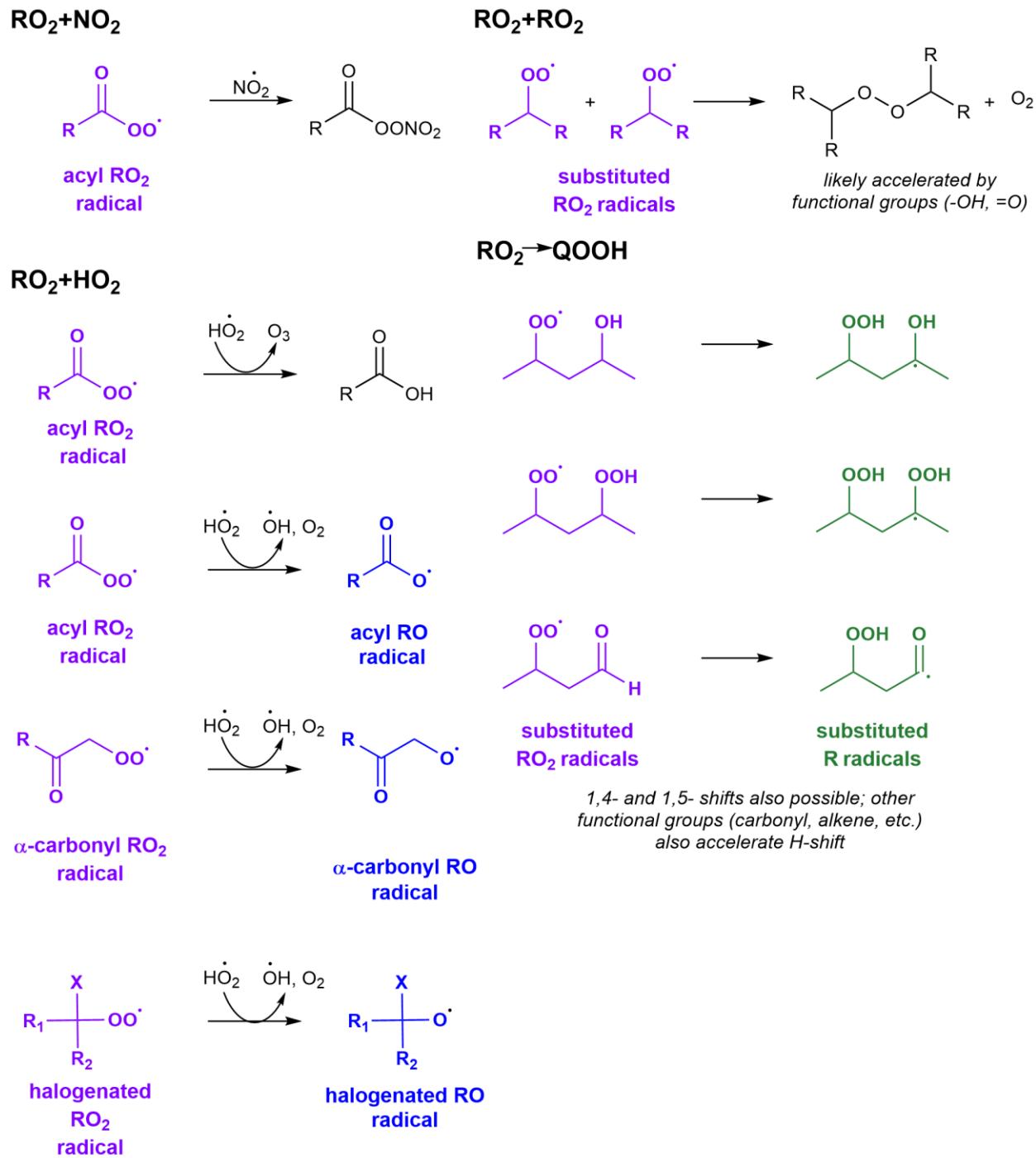


Figure 3: Known reactions available to only to functionalized intermediates, in which the functional groups alter chemistry by changing the potential energy landscape.

- RO₂+NO₂. One example of such a reaction long been known to be important in atmospheric chemistry is the reaction of acyl peroxy radicals (RC(=O)O₂) with NO₂. As noted above, when unfunctionalized RO₂ radicals react with NO₂ to form peroxy nitrates (ROONO₂), the products of this reaction rapidly dissociate back to RO₂ + NO₂, limiting their atmospheric importance (except at very low temperatures).²⁷ However, acyl peroxy radicals (RC(=O)O₂) have markedly different behavior: the adduct, a peroxyacyl nitrate (PAN, R(C=O)OOONO₂), is quite stable relative to the reactants, and thus has a lifetime on the order of minutes to weeks (depending on ambient temperature).³⁸ PANs are key species in the troposphere, as they act as reservoir for NO_x, allowing for its long-range transport to regions far away from pollution sources.

- RO₂+HO₂. The reaction of unfunctionalized RO₂ radicals with HO₂ is generally assumed to lead exclusively to a hydroperoxide product. However, the presence of electron-withdrawing groups (such as carbonyls or halogens) near the radical center can alter the reaction thermodynamics, and hence the products formed. In addition to the standard ROOH + O₂ route, channels forming ROH + O₃ and RO + OH + O₂, which are energetically unfavorable for alkyl-substituted RO₂ radicals, become possible.^{24,39,40} The latter channel (forming an RO and OH) is chain propagating, and thus has implications for OH radical cycling.

