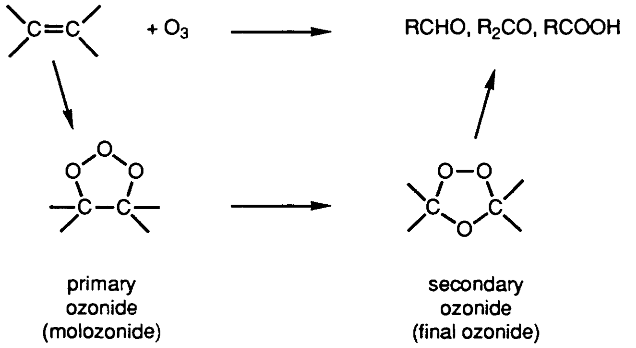
The Structure and Mechanism of Formation of Ozonides

Robert L. Kuczkowski
Department of Chemistry, University of Michigan, Ann Arbor, Michigan, 48109-1055, U.S.A.

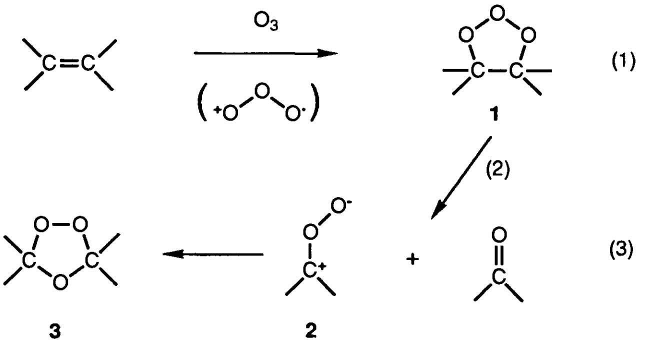
The cleavage of the alkene double bond by ozone to give aldehydes, ketones, and acids is a well known and widely utilized reaction.[1] It is also known that cyclic intermediates called ozonides precede the formation of these products during the course of the reaction (Scheme 1). However, few synthetic chemists have ever isolated an ozonide. It is an unnecessary diversion if the carbonyl containing compounds are the desired products. Moreover, ozonides have a reputation of being unstable and even explosive, although this latter characteristic varies markedly with alkene substrate. Nevertheless, investigators who are interested in the mechanism of ozonolysis isolate and characterize ozonides since they provide key information on the reaction process. This article will review the mechanism that describes the formation of these ozonides.

The identification of ozonides and the rationalization for their formation during ozonolysis was first described nearly 35 years ago. Using classical structure-proof methodology and trapping experiments, Rudolf Criegee and his co-workers isolated many ozonides and determined their structures.[2] This led Criegee to describe their formation with a three step mechanism, shown in Scheme 2. This proposal is so attractively simple that it is often included in undergraduate lectures. In its simplest form, the mechanism is usually explained using 1,3-dipolar cycloaddition concepts.[3] A more sophisticated description incorporates concepts from frontier molecular orbital theory.[4]

In terms of these paradigms, reaction 1 in Scheme 2 is a cycloaddition between the ozone 1,3-dipole and the alkene dipolarophile leading to (1), which is called a molozonide or primary ozonide. This is a symmetry allowed $2\pi + 4\pi$ cycloaddition. The orbital description of the reaction for ethylene and ozone is shown in Figure 1a; the strongest interaction involves the HOMO of the alkene and the LUMO of ozone. Figure 1b illustrates the idealized envelope transition state consistent with this orbital picture. The molozonide is very unstable and cleaves *via* a cycloreversion in reaction 2 to a stable carbonyl compound and an elusive carbonyl oxide (2), sometimes called the Criegee intermediate. The carbonyl oxide is isoelectronic with ozone and can be considered another 1,3-dipole. It quickly combines in reaction 3 with the internally generated carbonyl compound to produce (3) *via* a cycloaddition reaction which is formally analogous to the first step in the mechanism. Species (3) has several names in the literature: final ozonide, secondary ozonide or, as in this paper, simply ozonide. Ozonides can often be isolated and thoroughly characterized.



