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# Chapter 15

## SPECIFIC AND SELECTED SITE REACTIONS

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### INTRODUCTION

While numerous modifications of fatty acids have been attained at activated positions, *i.e.* the carboxyl group, the  $\alpha$ -position, the double bond, and allylic carbons, the capability of controlling reactions regiospecifically at less activated carbons has remained elusive. The uninterrupted, unactivated methylene groups of fatty acids have comparable reactivities that impose obstacles to targeting substituents or to rearranging molecules at precise positions in the chain. To overcome these difficulties, new reactions, techniques, and reagents must be developed to enable preparation of substituted derivatives at any/preselected position.

Many specifically substituted long chain derivatives of fatty acids are available only through total synthesis. In place of such inefficient methods, alternate routes have been developing that are termed "biomimetic" (1) or "enzyme mimetic" (2). While chemists have been utilizing enzymes in free cellular or supported (immobilized) systems (3-6), the biomimetic approach seeks techniques for aligning the reagent and substrate in proper spatial arrangements for reaction. It is in essence "imitating the style of enzyme-catalyzed processes in an effort to achieve some of the advantages that nature has realized by the use of enzymes" (1).

At present the few reactions directed to specific and selected sites involve inter- and intramolecular free radical attack by oxygen and nitrogen cations, oxidation of saturated species by photochemical and enzymatic techniques, and isomerizations of double and triple bonds. Although the reactions have been confined mainly to studies with small and medium chain length alkanes and fatty acids, they are, nevertheless, prototypes for extensions to the longer chain species. This review is therefore presented as an interim progress report on

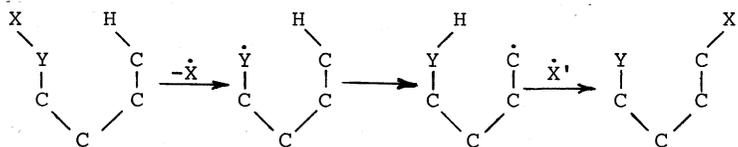
terminal, penultimate, and mid-chain functionalizations with the hope it will further stimulate new, imaginative developments in this challenging and essentially unexplored field of chemistry.

#### INTRAMOLECULAR ABSTRACTION OF HYDROGEN

Several factors influence the order of free radical hydrogen abstraction at different chain positions in saturated acids (7,8). Firstly, the general order of C-H abstractions is tertiary > secondary > primary. In long alkyl chains, the equivalent reactivity of the repetitive methylene groups (excluding the  $\alpha$ -methylene in fatty acids) has a statistical effect that leads to random methylene attack and a low probability of attack at the terminus. A second factor is the directive effect of functional groups toward electrophilic attack of radicals. A third factor is expressed by the reagent's reactivity which is determined by the effects of steric hindrance, electronic structure, and/or the nature of complexation with the substrate and solvent.

#### GENERAL 1,5 SHIFTS

Homolysis of a molecular bond (X-Y in *Scheme 1*) produces a free radical capable of abstracting a hydrogen atom within the molecule. Attack generally occurs at the C<sub>4</sub> carbon due to



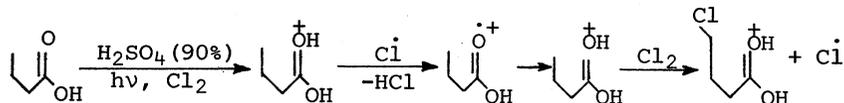
*Scheme 1*

favorable spatial orientations resulting in a 1,5-shift, although 1,4 and even less favorable 1,3 shifts may occur (7). The scheme is descriptive of the generation of oxygen radicals produced by nitrite photolysis (X = NO<sub>2</sub>; Y = O) (9), hypohalite cleavage (X = Cl, Br, I; Y = O) (10,11) or by lead tetraacetate (X = Pb(OAc)<sub>3</sub>, Y = O) (10). These reactions have received attention primarily in steroid research and little has been done to determine their usefulness with long chain aliphatic compounds.

