

Reactive Intermediates

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Criegee Intermediates Beyond Ozonolysis: Synthetic and Mechanistic Insights

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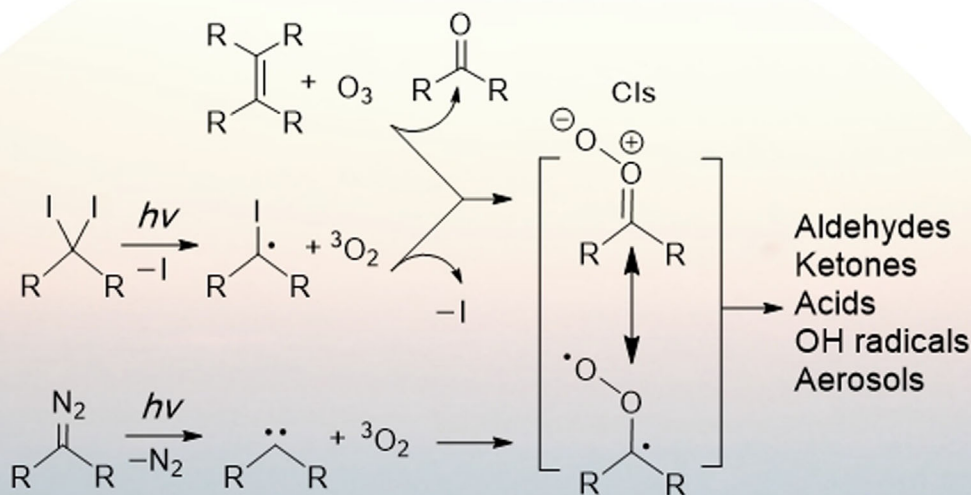
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ozonolysis



RUDOLF
CRIEGEE
1902-1975

After more than 70 years since their discovery, Criegee intermediates (CIs) are back at the forefront of modern chemistry of short-lived reactive intermediates. They play an important role in the mechanistic context of chemical synthesis, total synthesis, pharmaceuticals, and, most importantly, climate-controlling aerosol formation as well as atmospheric chemistry. This Minireview summarizes key aspects of CIs (from the mechanism of formation, for example, by ozonolysis of alkenes and photolysis methods employing diiodo and diazo compounds, to their electronic structures and chemical reactivity), highlights the most recent findings and some landmark results of gas-phase kinetics, and detection/measurements. The recent progress in synthetic and mechanistic studies in the chemistry of CIs provides a guide to illustrate the possibilities for further investigations in this exciting field.

1. General Introduction to Criegee Chemistry

1.1. Criegee Intermediates—A Legacy of Rudolf Criegee

The long struggle with ozone chemistry (discovered by Christian F. Schönbein in 1840) and investigations from the perspective of its applications in chemical synthesis have been described in a series of concise articles on the history of ozone.^[1] Beginning in 1904, Carl D. Harries (1866–1923) introduced ozone for the oxidative cleavage of multiple double bonds in hydrocarbons.^[2] Harries had established mechanistic aspects for determining the structures of organic compounds by utilizing ozonolysis, which many years later concluded in Criegee's unified mechanism of ozonolysis. The reaction of ozone with the double bonds in hydrocarbons produces short-lived unstable but important key intermediates, termed Criegee intermediates (CIs).^[3]

CIs, also called Criegee biradicals or Criegee zwitterions (also referred to as zwitterionic peroxides or commonly carbonyl oxides), were first postulated by R. Criegee,^[**] after whom they are named, who discovered their mechanism of formation and intermediacy in the ozonolysis of 9,10-octalin (Figure 1) in 1949.^[4]

The Criegee mechanism envisions a three-step sequential reaction process. The addition of ozone to the double bond (formation of a primary ozonide, POZ) is followed by dissociation into a carbonyl compound and a carbonyl oxide, called a “zwitterion” by Criegee (Figure 2). These two species then recombine with a reversed orientation to form the thermodynamically relatively stable, and isolable secondary ozonide (SOZ). These steps were later interpreted as 1,3-dipolar reactions. The presence of the carbonyl oxide, formed in the fragmentation of the ozonide, was proven by trapping with alcohols, which readily react as nucleophiles to form hydroperoxides. Hence, carbonyl oxides were considered polar (zwitterionic) in nature, which gave a decisive clue to the formation of CIs. Oxidative or reductive cleavage of the resulting ozonides give the corresponding aldehydes, ketones, alcohols, or carboxylic acids.

During the ozonolysis of 9,10-octalin, the 1,2,4-trioxolane structure cannot form because of steric constraints—instead a dimeric peroxide is rationalized in this particular system.^[4b] Criegee's important discovery is not the identification of ozonides but rather establishing the electronic structure and nature of the carbonyl oxide as the key intermediate in the formation of ozonides.


Much has happened since Criegee's pioneering mechanistic studies. Several landmark discoveries using advanced structural analysis and characterization methods have been achieved that have turned Criegee chemistry into one of the “hot topics” of the last few years. Although CIs are routinely encountered in organic synthe-


sis, recent studies show these exotic species play a much more prominent role in the chemistry of food, petrochemicals, and the environment than was previously believed.^[5] We have confined this literature survey to pioneering research contributions that advance CIs and their synthetic applications, and have discussed the role of these chemically active species in the field of atmospheric and environmental chemistry in

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[**] Rudolf Criegee (1902–1975), Director of the Institute of Organic Chemistry, carried out most of his research at the Karlsruhe Institute of Technology (then, Technische Hochschule Karlsruhe), even after his retirement in 1969 until his death on November 7, 1975. The renewed tremendous interest in ozone-organic chemistry is credited to R. Criegee, because of his pioneering precise investigations into the mechanism of the ozonolysis reaction.^[6] Among Criegee's prolific scientific works, one of his great scientific achievements was the elucidation of the reaction mechanism of the ozonolysis of double bonds,^[7] which has contributed enormously in different aspects to the progress of ozonation in organic chemistry.^[8,9]

terms of the formation of aerosols and condensed matter in the atmosphere. The emphasis is on research efforts from the last few years; earlier contributions are also included where relevant.

1.2. Mechanism of Formation, Structure, and Methods To Probe Criegee Intermediates

Criegee's famous and last article on the "Mechanism of Ozonolysis" and CIs was published in *Angewandte Chemie* in



From left to right: N. Rosenbaum, S. Bräse, Z. Hassan, and M. Stahlberger at the Commemoration of Rudolf Criegee in IOC, KIT. Zahid Hassan studied chemistry at HEJ Research Institute of Chemistry (M.Phil.), at the Leibniz University of Hannover, and received his Ph.D. at the Institute of Chemistry, Leibniz-Institute for Catalysis, University of Rostock, where he studied metal-mediated reactions. After an IBS Fellowship at the Centre for Self-Assembly and Complexity, POSTECH, in 2014 he started his independent career and held a faculty position at the University of Nizwa. Since 2017, he has been associated with the Institute of Organic Chemistry at the KIT and leads a team on cyclophane chemistry and synthetic materials. His research interests include mechanistic and synthetic applications of transition-metal catalysts and synthetic materials.

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Nicolai Rosenbaum obtained his B.Sc. in Chemistry from the Karlsruhe Institute of Technology (KIT) in 2015. After an internship at BASF SE in 2017, he finished his M.Sc. in Chemistry in the same year and currently is a Ph.D. student under the mentorship of Prof. S. Bräse, where he works on the stereoselective semisynthesis of the marine steroids gorgosterol and demethylgorgosterol.