Scheme 1



Scheme 2

This article will explore several questions of current interest about the basic three step Criegee mechanism. These range from evidence for the elusive intermediates (1) and (2), to fundamental tests of the cycloaddition process. For example, can it be ascertained whether the cycloadditions and cycloreversion are concerted reactions? What is the stereochemistry of the process and how is this incorporated into the mechanism? What role

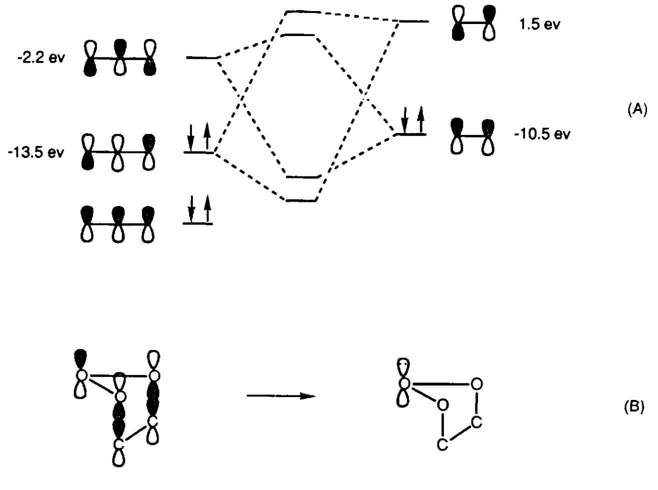
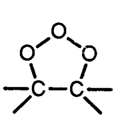


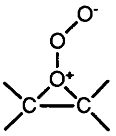
Figure 1 (a) HOMO–LUMO interaction diagram for the cycloaddition of ozone and ethylene. (b) Orbital overlaps in the idealized cycloaddition transition state.

Robert L. Kuczkowski was born in Buffalo, N.Y. where he attended Canisius College. The Ph.D. degree was received from Harvard University in 1964 under the mentorship of E. Bright Wilson, Jr. A NAS–NRC postdoctoral fellowship was held at the National Bureau of Standards (Washington, D.C.) in the Microwave and Infrared Spectroscopy Section. He joined the Chemistry Department at the University of Michigan in 1966 where he presently is Professor and Chair. His research interests include the heterogeneous catalysed oxidation of alkenes, the mechanism of ozonolysis, and structural studies by conventional and Fourier transform microwave spectroscopy.

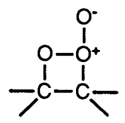
does the solvent and the solvent cage play in the reaction? Investigations which provide insight on these questions are the focus of this review. Several examples originate from the author's laboratory, where isotopic tracer experiments have been used extensively as a probe of the mechanism.



1



4

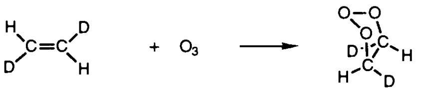


5

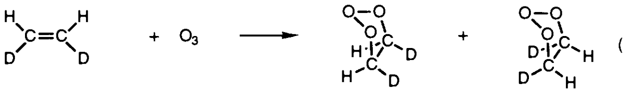
The primary ozonide (1) produced in the first step of the Criegee mechanism has been observed by NMR and IR at low temperatures for a variety of alkenes.[5] From these data, as well as the conversion of primary ozonides into 1,2-diols,[2] the cyclic 1,2,3-trioxolane structure has been inferred, although other forms such as (4) or (5) are not completely eliminated by such data. It is therefore satisfying that a definitive characterization of a primary ozonide by microwave spectroscopy has very recently been reported for the product between ozone and ethylene.[6] This primary ozonide was observed in the gas phase after the co-condensed reactants were allowed to warm. The structure of the primary ozonide is illustrated on the right side of the postulated reaction diagram in Figure 2. It is interesting that the envelope structure closely conforms to the postulated transition state for a concerted cycloaddition.

Even more remarkably, the van der Waals complex between ozone and ethylene has also recently been observed by microwave spectroscopy (Figure 2, left species).[7] The complex also resembles the postulated transition state in Figure 1b, strongly suggesting that it lies along the reaction coordinate for the cycloaddition. The structure of the transition state itself has been estimated using *ab initio* methods[8] (Figure 2, centre species); the O_3 and ethylene are separated by a distance of about 2 Å which is intermediate to those found in the weak van der Waals adduct and the primary ozonide.