#### OXYGEN CATION RADICALS

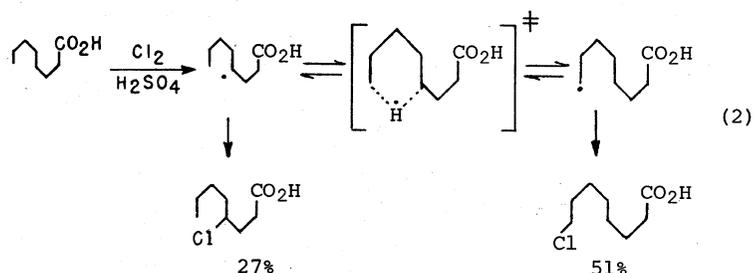
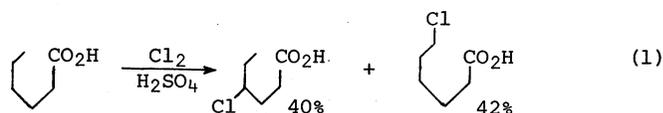
In acid media radicals capable of protonation may have their properties modified by the associated positive charge. An oxygen cation radical may be generated from carboxy acids

by protonation in acid media and subsequent electron abstraction by chlorine (12). Chlorination of the alkyl chain then occurs by free radical chain transfer (*Scheme 2*). The reaction resembles the McLafferty rearrangement in mass spectroscopy



*Scheme 2*

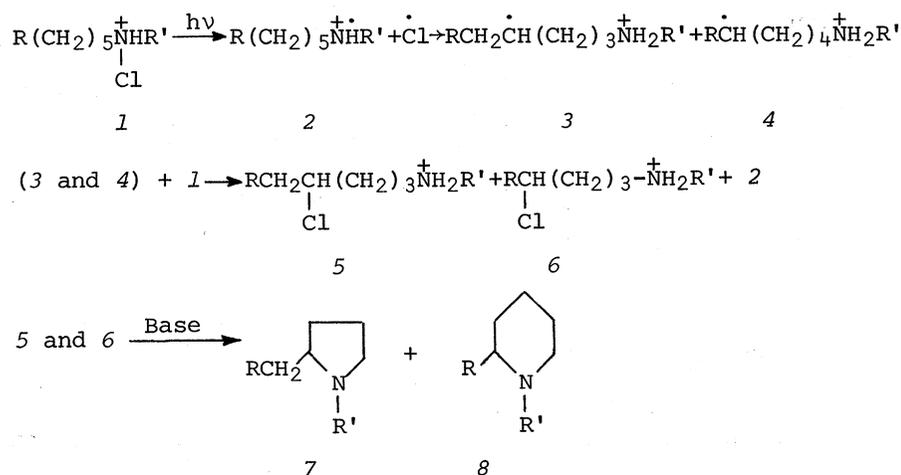
(12,13) whereby an oxygen radical cation abstracts hydrogen internally and selectively at C-4. However, a high degree of  $\omega$ -chlorination is also observed when longer chain acids are chlorinated in acid media (eq. 1 and 2). For octanoic acid, a 6-membered transition state initially introduces the radical



at C-4. A radical relay mechanism involving a subsequent 6-membered transition state could account for the preponderance of  $\omega$ -chloro products.  $\omega$ -Chlorination in hexanoic acid may be attributed to a 4-membered transition state. Clarification of the mechanistic details of these reactions may provide invaluable clues for practical extensions to longer chain carboxylic acids.

#### HOFFMAN-LÖFFLER-FREYTAG REARRANGEMENT

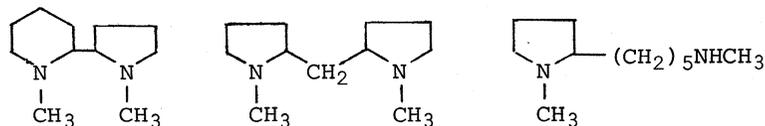
(A). *Nitrogen cation radicals from amines.* The Hoffmann-Löffler-Freytag reaction is a rearrangement by which N-haloamines are derivatized in acid media predominantly to 1,4-haloamines 5 and in minor amounts to 1,5-haloamines 6 (*Scheme 3*). Subsequent base cyclization of 5 and 6 affords pyrrolidine 7 and piperidine 8, respectively.