Stefan Bräse studied in Göttingen, Bangor (UK), and Marseille and received his Ph.D. in 1995 with Armin de Meijere in Göttingen. After postdoctoral research at Uppsala University (Jan E. Bäckvall) and The Scripps Research Institute (K. C. Nicolaou), he began his independent research career at the RWTH Aachen in 1997 (associated with Dieter Enders). In 2001, he finished his Habilitation and moved to the University of Bonn as a Professor for organic chemistry. Since 2003, he has been a Professor at the Karlsruhe Institute of Technology (KIT) and since 2012/2020 also Director of the Institute of Biological and Chemical Systems (ITG/IBCS) at the KIT. His research interests include asymmetric processes, combinatorial methods for biologically active compounds, synthetic functional materials, and digital workflows in chemistry and science.

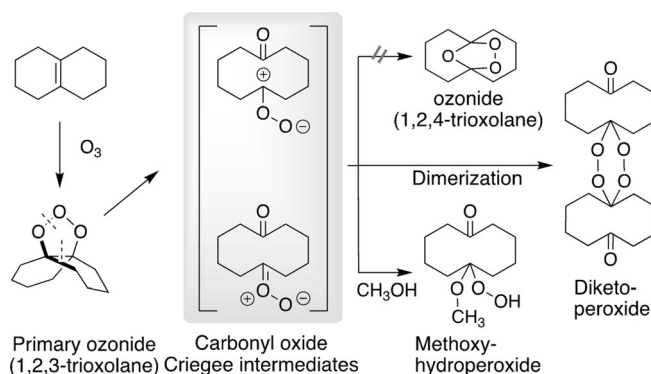


Figure 1. Mechanism of formation and intermediacy of CIs in the ozonolysis of 9,10-octalin as postulated by R. Criegee in 1949.^[4a]



Figure 2. R. Criegee (1902–1975). Photograph courtesy of the Institute of Organic Chemistry (IOC), Karlsruhe Institute of Technology (KIT), Karlsruhe.

1975.^[10] The proposed formation of ozonides (1,2,4-trioxolanes) from the reaction of alkenes and ozone can be described as a succession of three [2+3] or 1,3-dipolar cycloadditions or cycloreversions: the first 1,3-dipolar cycloaddition produces 1,2,3-trioxolanes (identical to the Harries ozonide formulation), the second step gives aldehyde or ketone oxides, and the third step produces 1,2,4-trioxolanes as isolable ozonides. Criegee, at the end of this article, specifically mentioned that many details about CIs remain open and need to be addressed, and ends with a question: "Will it become possible to at least detect a carbonyl oxide spectroscopically, or even to isolate one?"

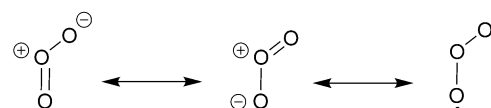
Criegee's pioneering mechanistic studies triggered intensive investigations.^[11] By the mid-1970s, the Criegee mechanism and the presence of carbonyl oxide had been confirmed; however, short-lived species, central to the mechanism of ozonolysis, had rarely been detected under normal laboratory

conditions. As a consequence of their quite elusive and fleeting existence, CIs escaped detection in reactions for decades. The understanding of CIs, obtained from indirect experimental evidence, and their true nature as zwitterions or diradical character has been controversial, and have remained a subject of long debate. The development of advanced methods for the preparation of CIs and the application of sophisticated experimental and computational techniques for their structural characterization has pushed Criegee chemistry beyond the historically known classical ozone-olefin experiment.

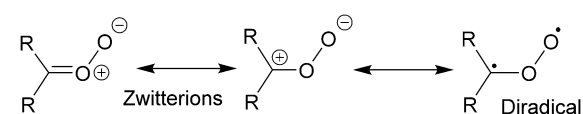
Since the fate of the CIs determines the final products, they can have a substantial impact beyond laboratory chemical synthesis. Hence, comprehensive advanced experimental and theoretical studies continued over the years on the detection, kinetics, and thermodynamics of chemical reactions involving CIs, which provided more insight and shaped our current understanding of CIs. For example, the spectroscopic detection and investigation of carbonyl oxide species using time-resolved laser-photolysis by W. Ando,^[12] J. C. Scaiano,^[13] Orville L. Chapman, and others led to a diradical structure being postulated.^[14] Matrix-isolation techniques and spectroscopic characterization performed by Ian R. Dunkin,^[15] W. Sander, and others have led to comprehensive details about the electronic nature of various carbonyl oxides.^[16] The direct detection of the simplest CIs and the spectroscopic characterization of several larger ones in gas-phase ozonolysis have provided more details on the nature, lifetime, reactivity, and electronic structure of the CIs, and showed they have a substantial zwitterionic rather than biradical character.^[17] The transient infrared absorption spectrum of the simplest gaseous CI species, formaldehyde oxide CH_2OO (produced from the iodomethyl radical (CH_2I) with O_2 in a flow reactor), has provided definitive proof of the zwitterionic identity. The direct detection/measurements of CIs in the gaseous phase have been useful for the kinetic and mechanistic investigations of the CIs.^[18] A general overview of the resonance structures of CIs and the generation of CIs through the historically known alkene ozonolysis versus photolysis method employing diiodo- and diazoalkanes is shown in Figure 3.

The observed O-O stretching band of CH_2OO at about 908 cm^{-1} is smaller than that of the corresponding band of CH_3OO at 1117 cm^{-1} . In contrast, the CO stretching band near 1286 cm^{-1} is larger than that of the corresponding band of CH_3OO at 902 cm^{-1} . These findings indicate a stronger C-O bond and a weaker O-O bond, and thus indicates the CIs have double bond character, which supports the zwitterionic rather than the biradical structural description of CH_2OO . In other experiments, the CI (CH_2OO) produced from the low-pressure photolytic reaction (248 nm, at 4 torr and 298 K) of CH_2I_2 with O_2 was studied by combining tunable synchrotron photoionization with multiplexed mass spectrometry, hence enabling the direct mass spectrometric detection of CH_2OO ($m/z = 46$) by photoionization.^[19] Formaldehyde oxide (CH_2OO) was previously observed in the chlorine-initiated gas-phase oxidation of dimethyl sulfoxide.^[19b] Further direct measurements and investigations of the chemical reactivity of the next heavier CI, that is, acetaldehyde oxide (CH_3CHOO ,

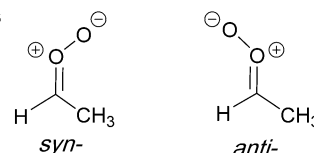
a) Chemical Structure of Ozone



b) Chemical Structure of Carbonyl Oxides (CIs)



c) CI Conformers



d) Generation and Fate of the CIs

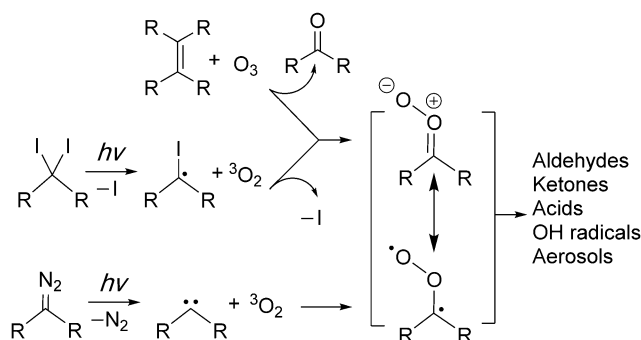


Figure 3. a) Resonance structures of O_3 ; b) CIs (zwitterions/diradicals); c) illustration of *syn*- and *anti*-CI conformers, and d) routes to generate CIs by ozonolysis of alkenes versus photolysis and fate of the CIs.