- RO₂+RO₂. As described above, RO₂ self- or cross-reaction is typically assumed to yield either 2 RO radicals, or closed-shell carbonyl and alcohol products. However, there have been a number of observations for more complex species (such as RO₂ radicals formed in the ozonolysis of cyclohexene and terpenes) that suggest that ROOR species may also be formed.^{41,42} Previously, even high-level electronic structure calculations had suggested that ROOR formation was not possible. Recently, however, with the use of multireference calculations, it has been shown that ROOR formation may occur on atmospherically-relevant timescales via a mechanism that includes a spin-forbidden intersystem crossing from a triplet to a singlet state.⁴³ Experimental evidence has shown that ROOR

production rates are significantly enhanced in the presence of oxygenated functional groups.⁴⁴ The role of functional groups in ROOR production is not fully understood, but it appears that oxygenated functional groups act as hydrogen bond donors and acceptors in the formation of the $\text{RO}_2 + \text{RO}_2$ reactive complex. With carbonyl or alcohol functional groups present, the accretion reaction occurs at rates that in some cases may compete with $\text{RO}_2 + \text{NO}$ and $\text{RO}_2 + \text{HO}_2$, forming low volatility products that may contribute to aerosol formation and growth.

- $\text{RO}_2 \rightarrow \text{QOOH}$. It has recently been shown that some functionalized RO_2 radicals may undergo intramolecular H-atom shift reactions. Such reactions have long been known to be important in low-temperature combustion chemistry, but were largely thought to be unimportant in the context of atmospheric chemistry, since the isomerization of unfunctionalized RO_2 radicals is too slow to compete with the standard bimolecular reaction pathways of RO_2 .²⁵ However, recent experimental and theoretical work has shown that functional groups can greatly accelerate RO_2 H-shift reactions, to the point where they can compete with, and even dominate over, standard RO_2 bimolecular reactions.^{26,45–48} If QOOH adds an additional O_2 , it forms an O_2QOOH , which can then undergo a second H-atom shift. This mechanism can regenerate OH, affecting radical cycling.⁴⁹ Alternatively, multiple, successive RO_2 isomerization reactions can lead to the generation of highly oxidized, low-volatility products that make an important contribution to new particle formation and total organic aerosol mass.⁵⁰

b. Reactions enabled by direct involvement of functional groups

The second category of reactions unique to functionalized species are those that directly involve the functional group itself. Since these reactions include atoms within the functional groups (i.e., they involve heteroatoms such as O or N atoms), they represent wholly new pathways, ones that are not available to unfunctionalized species. Rather than simply altering well depths and barrier heights on the

potential energy surface, entirely new transition states and products become available. Important known examples of such reactions are shown in Figure 4, and are discussed individually below.