Scheme 3

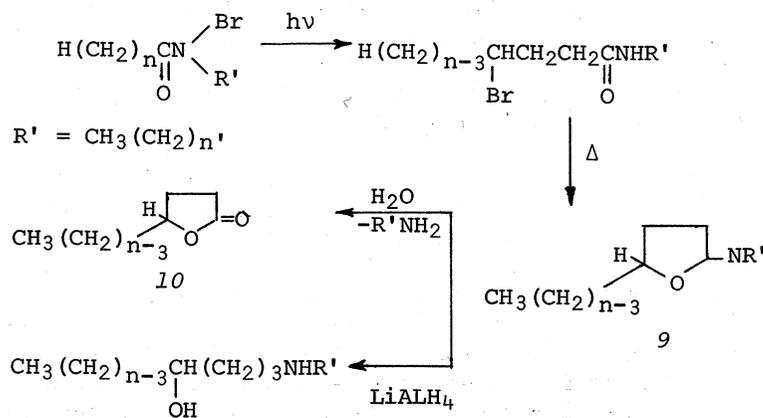
The reaction proceeds through a nitrogen cation radical  $\text{R}_2\overset{\oplus}{\text{N}}\text{H}^{\cdot}$  (aminium radical) which intramolecularly abstracts a sterically favored hydrogen atom (14). Chlorine abstraction by the alkyl radical from another molecule of N-chloroamine yields the haloamine product with regeneration of the aminium radical that continues the cycle in a chain propagation sequence. A more detailed description of the mechanism may be found in comprehensive reviews (15,16). The reaction offers a formal analogy to the McLafferty rearrangement (17).

A few examples with long chain fatty amines ( $\text{R} = \text{CH}_3(\text{CH}_2)_{12}$ ;  $\text{CH}_3(\text{CH}_2)_{10}$ ,  $\text{CH}_3\text{O}_2\text{C}(\text{CH}_2)_5$  and  $\text{R}' = \text{CH}_3$ ) have been reported (18). The reaction illustrates the predominance of the 5-membered pyrrolidine ring structure in this rearrangement even for diamines. The  $\omega, \omega'$ -dichlorodiamine,  $\text{CH}_3\text{NCl}(\text{CH}_2)_9\text{NClCH}_3$ , on rearrangement produced the following products in the ratio 5:65:30 in 80% overall yield.



(B). *Nitrogen radicals from amides.* N-Haloamide rearrangements are an extension of the Hoffmann-Löffler-Freytag reaction except that photolysis is generally in a neutral solution and halogen-hydrogen exchange is propagated by unprotonated nitrogen radical species (19). Hydrogen atom transfer from the alkyl chain involves a 1,5 shift from either the amine or acyl moiety. If  $n > 3$  and  $n' < 3$ , backbiting in a bromoamide forms  $\gamma$ -bromoamide that thermally cyclizes to 2-

iminotetrahydrofuran 9 (Scheme 4). The latter product hydrolyzes to lactone 10 or reduces with lithium aluminum hydride



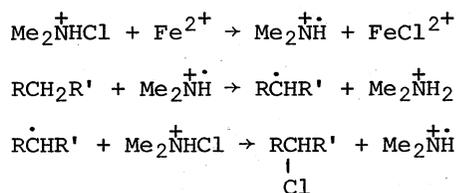
Scheme 4

to 4-hydroxyalkylamine 11. N-Chloroamides are similarly rearranged, but the resulting 4-chloroamides are more stable and cyclize less rapidly than the corresponding bromo analogs. The 4-chloroamides produce the nonhalogenated parent acylamide in significant amounts (19).

#### INTERMOLECULAR HYDROGEN ABSTRACTION

##### $\omega$ -1 SUBSTITUTION

*Nitrogen cation radical halogenation.* The nitrogen cation radical was first extended to intermolecular chlorination by Minisci and coworkers (Scheme 5) (20-23). They established the following significant characteristics of the reaction: (i) an unprecedentedly high selectivity of  $\omega$ -1 chlorination in aliphatic hydrocarbons and esters; (ii) monochlorination with



Scheme 5

little or no dichlorination; and (iii) selective chlorination of substrates such as hydrocarbons, alkyl halides, and alkylbenzenes which are generally insoluble in strong acid media

(80-90% H<sub>2</sub>SO<sub>4</sub>). Subsequent investigators also examined electronic and steric effects by variations of substitutions in the aminium radicals R<sub>2</sub>NH<sup>+</sup> (2,24). They further enlarged the scope of substrates to include acids, ethers, alcohols, amides, and alkanes (25).

The reaction is initiated chemically by Fe<sup>+2</sup> or other transition metals such as Cu<sup>+</sup>, Ti<sup>+3</sup>, Cr<sup>+2</sup> (23). In the photochemical reaction, the initiation process is not well defined since the protonated N-chloroamines have no appreciable UV absorption above 225 nm. Initiation may result from homolysis of trace impurities such as HCl, Cl<sub>2</sub>, or the free N-chloroamine (16).

