The Ozonolysis of Haloalkenes in Solution

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Abstract. A review of the ozonolysis of low molecular weight haloalkenes in solution is presented. The reaction products from the fluoroethylene series are discussed in detail. Secondary ozonides can be obtained from these alkenes although the yields decrease markedly with increased fluorination and diminish to negligible quantities with C_2F_4. Compared to alkylethylenes, a greater variety of products are obtained including some epoxides and fluorocyclopropanes. Yield data are supplemented by isotopic labeling results to elucidate the ozonolysis mechanism. The evidence indicates that the final ozonides are formed by the three step Criegee reaction mechanism although the stereoselectivity of the reaction differs from nonhaloalkenes.

The attack of a carbon–carbon double bond by ozone is "active oxygen" chemistry of broad interest and applications.[1] In many solution reactions, the final or secondary ozonide is the major product. Its formation is described by the three step Criegee mechanism[2] (Eq. 1) which in its "bare bones" form is familiar to organic chemists. Synthetic chemists usually reductively cleave the final ozonide to carbonyl or alcohol derivatives.

primary
ozonide

final
ozonide

(1)
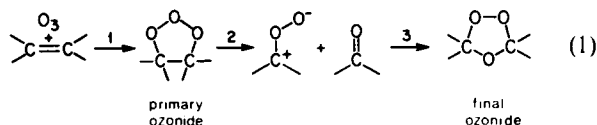
Current research on the mechanism of ozonide formation is directed towards questions concerning reaction concertedness, stereochemistry, solvent effects and energetics as well as extensions to new systems.[3]

When we searched the literature in the early 1970's for syntheses of fluoro ozonides with the intention of exploring their microwave spectra, it became apparent that virtually nothing had been reported about the ozonolysis of fluoroalkenes except for a few reports dealing with C_2F_4. Systematic investigations of other alkenes with halogen substitution at the C=C bond were also not very numerous.[4] Since then a more detailed picture has emerged from studies on haloalkenes with 2 to 4 carbon atoms at our laboratories, at Karlsruhe (Prof. K. Griesbaum et al.) and at Penn State (Prof. J. Heicklen et al.) along with contributions from other investigators on these and more complex substances. This review will principally focus on recent findings from the ozonolysis of small haloalkenes in solution. The similarities and differences to other alkenes will be emphasized and attention will be directed to the applicability of the Criegee mechanism to such systems.

REACTIVITY

There have been a number of reports which point to a decreased reactivity for ozone attack at a halogen substituted double bond.[5-7] One widely cited study of the

second order reaction kinetics between ozone and the chloroethylenes demonstrated that the rate constant for vinyl chloride is smaller by approximately 10^2 compared to alkenes like cis-2-butene, 1-pentene and styrene.[6a] In progressing from vinyl chloride to tetrachloroethylene, the rate constant further decreases by about 10^5.[6b] Recent measurements of activation parameters for $C_2H_2Cl_2$, C_2HCl_3 and C_2Cl_4 have also been carried out.[6b] There have been a variety of examples of compounds possessing both halogenated and nonhalogenated double bonds where ozone attacked exclusively at the nonhalogenated center.[7] The general trend of decreased reactivity towards ozone with increasing halogen substitution correlates with the electrophilic properties exhibited by ozone attack on a wide variety of alkenes containing both electron withdrawing and donating substituents.[1]

REACTION PRODUCTS

The products from the ozonolysis of the fluoroethylenes have recently been mapped in considerable detail.[8-13] A more diverse set of products has been identified compared to ethylene or propylene where the final ozonide is the predominant product. Scheme 1
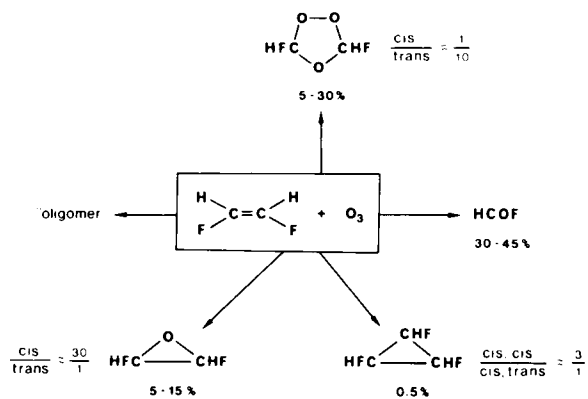
Scheme 1.