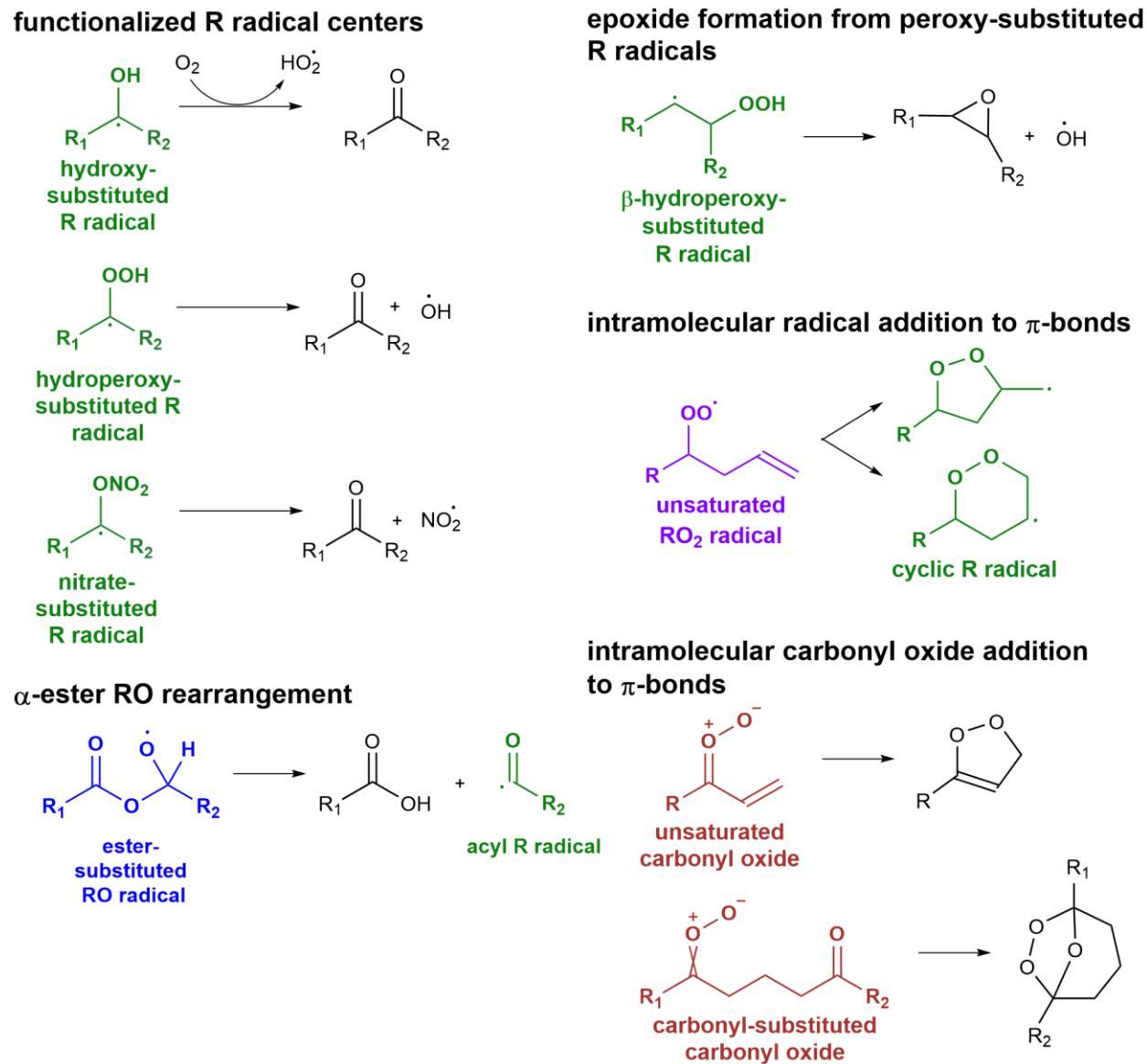


Figure 4: Known reactions available to only to functionalized intermediates, in which the functional group is directly involved in the reaction and therefore introduces a new pathway.

- **R radicals functionalized at the radical carbon.** As shown in Figure 1, unfunctionalized R radicals react with O₂ to yield RO₂ radicals; however, when there are functional groups on the radical-bearing carbon

other pathways may dominate. If the substituent is an alcohol (-OH) group, reaction with O₂ results in an H-atom abstraction from the -OH group, yielding a carbonyl and HO₂ coproduct.^{6,20,21} For other substituents, the O₂ coreactant might not even be involved: with a hydroperoxy (-OOH) or nitrate (-ONO₂) substituent, the R radical will decompose to a carbonyl plus an OH or NO₂ radical.^{6,20,21} These reactions have long been known, and are included in most atmospheric oxidation mechanisms.

- **α-Ester RO rearrangement.** Experiments and theoretical calculations have shown that RO radicals with α-ester functionality can undergo a novel decomposition reaction. This occurs by a concerted, single-step mechanism in which the H-atom α to both the alkoxy and ester groups is abstracted by the carbonyl oxygen of the ester and the ester C-O bond breaks.⁵¹ The reaction results in the formation of an organic acid and an acyl radical. It is quite fast, dominating over other unimolecular alkoxy radical reactions, and occurring on the same time scale as or faster than the reaction with O₂. A similar, β-ester RO rearrangement has also been observed, but is slower and thought to be only a minor pathway.⁵¹

- **Epoxide formation from -OOH substituted R radicals.** It has recently been shown that β-hydroperoxy substituted R radicals may form an epoxide and an OH radical. This pathway first gained attention as an important reaction in the low-NO (RO₂+HO₂-dominated) oxidation of isoprene.⁵² In this reaction, the isoprene hydroxy hydroperoxide (ISOPOOH, a first-generation product of the OH-initiated oxidation of isoprene) reacts with OH to form a highly substituted R radical. The -OOH group and the R-radical center then undergo a ring-closing reaction, forming an epoxide (isoprene epoxydiol, IEPOX) and regenerating the OH radical. The reaction happens only due to chemical activation, since the thermal rate is too slow to compete with the standard R + O₂ pathway. The resulting IEPOX species may then partition into the particle phase and undergo hydrolysis, forming a variety of lower- volatility and higher-solubility products, and contributing to SOA formation. This pathway is not unique to isoprene, nor to chemically activated systems: recently, it has been shown that additional functional groups (in particular alcohol substituents) can lower the barrier to epoxide formation to such an extent that even the thermal

epoxide formation process may be atmospherically important.⁵³ Similar reactions may also occur for other peroxide-containing functional groups; for example, radicals formed in the oxidation of PAN species may also undergo a ring-closing reaction, forming a lactone and an NO₃ radical.⁵⁴

- **Intramolecular radical addition to π-bonds.** Another class of reactions that directly involves functional groups is radical cyclization with π-bonds, in which a radical center (generally from an RO or RO₂ radical) attacks one end of a double bond. This mechanism has long been known to be important for RO₂ radicals formed in the oxidation of aromatic species;⁵⁵ more recent work has shown its importance for (non-aromatic) C=C bonds as well.^{24,56,57} This cyclization yields a cyclic R radical, which can then go on to add O₂, and thus can lead to the rapid oxidation of organic species. Recent computational work has suggested that a similar cyclization reaction may also occur for carbonyl-substituted RO₂ and RO radicals.^{58,59} Here, the radical center attacks the carbonyl carbon, yielding a cyclic alkoxy radical with an endocyclic peroxide or ether (for RO₂ or RO radicals, respectively).

- **Intramolecular carbonyl oxide addition to π-bonds.** Similarly, carbonyl oxides can also undergo intramolecular reaction with π-bonds. For large carbonyl oxides that contain aldehyde groups, such as those that are produced from the ozonolysis of monoterpenes and other large cyclic alkenes, the carbonyl oxide moiety can react extremely rapidly with the aldehyde to form a bicyclic secondary ozonide.⁶⁰ Additionally, carbonyl oxides with C=C double bonds can undergo an intramolecular cyclization reaction, yielding a dioxole species.⁶¹ In both cases, these pathways compete with the standard unimolecular channels, decreasing OH yields and impacting potential SOA formation.

The list of unique reactions of functionalized intermediates described here (and shown in Figure 3-4) is by no means complete. Over the years, additional examples of functionalized species following new chemical pathways have come to light, though these have received comparatively less attention than some of those described above, and their importance and exact mechanisms remain uncertain.

Moreover, it seems highly likely that there are many more reactions of functionalized intermediates that have yet to be identified or studied.

