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Stereochemistry of Reactions Involving
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LEVEL II

Final Report

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Professor of Chemistry

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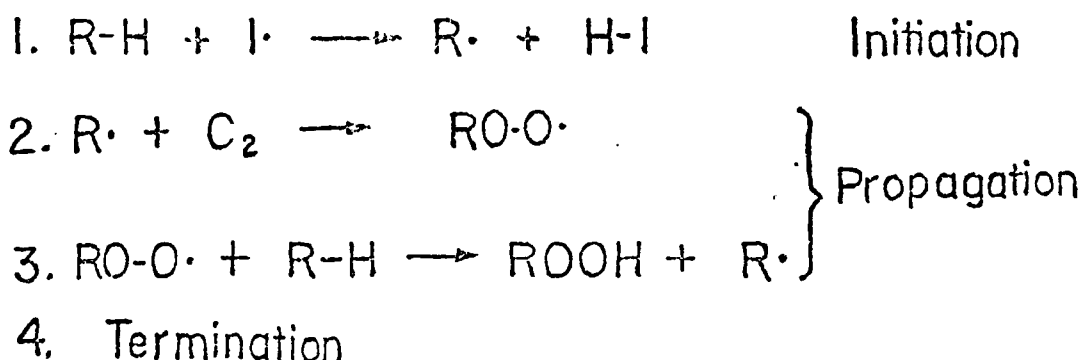
20. Abstract

Several aspects of chemistry related to autoxidation, peroxy free radicals, and peroxides have been explored. Methods for preparation of complex unsaturated hydroperoxides have been developed and peroxy radicals derived from these hydroperoxides were studied as models for polyunsaturated fatty acid and polyolefin (i.e., polybutadiene and polyisoprene) autoxidation. We have established that peroxy radical cyclization and bicyclization occurs in models of polyunsaturated fatty acid oxidation and a new type of cyclization, serial cyclization, has been observed in polybutadiene oxidation models. Kinetic and stereochemical aspects of these cyclization reactions have been explored. The free radical oxidation of polyunsaturated fatty acids has been studied mechanistically. In particular, we believe that the H atom donating ability of the medium in which oxidation occurs is an important factor in determining the partitioning of peroxy free radicals between competitive pathways (i.e., β scission and cyclization). The results of these studies provide a firm basis for understanding the degradation of materials, foodstuffs, etc.

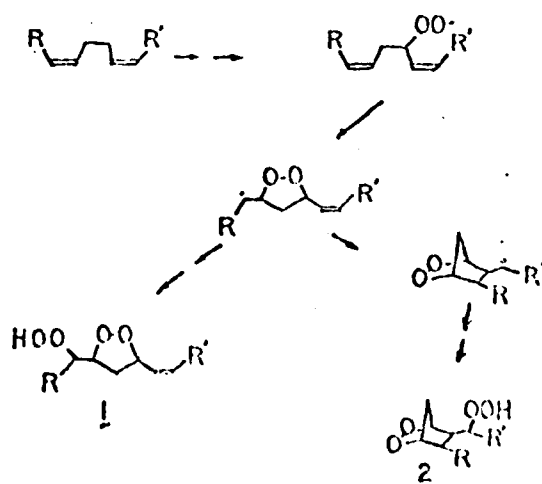
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a.) Statement of Problem Studied