summarizes the products which have been identified from cis-CHF=CHF.[8,9] It illustrates the typical yields for this particular alkene as well as the reaction pathways which must be considered for the fluoroalkenes in general.

The major products from the other fluoroethylenes also include the final ozonide, along with the cleavage product HFCO and/or F₂CO and solid or viscous liquid residues (uncharacterized oligomers). Perfluoroethylene is an exception to the other fluoroethylenes. Ozonolysis of this fluoroalkene over a wide range of $O_3 : C_2F_4$ molar ratios usually yields no final ozonide.[13] Only for $O_3 : C_2F_4$ ratios approaching unity was any perfluoroethylene ozonide identified in low yield. The yields of the ozonides and the carbonyl products are illustrated in Fig. 1. The variableness in the ozonide yields arises in part from a variation with solvent system as well as difficulties in reproducibility when dealing with volatile and unstable species. The results indicate a decrease in final ozonide yield and some increase in HFCO and F₂CO yield with increased fluorination if a liberal view towards the broad range in yields is tolerated.
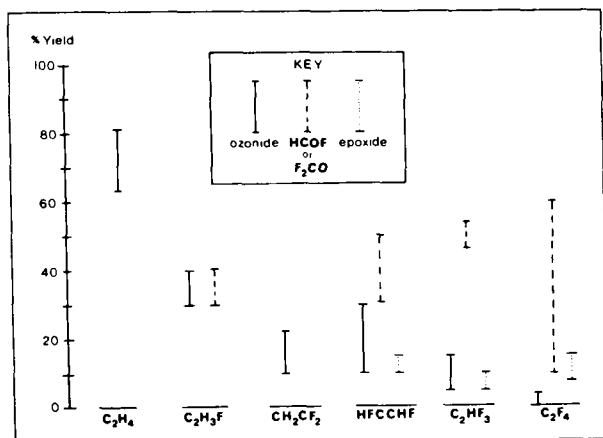

Fig. 1. The range of reported yields (Refs. 8–13) for the final ozonide, HCOF or F₂CO and epoxide from ozonolysis of fluoroethylenes.

In addition to the major products, some epoxide formation and trace amounts of fluorocyclopropanes (< 1%) are found when fluorine substitution occurs at both carbon atoms. Cross ozonides ($\leq 3\%$, Eq. 2) can also be isolated from the unsymmetrical alkenes with the exception of perfluoroethylene ozonide. This ozonide is evidently not formed from CH₂=CF₂ or CHF=CF₂ where it is expected as a cross ozonide.
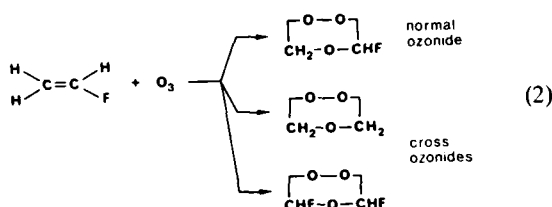

With vinyl fluoride, a variety of other species have been identified in trace quantities ($\leq 1\%$) which illustrate the additional reaction complications which enter with the haloalkenes.[12b,c] These products include

$$CH_3C(O)F, CH_2FC(O)F, cis\text{-}CHF\text{-}O\text{-}CHF,$$
$$(CH_2F)_2O \text{ and } CH_2FOC(O)H.$$
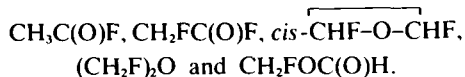
The latter two are known to arise from the decomposition of vinyl fluoride ozonide.[12] In the case of the epoxide, both carbon atoms can be traced back to the same C₂H₃F precursor (no carbon randomization).[12c] Therefore, it appears to arise after a fluorination process which probably occurs at the starting alkene.