The preference for ω-1 chlorination is attributed to the following factors (23): (i) the positive charge of the protonated functional group is inductively transmitted down the chain (with attenuation), causing an electrostatic repulsion of the attacking aminium cation radical. (ii) The difference in C-H bond dissociation energies between CH<sub>3</sub> and CH<sub>2</sub> groups favors the latter. (iii) The ω-1 effect results from less steric hindrance at the ω-1 position than at any of the remaining chain methylenes. Even hydrocarbons and haloalkanes, which have no protonatable functionality, show this selectivity but of lower degree than in protonated compounds. The second and third factors control selectivity in hydrocarbons and haloalkanes, while the electrostatic repulsion of halogen in the latter also has a contributing effect similar to the first factor.

Minisci (23) and Deno (16,24) investigated whether the type and degree of selectivity could be influenced by structural variations in the N-cation radical. The ω-1 preference is remarkably high (72-92%) for chain lengths up to C-8 (Table I). Increased branching in the N-chloroamine, e.g., N-chloro-di-*t*-butylamine vs. N-chloro-dimethylamine, improved slightly the degree of ω-1 selectivity. Bromination with N-bromodimethylamine gave results similar to chlorination (23).

Penultimate (ω-1) selectivity was high for fatty acids and esters of chain length C-5 to C-8 but diminished to approximately half for C-10 (Table I). Loss of selectivity arises from statistical dilution caused by increasing methylene additions and a corresponding rapid attenuation of the polar effect with increasing distance.

To determine whether ω-1 selectivity could be regained or enhanced in long chain fatty acids, Konen *et al.* (26) investigated several parameters, namely the nature of the acid medium, the diversity of substrates amenable to protonation, the structure of the N-chloroamine, and the method of initiation. When they submitted a series of even carbon homologous esters to constant reaction conditions, ω-1 selectivity to

TABLE I

Radical Chlorination of Saturated Aliphatic Compounds  
Via N-Chloroamines

R in R <sub>2</sub> NCl	% Isomer distribution				Ref.
<u>Alkanes</u>					
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>3</sub>				21
Me	1	56	29	14	
(i-Bu)	1	65	23	11	21
<u>1-Chloroalkanes</u>					
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -Cl				22
Me	5	88	7		
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -Cl				23
Me	4	77	16	3	
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -Cl				22
Me	2	73	20	4 1	
<u>Alcohols</u>					
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OH				25
(i-Pr)	6	90	2	2	
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OH				25
(i-Pr)	1	92	3	1 1 2	
<u>Ethers</u>					
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -OMe				23
Me	4	83	11	1 1	
(i-Pr)	8	92			25
<u>Acids</u>					
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CO <sub>2</sub> H				25
(i-Pr)	1	93	6		
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CO <sub>2</sub> H				25
(i-Pr)	1	80	14	5	
<u>Esters</u>					
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CO <sub>2</sub> Me				20
Me	14	86			
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CO <sub>2</sub> Me				20
Me	7	77	16		
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CO <sub>2</sub> Me				20
Me	4	78	13	5	
(i-Bu)	6	87	6	1	21
	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CO <sub>2</sub> Me				20
Me	3	72	20	4 1	
	4	80	15	1	21
	CH <sub>3</sub> -CH <sub>2</sub> -CO <sub>2</sub> Me				
Me	1	44	22	18 11 4	20
(i-Bu)	1	58	19	13 7 2	21

<sup>a</sup>Morpholino group represented by R<sub>2</sub>N.

TABLE II

Chlorination of Methyl Esters of Carboxylic Acids<sup>a,b</sup>

Substrate chain length	Product distribution <sup>c</sup>			
	$\sum_{\alpha}^{\omega-3}$	$\omega-2$	$\omega-1$	$\omega$
C <sub>6</sub>		3	82	15
C <sub>8</sub>	5	15	73	7
C <sub>10</sub>	21	20	55	4
C <sub>12</sub>	39	15	43	3
C <sub>14</sub>	60	11	27	2
C <sub>16</sub>	62	8	20	2
C <sub>18</sub>	80	5	14	1

<sup>a</sup>Data from Konen *et al.* (26). <sup>b</sup>N-chlorodiisopropylamine was used as the chlorinating agent; 97% sulfuric acid was the acid medium. <sup>c</sup>Determined by glc [SCOT-DEGS].

