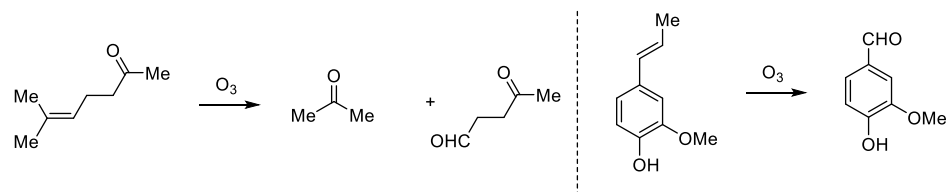


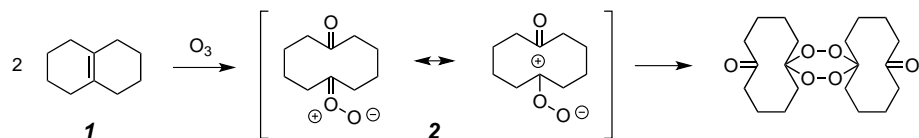
Early Ozonolysis of Alkenes to Ketones and Aldehydes [1905]

Harries first demonstrated oxidative cleavage of an alkene with ozone to form aldehydes and ketones in 1903¹ and proceeded to study the ozonolysis of organic compounds over the next two decades.²



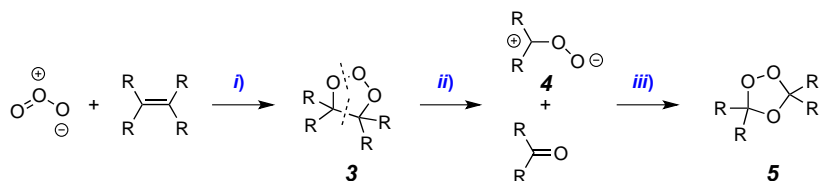
Criegee's First Proposal of the Carbonyl Oxide Species (aka the "Criegee Intermediate") [1949]

The first proposal of the key carbonyl oxide intermediate, now commonly referred to as the "Criegee intermediate", came in 1949, when Criegee observed dimerization upon treatment of the octahydronaphthalene **1** with ozone. This was rationalized as occurring through the carbonyl oxide intermediate **2**.³



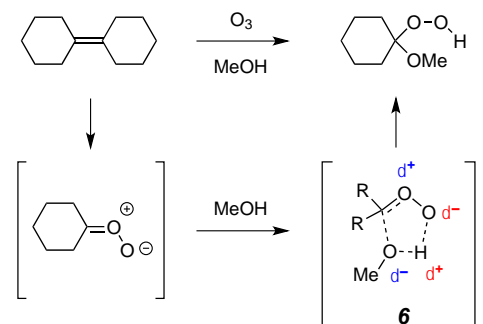
Criegee's First Proposal of the Three-step Mechanism [1951]

In a perspective Criegee wrote in 1975, he stated to have first proposed the classic three-step ozonolysis mechanism at an IUPAC Congress in New York in 1951. The overall process is rationalized by a series of 1,3-dipolar cycloaddition/cycloreversion/cycloaddition forming *i*) the primary ozonide (aka molozonide) **3**, *ii*) the carbonyl oxide **4** and carbonyl, and, finally, *iii*) the isolable 1,2,4-trioxolane **5**.⁴



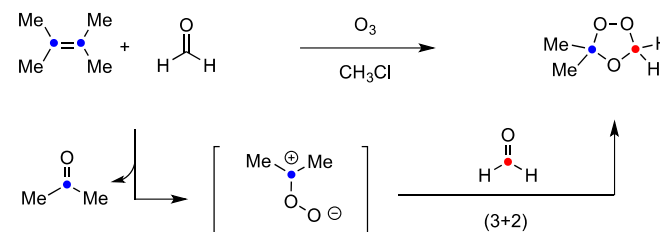
Trapping the Carbonyl Oxide with Alcohols [1953]

In 1953, Criegee observed the addition of alcohols across the presumed carbonyl oxide intermediate. The mode of addition was informative; the O–H bond of methanol was cleaved rather than a C–H bond, which suggested that a polar mechanism was operative. A radical process should favor cleavage of the weakest bond (i.e., the C–H), whereas a polar process would likely occur through proton transfer and nucleophilic attack by the oxygen atom (see TS **6**).⁵



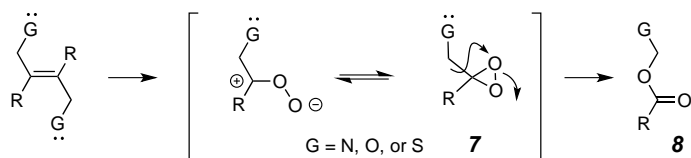
Trapping the Carbonyl Oxide with "Foreign" Carbonyls [1954]