$m/z = 60$), have also been carried out by pulse laser photolysis using photoionization time-resolved mass spectrometry (Figure 4).^[20]

After improvements to the experimental methods, the gas-phase ozonolysis of ethylene at atmospheric pressure and temperature using a high spectral resolution Fourier transform microwave spectroscopy has also been achieved, which enabled observation of the CH_2OO species.^[21] A detailed discussion on the physical chemistry of the CIs in the gas phase^[22] as well as the elegant spectroscopic methods and dynamic investigations to probe the structure-dependent chemical reactivity of CIs have been provided in recent tutorials and focused reviews.^[23] Computational studies and theoretical findings to understand substituted CIs (their geometric and electronic features), and investigations into the chemical reactivity of *syn*- and *anti*- CH_3CHOO conformers towards other species, for example, water, are excellent complements to the experimental results.^[24]

Crystallography can provide reliable structural evidence when studying intermediates that complement the spectral data of ozonolysis products. The crystalline sponge method (a coordination-driven, porous networks approach) has led to a rather new trend in structure analysis using X-ray crystallography. Using the crystalline sponge method, several

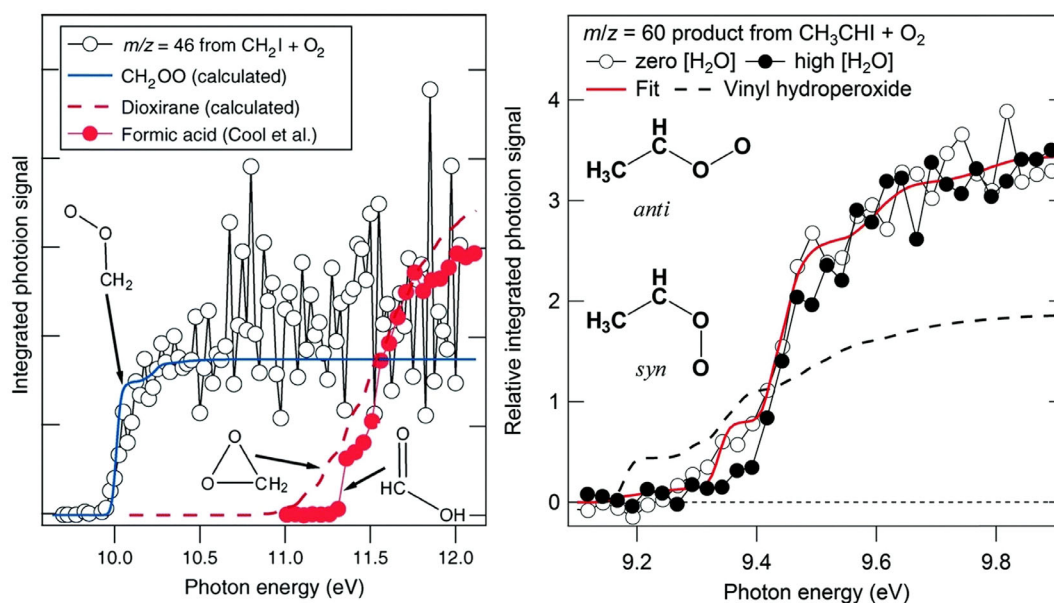


Figure 4. Left: Experimental photoionization efficiency spectrum of CI (CH_2OO); the calculated spectrum of dioxirane and experimental spectrum of formic acid (two isomers) are included for comparison. Reproduced from Ref. [19] with permission. Copyright 2012, *Science*, AAAS. Right: Experimental photoionization efficiency spectra of *anti*- and *syn*- CH_3CHOO conformers. Reproduced from Ref. [20] with permission. Copyright 2016, *Science*, AAAS.

ozonide intermediates have been visualized in the crystalline state.^[25] A porous coordination assembly $[(\text{ZnI}_2)_3(\text{tpt})_2 \cdot x(\text{solvent})]_n$ ($\text{tpt} = \text{tri}(4\text{-pyridyl})\text{-}1,3,5\text{-triazine}$) serves as the crystalline sponge, which bears defined cavities and encapsulates guest/target ozonides molecules that hardly crystallize under normal conditions (Figure 5).

Improved X-ray crystallographic analysis of bicyclic bridged secondary ozonids (prepared by an ozone-free synthesis approach and employing H_2O_2 sources as an oxidant) has also been carried out.^[26] The O–O bonds reported for some of the ozonides obtained from 1,5-dicarbonyl compounds and various H_2O_2 sources (as an oxidant) were even shorter than a few of the C–O bonds in the same molecules.

1.3. Criegee Intermediates and the Baeyer–Villiger (BV) Reaction

In addition to the classical ozonolysis of olefins, the term CIs is also used for an entirely different intermediate species in the Baeyer–Villiger (BV) reaction, which was discovered by Adolf von Baeyer and Victor Villiger in 1899.^[27] Notably, even though the mechanism of the BV reaction was a matter of debate for the first 50 years, several different mechanisms were suggested; however, it was Criegee who correctly described the formation of the intermediate (a nucleophilic attack of the oxidant on the carbonyl group), and it is now generally accepted as the tetrahedral Criegee intermediate.^[28] Comprehensive investigations into the BV rearrangement by experiments, computational studies, and stereoelectronic features of the previously elusive CIs obtained from ketones and peroxide derivatives as an oxidant (ozone-free synthesis approach of ozonides) in the BV reaction are well-documented, and serve as guidelines (Figure 6).^[29]

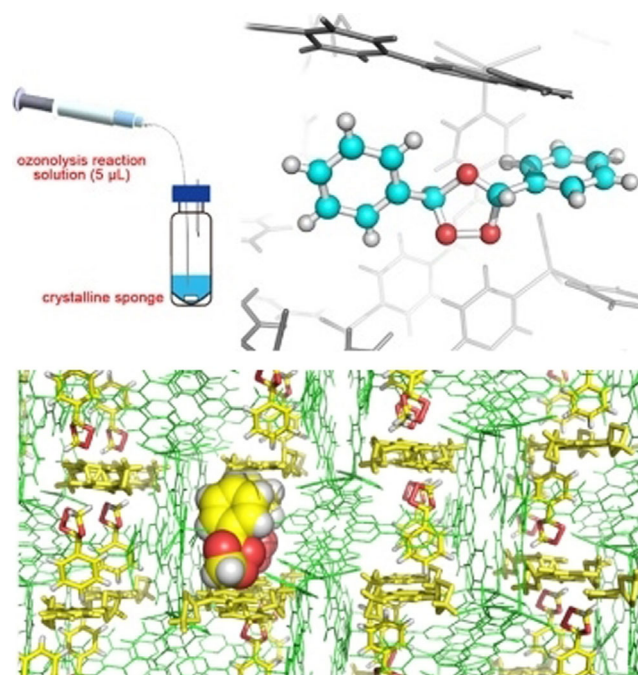


Figure 5. Top: X-ray structure analysis of ozonide intermediates by the crystalline sponge method. Bottom: Inclusion complex, where styrene ozonide (carbon and oxygen shown in yellow and red, respectively) is embedded in the host framework (green). Reproduced from Ref. [25] with permission. Copyright 2016, American Chemical Society.