The stereochemical test for a concerted cycloaddition,[3] *viz.* retention of configuration about the double bond, was also explored in the microwave study by ozonizing *trans*- or *cis*-ethylene-1,2-d_2. The *trans* species gave exclusively the *trans*-d_2 primary ozonide (reaction 4). The *cis* isomer gave an equimolar mixture of the *endo* and *exo* d_2-forms with no evidence for stereo randomization about the carbon–carbon double bond (reaction 5). This extensive set of structural data from experiment and theory is consistent with the many previous studies which inferred a concerted cycloaddition between ozone and the alkene.



(4)



(5)

Evidence for a concerted cycloreversion as the primary ozonide cleaves in the second step of the Criegee mechanism is considerably less direct.[1,5] One of the products of the cycloreversion, *viz.* the carbonyl oxide, is highly reactive which has impeded a study of this question. The carbonyl oxide had not been detected spectroscopically until recently when it was observed by IR in low temperature matrices[9,10] and by transient species UV techniques in solution.[11,12] Subsequent spectroscopic studies and electronic structure calculations of the simplest carbonyl oxide and substituted analogues have appeared,[13–15] as well as for the cyclic dioxirane isomer and the energetics of interconversion between the isomers.[16–19] However, during normal ozonolysis conditions, the carbonyl oxide concentration apparently never rises high enough to allow its detection and direct study. The principal evidence for its existence arises from trapping experiments. The carbonyl oxide is readily trapped[1,14] by carbonyl compounds, alcohols or, as shown recently, by an activated alkene containing an alkoxy group (Scheme 3).[20]

Because of the transitory nature of the carbonyl oxide, the evidence that the cycloreversion is concerted is much more inferential in nature. A rationale is constructed from the stereoselectivity which is usually evident in the ozonide product. This stereoselectivity can be summarized by the observation: the ozonolysis of *cis*(*trans*)-1,2-alkenes with bulky substituents yields more *cis*(*trans*)-ozonides respectively (reaction 6). Since the first step of the Criegee mechanism is stereospecific (Figure 1b), the stereoselectivity must arise in the second or third steps, or both. In the second step, stereo effects are readily incorporated by postulating *syn–anti* isomerism in the carbonyl oxide

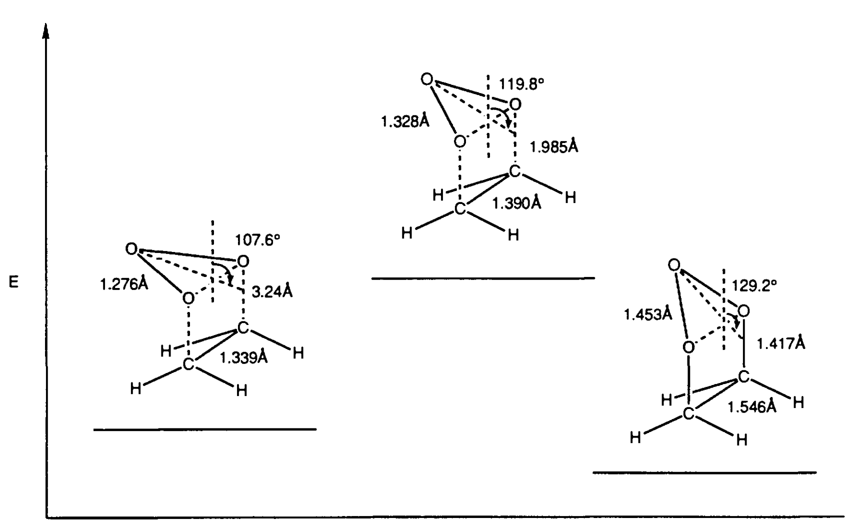
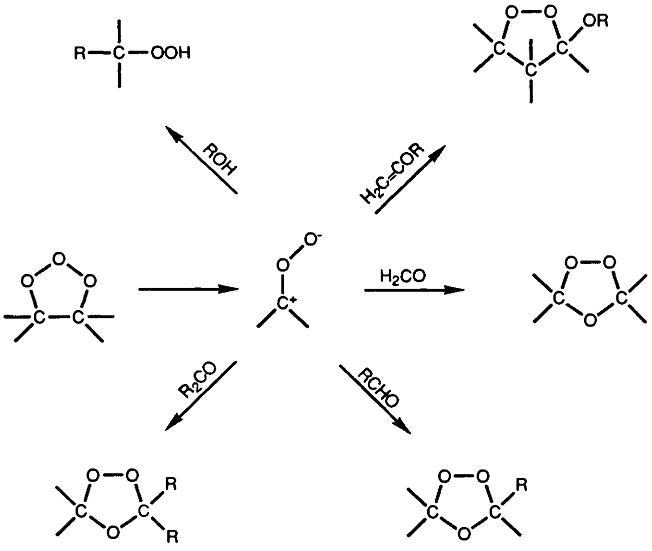
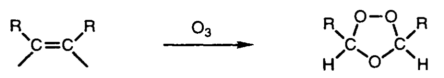