By 1954, Criegee had observed ozonolyses in which the recovered ozonide was comprised of one fragment from the starting alkene and one fragment from a "foreign" or external carbonyl compound present in the reaction mixture from the outset. This suggested an intermediate having a sufficiently long lifetime to encounter a carbonyl compound other than the one produced in the initial cycloreversion step [cf. *ii*), above].⁶



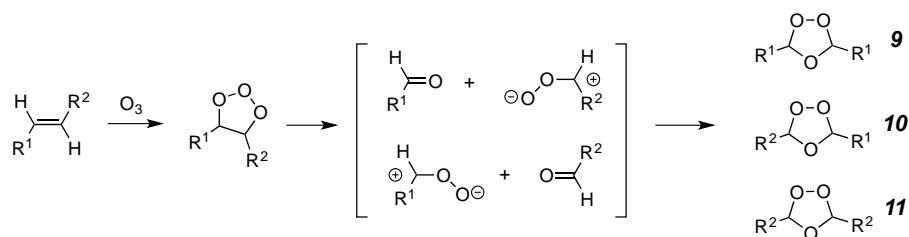
Rearrangements of Carbonyl Oxides [1957]

Bailey observed a series of “anomalous ozonolyses” of alkenes bearing allylic heteroatom substituents (N, O, or S, denoted by generic atom G). A peroxide rearrangement to form esters **8** was observed, rationalized by a carbonyl oxide to dioxirane (**7**) interconversion.⁷



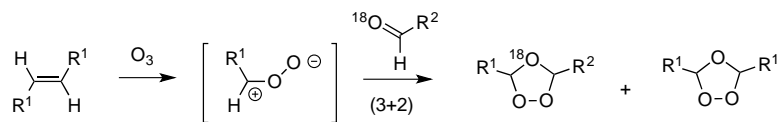
Crossover Experiments [1963-1965]

In the case of unsymmetrically substituted alkenes, the formation of not only the unsymmetrical ozonide **10** but the symmetrical analogs **9** and **11**, in nearly statistical amounts (1:2:1), shows that the carbonyl oxide does not re-add to its aldehyde counterpart before that pair separates and randomizes into solution.^{8,9,10}

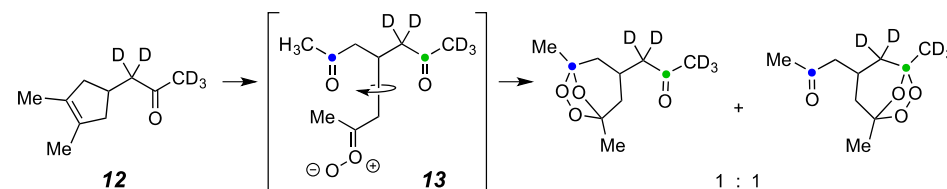


Isotopic Labeling Studies [1968-1975]

• *origin of atoms in a product via, here, a double-label experiment*: Using an ¹⁸O-labeled “foreign” aldehyde, Fliszar¹¹ and Kuczkowski¹² showed i) that the carbonyl oxygen atom was incorporated as the ether bridge of the 1,2,4-trioxolane product and ii) that the R² and ¹⁸O labels remained intact in the product, refuting a mechanistic proposal at the time to the contrary.

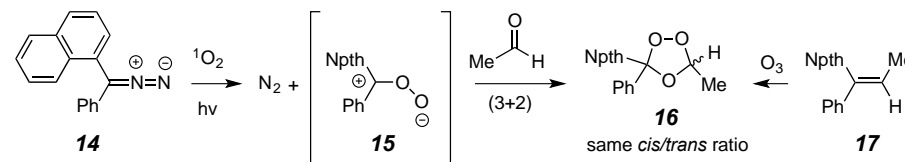


• *symmetrization of an intermediate*: In an elegantly designed experiment, Criegee¹³ used the deuterated cyclopentenyl ketone **12** to support the intermediacy of the carbonyl oxide **13**, symmetrical except for the isotopic labeling. 1,3-Dipolar addition to either the **unlabeled ketone** or the **labeled ketone** with equal ease demonstrated that the carbonyl oxide had time to undergo symmetrizing bond rotation.



Alternative Synthesis of the Carbonyl Oxide Intermediate [1973]

The photooxidation of the carbene from the naphthyl diazomethane derivative **14** in the presence of acetaldehyde gave the same mixture of *cis*- and *trans*-trioxolanes **16** as was formed by ozonolysis of the alkene **17**. This strongly supports the common intermediacy of the carbonyl oxide **15** in both reactions.¹⁴



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