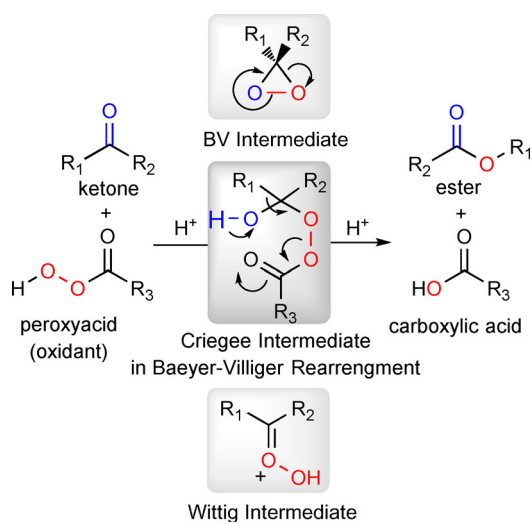


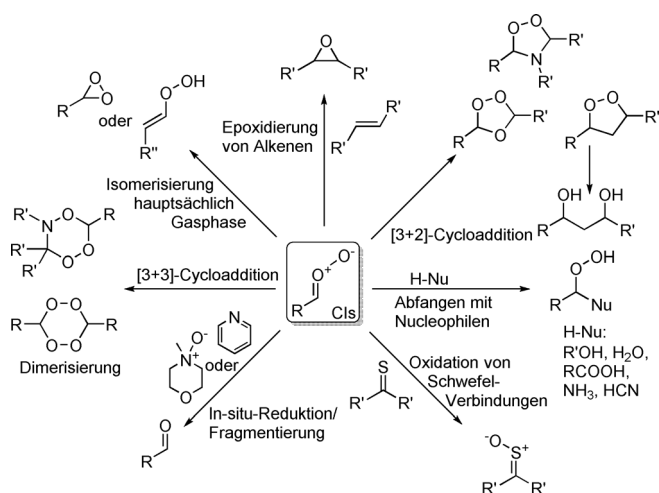
Figure 6. General representation of the tetrahedral Criegee intermediate and reactive species in the peracid-promoted Baeyer–Villiger oxidation reaction.

2. CIs and Their Synthetic Applications

2.1. Criegee Intermediates in Organic Synthesis

CIs possess a rich chemistry beyond their role in the ozonolysis of alkenes. This includes cycloadditions, nucleophilic trapping, oxygen-transfer reactions, and isomerizations.^[30] Advances in alkene ozonolysis and the development of new reaction procedures have been the subject of a recent focused review.^[31] The basic science of CIs/ozonolysis chemistry is well-documented and some of the most common synthetic transformations involving CIs are summarized in Scheme 1.

The mechanism of the reaction of CIs is expected to be similar to that of ozone, since both are known to be mostly



Scheme 1. Common synthetic transformations involving CIs.

zwitterionic with a relatively low contribution of biradical character and both react through a 1,3-dipolar mechanism.

Cycloadditions are the predominate reactions of CIs alongside nucleophilic trapping. CIs are allyl-type 1,3-dipoles and react with dipolarophiles. A wide variety of chemical transformations have been investigated that have aimed to exploit key ozonolysis intermediates as synthetic handles.^[32]

The formation of a carbonyl oxide depends on the substituents on the primary ozonide and usually leads to a product mixture. The Griesbaum co-ozonolysis, which allows the synthesis of well-defined 1,2,4-trioxolanes, will be discussed in the next section.^[33] The cycloaddition of CIs derived from cycloalkenes to the α -carbonyl group of methyl pyruvate yields terminally differentiated compounds.^[34] The addition to alkenes results in 1,2-dioxolanes,^[35] which can be reduced to give 1,3-diols.^[36] Esters^[37] and similar related compounds^[38,39] can undergo [3+2] cycloadditions with CIs, although their chemical reactivity is lower. Similar to aldehydes, imines react to yield 1,2,4-dioxazolidines.^[40,41] Furthermore, CIs can add to 1,3-dipoles in a [3+3] cycloaddition. The dimerization of carbonyl oxides falls into this category and presents a usually unwanted side reaction, especially in the ozonolysis of highly substituted alkenes. The reaction with nitrones yields dihydro-1,2,4,5-trioxazines.^[42,43]

Nucleophilic trapping represents the second most important reaction pathway of CIs. By using methanol as a solvent in the ozonolysis, the CIs yield α -methoxy hydroperoxides instead of secondary ozonides, thus preventing side reactions, such as the formation of 1,2,4,5-tetroxanes or rearrangements. Higher alcohols, water, and carboxylic acids are less reactive. The trapping of intramolecular nucleophiles has been used to synthesize tetrahydrofurans,^[44] or to convert octalins into macrolides.^[45] Ammonia, amines, and hydrogen cyanide are other nucleophiles that can be used to trap CIs, as evidenced by the ozonolysis of indenes in the presence of primary amines.^[46] This presents another route to 1,2,4-dioxazolidines. CIs can also be trapped by aprotic nucleophiles such as amine *N*-oxides and pyridine.^[47] The formed species are unstable and yield aldehydes, which can be used in ozonolysis for in situ reductions. The isomerization of CIs proceeds through two major pathways: rearrangement to dioxiranes and tautomerization.^[31] The rearrangement of CIs is thermodynamically favorable, but connected with a high activation barrier, which usually prevents the rearrangement in the liquid phase. However, they can be isomerized photochemically, and the rearrangement is much more common in the gas phase. The tautomerization pathway is available for carbonyl oxides with α -protons, and products arising from this pathway can frequently be found in ozonolysis reactions. As for the rearrangement of dioxiranes, tautomerization is predominant in the gas phase. Oxygen-transfer reactions of CIs are mechanistically categorized as oxidations. Alkenes can be epoxidized by CIs generated from the corresponding diazo compounds.^[48] Similarly, the electron-poor tetracyanoethylene can reduce CIs in situ during ozonolysis. Furthermore, CIs have been reported to oxidize alkanes directly, that is, tetrachlorocyclopentadienone *O*-oxide prepared by the photolysis of tetrachlorodiazocyclopentadiene was identified as an oxygen atom transfer reagent (photooxidation of cyclo-

hexane into cyclohexanol and cyclohexanone).^[49] A carbonyl oxide intermediate generated by the oxidation of diazofluorene was reported to undergo a metalloporphyrin-catalyzed oxidation of hydrocarbons, sulfides, and anisole into alcohols, sulfoxides, and methoxyphenol, respectively.^[50] CIs have also been known to oxidize thioketones and yield the corresponding thione-*S*-oxides.^[51] The gas-phase chemistry of CIs is discussed in Section 3.

