



# **TOPICS IN LIPID CHEMISTRY**

**VOLUME 2**

**Edited by**

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LIPID CHEMISTRY**

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## PREFACE

The second volume in this series continues the policy set out in the first volume of having reviews written by those who are themselves involved in the work they describe. I have tried to select significant topics which have not been reviewed elsewhere, and this volume contains articles on ozonolysis, allylic halogenation and autoxidation, the nitrogen and sulphur analogues of epoxy and polyhydroxy acids, natural alkyl-branched long-chain acids, and olefin reactions occurring through transition metal intermediates. This last is an attempt to set out, for lipid chemists, reactions which have been successfully applied to olefinic hydrocarbons and may be capable of extension to unsaturated esters. The manuscripts were received in the period September, 1969 to June, 1970 and the authors have been given the opportunity to insert additional relevant papers in the list of references, but not in the text.

The plan to offer a further service to readers is continued and extended and in addition to a further list of relevant books and reviews this volume contains a tabulation on NMR data. Comment on this development and ideas for other useful data which might be collated will be welcomed by the editor.

*September, 1970*

F. D. GUNSTONE.  
St. Andrews

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# 1

## OZONOLYSIS

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## A. INTRODUCTION

Ever since the turn of the century when Harries started his pioneering investigations on the organic chemistry of ozone and when Molinari ozonised oleic acid, interest in ozone and its uses has steadily increased. Long (1940) and Bailey (1958b) have reviewed ozonisation in broad scope and detail, covering many aspects of organic reactions



of ozone. Maggiolo (1962) described organic ozone reactions in lesser detail but also discussed experimental techniques. Kadesch (1963) summarised ozonolysis of unsaturated fatty acids and their derivatives, and Bischoff and Rieche (1965) described synthetic and technical uses for ozone. Other reviews include those of Menyailo and Pospelov (1967) on the reactions of ozone with alkenes, of Murray (1969) on mechanism with a tabulation of properties for the known ozonides of alkenes and cycloalkenes, and of Belew (1969) on the preparative aspects of ozonisation in organic chemistry. Papers from the International Ozone Conference, Chicago, 1956, cover many aspects of ozone chemistry in addition to those of organic chemistry. Manley and Niegowski (1967) have reported in general the properties, reactions—inorganic as well as organic—and uses for ozone. Schulz and Kirschke (1967) have described the formation and properties of ozonides and of dimeric cyclic peroxides formed by the reaction of ozone with olefins. In his most recent review, Criegee (1968) described also some of his unpublished work on the formation of substituted cyclobutenes by decomposition of bi- and tricyclic olefin ozonides.

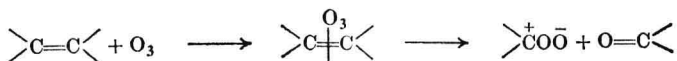
This chapter concerns the ozonolysis (i.e., ozonisation with cleavage) of olefins—unsaturated fatty acids in particular—and surveys the current status of theoretical aspects, analytical applications, and preparative uses. Emphasis will be on research conducted during the 1960's. There have been startling (no doubt literally as well as figuratively) developments in ozonide chemistry during this period. This progress can be ascribed in great part to the stimuli provided by the research and mechanistic proposals of Criegee (1957). Other stimulants were provided by new tools for the analysis of isomeric ozonide mixtures: gas-liquid partition chromatography (GLPC), thin-layer chromatography (TLC), and nuclear magnetic resonance (NMR).

## B. THEORETICAL ASPECTS

### 1. Criegee's Mechanism

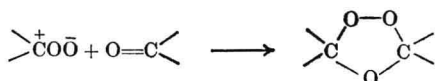
Briefly stated, Criegee's mechanism postulates the existence of a zwitterion formed along with a carbonyl fragment by the cleavage of a *primärozonid*.

Criegee had little to say about the structure of the *primärozonid*, which could only be a transitory intermediate at the temperatures

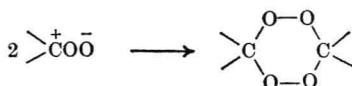


ordinarily used in ozonolyses. Once formed, the zwitterion can then undergo a variety of subsequent reactions depending on the polarity of the solvent, on whether or not the solvent is a reactive or participating one, on electronic effects of substituents, and on steric effects. These reactions form various ozonolysis products having widely differing properties.