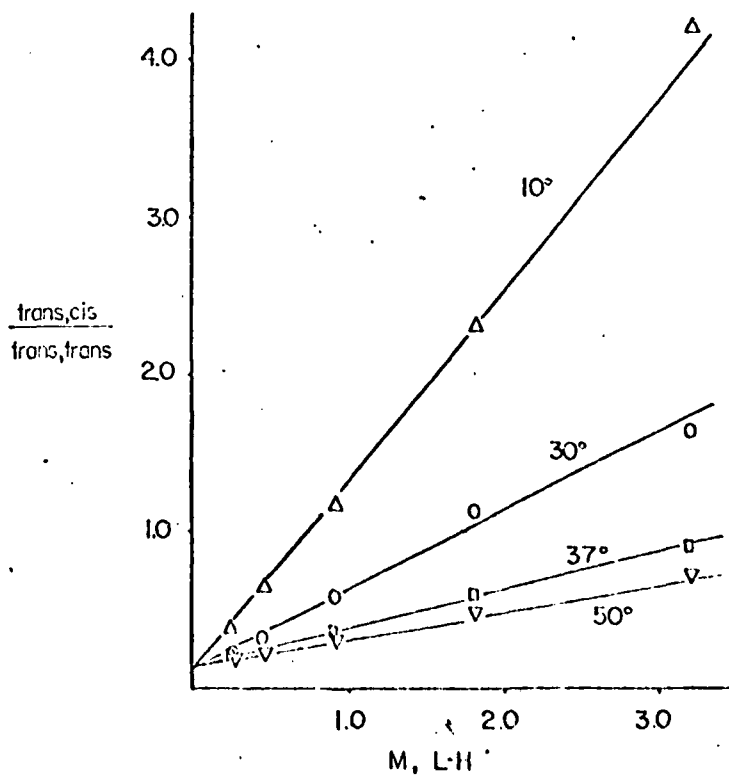
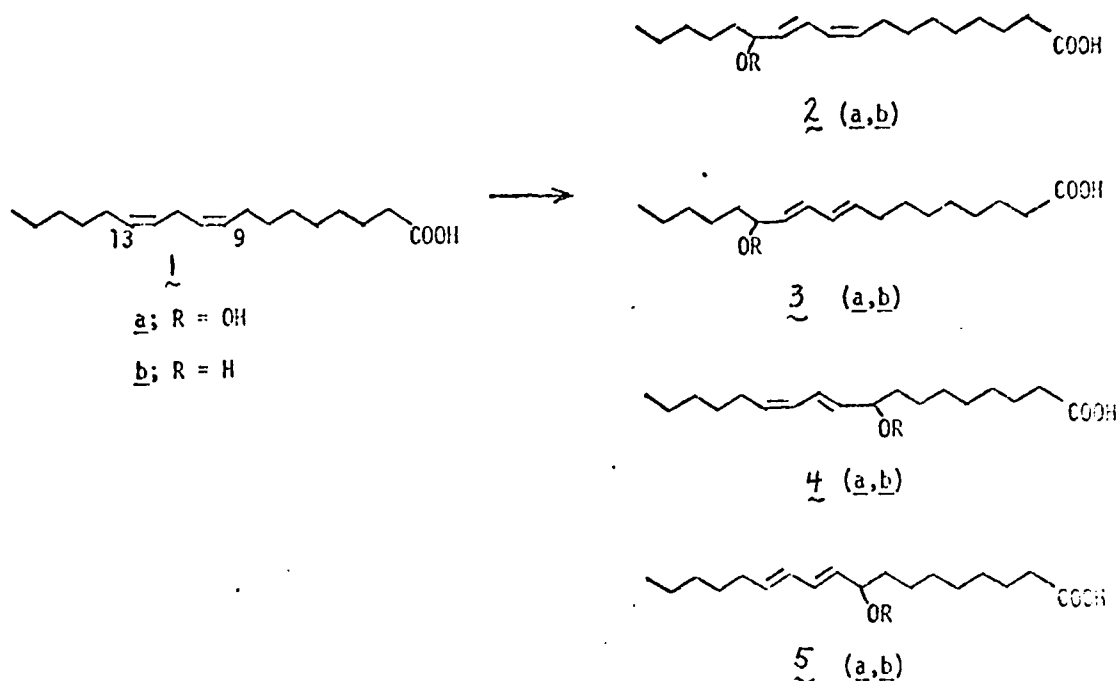
The destruction of organic substrates by molecular oxygen is perhaps one of the most important organic reactions. Natural and synthetic polymers, biological materials such as lipids, and for that matter, any organic molecule exposed to the atmosphere may react with ground state molecular oxygen. It is no surprise then, that extensive investigations have focused on the kinetics of organic substrate oxidation by O_2 . The "hydroperoxide mechanism" for autoxidation which is now generally accepted is outlined below.