TABLE III

Chlorination of Fatty Acid Derivatives of C-10 Chain Length<sup>a,b</sup>

Substrate functionality	Conc. <sup>d</sup>	Conv.	Distribution (%) <sup>c</sup>					
			5Cl	6Cl	7Cl	8Cl	9Cl	10Cl
Acid	1	63	2	8	16	28	42	4
	2	73	2	7	13	19	54	4
	3	63	3	8	14	18	52	4
Ester	1	73	3	10	17	28	36	5
	2	79	2	7	14	20	53	4
	3	74	3	8	14	19	52	4
Amide	1	68	2	11	17	29	36	5
	2	78	2	6	14	20	55	4
	3	68	2	7	14	19	54	4

<sup>a</sup>Data from Konen *et al.* (26). <sup>b</sup>N-chlorodiisopropylamine, 97% H<sub>2</sub>SO<sub>4</sub>. <sup>c</sup>Analyzed by glc [SCOT, DEGS]. <sup>d</sup>Molar concentration of substrate in 97% H<sub>2</sub>SO<sub>4</sub>.

chlorination diminished with chain extension from C-6 (82%) to C-18 (14%) (Table II). The type of functionality, *i.e.*, acid, ester, or amide in a C-10 chain, did not affect the product distribution (Table III). However, the  $\omega-1$  and  $\omega-2$  selectivities were sensitive to concentration effects of the substrate in sulfuric acid. For all three substrates studied,  $\omega-2$  and other substitutions increased at the expense of  $\omega-1$  in the more dilute substrate solution (1M). Elucidation of the gen-

eral effects of concentration of each reactant was thereby indicated to be essential.

Increasing the water content in concentrated sulfuric acid from 3 to 20% diminished  $\omega$ -1 selectivity slightly, but greatly lowered the overall conversion to chlorinated products from 80 to 22% (Table IV). Decreasing the ratio of N-chloroamine had no effect on selectivity, although conversions declined as would be expected for insufficient stoichiometric proportions. The product distribution and conversion were unaltered on decreasing ferrous sulfate initiator in the metal catalyzed reaction from 25 mole percent to catalytic quantities (2.5 mole %). Consequently, the large amounts of initiator generally used by other workers is unnecessary.

A more detailed examination of the substrate concentration effect on selectivity and conversion also established their dependence on the substrate's chain length (Table V). In methyl octanoate,  $\omega$ -1 selectivity was unaltered upon increasing concentrations from 1M to 4M, whereas conversion fell precipitously from 90 to 20%. Both selectivity and conversions diminished in solutions below 1M. Similar results were qualitatively experienced with the longer chain lengths, except conversions were poor for methyl decanoate at 4M and for methyl dodecanoate at 3M. These data reveal the importance of concentration effects on selectivity and conversion.

The increasing complexity that arises in the isomeric product mixtures with increasing chain length of homologues makes it imperative that the analytical method be capable of high resolution and quantification. It is therefore desirable to minimize product treatment following termination of the reaction to preclude loss and to ensure detection of unexpected sensitive products that would otherwise be overlooked. For example,  $\gamma$  and  $\delta$  lactones were detected in the mixtures of products derived from reactions conducted at low molar concentrations of the esters (26). These lactones had not been previously reported as products of chlorinations. The lactones originated from the chlorinated esters by prolonged solvation in the strong acid solution. They are not products in the iron-initiated chlorinations because of the rapidity of reaction.

*Micellar substitutions.* Solvents are highly important for controlling reactions. In  $\omega$ -1 substitutions a strong acid solvent protonates the carboxylic acid group with enhancement in selectivity by electrostatic repulsion of the N-cation radical toward the tail end of the nonpolar hydrocarbon chain (16,23). Deno and Jedziniak (27) postulated that the interactions of fat compounds with solvents could induce enfoldments of the long chain. They predicated their concept

TABLE IV

Chlorination of Methyl Decanoate by  
N-Chloro Diisopropylamine<sup>a</sup>

Variable	%	Isomer distribution (%)					
		Conversion	5Cl	6Cl	7Cl	8Cl	9Cl
H <sub>2</sub> SO <sub>4</sub> Conc.							
80%	22	4	10	14	20	49	3
90	68	3	8	13	18	53	6
97	80	2	7	14	19	55	4
N-Cl amine ratio <sup>b</sup>							
1/2	42	}	2	6	13	19	55
3/4	61						
1/1	78						
FeSO <sub>4</sub> Ratio <sup>c</sup>							
1/4	76	}	2	6	13	19	56
1/8	83						
1/40	76						

<sup>a</sup>Data from Konen *et al.* (26). <sup>b</sup>Ratio of N-chloroamine to methyl decanoate. <sup>c</sup>Ratio of FeSO<sub>4</sub> to methyl decanoate.