IV. Challenges and Advances in Investigating the chemistry of functionalized reactive intermediates

The study of the chemistry of functionalized intermediates, and especially the discovery of new reactions of such intermediates, poses a number of major challenges, both experimentally and theoretically. Here, we describe some of these challenges, as well as a selection of experimental and theoretical approaches that show promise as tools for uncovering this chemistry. In some cases, the approaches described have already unearthed examples of new chemistry. In other cases, the approaches have not yet been applied for the study of functionalized species, but rather provide a promising avenue for future research in this direction.

a. Experimental Challenges and Advances: Generation of Reactive Intermediates

Well-controlled laboratory investigations of atmospheric oxidation chemistry have been critical in elucidating key reaction pathways. Most often, these studies involve the reaction of a volatile organic compound of interest and an atmospheric oxidant. The reaction takes place in an environmental chamber or in a flow reactor, under controlled conditions (temperature, pressure, relative humidity, etc.) and with known amounts of reactants present. The majority of these studies have focused on the first one or two oxidation generations of hydrocarbons or monofunctional species. Hence, the most detailed mechanistic information is available for the early-generation oxidation reactions of these relatively simple species.

The study of the chemistry of more functionalized species can be substantially more challenging, since these tend to be formed later in the oxidation process. Even when the timescales for their formation is accessed, it can be difficult to isolate their chemistry, because they are formed within a

complex mixture of a large number of species formed via many pathways. It is possible to better isolate the chemistry of such intermediates by examining the oxidation of already-functionalized molecules, but such compounds tend not to be readily available. Further, laboratory studies tend to be run at high concentrations (of VOCs, oxidants, and NO_x); this can provide large concentrations of products, but may also lead to biases in the specific chemistry observed.

Recently however, a number of advances begun to address these challenges, allowing for the detailed investigation of the chemistry of more functionalized species. The synthesis of key functionalized species has enabled the explicit study of later generations of oxidation. For example, thanks to collaboration with synthetic chemists, isoprene hydroxyhydroperoxide (ISOOPOOH) is now generally available for atmospheric chemistry studies;⁶² this advance has enabled detailed investigation of the chemistry of this key intermediate in isoprene oxidation.

Recent work has also focused on improving the control of reaction conditions in reactors (flow tubes and environmental chambers). These efforts have been responsible for a number of the recent advances in understanding the new chemistry described above (Section 3). As an example, traditional studies of RO₂ chemistry were run with very high NO or HO₂ levels, ensuring that bimolecular reactions would dominate. However, more recent experiments carried out under very low concentrations of such species^{46,49} have established the importance of the unimolecular chemistry of functionalized RO₂ radicals, fundamentally altering our understanding of RO₂ reactivity.

Beyond this, photoinduced generation of reactive intermediate species without the use of an oxidant, typically performed in flow reactors or in jets under vacuum conditions, has allowed for more selective investigations of particular key reaction steps and the intermediates that lead to them. This includes the photolysis of alkyl iodides for R and RO₂ radicals,⁶³ of alkyl nitrites to form RO radicals,⁶⁴ and of diiodo compounds to form carbonyl oxides.⁶⁵ To date, most investigations of this type have been

limited to small and/or unfunctionalized reactive intermediates, largely due to the fact that precursors to large, functionalized radicals are not commercially available. Such limitations can be overcome via the synthesis of functionalized photolytic precursors (e.g., alkene-substituted carbonyl oxides.^{66,67}), which is likely to be a useful approach going forward.

b. Experimental Challenges and Advances: Analytical Techniques

Analytical techniques for the detection and molecular-level identification of reaction intermediates and products are critical to the study of the chemistry of reactive species in the atmosphere. The measurement of (multi)functional species poses a number of analytical challenges that have long limited our understanding of their chemistry. These include: high reactivity (which leads to short lifetimes and hence low concentrations), low volatility (which can lead to rapid loss to surfaces or inlets), thermal instability (leading to degradation at the elevated temperatures of many analytical techniques), high chemical complexity (since the number of possible isomers increases dramatically with increased molecular size and functionalization), and a lack of authentic standards for verification or calibration.

The most useful detection techniques are those that provide structural information (enabling an understanding of which bonds are breaking and forming), as well as quantitative measurements of concentrations (enabling determination of rate constants and branching ratios). They must also be sensitive enough to detect species in very low concentrations, involve relatively few surfaces, and avoid sample heating. While most studies of the chemistry of reactive intermediates infer this chemistry by measuring molecular products, a more direct approach involves the measurement of the reactive intermediates (R, RO, RO₂, and carbonyl oxide) themselves. Such a capability is limited to relatively few techniques, due to the short lifetimes (and hence low concentrations) of such intermediates. Often, this detection of reactive intermediates requires an additional ‘trapping’ step, via techniques such as jet cooling,⁶⁸ cryogenic freezing,⁶⁹ or derivatization.^{70,71}

In recent years, a variety of analytical approaches have been developed (and/or have become commercially available) that fulfill these requirements. Here, we provide an overview of analytical techniques that either have contributed to newly reported pathways associated with functionalized intermediates, or are promising for future investigations of such chemistry. We divide these approaches into three categories: purely mass spectrometric (MS) approaches, purely spectroscopic approaches, and multidimensional approaches.

Pure Mass Spectrometric Approaches

Mass spectrometry (MS) is a powerful tool for investigating gas-phase atmospheric chemistry, as it tends to be quite general, and so enables the characterization of a wide range of organic species. The specific species that can be measured by a given MS system is largely determined by the ionization technique used. Historically, real-time gas-phase MS has relied on so-called “hard” ionization techniques such as electron impact. These techniques are quite sensitive and general, but have the disadvantage of causing substantial fragmentation. Therefore, while useful for measuring ensemble properties such as elemental ratios, they can preclude the identification of individual compounds by their molecular formulas, especially in the absence of chromatographic separation or authentic standards.