Despite the numerous studies on autoxidation and inhibition, surprisingly little research has been directed towards product study in autoxidation. It is true that for simple molecules like isopropylbenzene the primary autoxidation product is the tertiary hydroperoxide. However, if the organic substrate has several centers of unsaturation, the simple hydroperoxide product may not be found and in its place, cyclic peroxides are formed. For example, squalene absorbs two moles of oxygen upon autoxidation and one of these oxygen molecules is incorporated as a peroxide, rather than a hydroperoxide group. Although no rigorous structure proof was offered for the squalene oxidation product, it seems likely on the basis of subsequent work that the principal product of squalene autoxidation is one of the cyclic peroxides (1 or 2) formed by the mechanism described below:



For some six years we have been involved in studies related to the mechanism of autoxidation and the synthesis of biologically important peroxides. These studies have resulted in the first syntheses of the important biological compound PGH_2 and PGG_2 and have provided mechanistic information about autoxidation of fatty acids, phospholipids, and polymer models. In this final report, two aspects of these studies are discussed, namely, (1) a unified mechanism for lipid autoxidation, and (2) a description of the stereochemical requirements of the $\text{S}_\text{H}2$ reaction.

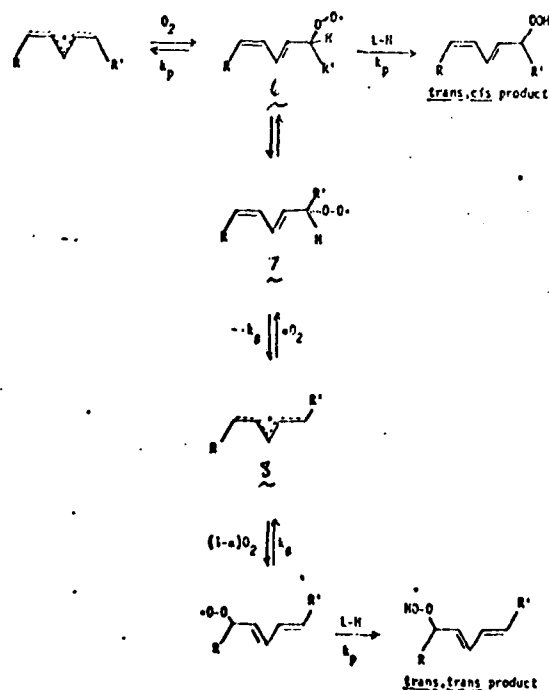


b.) Summary of the Most Important Results

1) Reversibility of Oxygen Entrapment in Autoxidation:

In the autoxidation of linoleic acid, both trans,cis and trans,trans hydroperoxides are formed. Thus, linoleic acid, 1, leads to four different hydroperoxides, 2a-5a. Two of these, 2a and 4a have the trans,cis geometry while 3a and 5a are trans,trans diene isomers. We have recently published a study of factors controlling the product distribution of 2-5. We find, in short, that the ratio of trans,cis/trans,trans products (2+4/3+5) formed during the initial stages (<2%) of oxidation is dependent on temperature and the concentration of linoleic acid. This ratio (2+4/3+5) varies from 4.2 (neat linoleic acid oxidations at 10°C) to 0.23 (0.24 linoleic acid in benzene at 50°C). The trans,cis/trans,trans ratio is presented in Figure 2 as a function of [L-H] (the concentration of linoleic acid in the oxidation) and temperature. Appropriate controls have been run to insure that the product ratios observed are independent of extent of oxidation (within the 2% oxidation range) and O₂ pressure.

The essential competition that accounts for the observed trans,cis/trans,trans ratio is β scission at peroxy radical conformer 7 (leading ultimately to a trans,trans product) vs. H atom abstraction by radical conformer pair 6/7 to give the trans,cis product.



A kinetic derivation describing this system gives:

$$\frac{\text{trans,cis}}{\text{trans,trans}} = \frac{k_p [\text{L-H}]}{k_\beta (1-\alpha)} + \frac{\alpha}{(1-\alpha)} \quad \text{Eq. 1}$$

That is, the product ratio depends on [L-H] as is observed in Figure 2 and the valuable kinetic parameters k_β and α can be extracted from the data. (α is the partition factor of radical β between the trans,cis and trans,trans manifold.) Further, estimates of $\Delta H_\beta^\ddagger$, the enthalpy of the β scission process, can be obtained from temperature dependence data and $\Delta H_\beta^\ddagger$ is calculated to be in the 16-18 kcal/mole range. We should note that Benson had proposed in a classic paper that peroxy radical β scission is an important reaction in autoxidation. We have simply shown that this β scission process has a profound influence on product stereochemistry. We should also note that linoleic acid is the only good H atom donor available in this autoxidation system but in reality $k_p[\text{L-H}]$ in Eq. 1 should be replaced by a summation term that includes all H atom donors,

$$\sum_{n=1}^i k_p^n [\text{R}_n\text{-H}] = \text{KP}.$$

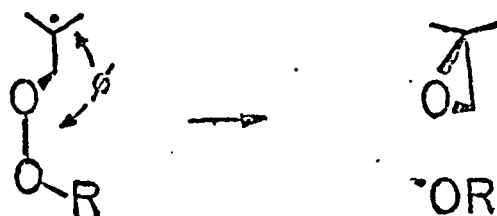
We have chosen to define this important parameter as KP and it represents the total H atom donating ability of the medium of autoxidation.