TABLE V

Percent Isomer Distribution Using  
N-Chlorodiisopropyl Amine in H<sub>2</sub>SO<sub>4</sub><sup>a</sup>

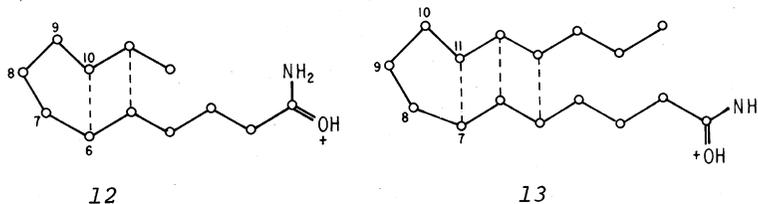
Substrate	Conc. (M)	%			
		Conversion	$\omega$ -2	$\omega$ -1	$\omega$
Methyl octanoate	0.5	70	}	22	65
	1.0	90			
	2.0	90			
	3.0	80			
	4.0	20			
Methyl decanoate	1.0	70	}	28	40
	2.0	80			
	3.0	60			
	4.0	15			
Methyl dodecanoate	1.0	65	}	15	43
	2.0	70			
	3.0	20			

<sup>a</sup>Data taken from Konen *et al.* (26).

on the conformational effects envisioned in enzyme systems for directing product formation.

Octanoamide was selectively chlorinated at  $\omega$ -1 (70% of product) in 70-90% H<sub>2</sub>SO<sub>4</sub> (28). The longer chain dodecanoamide

was also remotely chlorinated in 70% acetic acid - 30% sulfuric acid, although  $\omega$ -1 preference was reduced to 39% (27). When the polarity of the solvent was increased (20% H<sub>2</sub>O, 80% H<sub>2</sub>SO<sub>4</sub>), the conformations in dodecanoamide (Structure 12) were altered, shifting substitution toward the middle of the chain. Chlorination at  $\omega$ -1 fell to 8% and the bulk of chlorinations (88%) encompassed the C<sub>6</sub>-C<sub>10</sub> region. Predominant mid-chain halogenation was observed for hexadecanoamide (palmitamide) in 70% acetic acid - 30% sulfuric acid.



The interpretation of this phenomenon is based on the concept of enfolding of the long chain amides 12 and 13 under highly polar conditions. Deno and Taft (29) have determined that 80% H<sub>2</sub>SO<sub>4</sub> behaves like a fused salt (H<sub>3</sub>O<sup>+</sup>HSO<sub>4</sub><sup>-</sup>) of high dielectric constant. Charge repulsion from the polar head to nonpolar tail enhances chlorination at the less repelled central region of the enfolded chain. The existence of amide micelles is postulated to shield the chain from reaction with R<sub>2</sub>NH so that reaction on enfolded amide occurs at the periphery of the micelle (27).

A micellar approach to the substitution of long chain hydrocarbons, specifically for chain extension by methyl radical addition to the terminal methyl group, was earlier conceived by Wilson (30,31). This concept was proposed in explanation of the cosmic origin of linear hydrocarbons and fatty acids in meteorites. Wilson's proposal of a nonbiological mechanism of synthesis involves crowding hydrocarbon chains on a solid matrix like straws in a box (Figure 1) analogous to Langmuir's films of oriented fatty acids (32). The clustered chains imprison the methylene groups leaving only the terminal methyl groups exposed to free radical attack. The feasibility of this concept was experimentally demonstrated by passage of methyl radicals (pyrolysis of di-*t*-butyl peroxide) or ethyl radicals (pyrolysis of lead tetraethyl) (33) over oriented films of palmitic acid (31) or potassium palmitate (34,35). A homologous fatty acid mixture containing chain lengths up to C-22 was formed. When free radicals were generated by corona discharge through an atmosphere of oxygen, hydrogen, or methane, the film of fatty acid molecules polymerized to solid, insoluble products.