#### *Ozonides*



#### *Dimer Peroxides*



#### *Polymeric Peroxides*



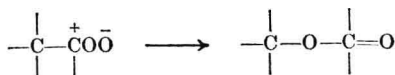
#### *Alkoxy Hydroperoxides*



#### *Acyloxy Hydroperoxides*



#### *Rearrangement*



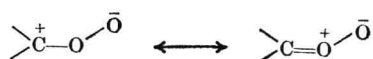
The term ozonide is applied properly only to the 1,2,4-trioxolane structure; it is only one of the many different types of ozonolysis products illustrated above. In forming an ozonide, the zwitterion may react with foreign aldehydes, as well as the one formed along with the zwitterion during ozonolysis.

Existence of the zwitterion as a transitory intermediate has been confirmed by isolation and characterisation of the various peroxidic

ozonolysis products outlined above in simplest form. However, rearrangement of the zwitterion to anomalous nonperoxidic ozonolysis products is questionable, and such products more probably arise by peracid oxidation of aldehydes in the Baeyer-Villager reaction.

Criegee's mechanism has been extremely helpful in explaining many aspects of ozonolysis, but Criegee (1962) himself has raised several questions that are the consequence of the mechanism:

1. What is the nature and structure of the *primärozonid*?
2. What is the nature of cleavage of the *primärozonid*?
3. Does the zwitterion have stereoisomeric forms as a consequence of resonance?



4. Are the reactions of the zwitterion reversible?
5. Why do *cis*- and *trans*-olefins not always produce the same products?
6. What is the configuration of stereoisomeric ozonides?
7. What is the role of solvents?
8. What are the conditions for the formation of polymeric ozonides?

Some answers to these questions will be found in the research reviewed in this chapter.

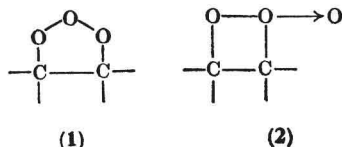
## 2. The *Primärozonid* or Molozonide

*Primärozonid*, initial ozonide, primary ozonide, and molozonide are synonymous terms used by various authors. The concept of such a substance was originated by Staudinger (1925), who proposed calling it the molozonide. Although Staudinger assigned a structure now known to be wrong, Greenwood (1964) has continued to use the term molozonide. Since other possibilities exist for initial products in the attack of ozone on a double bond, such as a  $\pi$  or a  $\sigma$  complex, the term molozonide will also be used here to avoid confusion.

Criegee and Schröder (1960) were first to report a molozonide, which they obtained by ozonising *trans*-1,2-di-*t*-butylethylene in pentane at  $-75^\circ$ . The crystalline molozonide, when allowed to warm, evolved considerable heat and formed a mixture of ozonide and polymeric peroxides. Reaction of the molozonide with methanol produced

a methoxy hydroperoxide, and reaction with sodium in liquid ammonia or with isopropyl magnesium bromide yielded racemic *t*-butylene glycol. Other reducing agents gave mainly trimethylacetaldehyde or neopentyl alcohol.

Formation of the glycol was evidence for an intact C—C bond from the double bond in the original compound but provided no clue to the structure for the molozonide. The most rational structures are the 1,2,3-trioxolane (1) or that (2) proposed by Staudinger (1925).



The 1,2,3-trioxolane structure (1) was confirmed by Bailey, Thompson, and Shoulders (1966), who obtained by low-temperature NMR two singlet peaks, one for the methyl protons and one for the methine protons, in the expected ratio of 9 : 1.

Greenwood (1964) produced the 1,2,3-trioxolane compounds, stable up to  $-85^{\circ}$ , from *trans*-pent-2-ene and *trans*-hex-3-ene as a consequence of stereospecific *cis* addition of ozone. Each of these initial ozonides gave an  $\alpha$ -diol by reaction with isopropyl magnesium bromide: *threo*-*dl*-pentane-2,3-diol and *dl*-hexane-3,4-diol. Smaller amounts of methyl- and ethyl-isopropyl-carbinol were also derived from *trans*-pent-2-ene and of isobutyl alcohol and *n*-propylisopropylcarbinol from *trans*-hex-3-ene. These products presumably arose by the action of Grignard reagent on the small amounts of true ozonide present. Greenwood and Haske (1965a) found that reaction of isopropyl magnesium bromide with the pure ozonide from *cis*-hex-3-ene produced ethylisopropyl carbinol in only 69 per cent yield, the balance of the reaction having produced smaller amounts of propane, propene, and isopropyl alcohol.