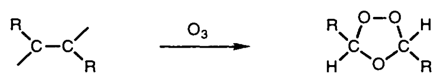
Figure 2 Structures of the van der Waals complex between ozone and ethylene (left),[6] the reaction transition state (middle),[8] and the primary ozone product (right)[7] plotted along a hypothetical cycloaddition reaction coordinate.



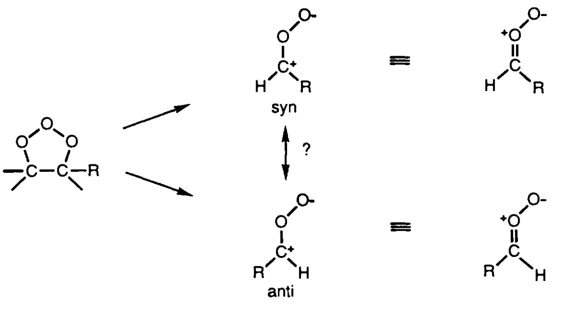
Scheme 3



(6a)



(6b)



(7a)

(7b)

(reaction 7).[21] This is consistent with the electronic properties of a carbonyl oxide which has a three-centre π orbital perpendicular to the molecular plane similar to isoelectronic ozone, resulting in a high barrier to *syn–anti* equilibration. A cycloreversion from the envelope transition state, which is preferred on orbital alignment grounds for a concerted process, could readily lead to a preference for either the *syn* or *anti* conformer (Figure 3). The isomer preference and extent of stereoselectivity depends on substituent steric effects, secondary orbital interactions, anomeric interactions *etc.* In the case of *trans* alkenes with bulky substituents, it has been postulated that the cycloreversion yields *syn* carbonyl oxides.[22] This was based on steric arguments which orient the substituents diaxial in the envelope transition state, an orientation favourable to formation of the *syn* carbonyl oxide upon decomposition. By a similar rationale, *cis* alkenes would produce *anti* carbonyl oxides. However, it has so far proven to be impossible to devise a straightforward test of the stereochemical properties of the carbonyl oxide in order to examine this hypothesis.

The cycloaddition between the carbonyl oxide and the carbonyl compound resulting in the ozonide in the third step of the Criegee mechanism should also occur *via* a putative envelope transition state according to orbital overlap arguments. Thus a *syn* (or *anti*) carbonyl oxide will react with an aldehyde in either an *endo* or *exo* transition state to give *cis* or *trans* ozonide (Figure 4). This third step, like the second, can also occur with varying degrees of stereoselectivity dependent on substituent interactions, electronic effects *etc.* In this manner, the stereoselectivity in the overall ozonolysis process can be rationalized in a manner consistent with simple orbital overlap arguments for a $3+2$ cycloaddition reaction. Although this general outline lays the basis for a rationale to incorporate stereochemistry in the ozonolysis reaction, the detailed argumentation for a particular system is often *ad hoc* and specific to the problem at hand. A set of rules have been devised as a guide to stereochemical predictions;[5,22] they are more the nature of a working hypothesis rather than well tested hard and fast laws.