These more unusual, but low yield products from vinyl fluoride presage the rich variety of products that have been identified from 2,3-dibromo-2-butene[14] and 2,3-dichloro-2-butene.[15] The reactions of the latter species are outlined in Scheme 2. While the final ozonide was not
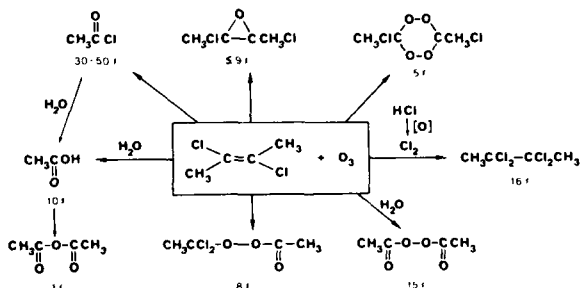
Scheme 2.

isolated from CH₃CCl=CClCH₃ (or the dibromo alkene), the two products containing a peroxy link may be derived from it. The cyclic diperoxy species is the expected product from dimerization reactions of the Criegee intermediate, CH₃CCl-O-O, the usual cleavage product of the primary ozonide. The epoxide, acetyl chloride and its derivatives are analogous to products obtained from the fluoroalkenes. A noteworthy contrast between the fluoroethylenes and the dichloro and dibromobutenes is the apparently higher yield of products derived from hydrolysis reactions of C-Cl or C-Br bonds or from halogenation processes at some stage. The latter reactions presumably arise from the greater ease of producing active Cl or Br in the presence of ozone.

REACTION MECHANISMS

A plausible reaction mechanism is derived in the first instance from consideration of the products combined with chemically sound reaction principles. This often suggests additional experiments or calculations specifically designed to test aspects of the model. The product analysis from the fluoroalkenes and halobutenes indicates that complete alkene cleavage products are formed, specifically the ozonide and haloaldehydes, as well as epoxides and cyclopropanes which might be derived by simple addition to the alkene double bond. A third group of products are derived from decomposition reactions, hydrolysis reactions and other complications resulting from halogen rearrangements or halogenation of reactants or products. Follow up efforts have been made to better establish the pathways to these products with the greatest amount of attention and success associated with the mechanism of ozonide production.

The Criegee mechanism of ozonolysis (Eq. 1) can be described as a three step cycloaddition, cycloreversion, cycloaddition process.[16,17] It rationalizes many aspects of the ozonolysis of alkyl and aryl alkenes and is the starting

point for the haloalkene analysis. This process is illustrated in Scheme 3 for reactions and products associated with ozonolysis of vinyl fluoride and mixtures of it with other alkenes or aldehydes.[12]
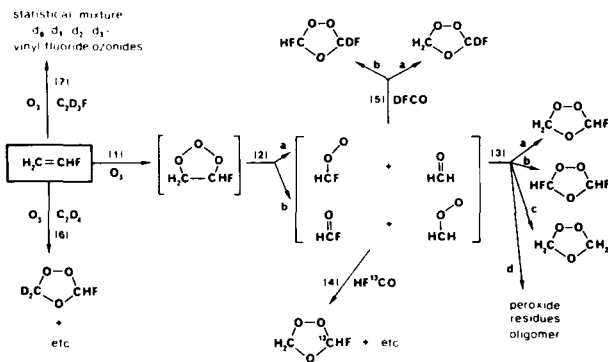

Scheme 3.