Neither Criegee nor Greenwood found evidence for the existence of *cis*-molozonides in the work cited above. However, Greenwood and Haske (1965b) observed precipitation of a white solid during ozonisation of a dilute solution of *cis*-hex-3-ene in pentane at  $-112^{\circ}$ . This solid was highly explosive and too unstable for further investigation. Steric factors are probably important in this instability, since *cis* alkyl groups at positions 4 and 5 of the 1,2,3-trioxolane ring are permitted little rotational freedom in consideration of the

orbitals for the lone pair of electrons on the oxygen atoms (Greenwood, 1964; Durham and Greenwood, 1968a).

In extending studies on molozonide formation in ether solutions to *cis*- and *trans*-butene, but-1-ene, and ethylene, Greenwood (1965) found that alk-1-enes gave considerably less  $\alpha$ -diols than did the *trans*-alkenes and that ethylene gave no  $\alpha$ -diol. The steric factors already described are not important in the alk-1-enes or ethylene and cannot be held responsible for the lack of molozonide and  $\alpha$ -diol formation. Greenwood proposed that there is a solvent effect in the rearrangement of *cis*-molozonides and the molozonides from alk-1-enes and ethylene, which are less hindered in nucleophilic attack by the ether solvent than are the *trans*-molozonides. Ether also brings about more pronounced crossed ozonide formation, as with pent-2-ene (Greenwood, 1966).

Durham and Greenwood (1967) observed NMR spectra for molozonides from the *trans* isomers of but-2-ene, pent-2-ene, and hex-3-ene at  $-130^\circ$  in dichlorodifluoromethane and again confirmed the 1,2,3-trioxolane structure. When the solutions were warmed to  $-100^\circ$ , the molozonide methine peak gradually diminished as the ozonide peak increased until at  $-90^\circ$  the molozonide peak had completely disappeared. At  $-70^\circ$  the spectra verified the usual ozonolysis products of ozonide, aldehyde and oligomer. The *cis* isomers formed products at  $-130^\circ$  which had methine peaks at  $5.05\text{--}4.87\delta$ , assignable to the ozonide, and at  $4.52\text{--}4.35\delta$ , assignable to the molozonide (Durham and Greenwood, 1968b). The *cis*-molozonide was not stable even at  $-130^\circ$  and was no longer detected after 2 hours, in contrast to the relative stability of *trans*-molozonides at this temperature. The *cis*-molozonide formed more oligomeric products at  $-130^\circ$  than normally found at higher temperatures, undoubtedly because of the greater lifetime of the transient molozonide. No isomerisation was observed between *cis*-molozonide (methine peak at  $4.5\delta$ ) and *trans*-molozonide (methine peak at  $4.1\delta$ ).

Because the molozonide has a measurable half-life at low temperatures, the kinetics of molozonide decomposition can be investigated. Hopefully, the kinetics would throw some light on the mechanism of ozonide formation. Razumovskii and Berezova (1968) reported a first-order reaction with  $k = 0.9 \times 10^{-2} \text{ sec}^{-1}$  at  $-100^\circ$  for the molozonide of hex-1-ene. Greenwood and Durham (1969) utilised low-temperature NMR and also found a first-order reaction but with  $k = 5.4 \times 10^{-4} \text{ sec}^{-1}$  at  $-100^\circ$  for the molozonide of *trans*-hex-3-ene.

Activation energies of 7 kcal and 8 kcal/mole were calculated for the molozonide decomposition of hex-1-ene and *trans*-hex-3-ene, respectively. *First-order kinetics do not support reactions of the molozonide with other cleavage products as a pathway to the ozonide.*

In their kinetic studies, Greenwood and Durham detected a marked solvent effect. In dichlorodifluoromethane, ozonide and oligomer were formed during early stages of the decomposition, with propionaldehyde appearing in a small amount later while ozonide predominated. In deuterated dimethyl ether, aldehyde formation started immediately and levelled off at a concentration twice that in dichlorodifluoromethane; oligomer was the principal product.