The development (and commercialization) of real-time “soft” ionization techniques, which involve lower-energy ionization processes that limit fragmentation and provide measurements of intact species, has represented a revolution in the study of the chemistry of reactive intermediates. One such technique is fixed vacuum ultraviolet (VUV) photoionization, which involves the use of a lamp, laser, or synchrotron light source fixed at a particular energy (usually on the order of 10-11 eV) as an ionization source.⁷² While such approaches have tended to suffer from low photon fluxes, advances in the design

of VUV lamp sources have allowed for higher photon fluxes and thus higher sensitivities (1-10 pptv),⁷³ making these instruments promising for future studies of oxidation chemistry.

Probably the most important “soft ionization” technique for the study of reactive intermediates in the atmosphere has been chemical ionization mass spectrometry (CIMS), in which ionization is initiated by gas-phase reagent ions. The ensuing reaction between ion and analyte (typically proton transfer, charge transfer, or adduct formation) leads to the formation of a stable product ion with very little fragmentation. CIMS techniques can be highly sensitive, with real-time sensitivities on the order of pptv or better. A variety of choices for reagent ions are available, enabling the detection of different types of species and with different degrees of selectivity.⁷⁴ Protonated water clusters are a widely-used CIMS reagent that enables the detection of a broad range of organic species, namely those with proton affinity higher than water (which covers nearly all VOCs other than alkanes and small alkenes).⁷⁵ Recent work has used other reagent ions that enable the selective detection of functionalized (and even multifunctional) species, such as CF₃O-,⁷⁶ I-,⁷⁷ NO₃-,⁵⁰ and CH₃COO-.⁷⁸ These have been particularly important in elucidating many of the reactions of functionalized species shown in Figures 3-4, such as RO₂ → QOOH chemistry^{45,46} and epoxide formation.⁵² While most CIMS measurements have focused on molecular products of atmospheric reactions, CIMS methods may also be used to detect reactive intermediates themselves; for example, functionalized RO₂ radicals have been directly detected by chemical ionization,^{42,79} and both RO₂ radicals and carbonyl oxides have been detected via the use of chemical derivatization prior to CIMS detection.^{70,71}

CIMS (and other soft ionization) techniques are particularly powerful when coupled with other advanced mass spectrometric approaches. This includes the use of high-mass-resolution MS, which enables the unambiguous determination of chemical formulas, and approaches (such as time-of-flight or orbitrap MS) that enables the near-instantaneous measurement of the entire mass spectrum. Further, tandem mass spectrometry (MS/MS) can provide additional structural information beyond what is

provided by chemical formulas alone, namely functional group information. For example, CIMS combined with MS/MS was a critical tool in elucidating epoxide formation (Section 3).⁵² very recent work has used this approach for the structure-specific detection of functionalized RO₂ radicals as well.⁸⁰ A major challenge for CIMS techniques is in quantification, as sensitivity can be highly dependent on molecular structure, and authentic standards tend not to be available. Sensitivities can be constrained from known (or measured) ion-molecule kinetics or thermodynamics,^{81,82} but uncertainties remain high; this remains an important area for future work.

Pure Spectroscopic Methods

There is a long history of spectroscopic methods used for the elucidation of atmospheric mechanisms and the measurement of kinetics of atmospheric reactions. Conventional spectroscopic methods like Fourier-transform infrared spectroscopy (FTIR), broadband ultraviolet and visible (UV/Vis) absorption methods, and a variety of pump-probe spectroscopy techniques have been indispensable in extracting kinetic and mechanistic information from simple atmospheric chemical systems. However, these techniques often do not provide high time resolution, sensitivity, or structural information, limiting their utility for the study of complex reactive intermediates. As a result, in recent years such spectroscopic techniques have generally seen less in use in atmospheric organic chemistry than mass spectrometry. However, some recently-developed spectroscopic methods address many of these shortcomings, and thus represent promising approaches to understanding the complex mechanisms involved in the oxidation of functionalized species.

One example is Frequency Comb Infrared Spectroscopy, a broadband and high-resolution approach that provides structural information on a variety of species present in a complex mixture.^{83,84} The high spectral resolution means that even substantially overlapping spectra signals can be deconvolved, and the recent coupling of cavity-enhanced frequency comb spectroscopy to fast, spatially-dispersive

detection schemes enables extremely low detection limits and microsecond time resolution, making these methods ideal for the study of reactive intermediates and their chemistry. Though so far frequency comb spectroscopy has not been applied to the chemistry of large functionalized intermediates, its application to the chemistry of smaller intermediates has already yielded evidence of some unexpected chemical pathways, due to its unique ability to probe precursors, intermediates, and products simultaneously and with great structural specificity.⁸⁵ Applying frequency comb infrared spectroscopy (or indeed any high-resolution rovibrational spectroscopic method) to large, multifunctional species is likely to be quite challenging, due to the large number of vibrational degrees of freedom; this increases both the likelihood of spectral broadening due to vibrational couplings, and the difficulty in assigning spectra. Nonetheless, frequency comb spectroscopy is a promising approach, particularly for simplified systems (i.e., experiments that involve photolytic intermediate generation) that limit the complexity of observed spectra.