2) Stereochemistry of the S_H2 Reaction on Peroxide

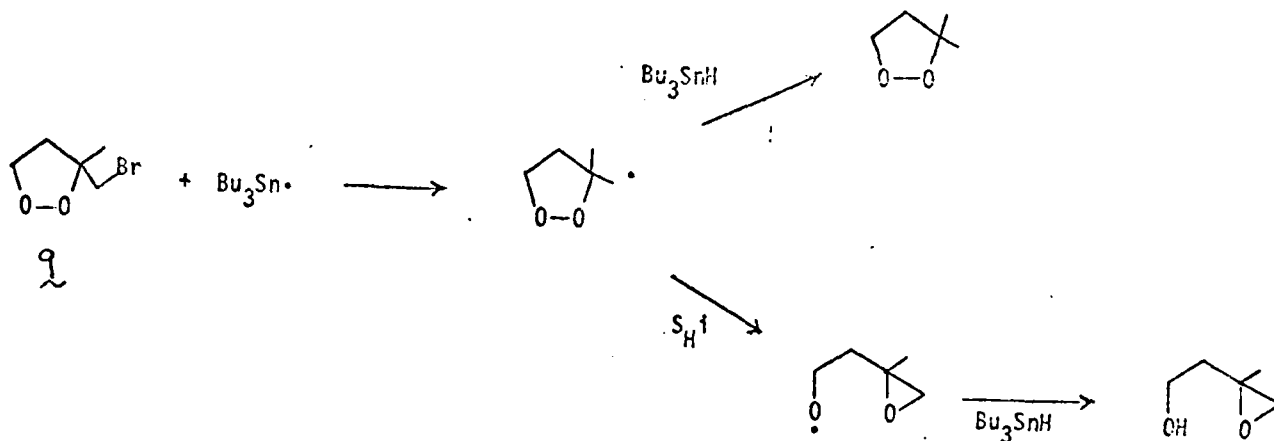
Little is known about the stereochemical requirements of the S_H2 reaction. An S_N2 type transition state has been proposed and strong evidence has been presented that suggests that halogen atom attack on cyclopropane carbon occurs with stereochemical inversion. The S_H2 reaction is apparently extremely sensitive to steric hindrance, and attack on carbon is limited to the strained cyclopropane series. Radical attack on heteroatoms such as O, N, or S is a much more common event, possibly because the steric hindrance of attack is much less for these di- and tri-valent atoms than it is for substitution at tetravalent carbon. Skell

suggests that "perhaps this type of displacement" (inversion) "will be found to be important for an unhindered substrate".

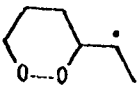
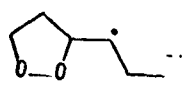
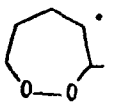
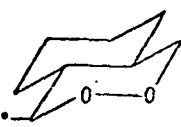
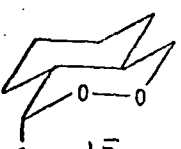
The $S_{\text{H}}\text{i}$ reaction reported here (Scheme 1) offers the possibility of studying the geometric requirements of $S_{\text{H}}2$ attack on the peroxide linkage since the attacking radical center and the peroxide bond are geometrically fixed by the cyclic peroxide molecular frame. We suggest that the critical geometric parameter for the $S_{\text{H}}\text{i}$ reaction is the dihedral angle, ϕ , about the O-C bond between the attacking radical and the leaving oxygen. Further, we propose that for maximum reactivity, this dihedral angle must be 180° . Our evidence in support of this hypothesis has been published in two recent papers, the results of which are summarized here.