The direct evidence for the primary ozonide formed in the first reaction step (Scheme 3, reaction 1) is not extensive. There is some spectral evidence by matrix IR for the primary ozonide of vinyl chloride[1X] and the primary ozonide of 1,2-dichloroacenaphthylene is stable enough to be isolated.[19] A transient primary ozonide also seems plausible by analogy with nonhalo alkenes where it has been observed at low temperatures by NMR or IR. Even crystals of the primary ozonide and 1,2-diol derivatives have been isolated in several cases.[1,20]

The cleavage of the primary ozonide to produce a carbonyl oxide and aldehyde is consistent with the normal reaction products represented in reactions 3a–3d in Scheme 3. Isotopic reactions 4 and 5a are consistent with a trapping of H₂COO precursor while 5b provides support for the intermediacy of HFCOO. The products of reactions 6 and 7 can also be explained by the presence of H₂COO and/or HFCOO in solution. It is evident that extensive scrambling of the cleavage products produced in reactions 2a and 2b occurs leading to a high proportion of ozonide formation outside the original solvent cage (e.g. reactions 6 and 7).

Additional evidence which suggests that the primary ozonide cleaves to produce both possible carbonyl oxides (reactions 2a and 2b) is provided by the formation of cross ozonides (reactions 3b and 3c). However, the two cleavage reactions probably occur in unequal amounts. The relative yields of the two cross ozonides along with other trapping experiments suggest that the H₂COO cleavage direction (reaction 2a) is favored to the extent of 75–90%.

Trapping experiments with monochloro alkenes including vinyl chloride[21] in methanol provide firm evidence that the cleavage direction of the primary ozonide usually favors production of the nonhalogenated carbonyl oxide. This cleavage preference is almost quantitative for some cases as illustrated by a selected example in Eq. (3).


(3)

(95 % yield)
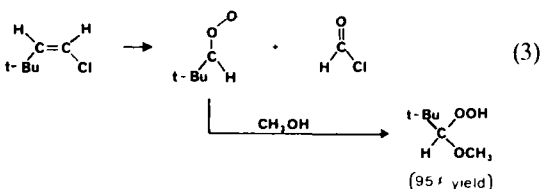
There have been several trapping experiments conducted with the 1,2-difluoroethylene isomers using H₂CO or DCOF. These yield the appropriate ozonide expected from the combination of HFCOO with the added al-' dehyde.[12c] An especially noteworthy result occurs with H₂C¹⁸O and HFC=CHF mixtures as shown in Eq. (4).


(4)
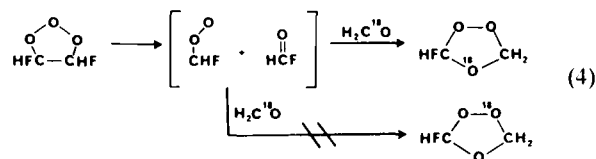
The position of the ¹⁸O label in the ozonide is consistent with the open carbonyl oxide form for the Criegee intermediate but is more troublesome for a cyclic dioxirane structure. Such a structural isomer would undoubtedly have a weak peroxy bond and reaction with H₂C¹⁸O should lead to ¹⁸O labeling at the peroxy site in the ozonide ring.

Another notable reaction (Eq. 5) provides evidence for the intermediacy of CF₂OO.[10]

(5)
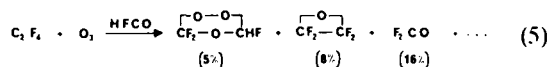
The absence of perfluoroethylene ozonide in the C₂F₄ reaction and the low production of ozonides in general as fluorine content increases suggest a decrease in 1,3-dipolar reactivity for fluorinated carbonyl oxides. It also indicates a successive lowering of the dipolarphilicity in the series H₂CO, HFCO and F₂CO.[10,12c]

An interesting aspect of the fluoroalkene story is the stereochemistry of the reaction as revealed in the production of cis- and trans-difluoroethylene ozonide. These species can be obtained as the normal ozonide or a cross ozonide from C₂H₃F, C₂H₂F₂ and C₂HF₃ (Scheme 4).
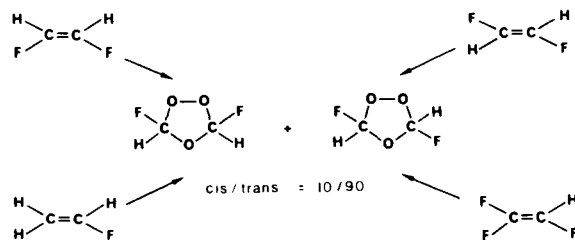

Scheme 4.