High-resolution microwave spectroscopy is another promising tool for the analysis of atmospheric oxidation reaction systems, as it provides structure-specific information and can have very high sensitivity. Further, the calculation of frequencies and intensities of pure rotational transitions is less expensive than of rovibrational ones, aiding in determination of structure and concentration. With the relatively recent advent of broadband, chirped-pulse Fourier transform microwave spectrometry (CP-FTMW), extremely high resolution microwave spectra are now accessible on very short timescales, allowing for the microwave spectroscopy of complex reaction systems.⁸⁶ Recently CP-FTMW spectroscopy was coupled to a cryogenic buffer gas cell, enabling the identification and quantification of key first-generation products from complex oxidation reactions such as isoprene ozonolysis.⁸⁷ While this approach has not yet been applied for more complex or later-generation chemistry, such work demonstrates the potential of high-resolution microwave spectroscopy for elucidating the chemistry of complex reactive intermediates.

Multidimensional Approaches

Despite the advances described above, the pure mass spectrometric techniques or pure spectroscopic techniques often do not provide enough information to fully resolve chemical structures of detected species, especially in complex mixtures. Multidimensional detection methods, which add one or more additional axes of information to a given technique, offer the possibility of providing structural (isomer resolved) detection. Such multidimensional approaches include MS/MS methods, described above; others include the separation of analytes prior to mass spectrometric detection, or the combination of mass spectrometry and spectroscopy.

The separation of compounds within complex mixtures prior to mass-spectrometric detection provides measurements of individual species, as well as isomer-resolved measurements. Near real-time measurements that rely on this approach include gas chromatography-mass spectrometry (GC-MS) and ion mobility spectrometry-mass spectrometry (IMS-MS). GC-MS measurements, in which compounds are separated first by column retention time, and then by mass, have long been used in atmospheric chemistry, but the technique traditionally has relied on hard ionization techniques (such as electron impact), and has been unable to detect functionalized (polar) species due to their loss on heated metal surfaces. However, GC-MS has recently been coupled to soft ionization techniques, including chemical ionization⁸⁸ and VUV photoionization⁸⁹ enabling isomer-level resolution even (when no metal surfaces are present) of highly functionalized species. Similarly, IMS-MS enables the separation of species according to the mobility of their ions through the bath gas (which is a function of ion size, shape, and conformation).⁹⁰ While these separation techniques (GC-MS and IMS-MS) provide far more chemical information than what pure mass spectrometric approaches can provide, they face some limitations. They generally have lower time resolution than their pure MS counterparts, due to the time associated with the separation; they have also not yet been used for the direct detection of reactive intermediates.

There are also a number of combined spectroscopic-mass spectrometric techniques that provide information on both mass (chemical formula) and structure, enabling isomer-specific detection. These methods generally use tunable light for ionization or detection, so that the photon wavelength provides an additional dimension of structural information. Some of the techniques that couple spectroscopy to mass-spectrometric detection are tailored for the probing of a few particularly relevant species or processes (e.g. resonance-enhanced multiphoton ionization (REMPI) mass spectrometry, and various action spectroscopy techniques), or lack time resolution and so are best suited for offline studies (e.g. infrared multiphoton dissociation spectroscopy of trapped ions).⁹¹ However, the use of tunable vacuum ultraviolet (VUV) light coupled to multiplexed, highly time-resolved mass spectrometry has been demonstrated to be a general, real-time approach to the study of reactive intermediates and their products.⁹² Here, tunable VUV light from a synchrotron light source is used to measure the photoionization spectrum across a range of masses simultaneously. The result is a time-, frequency-, and mass-resolved dataset that provides both kinetic and structural information. This detection technique has been coupled to flash-photolytic generation of key radical intermediates, and has allowed for the direct detection of several previously unobserved reactive intermediates such as carbonyl oxides⁹³ and the QOOH radical,⁹⁴ enabling the direct study of their reaction kinetics.

c. Theoretical Challenges and Advances

The chemistry of functionalized intermediates cannot be fully elucidated from experimental studies alone, given the challenges, time, and expense associated with such studies, as well as the enormous breadth of possible intermediates and reactions involved. Thus, theoretical calculations play a central and complementary role in investigating this chemistry. Detailed theoretical calculations of the reactivities of functionalized intermediates can be used to identify new reactions, mechanistically interpret experimental results, and generalize results to wider range of structures and reactions conditions. In addition, the various experimental approaches described above rely heavily on

complementary theoretical studies: theory can aid in the structural interpretation of mass spectrometric data, in the prediction of ion-molecule chemistry and fragmentation in chemical ionization mass spectrometry, and in the assignment of spectroscopic transitions. These investigations require the prediction of accurate and complete potential energy surfaces, including the energies and molecular properties of key stationary points. In order to achieve accurate predictions of kinetics and branching ratios, accurate descriptions of the dynamics across those potential energy surfaces are also critical. However, the computational study of functionalized intermediates also presents a number of challenges, as outlined below.