A series of β -bromo peroxides were reacted with $\text{Bu}_3\text{Sn-H}$ affording the corresponding alkyl radicals. As an example, the bromide 9 was shown to react as follows:

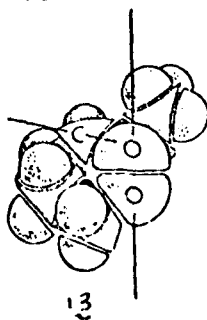


By carrying out reactions with different concentrations of $\text{Bu}_3\text{Sn-H}$, the rate constant for $S_{\text{H}}\text{i}$ can be determined. These rate constants, $k_{S_{\text{H}}\text{i}}$, for a series of radicals are shown below.

	$k_{S_H1} \text{ (sec}^{-1}\text{)}$
 <u>10</u>	1×10^4
 <u>11</u>	8.7×10^5
 <u>12</u>	7.5×10^4
 <u>13</u>	< 1
 <u>14</u>	1.2×10^4
 <u>15</u>	< 10

Rate constants for k_{S_H1} range generally from 10^4 - 10^6 sec^{-1} for the series of radic

radicals 10-15 with two exceptions, radicals 13 and 15. In both of those species, the attacking radical cannot approach the peroxide bond with $\phi \approx 180^\circ$ because of geometric constraints. In 13, for example, the angle ϕ is 100° at a maximum while in radical 15, the radical center is fixed with $\phi \approx 60^\circ$. Note that the epimeric radical to 15, 14 (which has equatorial substitution and $\phi \approx 180^\circ$), has a "normal" k_{S_H1} .



We conclude from these studies that radical substitution on the peroxide bond does, indeed, follow a colinear approach pathway. The S_H2 and S_N2 pathways for reaction on first-row elements are thus apparently similar, with back-side displacement being the rule.

c.) List of Publications

- "The Chemistry of Cyclic Peroxides: The Formation and Decomposition of Prostaglandin Endoperoxide Analogs", Ned A. Porter, John R. Nixon, and Dennis W. Gilmore, Organic Free Radicals, ed., William A. Pryor, American Chemical Society, Washington, D. C., pp. 89-101, 1978.
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- "Cyclic Peroxides by Intramolecular Peroxymercuration of Unsaturated Hydroperoxides", J. R. Nixon, M. A. Cudd and N. A. Porter, J. Org. Chem., 43, 4048(1978).
- "Separation and Purification of Lecithins by High Pressure Liquid Chromatography, N. A. Porter, R. A. Wolf, and J. R. Nixon, Lipids, 14, 20(1979).
- "Prostaglandin Endoperoxide", N. A. Porter, Free Radicals in Biology, Vol. IV, ed., William A. Pryor, Academic Press, Inc., New York, N.Y., pp. 261-291, 1980.
- "Synthesis of Prostaglandin H", Ned A. Porter, Jim D. Byers, Katherine M. Holden, and Daniel B. Menzel, J. Amer. Chem. Soc., 101, 4319(1979).
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- "The Autoxidation of Arachidonic Acid: Formation of the Proposed SRS-A Intermediate", Ned A. Porter, Richard A. Wolf, Elizabeth M. Yarbrow, and Hugo Weenen, Biochem. and Biophys. Res. Comm., 89, 1058(1979).
- "A Fixed Geometry Study of the S₂ Reaction on the Peroxide Bond", Ned A. Porter, M. Amelia Cudd, Richard W. Miller and Andrew T. McPhail, J. Amer. Chem. Soc., 102, 414(1980).
- "Prostaglandin G₂", Ned A. Porter, Jim D. Byers, A. E. Ali, and Thomas A. Eling, J. Amer. Chem. Soc., 102, 1181(1980).
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- "The Autoxidation of Poly-Unsaturated Lipids: Factors Controlling the Stereochemistry of Product Hydroperoxides", Ned A. Porter, Bruce A. Weber, Hugo Weenen and Jamil A. Khan, J. Amer. Chem. Soc., 102, 5597(1980).
- "Serial Cyclization of Peroxy Free Radicals: Models for Polyolefin Oxidation", Ned A. Porter, A. Nicholas Roe, and Andrew T. McPhail, J. Amer. Chem. Soc., 102, 5912(1980).

d.) List of Participating Personnel

		Ph.D. earned
M. Amelia Cudd	graduate student	1980
A. Nicholas Roe	graduate student	--
James Logan	graduate student	--
Carl B. Ziegler, Jr.	graduate student	1981
David Roberts	graduate student	--