However, all four starting alkenes lead to a similar cis/trans ratio of about 10/90 (±2%) for the difluoro ozonide. Stereochemical control in the Criegee mechanism (Eq. 1) can occur via stereospecific addition of O₃ in step 1, preferential cleavage to a syn or anti carbonyl oxide in step 2 along with further stereoselectivity in the recombination step 3. According to the arguments developed for alkylethylenes, the syn carbonyl oxide is preferred from trans alkenes and the anti isomer from cis alkenes. Furthermore, the syn carbonyl oxide leads to trans ozonides while an anti isomer results in cis ozonide.[16,17] This rationale has to be modified (or discarded) for the fluoroalkene series since the trans isomer is predominant for all reactions. One possibility is that cleavage of the primary ozonide occurs by a cycloreversion such as in Eq. (6) which places the fluorine in an

axial position, consistent with an anomeric effect.[8,12d] This would give predominantly the syn carbonyl oxide and *trans* final ozonide. Another possibility is that the carbonyl oxide, HFCOO (regardless of its syn or anti configuration), and HFCO react preferentially trans in step 3 due to F...F repulsions in the transition state. Calculations of the reaction energetics suggest that both of these explanations are applicable.[22]


(6)
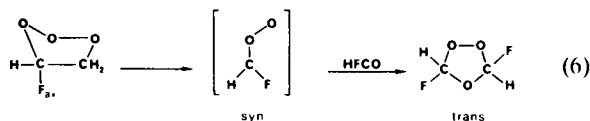
In summary, considerable evidence establishes the formation of ozonides from the fluoroalkenes and indicates that they are formed by a Criegee reaction process. A variety of experiments suggests that the cleavage of these alkenes produce the expected carbonyl oxides including both halogenated and nonhalogenated species. These carbonyl oxides react and can be trapped resulting in ozonides which are readily rationalized. However, the yields of ozonides decrease with increased fluorine substitution due in part to the lowered reactivity of the primary ozonide cleavage products. Finally, the overall stereoselectivity from alkene to ozonide differs from simple alkyl ethylenes requiring some amendments to the usual stereochemical rationale of the Criegee process.

Additional stereochemical and labeling data also provide some mechanistic insights on the epoxide and cyclopropane production in the fluoroalkene ozonolyses. Reaction of CHF=CHF + CDF=CDF mixtures with ozone show no scrambling of the carbon moieties in the epoxides.[8] Therefore, the carbon–carbon bond remains intact upon epoxidation eliminating their production via decomposition of a final ozonide or by the other two processes shown in Eq. (7).

(7)
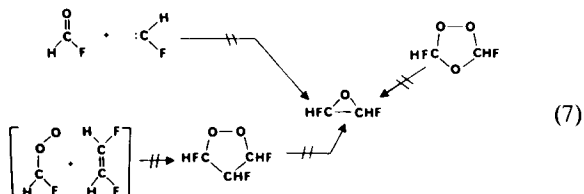
The epoxidation of *cis-* and *trans*-CHF=CHF proceeds with high stereospecificity. For example, in a CF$_3$Cl solvent, the *cis* and *trans* epoxides are formed in the ratio of 97/3 and 5/95 from the *cis* and *trans* alkenes, respectively. The small loss of configuration does not apparently take place by an isomerization of the alkene or epoxide. It appears intrinsic to the epoxidation process and suggests that they do not form by a completely concerted process but via pathways where rotation about the carbon–carbon bond competes, albeit poorly, with ring closure. For *cis*-CHF=CHF, either partial or complete cleavage processes are consistent with the data as illustrated in Eq. (8).