Predicting potential energy surfaces

A major challenge in the theoretical prediction of reactivity is the full exploration of chemical space, which involves identifying all relevant potential energy wells and transition states. For complex functionalized species, the number of potential pathways, and associated transition states, intermediates, and products may be quite large. In theory, full-dimensional explorations of potential energy surfaces will find all possible reaction pathways, but at present such explorations are not computationally feasible. Instead, investigations of new reaction channels have generally relied on chemical intuition. However, this approach risks missing new and/or unexpected pathways. One approach for addressing this challenge is automated mechanism generation, which enables systematic explorations of all possible pathways based on known thermochemistry or chemical heuristics (rather than detailed quantum chemical calculations).⁹⁵ Recently one such generator (the Reaction Mechanism Generator, originally developed for use in combustion systems⁹⁶) was used to search for new reactions of atmospheric intermediates.⁵⁹ This approach was used to efficiently explore a large area of atmospherically-relevant chemical space, and uncovered some new reactions as promising targets for future study.⁵⁹

Once all pathways for a given system are found, the next challenge is accurately describing the associated energetic barriers and well depths, as well as the geometries and relevant molecular properties (e.g., vibrational frequencies and rotational constants). At atmospheric temperatures, the accuracy of predicted reaction rates (and their dependence on temperature and pressure) relies critically on the accuracy of the calculated energetics of the potential energy surface. Achieving sufficiently high accuracy is quite challenging, particularly for complex functionalized species. First, they tend to be quite large, with more than 5 (and often more than 10) heavy atoms. Quantum mechanical calculations of such systems can be exceedingly expensive, such that the most accurate computational methods (such as coupled cluster calculations) are not currently feasible.⁹⁷ Further, many atmospherically relevant species have substantial multireference character, further complicating accurate calculations of their energies.⁹⁷ Nevertheless, given the recent improvements in relatively inexpensive density-functional theory calculations, as well as the increasing availability of high-performance computing resources, chemically accurate calculations of large functionalized species are rapidly becoming more achievable.

Predicting kinetics and branching ratios

Even if we could perfectly describe the energetics associated with potential energy surfaces (and the associated molecular properties of relevant stationary points), accurate predictions of kinetics and branching ratios require accurate descriptions of the dynamics over those surfaces. Statistical-dynamical approaches such as transition state theory (TST) and Rice-Ramsperger-Kassel-Marcus (RRKM) theory have enabled the calculation of rates of many elementary reaction steps, and the inclusion of the effects of quantum mechanical tunneling in such calculations has allowed for further accuracy, particularly for the rate constants associated with H-atom shifts. However, the complexity of organic intermediates and the low temperatures of the atmosphere introduce a number of additional computational challenges.

Functionalized reactive intermediates are typically large, complex, and flexible, and are therefore likely to be present as a number of conformers at atmospheric temperatures. Accurate kinetic calculations require that the full ensemble of populated conformers is considered in any TST modeling, especially since the lowest-energy conformer may not be connected to the lowest energy transition state via an intrinsic reaction coordinate.⁹⁸ For example, it has been shown that single-conformer treatments of RO₂ radical H-atom shift rate constant calculations can result in overestimates by up to several orders of magnitude.⁹⁹ Multi-conformer transition state theory (MC-TST), which treats the overall rate constant as Boltzmann-weighted sum of the intrinsic reaction coordinate rate constants of reactant conformers, is a promising approach to addressing this issue.⁹⁸ While this approach requires potentially expensive conformational searches, a cost-effective implementation of MC-TST was recently developed for RO₂ H-atom shifts.⁹⁹ This same approach should be broadly applicable to a wider range of reaction classes as well, enabling a rigorous treatment of multi-conformer effects with relatively low computational cost.

Further, because the chemistry of functionalized reactive intermediates often takes place above multi-well potential energy surfaces,¹⁰⁰ intermediates may be formed chemically activated, with non-Boltzmann energy distributions. In these cases, reaction time scales can often be similar to or faster than thermal relaxation time scales, and simple TST approaches cannot accurately describe their kinetics. Such cases are best described using master equation modeling approaches,^{101,102} which combine energy-resolved rate constants and descriptions of collisional energy transfer to account for the competition between reaction and thermalization of non-equilibrium populations. This enables the calculation of kinetics and products of complex, multichannel/multiwell reaction systems; examples include aromatic oxidation¹⁰³ and isoprene ozonolysis.¹⁰⁴ Such calculations can also allow for the extension of a small number of well-studied rates and branching ratios to cover a wider range of species and reactions over a range of reaction conditions that have not been examined in detail.

The accurate, complete theoretical determination of the chemistry of even a single complex organic species is currently quite difficult to achieve: it requires finding all major stationary points on a potential energy surface, calculating the energies and properties of each (including multiple conformers) accurately, and transferring those parameters into a master equation model. As a result, such work has typically been the purview of computational chemists, examining individual reactions and reaction networks essentially one at a time. However, recent increases in computing power, as well as the availability of user-friendly software packages, have made such calculations more accessible.^{105–107} Further, recent work has taken on the task of automating and coupling each step of this process. As a result, the automated investigations of the full, complex network of reactions involved in oxidation of single species are now within reach (albeit still very computationally expensive).^{108–110} To date this approach has been applied only to investigations of hydrocarbon oxidation mechanisms under combustion conditions,^{108–110} predicting kinetics under atmospheric conditions is more challenging, due to the more stringent accuracy requirements on the predicted potential energy surfaces. Nonetheless this general approach offers promise for predicting the detailed chemistry of functionalized atmospheric organic species.

V. Conclusion and Future Outlook

The chemistry of functionalized reactive intermediates (R, RO, RO₂, and carbonyl oxides) is central to the lifecycle and ultimate impacts of atmospheric organic carbon. The reactivity of these intermediates can vary from those of the better-studied chemistry of their unfunctionalized counterparts, as a result of two effects: changes to the energetics (barrier heights and exothermicities) of the reactions, and the introduction of new reaction pathways that directly involve the functional group(s). Recent studies, enabled by advances in experimental and theoretical approaches, have elucidated a number of new pathways available to functionalized intermediates. These pathways include intramolecular H-atom abstraction reactions of RO₂, the addition of peroxy radicals to double bonds, the formation of epoxides

from hydroperoxyl-substituted R radicals, and others (Fig 3-4); these have had a major impact on our understanding of key atmospheric chemical processes, such as radical cycling and secondary organic aerosol formation. It seems likely that as-yet undiscovered reactions exist, possibly involving specific chemical structures or combinations of multiple functional groups.