The concerted nature of the third step of the Criegee reaction has been explored using a phenomenon called kinetic secondary isotope effects. Secondary isotope effects are observed when deuterium is substituted at a site at which other new bonds are being formed or broken in the reaction transition state. Basically, the zero point vibrational energies of the reactants and transition states are affected differently when deuterium substi-

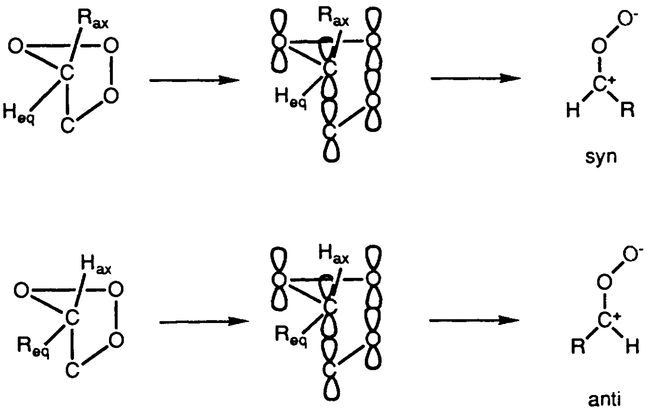


Figure 3 Envelope transition states for the cleavage of the primary ozonide leading to carbonyl oxide isomers.

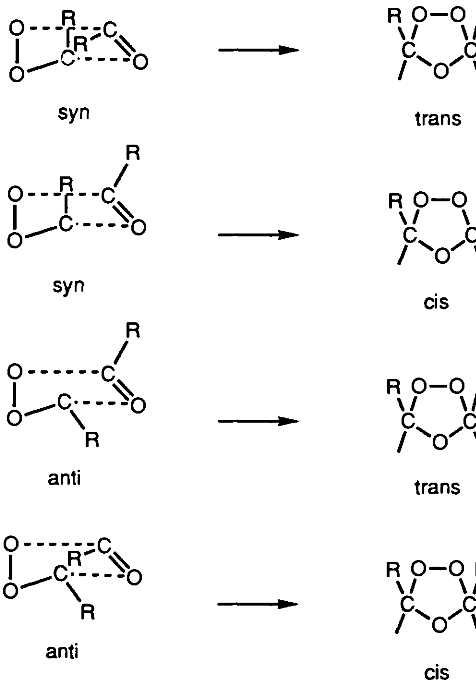
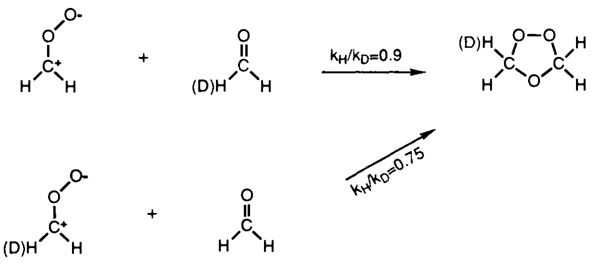


Figure 4 Envelope transition states for the cycloaddition of the carbonyl oxide and carbonyl compound producing the final ozonide isomers.

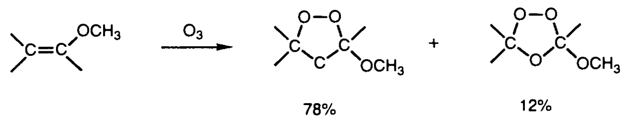
tution occurs at the reaction site, leading to a change in the kinetics of the reaction of approximately 10–20% per deuterium atom substitution. It was observed using HDCO or D_2CO as the aldehyde trap and HDCOO as the dipolarophile[23,24] (reactions 8 and 9) that secondary isotope effects occur due to deuterium substitution in both the aldehyde and the carbonyl oxide during the third step. This is consistent with the carbon atoms in both species being involved in the transition state, which implies a concerted cycloaddition.



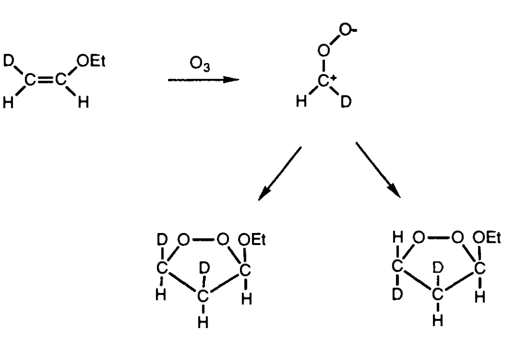
(8)

(9)

Recently, the stereochemical test for a concerted cycloaddition has also been investigated for the reaction of the carbonyl oxide with a dipolarophile. This became possible with the discovery that carbonyl oxides will trap an activated alkene containing an alkoxy substituent.[20] The product was a 1,2-alkoxy dioxolane along with the expected ozonide (reaction 10, relative yields). It was apparent when the alkene was stereo labelled with deuterium, that retention of stereochemistry about the double bond occurred when the alkene was trapped by the carbonyl oxide (reaction 11, relative yields).[25] This was the first example where stereospecificity, implying concertedness, was directly observed for a reaction of a carbonyl oxide with a substrate. At the same time, the deuterium substitution at C-5 (the end carbon *sans* OR substituent) occurred stereoselectively. This latter result can be explained by stereoselective production of *syn* and *anti*-HDCOO in step 2 of the Criegee mechanism.