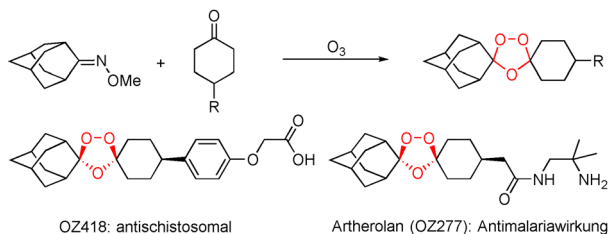
2.2. Synthetic Applications of CIs in Total Synthesis and Pharmaceuticals

Applications of CIs in the synthesis of natural products and drugs are mostly limited to their role in the ozonolysis of alkenes. The CIs formed in the oxidative cleavage of a C=C bond by ozonolysis are used:

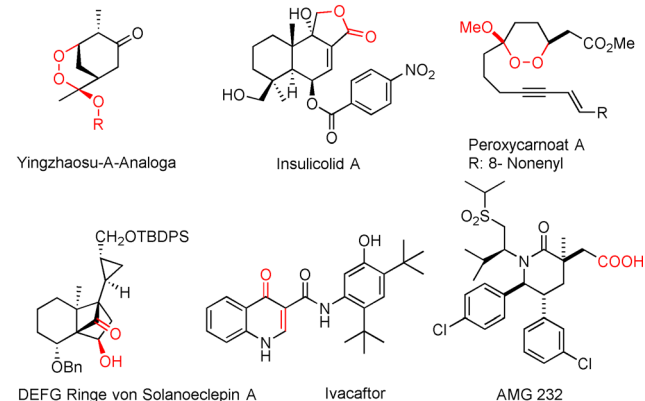
- 1) for skeletal modifications/carbonyl group generation,
- 2) as a bond-breaking tool to reveal masked functionalities (e.g. unmasking of a precursor of the prostaglandin receptor antagonist S-575,^[52] transformation of eugenol (natural component of cloves) into its aldehyde, and synthesis of the F-ring of halichondrin B by ozonolytic desymmetrization of a C2-symmetric dihydroxycyclohexene),^[53]
- 3) for removing protecting groups.^[31]

An outstanding example that does not follow the traditional path is the Griesbaum co-ozonolysis (Scheme 2), which was developed by K. Griesbaum (1932–2019) and co-workers

a) Griesbaum-Co-Ozonolyse:



b) Naturstoffe und Wirkstoffsynthesen mit Bezug zu CIs und Ozonolyse:



Scheme 2. a) The Griesbaum co-ozonolysis and illustrative examples of bioactive ozonides. b) Related products and drug syntheses involving CIs/ozonides (groups and bonds arising from ozonides are shown in red).

in 1995 in Karlsruhe, whereby an *O*-methyl oxime is ozonized in the presence of a cyclic or acyclic carbonyl compound.^[54] The oxime selectively forms a carbonyl oxide, which in turn can add to a ketone to give relatively stable and isolable 1,2,4-trioxolanes. These ozonides and related products are of interest because of their pharmacological activity.^[55–57]

The total synthesis of Yingzhaosu A (an antimalarial natural product) was investigated by O'Neill et al., who used the nucleophilic trapping of carbonyl oxides to install the required endoperoxide.^[58] The total synthesis of Baulamyacin A (an antibiotic polyketide) was performed using dry ozonolysis to unmask a carboxylic acid.^[59] Dry ozonolysis can be performed on a substrate absorbed on silica gel at low temperatures. Higher effective ozone concentrations can be reached, which allows ozonolyses that are difficult to achieve in solution; furthermore, since the substrates are immobilized, the formation of oligomeric ozonides is prevented. Skeletal modifications by ozonolysis were performed in the total syntheses of peroxyacarnoaates A and D,^[60] insulicolide A,^[61] and in the preparation of a key intermediate for the total synthesis of heme by Taber and Nakajima.^[62] Sun et al. used ozonolysis to reveal a masked aldehyde, as well as to remove an alkene employed as a protective group.^[63] Examples of pharmaceutical importance are the ozonolysis of bioengineered heparin to remove C=C bonds without loss of activity,^[64] and the preparation of the cystic fibrosis medicine Ivacaftor in a multistep continuous-flow process incorporating ozonolysis.^[65]

Other examples of CIs being used in various steps in the total synthesis of insect pheromones and juvenoids have been reported.^[66] It is also worth mentioning that ozonolysis of natural products has been used extensively in the past as a tool for structure elucidation.^[67,68] Analysis of the thereby generated fragments enables the localization of C=C double bonds to be deduced and to establish the structure of the molecule in question. A growing number of research papers appear every year with Criegee intermediates/ozonolysis as a keyword, combined with other versatile chemical reactions, for example, metal-mediated couplings and solid-phase synthesis.^[69]

2.3. Advanced Methods and Reactor Design for Exploiting CIs in Synthesis and Materials Modulation

Despite the progress, exploiting CIs in chemical synthesis on a larger scale still remains challenging because of safety issues, thus limiting its practical potential. Considering the formation of potentially explosive ozonide and/or peroxide intermediates and the toxicity of the CIs precursor, O₃ itself, traditional workup procedures have certain limitations.^[70] Through advancing methods, instrumental improvements, and automated up-scaling production, certain practical applications have become possible. For example, Hübner et al. developed an ozonolysis-reduction sequence in a microstructured device (microplant) for the synthesis of vitamin D precursors.^[71] The use of two individual microreactors in a continuous-flow setup provided a safe/controlled multistep process. Cochran et al. developed a commercial process by

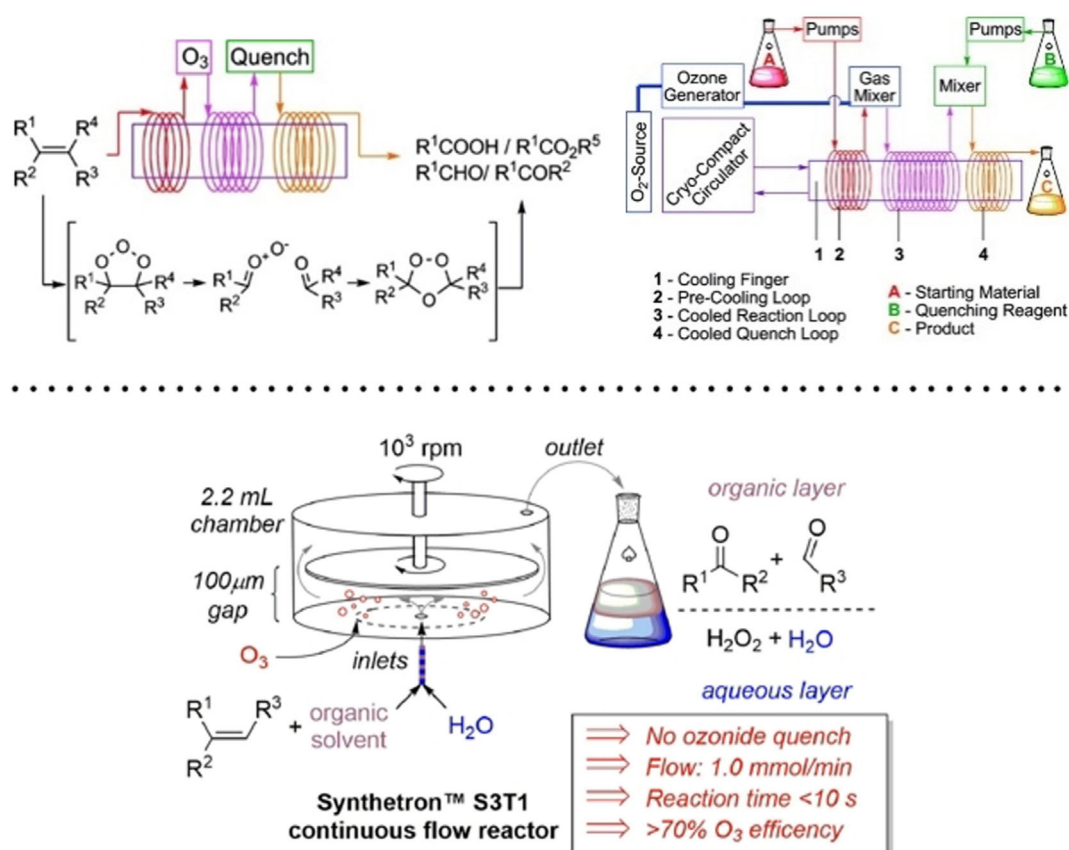


Figure 7. Top: Schematic illustration of the flow ozonolysis reactor. Reproduced from Ref. [73] with permission Copyright 2010, American Chemical Society. Bottom: Diagram of the Synthetron™ S3T1 flow reactor. Reproduced from Ref. [75a] with permission. Copyright 2016, Elsevier Ltd.