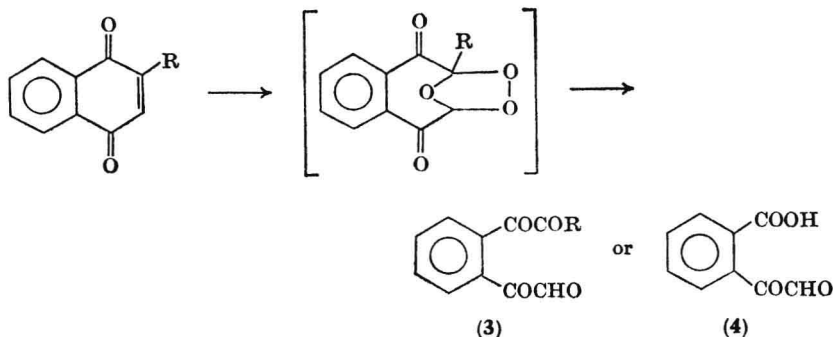
Confirmation for the existence of the 1,2,3-trioxolane structure strongly supports 1,3-dipolar cycloaddition as the mechanism for ozone attack on the double bond (Huisgen, 1963).

### 3. Molozonide Direction of Cleavage

Fragmentation of a molozonide from an unsymmetrical olefin can occur in two ways so that two different zwitterions are possible. In a long-chain olefin having substituents far removed from the double bond, the statistical distribution should be 1:1 like a symmetrical olefin. However, substituents near the double bond can have both electronic and steric effects, which result in a ratio other than 1:1. Several models are available for investigating the relative amounts of each zwitterion.

Bernatek, Kolsaker, and Ledaal (1963) proposed to measure formation of a specific zwitterion by measuring the amount of anomalous nonperoxidic ozonolysis product thought to form by rearrangement of the zwitterion. Since such anomalous products more probably are derived by a Baeyer-Villager type reaction, their results, although still of interest, are actually not applicable to the problem of molozonide direction of cleavage. They established a Hammett-type relationship between the substituent constant and amount of anomalous ozonolysis products for several 2-substituted naphthoquinones in the reaction below.

Phenylglyoxal-*o*-carboxylic acid (4), the anomalous ozonolysis product (Bernatek, 1958) is formed with loss of a carbon atom. Formation of compound (4) was greatest with R = OH (90 per cent), followed by decreasing amounts as R was Cl (78 per cent), OCOCH<sub>3</sub> (71 per cent), NHCOCH<sub>3</sub> (14 per cent), NH<sub>2</sub> (4.6 per cent), and CH<sub>3</sub>



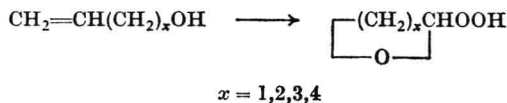
(2.5 per cent). The Hammett relationship applied also to the products from unsymmetrical derivatives of 1,2-dibenzoyl ethylene (Bailey, Mainthia, and Abshire, 1960) and to phenylacetylene and phenylpropyne (Bailey, Chang, and Kwie, 1962) as reported by Ledaal (1966).

Ozonolysis of phenylacetylene and phenylpropyne in an alcohol produced the hydroperoxides (5) and (6) in the respective yields of 25 and 75 per cent (Bailey *et al.* 1962). Although hydroperoxide (5)



was isolable, compound (6) was not, and the amounts formed were calculated from their thermal decomposition products.

Schulz and Becker (1964) found that the longer chain fragment forms the zwitterion in a series of alcohols with terminal unsaturation as shown by the *O*-heterocyclic hydroperoxide. The tetrahydrofuran

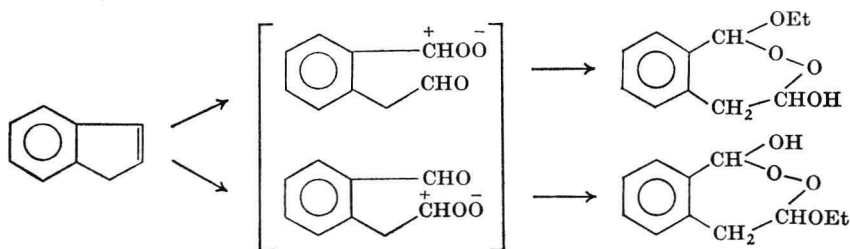


hydroperoxide ( $x = 3$ ) formed in 76 per cent yield. The oxetane ( $x = 2$ ) and oxirane ( $x = 1$ ) hydroperoxide yields were small and the major products were polymeric. Phthalan hydroperoxide was isolated in quantitative yield from the ozonolysis of 2,2'-bis(hydroxymethyl)-stilbene (Rieche, Schulz, and Becker, 1965).

Kolsaker and Bailey (1967) attempted to determine the ratio for substituted cinnamic esters and acids by ozonolysis in methanol.