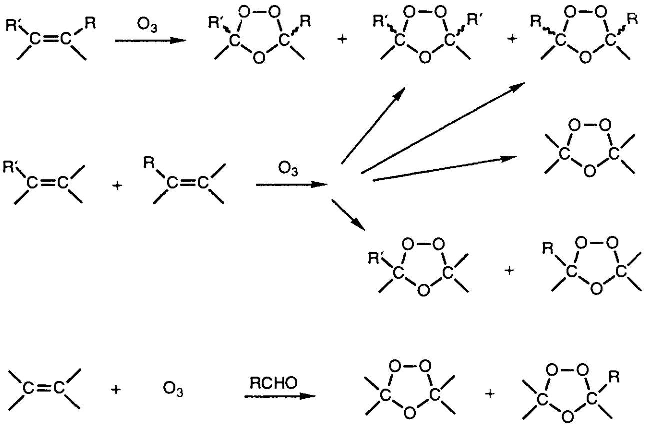
(10)



(11)

Similar results have been obtained with the ozonolysis of (*E*)- or (*Z*)-$CH_3CH{=}CHOEt$.[26] These results, along with the kinetic secondary isotope effect data, the stereoselectivity discussed above, and thermochemical reasoning[27] are the principal experimental evidence for concertedness in the third step of the Criegee mechanism. It should be noted that there is evidence that a non-concerted or stepwise cycloaddition probably also occurs when conditions are propitious as in the case of more substituted and complex alkenes or in certain solvents. This body of data has been discussed recently.[14]

Additional insights on the third step can also be garnered with cross ozonide formation and aldehyde insertion experiments. The former technique examines the ozonide product distribution when an unsymmetrical alkene (reaction 12) or mixtures of alkenes are ozonized (reaction 13). Insertion experiments involve the ozonolysis of a mixture of an alkene and foreign aldehyde (*i.e.* one not generated in the reaction itself, reaction 14). Such experiments can explore steric effects, electronic effects, and solvent cage effects. An example of each of these applications will be given.

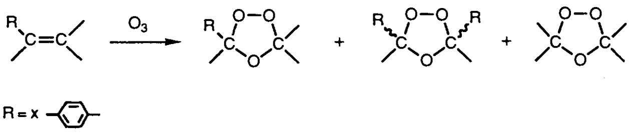


(12)

(13)

(14)

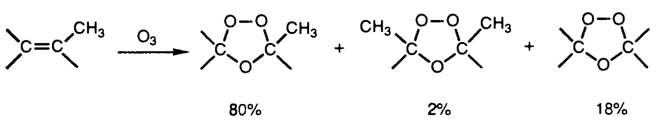
A body of data from the ozonolysis of unsymmetrical *cis*-alkenes (reaction 12) reveals that when the bulk of the substituents are different (R > R'), the heavy molecular weight ozonide cross product (RR) will contain more *cis* isomer while the low molecular weight ozonide (R'R') will contain more *trans* isomer.[5,21] The *cis*/*trans* product ratio for the normal ozonide (RR') will usually fall in between the two cross ozonides. The explanation for this behaviour is complex. It assumes the production of different *syn*/*anti* ratios for the two carbonyl oxides, RHCOO and R'HCOO, which are produced in the cycloreversion decomposition of the primary ozonide. Steric effects in the envelope transition state leading to the carbonyl oxides are the basis for the differential carbonyl oxide isomer production. The literature should be considered for a more detailed discussion.[5,21,22,27b]