The identification and characterization of this unique chemistry represents central challenges in both atmospheric and physical chemistry, and requires research at the intersection of these fields. Virtually all aspects of the reactivity of these intermediates, and their experimental and theoretical study, involve physical chemistry tools and concepts: the measurement and prediction of reaction kinetics and products; the determination of potential energy surfaces and the behavior of species given these surfaces (e.g., chemical activation and tunneling); and even the analytical techniques themselves (which involve the interactions of photons and molecules, ions and molecules, etc.). At the same time, the relevant chemical systems to study are determined by atmospheric chemistry: the chemical structures and the reaction conditions need to be relevant to those of the real atmosphere in order to have an appreciable impact on atmospheric oxidation. Improved understanding of the detailed chemistry of functionalized atmospheric intermediates requires a focus on the reactivity of species which serve as important branch points in atmospheric oxidation processes, particularly over the conditions of the lower troposphere (e.g., 250-310 K, 0.7-1.0 atm, and 21% [O₂]).

Future progress in elucidating this chemistry requires continued advances in all the steps of its study: from the identification of target reactions to study, to the experimental and theoretical study of the intermediates and their reactivities, to the generalization of results so that new chemistry can be included in 3D models of the atmosphere. First, given the very large size of chemical space involved, the identification of target systems with the potential for new chemistry is a non-trivial task. Historically, new chemistry of functionalized species has been initially identified and targeted as a result of some combination of chemical intuition (recognizing the potential for a given reaction to occur) and

unexplained observations that prompted further investigation. However, this approach risks missing key classes of reactions, particularly for multifunctional species, and so more methodical approaches to examine reactivity would be preferable. The development and use of such techniques, which could include relatively simple chemical heuristic methods for scanning chemical space,⁵⁹ more complex on-the-fly quantum chemical calculations,¹⁰⁸ and machine-learning based approaches,¹¹¹ are still in their infancy, particularly as applied to atmospheric systems, but offer major opportunities for identifying new potential reactions.

Recent improvements in our understanding of the chemistry of key atmospheric intermediates has been driven by, and will continue to be driven by, advances in both experimental and theoretical approaches (section IV). Future laboratory work, both oxidation experiments (using chambers or flow systems) and more targeted studies involving the direct generation of reactive intermediates, will certainly benefit from further advances in analytical techniques. Particularly useful will be new techniques that provide real-time information on the detailed structures (or at least functional-group distributions) of individual species, as well as those that enable the direct detection of short-lived reactive intermediates. In addition, collaboration with synthetic chemists will be crucial: chemical synthesis can provide new precursors to functionalized intermediate species, enabling new detailed experimental studies of their reactivity, as well as authentic standards to aid in identification and quantification. Data-analysis approaches that efficiently mine existing or new complex experimental datasets may also prove useful for identifying and characterizing novel reaction pathways of functionalized intermediates.

In parallel, advances in theoretical approaches will continue to develop our understanding of this chemistry. Increasingly accurate calculations of potential energy surfaces (namely barrier heights and free energies of reaction), arising from improvements in levels of theory, basis sets, and computing power, will continue to enable better determinations of rates and branching ratios for large, complex

intermediates. Moreover, these determinations will also improve with the further development of computationally-efficient approaches for simulating the effects of key chemical features of complex organic reactions, such as multiple conformers, tunneling, chemical activation, and low-lying excited states, on the reactivity of atmospheric intermediates.

Even with these experimental and theoretical advances, the immense breadth and complexity of the relevant chemical space means that the detailed, quantitative characterization of every reactive intermediate that might play an important role in atmospheric oxidation is not possible. And even if it were, the explicit inclusion of each reaction would be too computationally expensive for most large-scale 3D models of the atmosphere (chemical transport models and earth system models). Therefore, future work must focus not just on characterizing the chemistry of individual intermediates, but also on more effectively generalizing quantitative results to a wide array of species. This includes “lumping” of intermediates that are similar in terms of their structures, reaction kinetics, and product distributions, as well as the further development of structure-activity relationships (SARs) for predicting the reactivity of species spanning a range of structures. While SARs have traditionally been based on laboratory measurements,²⁹ the development of SARs that are based on theory (or ideally both theory and experiment) represent a promising new and flexible direction for reactivity prediction.²² A particular challenge is ensuring that SAR predictions are accurate for multifunctional species, for which existing data tend to be sparse.

More generally, many recent improvements in our understanding of the chemistry of functionalized intermediates have involved a combination of experimental and theoretical study;^{45,50,52} the value and impact of connecting experimental and theoretical approaches will likely only increase going forward. Given the limitations and challenges associated with theoretical calculations of these kinds of large systems, experiments are critical for the generation of accurate data; but experimental investigations themselves must also be informed by theory, for choosing target systems and interpreting results. And

while quantum-chemical calculations must be benchmarked against experiment, they can then be used to extend experimental results to additional reaction systems and reaction conditions. Theoretical approaches also directly aid in the experiments themselves: for example, quantum-chemical calculations can aid in the interpretation of mass spectrometric and spectroscopic data, by assigning spectra, inferring structure, and estimating sensitivities.⁹⁷ Close collaborations between experimentalists and theoreticians is critical in developing an improved mechanistic understanding of the reactivity of complex, functionalized molecules in the atmosphere; this will lead to more accurate model representations of critical atmospheric processes such as ozone formation, radical cycling, and SOA generation, and ultimately an improved ability to predict present-day and future air quality and climate.

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