Film orientation of a fatty acid on a solid substrate

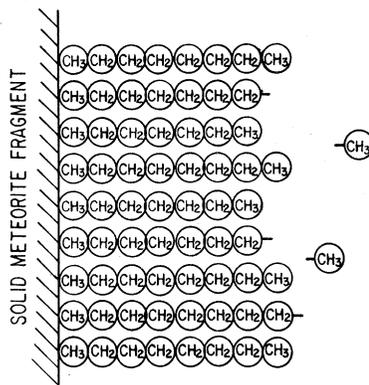


Fig. 1. Wilson's (30,31) proposed mechanism for extra-terrestrial synthesis of straight chain hydrocarbons. Reproduced with permission from *Nature* 196:71 (1962).

was later examined by Deno and coworkers (36) and Eden and Shaked (37). Fatty acids (butyric, hexanoic, octanoic, and stearic), adsorbed on alumina, were chlorinated in low conversions to yield a distribution of monochloro acids. The data of these workers are assembled in Table VI. Selectivity was high for  $\omega$  as well as for  $\omega-1$ . In homogeneous solution, chlorination with free chlorine gave diminished selectivity and increasing randomization. Less reactive halogen like chlorine in association with benzene (38-40) or *t*-butyl hypochlorite was applied by Deno (36) to octanoic acid;  $\omega$  chlorination was reduced with no enhancement in  $\omega-1$  selectivity.

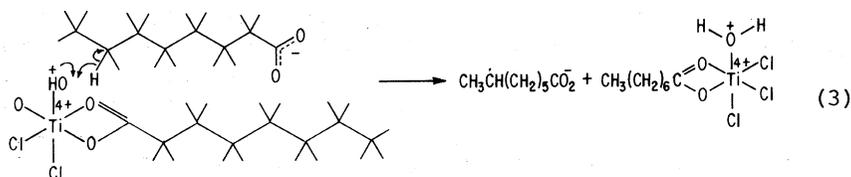
*Oxidation.* Selective substitutions at  $\omega-1$  or mid-chain positions with functionalities other than halogen have been sparse. In a regioselective oxidation of aliphatic acids, Hewgill and Proudfoot (8) determined the esr characteristics of aliphatic chain radicals produced by OH radicals. The hydroxyl radicals were generated by  $\text{TiCl}_3/\text{H}_2\text{O}_2$ . Remote ( $\omega-1$ ) radical formation was the rule in either acidic or basic media, although short chain acids (C-3 and C-4) also produced the  $\beta$ -radical in acidic and  $\alpha$ -radical in alkaline solutions. The mechanism, illustrated with octanoic acid for reaction in basic solution was proposed to involve a complex of the carboxylic acid, OH radical and  $\text{TiCl}_3$  (eq. 3). In the region below the critical micelle concentration, the complexed molecule was linearly aligned head to tail to another octanoate molecule, an arrangement in favor of  $\omega-1$  selections. Abstraction from the  $\alpha$ -carbon was also obtained in the basic

TABLE VI

## Chlorination of Fatty Acids Adsorbed on Alumina

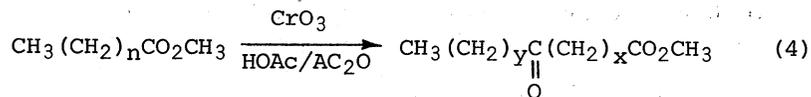
	$\omega$	$\omega-1$	$\omega-2$	$\omega-3$	$\omega-4$	$\omega-5$	$\omega-6$
Butyric <sup>a</sup>	52	47	1				
Hexanoic <sup>a,b</sup>	31 (18)	36 (37)	27 (28)	4 (13)	1 (4)		
Octanoic <sup>a,b</sup>	33 (17)	30 (24)	20 (19)	8 (15)	5 (15)	3 (9)	1 (1.5)
Stearic <sup>c</sup>	41.5	50	8.5				

<sup>a</sup>Data from Deno *et al.* (36). <sup>b</sup>Data in parentheses are for homogeneous chlorination in  $\text{CCl}_4$  and listed for comparison. <sup>c</sup>Data from Eden and Shaked (37).



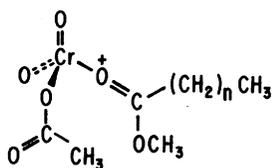
medium. Unfortunately, quantitative measurement of the hydroxylated products was not determined since this work was not oriented with the aim of acquiring preparative data.