(15)

x = *p*-NO_2	62.8%	22.3%	14.8%
x = H	93.3	1.5	5.2
x = CH_3	95.1	0.6	4.4

A striking difference in the normal and cross ozonide product distribution (relative amounts) is observed when *para*-substituted styrene substrates are ozonized as exemplified in reaction 15.[28] This is probably the result of electronic effects which influence the cleavage direction of the primary ozonide (*i.e.* the relative amounts of H_2COO and RHCOO which are produced) and the recombination kinetics of the carbonyl oxides with the two aldehydes which are present (H_2CO,RHCO). The results can be accounted for by a kinetic scheme in which the rate constants in the primary ozonide cleavage step and the recombination step vary systematically with change in electronic properties of the substituents. For example, the increase in the amounts of styrene ozonide and decrease in cross ozonides with increase in the electron withdrawing character of the substituents correlate with a Hammett σ of 1.4. This indicates that accentuation of positive charge at the reactive carbon centre of the carbonyl oxide and the benzaldehyde involved in bond formation assist the formation of the styrene ozonide. This observation also



(16)

holds for the reaction of the diphenyl substituted carbonyl oxide with a series of *para*-substituted benzaldehydes.[29]

Another interesting observation involves the yields of ozonides (relative amounts) when propylene is ozonized.[30] Reaction 16 describes a typical result. The relative amounts of the products are fairly insensitive to temperature and solvent polarity. On the other hand, using C_2H_4/C_2D_4 mixtures, the amounts of the cross ozonide, ethylene-1,1-d_2 ozonide, varied from about 3% in non-polar solvent to almost 40% in a polar solvent.[23] The explanation for these results must take into account several factors including cleavage direction competition (to CH_3CHOO and CH_2O *versus* H_2COO and CH_3CHO in reaction 16), kinetic effects in the recombination steps, and kinetic secondary isotope effects in the reactions involving CD_2O and CD_2OO. Nevertheless, a difference in the cross ozonide formation with solvent polarity is readily apparent between the propylene and ethylene substrates. Kinetic modelling indicated that ozonide formation in the propylene system occurred almost entirely outside the original solvent cage while this was the case only in polar solvents for the ethylene ozonolysis. Thus, substitution of H with a methyl group in the simplest carbonyl oxide significantly affects the reaction kinetics in the original solvent cage. An increased stability for CH_3COO compared to H_2COO is one possible explanation for the results.

These examples underscore the subtle complexities that affect ozonide yields when alkenes are cleaved by ozone. Basically, the ozonolysis mechanism is a network of competing reactions and processes for which the kinetics at each step must be considered. When one reflects that small differences in reaction energetics for competing kinetic processes can lead to marked effects on yields, then much of the reaction diversity with change in conditions, substituents, and solvent can be appreciated. For example, the ratio of the yields of propylene ozonide to ethylene ozonide in reaction 16 might be explained by activation energy differences of about 0.5 kcal/mol in the third step of the mechanism while the energy difference resulting in unequal *cis–trans* ozonide stereo ratios in reaction 12 can be even smaller. Consequently, very modest energy changes will markedly affect competitive processes resulting in complex and often puzzling results. This is a sobering realization since solvent interactions, zero point energy effects in competing transition states, and other hard-to-identify factors (because they are small) may enter into a complete microscopic understanding of the details of the ozonolysis reaction.

In spite of such obfuscations, great progress has been made in elucidating the bare bones Criegee mechanism and in understanding puzzling aspects of the ozonolysis reaction using traditional physical organic techniques and reasoning. Aided by such work and the ever advancing sophistication in chemical analysis techniques, including theoretical approaches which include solvent effects in reaction simulations, we expect that our understanding of this fascinating reaction will continue to grow. Perhaps some day ultrafast laser techniques will allow the study of incipient carbon–oxygen bond formation when ozone reacts with ethylene!

Acknowledgements. The work carried out in the author's laboratory was supported by grants from the American Chemical Society-Petroleum Research Fund and the National Science Foundation. The author is pleased to acknowledge the contributions of his co-workers mentioned in the references and particularly Professor C. W. Gillies who first initiated the study of the ozonolysis mechanism at Michigan and has recently observed spectroscopically the primary ozonide of ethylene and the pre-reaction complex between ethlylene and ozone.