employing a green, ozonolysis-Pinnick tandem transformation for the synthesis of a cancer drug candidate in high purity.^[72] The tandem reaction can be realized in a continuous-flow ozonolysis process in a safe laboratory-scale reactor,^[73] and batch-wise processing of complex organic substrates provides the desired carbonyl products on a multigram scale.^[74] The flow ozonolysis reactor setup (Figure 7) is suitable for safe ozonolysis/quenching at atmospheric pressure and -25°C to room temperature, at flow rates of 0.2–2.0 mL min⁻¹, whereas previous flow set-ups required the use of additional quenching reagents. Similarly, a new method for the efficient biphasic ozonolysis of alkenes in EtOAc/H₂O using a high-throughput film-shear flow reactor set up, with certain improvements, has recently been developed. Here, the water acts as a mild in situ reducing agent for the carbonyl oxide intermediate to yield aldehydes and ketones together with H₂O₂ directly from the reaction mixture on a multigram scale with reaction times of <10 s without a secondary quench step (Figure 7, bottom).^[75] The flow reactor set-up uses a shearing microfluidic mixing chamber that can effectively mix biphasic media so that the carbonyl oxide can react with water during ozonolysis. A collection flask with Na₂SO₃ quenches the H₂O₂ in the aqueous layer.

From the perspective of materials applications, post-synthetic modification of polymers is a commonly used tool to modify their surface with polar groups such as aldehydes and

carboxylic acids.^[76] These can, in turn, be used to tailor the polymer surface by further functionalization^[77] or to graft another polymer,^[78] and the structure of the polymer can be modified.^[79] Ozonolysis at the solid–gas interface can be performed for the post-synthetic modification of a diverse class of coordination-driven materials bearing olefin functionalities, such as metal–organic frameworks (MOFs).^[80] This solvent-free post-synthetic transformation offers new opportunities at the solid–gas interface and for material modulation with diverse application possibilities (Figure 8).

Ozonolysis also provides the means to investigate the degradation of polymers.^[81–83] Identifying possible pathways and degradation products allows the design of tailor-made

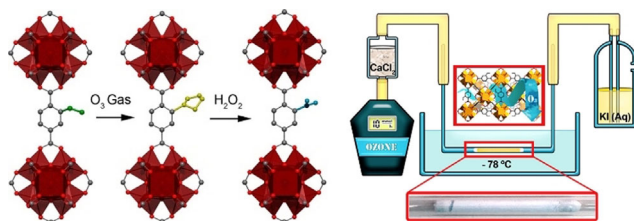


Figure 8. Left: Depiction of the postsynthetic modifications of MOFs. Right: Setup used for the ozonolysis of solid-state MOF crystals. Reproduced from Ref. [80] with permission. Copyright 2018, American Chemical Society.

polymers—either to be more durable or to be degraded more easily—as demonstrated by Tsuji et al.^[84] They designed a curable resin that is degradable by ozonolysis. In addition to polymers, carbon black^[85] and other carbon allotropes can be subjected to post-synthetic modification.^[86,87] The ozonolysis of polymers has been exploited for structure elucidation.^[88,89] The ozonolysis of vegetable oils leads to polyfunctional monomers that can be used to synthesize hyperbranched polymers.^[90] We would like to add that post-synthetic modifications are not limited to the few above-mentioned examples.

3. CIs and Atmospheric Chemistry

The role of CI species in aerosols and condensed matter in the atmosphere has been the subject of extensive recent investigations.^[91] The large body of experimental work and the conclusions regarding the chemical reactions of CIs with biogenic and anthropogenic hydrocarbons, such as alkenes, and oxides in the atmosphere are today more relevant than ever before.^[92] Understanding the fate of CIs through unimolecular, self-, and bimolecular mechanisms is a prerequisite for modeling climate-controlling atmospheric aerosol formation.^[93] Recent findings regarding CIs and their gas-phase reactions^[94] suggest that CIs may play a more prominent role in atmospheric chemistry than was previously assumed.^[95] Hence, from the perspective of photochemical smog, CIs formed during ozonolysis have crucial implications for climate change and tropospheric chemistry.^[96] Most of the ozone-dependent atmospheric processes rely on the reactivity of ozone towards UV light or radicals; however, ozonolysis is also a considerable factor. As the fine machinery of atmospheric mechanisms is crucial for making the Earth a habitable planet, it is important to understand how emissions impact this system, especially considering the current challenges of climate change. Atmospheric chemical mechanisms are beyond the mandate of this Minireview. Further insights into the new frontiers of chemistry–climate interactions have been highlighted in recent special reviews and themed issues.^[96–98]

3.1. Atmospheric Biogenic and Anthropogenic Hydrocarbons

Aside from its role as a UV scavenger, atmospheric ozone engages in reactions with volatile organic compounds (VOCs) bearing unsaturated bonds that are emitted by plants and occur as a result of other life activities. The composition of these VOCs varies considerably; thus, the oxidation products obtained by ozonolysis of these VOCs have a vast impact on the area's atmospheric processes. In rural areas, the production of terpenes by vegetation (Figure 9) results in high amounts of terpenoid VOCs, for example, isoprene.^[99] The emission of unsaturated VOCs is assumed to be a strategy of plants to protect them against ozone damage.^[100] Another example of biogenic VOCs (BVOCs) is methacrolein. Unnatural olefins such as styrene or cyclohexene are predominant VOCs which are emitted from a variety of anthropogenic sources.^[101]

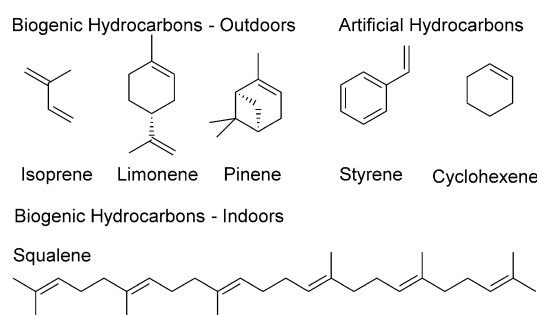


Figure 9. Some biogenic and anthropogenic VOCs with double bonds.