They concluded that work-up conditions (acidic, basic or neutral) greatly influenced the extent to which abnormal phenolic compounds were formed and that the rearrangement to phenol occurred at the methoxy hydroperoxide stage rather than the molozonide or zwitterion stage. As a consequence, they were unable to determine the effect of substituents on direction of zwitterion formation.

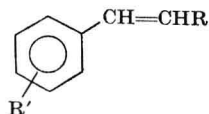
Fliszár, Belzecki, and Chylińska (1967) showed that the molozonide from indene, when formed in ethanol, cleaved equally in each direction by chromatographic separation of the two alkoxy peroxides formed.



Fliszár and Granger (1969) studied the direction of cleavage for a series of ring- and side chain-substituted vinyl benzenes (Table 1).

TABLE 1

*Fraction of  $R'C_6H_4CHO$  formed in ozonolysis in  $CH_3OH/CCl_4$  at  $25^\circ$  of:*



R'	R						
	COOCH <sub>3</sub>	CH <sub>2</sub> OH	H	C <sub>6</sub> H <sub>5</sub>	COOH	CH <sub>3</sub>	COCH <sub>3</sub>
<i>p</i> -NO <sub>2</sub>	—	—	0.86	0.91	—	—	—
<i>m</i> -NO <sub>2</sub>	—	—	0.84	—	—	—	—
<i>m</i> -Cl	0.42	—	0.67	—	0.84	—	—
<i>p</i> -Cl	0.36	0.40	0.57	0.64	—	0.90	—
H	0.23	0.26	0.41	0.500	0.61	0.82	0.90
<i>p</i> -CH <sub>3</sub>	—	—	0.29	0.39	0.46	—	—
3,4-CH <sub>2</sub> O <sub>2</sub>	—	—	—	—	—	0.75	0.85
<i>p</i> -OCH <sub>3</sub>	—	—	0.21	—	0.39	0.68	0.80

Source: Fliszár and Granger (1969).

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They concluded that the zwitterion formed preferentially is the one that stabilises the carbo-cation by an increase in electron density by inductive and mesomeric effects in the side-chain substituent. The relative efficiencies of  $\beta$ -substituents for stabilisation of the zwitterion occurred in the order



The unusual effects of the  $\text{COCH}_3$  and  $\text{COOH}$  groups are explained by resonance stabilisation. For a series of compounds with various



where  $\text{X} = \text{CH}_3$  or  $\text{OH}$

ring substituents, the proportion of aromatic aldehyde ( $x$ ) *vs.* aliphatic aldehyde is related to Hammett's  $\sigma$  and  $\rho$  constants by the equation (Fliszár and Renard, 1967):

$$\log[x/(1-x)] = -\Delta G_0^+ / 2.3RT + (\rho_a - \rho_b)\sigma$$

A similar correlation was established by Razumovsky and Yur'ev (1967). The reaction was followed by infrared (i.r.) measurement of the aromatic aldehyde formed in carbon tetrachloride solution 1 molar in methanol. Acetaldehyde did not interfere because of its rapid transformation to its hemiacetal, a reaction that did not occur with the aromatic aldehyde under the conditions used.

Keaveney, Berger, and Pappas (1967) determined the direction of cleavage for the molozonides formed in methanol of three vinyl benzenes. Benzaldehyde and the aliphatic methoxy hydroperoxide were produced in 46 per cent yield from styrene, 91 per cent from propenylbenzene, and 97 per cent yield from 2-methylpropenylbenzene. Chemical and GLPC methods were used for analysis. Keaveney and Pappas (1969) used NMR to determine amounts of the methoxy hydroperoxide compounds and benzaldehyde. The chemical shifts for the hydroperoxy and benzaldehyde protons in methanol solution are sufficiently deshielded to produce reasonably sharp singlets. The proportion (in mole per cent) of benzaldehyde formed by ozonolysis in methanol of several vinyl benzenes with substituents both in the ring and in the side chain were:  $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}=\text{CH}_2$ , 20;  $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$ , 29;  $p\text{-ClC}_6\text{H}_4\text{CH}=\text{CH}_2$ , 63;  $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}=\text{CHCH}_3$ , 69;  $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}=\text{CHCH}_3$ , 88;  $p\text{-ClC}_6\text{H}_4\text{CH}=\text{CHCH}_3$ , 92; and  $p\text{-HOC}_6\text{H}_4\text{CH}=\text{CHCH}_3$ , 64.