References

1 P. S. Bailey, 'Ozonation in Organic Chemistry', Academic Press, N.Y. Vol. 1, 1978; Vol. 2, 1982.
2 R. Criegee, *Angew. Chem.*, 1975, **87**, 765; *Int. Ed. Engl.*, 1975, **14**, 745.
3 R. Huisgen, in '1,3-Dipolar Cycloaddition Chemistry', ed. A. Padwa, Wiley, New York, 1984, Vol. 1, Chapter 1.
4 K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, 1973, **95**, 7287.
5 R. L. Kuczkowski, in '1,3-Dipolar Cycloaddition Chemistry', ed. A. Padwa, Wiley, New York, 1984, Vol. 2, Ch. 11.
6 J. Z. Gillies, C. W. Gillies, R. D. Suenram, and F. J. Lovas, *J. Am. Chem. Soc.*, 1988, **110**, 7991.
7 C. W. Gillies, J. Z. Gillies, R. D. Suenram, F. J. Lovas, E. Kraka, and D. Cremer, *J. Am. Chem. Soc.*, 1991, **113**, 2412.
8 M. L. McKee and C. M. Rohlfing, *J. Am. Chem. Soc.*, 1989, **111**, 2497.
9 O. L. Chapman and T. C. Hess, *J. Am. Chem. Soc.*, 1984, **106**, 1842.
10 G. A. Bell and I. R. Dunkin, *J. Chem. Soc., Chem. Commun.*, 1983, 1213.
11 H. L. Casal, S. E. Sugamori, and J. C. Scaiano, *J. Am. Chem. Soc.*, 1984, **106**, 7623.
12 H. L. Casal, M. Tanner, N. H. Werstiuk, and J. C. Scaiano, *J. Am. Chem. Soc.*, 1985, **107**, 4616.
13 W. Sander, *Angew. Chem.*, 1990, **102**, 362; *Int. Ed. Engl.*, 1990, **29**, 344.
14 W. H. Bunnelle, *Chem. Rev.*, 1991, **91**, 335.
15 D. Cremer, T. Schmidt, W. Stander, and P. Bischof, *J. Org. Chem.*, 1989, **54**, 2515.
16 R. D. Suenram and F. J. Lovas, *J. Am. Chem. Soc.*, 1978, **100**, 5117.
17 W. Adam, Y.-Y. Chan, D. Cremer, J. Gauss, D. Scheutzow, and M. Schindler, *J. Org. Chem.*, 1987, **52**, 2800.
18 J. Gauss and D. Cremer, *Chem. Phys. Lett.*, 1987, **133**, 420.
19 D. Cremer, T. Schmidt, J. Gauss, and T. P. Radhakrishnan, *Angew. Chem.*, 1988, **100**, 431; *Int. Ed. Engl.*, 1988, **27**, 427.
20 H. Keul, H. S. Choi, and R. L. Kuczkowski, *J. Org. Chem.*, 1985, **50**, 3365.
21 (*a*) N. C. Bailey, J. A. Thompson, C. E. Hudson, and P. S. Bailey, *J. Am. Chem. Soc.*, 1968, **90**, 1822; (*b*) P. S. Bailey and T. M. Ferrell, *J. Am. Chem. Soc.*, 1978, **100**, 899.
22 R. P. Lattimer, R. L. Kuczkowski, and C. W. Gillies, *J. Am. Chem. Soc.*, 1974, **96**, 348.
23 G. D. Fong and R. L. Kuczkowski, *J. Am. Chem. Soc.*, 1980, **102**, 4763.
24 J.-I. Choe, M. K. Painter, and R. L. Kuczkowski, *J. Am. Chem. Soc.*, 1984, **106**, 2891.
25 H. Keul and R. L. Kuczkowski, *J. Org. Chem.*, 1985, **50**, 3371.
26 B. J. Wojciechowski, W. H. Pearson, and R. L. Kuczkowski, *J. Org. Chem.*, 1989, **54**, 115.
27 (*a*) P. S. Nangia and S. W. Benson, *J. Am. Chem. Soc.*, 1980, **102**, 3105; (*b*) D. Cremer, *J. Am. Chem. Soc.*, 1981, **103**, 3619.
28 M. K. Painter, H. S. Choi, K. W. Hillig II, and R. L. Kuczkowski, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1025.
29 R. W. Murray and M. M. Morgan, *J. Org. Chem.*, 1991, **56**, 684.
30 J.-I. Choe, M. Srinivasan, and R. L. Kuczkowski, *J. Am. Chem. Soc.*, 1983, **105**, 4703.