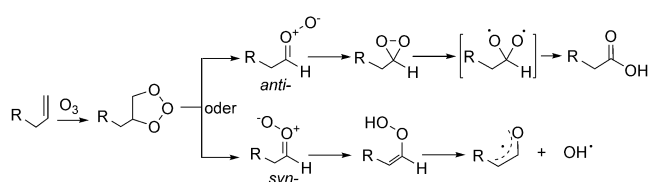
Even though ozone is considered to mainly influence tropospheric chemistry, it does also have a considerable impact on indoor chemical processes and air quality. Depending on factors such as ventilation or the presence of ozone-emitting devices such as printers, the indoor ozone concentration can reach up to 70% of outdoor levels.^[102] Artificial VOCs mainly consist of residues emitted from clothing, furniture, and cleaning products.^[103]

3.2. CIs and Their Impact on the Tropospheric Chemistry

In liquid-phase ozonolysis, the primary ozonide decomposes to a CI and an aldehyde, which subsequently recombine to form a secondary ozonide. In atmospheric ozonolysis, however, recombination is not the main way CIs react further. As a consequence of the high convection in the gas phase and the resulting lower availability of reaction partners, other pathways dominate, despite often having lower rate constants than SO₂ formation. The fate of excited CIs can be divided into either unimolecular decomposition or stabilization through collisional energy transfer to generate stabilized CIs and their follow-up chemistry. Both pathways lead to the formation of a variety of compounds that have an influence on the tropospheric chemistry.^[104]

The occurrence of CIs resulting from the ozonolysis of isoprene is intricately linked to the formation of OH radicals, which are often referred to as the atmosphere's detergent. The main source of OH[•] is the photolysis of ozone, which produces the O(¹D) atoms that in turn react with water to generate OH[•]. As this process is light-dependent, the OH[•] concentration decreases at night and in the winter. As ozonolysis proceeds without the need for light, this is the main source for the night-time production of OH[•].^[105] Thus, the OH[•] yield of reaction cascades resulting from CIs is particularly important for the atmospheric equilibrium as well as for understanding pollution phenomena arising from disturbances in these processes. The unimolecular decomposition pathways of the simple CIs are described in Scheme 3. Details on the formation of peroxides by the ozonolysis of alkenes and the formation of radicals by homolytic O–O bond cleavage of peroxides are well-documented in a recent report.^[106]

In the case of the simplest CI (CH₂OO), Beames et al. reported that the rates of the unimolecular photodecompo-



Scheme 3. Unimolecular decomposition pathways of *syn*- and *anti*-CIs.

sition to H_2CO and excited $\text{O}(^1\text{D})$ products are comparable to bimolecular reactions with other atmospheric substances. The production of $\text{O}(^1\text{D})$ products can in turn lead to the formation of OH radical products through reaction with molecular oxygen and water vapor.^[107] Several other spectroscopic investigations on the photochemistry of CIs have recently been reported.^[108] The crucial factor for which pathway is dominant for a specific CI is its conformation.^[109] Depending on the orientation of the oxygen atom of the carbonyl oxide relative to the organic residue, the substrate is either a *syn*- or an *anti*-CI. In *syn*-CIs, the proximity of the terminal oxygen atom to an α -hydrogen atom enables an internal H-shift and leads to the formation of vinylhydroperoxides, which will subsequently decompose to OH^\bullet and the respective aldehyde radical. The *anti*-CIs, on the other hand, are more prone to cyclization to a dioxirane intermediate. This dioxirane rearranges to give the respective carboxylic acid. Thus, the yield of OH^\bullet is significantly higher from the *syn* conformer. However, a recent study by Novelli et al. suggests that other decomposition pathways that lead to OH^\bullet formation might also be relevant for *anti*-CIs.^[110] For even more complex residues with additional functional groups, for example, more unsaturated carbon-carbon bonds, intramolecular cycloadditions further enhance the spectrum of the CI reactivity. In 2018, Barber et al. investigated the fate of the C_4 CI resulting from the ozonolysis of isoprene, namely methyl vinyl ketone oxide, and identified several decomposition pathways and important products depending on the initial CI conformation.^[111]

Through collisional stabilization, CIs can evade the unimolecular decomposition and transfer their energy to other molecules to become stabilized CIs. These subsequently undergo a variety of further transformations through bimolecular reactions. Possible reaction partners include water, SO_2 , NO_x , or atmospheric organic acids. In 2012, Mauldin et al. reported on the role of CIs as atmospheric oxidants of anthropogenic SO_2 to produce gaseous sulfuric acid and carbonyl compounds.^[112] The rate constants for the reactions of BVOC-derived CIs with SO_2 are relatively higher, thus making this bimolecular pathway relevant for the fate of CIs.^[113] As the presence of sulfuric acid in the atmosphere is one of the major causes of acid rain, the oxidizing potential of CIs has an important environmental impact. Similarly, CIs can also oxidize NO to NO_2 .^[114] This process contributes to the non-ozone-induced formation of NO_2 and can disturb the photostationary equilibrium of O_3 , NO , and NO_2 , which leads to smog.

In analogy to this, the reaction with NO_2 would yield NO_3 ; however, investigations by Caravan et al. show that the

oxidation of NO_2 to NO_3 is not the dominant pathway. Instead, they observed the formation of Criegee- NO_2 adducts.^[115] The reaction of CIs with water was reported to have significantly lower rate constants compared to their reactions with SO_2 or NO_x , but because of the higher atmospheric abundance of water vapors, this is one of the major reaction pathways of CIs.^[116] The resulting α -hydroxyalkyl hydroperoxides can subsequently decompose to their respective carbonyl compounds and H_2O_2 .^[117] Atmospheric organic acids similarly react with CIs to yield α -hydroxyalkyl hydroperoxide esters, which undergo broad follow-up reactions and are also able to produce H_2O_2 .^[118] Inorganic acids such as HCl and HNO_3 have also been reported to be relevant reaction partners for CIs.^[119]

The reaction of CIs with carbonyl compounds in a 1,3-dipolar cycloaddition is still an important pathway regarding the fate of atmospheric CIs. Depending on the structure of the CIs, SOZ formation can occur intermolecularly.^[120] Intermolecular reactions with aldehydes or ketones have been reported.^[121] The resulting species stemming from volatile molecules are often oxidized to less volatile ones and remain in the atmosphere. Thus, they are referred to as secondary organic aerosols (SOAs).^[122] For example, Kristensen et al. reported on the impact of high-molecular-weight esters resulting from terpene ozonolysis on the composition of SOAs in boreal areas.^[123] Pun et al. examined the structure-activity relationship in the reaction of CIs with a variety of acids as a function of their volatility. These results show that in most cases, products with high molecular masses and comparable low volatilities are formed, thus contributing to the formation of SOAs. Other, more volatile products can act as nucleating agents for SOAs. The reaction of CIs and carboxylic acids constitutes a sink for atmospheric RCOOH and, thus, could provide an efficient process for the removal of gas-phase organic acids.^[124] The influence of extremely low volatility hydrocarbons (ELVOCs) and SOAs on atmospheric particle growth and cloud formation has been envisioned.^[125] In particular, the smaller monoterpene-derived SOAs with a lower molecular weight are excellent cloud condensation nuclei as a result of their increased water solubility. These aspects emphasize the far-reaching impact of CIs on climate and show how CIs add to the production of OH radicals or the scavenging of pollutants. The complex machinery of these atmospheric processes can, however, be brought out of balance by an increased formation of CIs as a result of higher emissions of VOCs or ozone and by higher amounts of atmospheric pollutants such as SO_2 , NO_x , and acids, which might result in negative weather phenomena such as acid rain or smog formation.