(8)
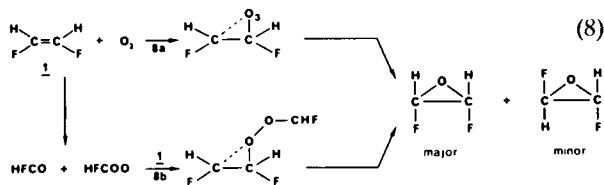
However, in the case of perfluoroethylene ozonolysis, the reaction stoichiometry is given by Eq. (9) in the limit

(9)
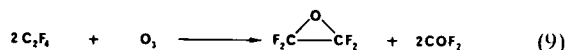
of low ozone:alkene mole ratios. This result argues compellingly against a partial cleavage mechanism (reaction 8a) where one mole of alkene reacts with one mole of ozone to produce one mole of epoxide and one mole of oxygen.[23] It is consistent with a complete cleavage process such as reaction 8b. Nevertheless, the species responsible for the epoxidation in CHF=CHF, CHF=CF$_2$ and CF$_2$=CF$_2$ ozonolyses is still not clear.

Cyclopropane formation in the fluoroethylene ozonolyses has been rationalized through either direct fluorocarbene or fluorocarbenoid addition to the appropriate alkene. Stereochemical[9] and isotopic[24] results for the CHF=CHF alkenes show that this addition proceeds in a concerted fashion as shown in Eqs. (10a) and (10b).

(10a)

(10b)
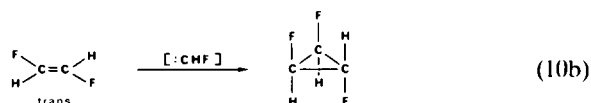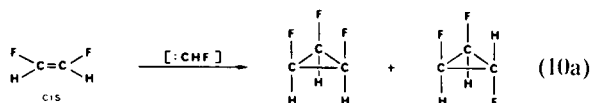
The immediate source of the carbene or identity of the carbenoid is not clearly established. However, isotopic studies have shown that decomposition of the epoxide is not the source.[8] In the case of perfluoroethylene, it was suggested that the carbonyl oxide, CF$_2$O$_2$, might decompose to :CF$_2$ (carbene) and oxygen.[13]

Mechanistic schemes in the case of the bromo and chlorobutenes mentioned earlier must account for an even greater variety of reactions than for the fluoroalkenes. Plausible proposals have been described to account for the rich set of products illustrated in Scheme 2.[14,15] These reaction processes will not be rationalized in detail here except to note that many of them can be derived from subsequent reactions of the carbonyl and carbonyl oxide moiety. In other words, the first two steps of the Criegee reaction process presumably occur followed by reactions of the Criegee cleavage products, unstable ozonides and cyclic diperoxides. These subsequent reactions can rationalize the appearance of many of the more complex products.

SUMMARY

A clearer understanding of the ozonolysis of haloalkenes has developed the last decade. Some general patterns have begun to emerge but much still can be learned. It is apparent that the Criegee mechanism is a useful starting point and that double bond cleavage is a prevalent process. However, a plethora of nonozonide products indicates other competing reactions occur which are largely absent in most nonhaloalkene ozonolyses. These complications and the concomitant reaction diversity may diminish the practical utility of this reaction class to synthetic chemists. It, of course, increases the challenges to the experimentalists who probe the reaction process. The necessity for small-scale reactions due to the peroxidic nature of the product milieu also provides its own challenges. Still, the satisfaction and potential usefulness associated with exploring

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haloalkene ozonolysis chemistry which is not yet "old hat" is sure to stimulate further inroads in this area over the next decade.

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