3.3. Climate-Controlling Organic Aerosols, Photochemical Smog, and the Role of CIs

In general, smog describes an increased concentration of aerial pollutants arising from meteorological phenomena. Unlike the smog commonly encountered in colder climates, photochemical smog or summer smog does not refer to air pollution arising from SO_2 or dust particles, but rather an

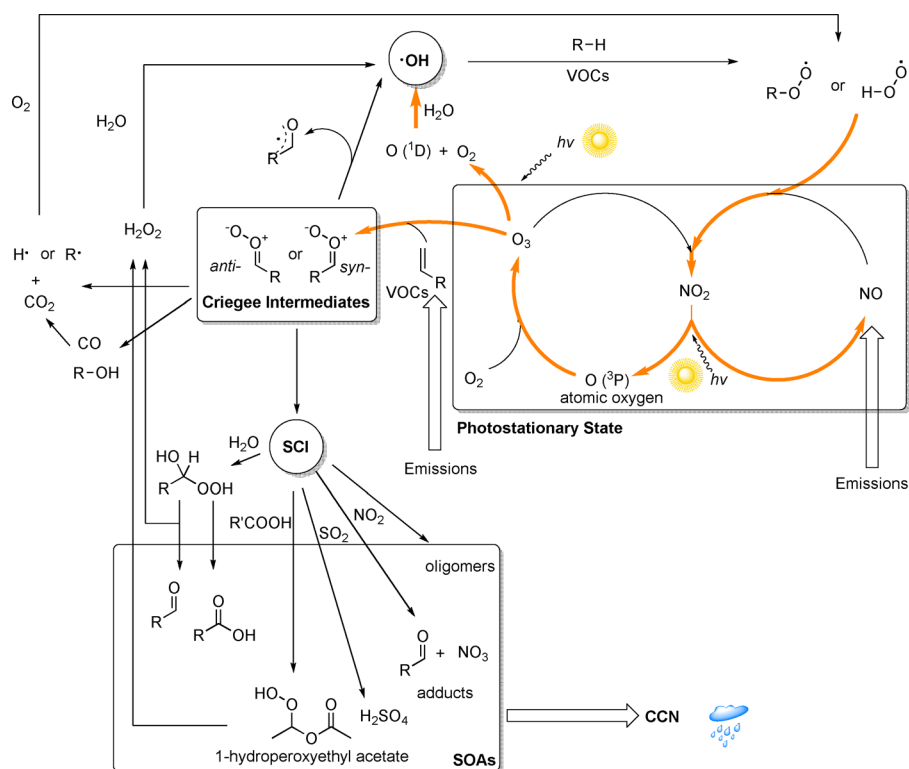


Figure 10. Atmospheric fate of CIs, SCI (stabilized CIs), and their role in the generation of photochemical smog. Orange arrows indicate processes amplified in smog formation.

increased concentration of oxidizing agents as a result of a variety of reactions that occur under specific conditions. The prerequisites for photochemical smog are UV irradiation, NO_x , and VOCs. The photolysis of NO_x leads to a series of reactions that ultimately increase the ozone concentration in the lower troposphere, as shown in Figure 10. Under normal circumstances, NO, NO_2 , and O_3 are in a photostationary state, in which NO emitted from vehicles is oxidized to NO_2 by O_3 . Through UV irradiation, NO_2 is photolyzed to generate NO and $\text{O}(^3\text{O}_2)$, which in turn reacts with O_2 to regenerate O_3 . In this way, the concentration of ground-level ozone remains constant. However, as soon as NO is oxidized to NO_2 by any other source, this equilibrium is disturbed, and more ozone is generated than consumed. The excess O_3 is subsequently photolyzed to O_2 and $\text{O}(^1\text{D})$, which reacts with water under the formation of OH radicals. OH \cdot plays a key role in many atmospheric processes. One of them is the oxidation of atmospheric hydrocarbons to peroxy radicals, which can also oxidize NO to NO_2 . Thus, even more NO_2 is generated from non- O_3 -consuming pathways, thereby resulting in an accumulation of O_3 . One possible sink for the ozone excess is the ozonolysis of olefinic VOCs, as O_3 is consumed in this process. The resulting CIs, however, are not the end of the line and will react further, which leads to the formation of ground-level SOAs, cloud condensation nuclei (CCN), and haze particles.

4. Conclusion

Although CIs are long-known species that were postulated seven decades ago, the recent findings regarding CIs and their tremendously exciting roles in synthetic and atmospheric chemistry made us realize: One can discover new things by carefully reviewing old work. With the advancement of sophisticated experimental methods for generation, and characterization techniques, most fleeting intermediates can be illuminated for timescales of 10^3 ms, μs , ns, ps, and fs, timescales that were only postulated in the early days of physical organic chemistry.^[126] In the last few years, intensive efforts have been dedicated to innovative synthetic methods for CI generation, characterization, and investigations on their reactivity. New experimental techniques have been developed for the generation of CIs and for examining their chemical structures as well as properties. The direct detection of CIs in the gas phase and their precise spectroscopic characterization have provided in-depth details on their nature, lifetime, reactivity, and electronic structure, and have shown that they have a substantial zwitterionic rather than a biradical character.

For higher accuracy, combining computations with experiments has become a powerful tool to understand and predict chemical reactivity. Computational chemistry is widely used to understand electronic structures and properties as well as support the interpretation of reactive intermediates. Structures of CIs can be calculated with a high degree of accuracy by mechanistic investigations based on quantum chemical calculations; indeed, such calculations are now becoming

routine and can predict the selective formation of particular intermediates.

The recent research interest in climate-controlling organic aerosols has shown that Criegee's work has lost none of its validity. The fate of CIs in the atmosphere and understanding their particular impact on the environment need detailed systematic investigations, both experimentally and theoretically, beyond small CI precursors and structure-dependent chemical reactivity. To explore new perspectives in Criegee chemistry—from developing new experimental methods to generate CIs to structural characterization and chemical reactivities—utilizing multidisciplinary research approaches by combining insights from organic/physical chemistry and atmospheric chemistry aided by advanced computational calculations and modeling would further advance the understanding of this field.

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Conflict of interest

The authors declare no conflict of interest.

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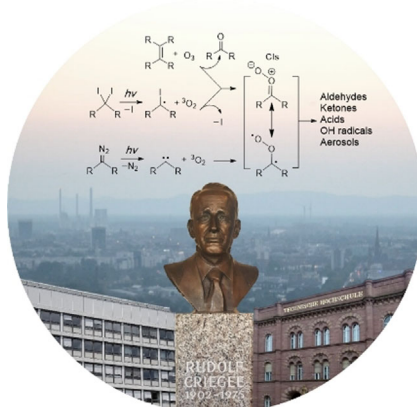
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Minireviews

Reactive Intermediates

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Criegee Intermediates Beyond
Ozonolysis: Synthetic and Mechanistic
Insights



After more than seven decades, Criegee intermediates (CIs) are back at the forefront of modern chemistry. They play an important role in the mechanisms of chemical reactions, total synthesis, pharmaceuticals, climate-controlling aerosol formation, as well as atmospheric chemistry. This Minireview summarizes key aspects of CIs, highlights recent progress in CI chemistry, and illustrates possibilities for further investigations.