Isomeric keto esters were obtained by chromium trioxide oxidation of long chain esters (methyl esters of decanoic, myristic, palmitic, stearic, and docosonoic acids) in acetic acid-acetic anhydride solutions (eq. 4) (41). The mechanism

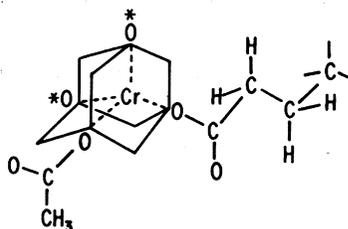


of oxidation was indicated to engage a chromium oxide-acetyl-substrate cationic complex 14 with acetate counter anion. The sites predominantly oxidized in methyl stearate clustered at C-5 to C-10 and in methyl docosonoate at C-6 to C-10 and C-18 to C-20 ( $\omega-2$ ). These two carboxylic esters reacted more regioselectively than the lower homologues. An intramolecular mechanism based on a Monte Carlo method of random walks in a diamond lattice (42,43) was proposed to account for mid-chain oxidation by chromium trioxide (44). Briefly, the mechanism involves an adamantane structure 14b with the  $\text{Cr}^{\text{VI}}$  atom (in tetrahedral complexation with the oxygen atoms) at its center (44). The chromium atom, with the four oxygen atoms positioned

at the tertiary intersections, enclose a space volume that presents a steric barrier to the long alkyl chain. Reactive conformations of the flexible chain through segmental rotation (related to the configurational entropy for reaction) induce regioselective oxidation of methylene sites by either of the two reactive (starred) oxygen atoms.



14a



14b

Electrophilic hydroxylation of aliphatic hydrocarbons proceeds readily by incipient hydroxyl cation  $\text{OH}^+$  in strong acid media. The  $\text{OH}^+$  species is formed from protonated hydrogen peroxide,  $\text{H}_3\text{O}_2^+$ , and arises in the course of insertion in the  $\sigma$  bonds in alkanes (45). Oxidation of secondary and tertiary C-H bonds by trifluoroperoxyacetic acid as a source of  $\text{OH}^+$  was first noted in reactions with pentane and tertiary alkanes by Frommer and Ullrich (46). Deno subsequently hydroxylated cyclohexane, 1-octanol, and palmitic acid in high yield with no oxidation of the incorporated or parent functionalities (47). 1-Octanol gave a mixture of diol products as their bis trifluoroacetates in 59% yield in the following distribution: 1,8 - (3%); 1,7 - (51%); 1,6 - (25%); 1,5 - (14%); and 1,4 - (7%). Palmitic acid converted to a 70% yield of hydroxypalmitic acids in which the hydroxyl functionality was distributed in the range of C-5 to C-15.

Olah and coworkers (45) investigated in depth the oxidation of simple alkanes with hydrogen peroxide in strong acids ( $\text{HF}$ ;  $\text{FSO}_3\text{H}$ ;  $\text{H}_2\text{SO}_4$ ) and in superacids, e.g., ( $\text{FSO}_3\text{H}-\text{SbF}_6$ , which Olah termed Magic Acid, and the combination Magic Acid -  $\text{SO}_2\text{ClF}$ ). The details of oxidation of branched chain alkanes, on which the study was focused, exceed the scope of this review. The longest straight chain alkane examined was butane in which secondary C-H was preferentially attacked. The vigorous oxidation resulted in rearrangements and formation of mixtures of alcohols, ketones, and carboxylic acids. No extension of the reaction for the selective introduction of oxygen into aliphatic acids was attempted.

Nevertheless, vigorous degradative oxidation of a saturated acid to a mixture of dicarboxylic acids does follow the selectivity route (48). Thermal ( $90^\circ$ ) nitric acid oxidation of palmitic acid at low conversion (6%) and short reaction

TABLE VII

Relative Yields of Dicarboxylic Acids from  
Hexadecanoic Acid<sup>a,b</sup>

Reaction time, % reaction	Number of carbons in dicarboxylic acid											
	4	5	6	7	8	9	10	11	12	13	14	15
4 hr., 6%	0	3	4	4	5	7	13	13	15	16	11	9
24 hr., 80%	3	4	7	12	20	20	14	9	6	3	2	
120 hr., 100%	8	16	24	26	16	8	2					

<sup>a</sup>Taken from Deno et al. (48). <sup>b</sup>Oxidation using 70% HNO<sub>3</sub> at 90°.

TABLE VIII

Chlorination of Dicarboxylic Acids in Sulfuric Acid (85%)<sup>a,b</sup>

Substrate	Isomer distribution <sup>c</sup>					% Conversion <sup>c</sup>
	α	β	γ	δ	ε	
Hexanedioic	4	96				2
Heptanedioic		3	97			11
Octanedioic		4	96			45
Nonanedioic		2	40	58		72
Decanedioic		1	14	85		96
Dodecanedioic			2	32	66	96

<sup>a</sup>Taken from Kämper et al. (49). <sup>b</sup>Chlorination with N-chlorodiisopropylamine. <sup>c</sup>Determined by glc via the dimethyl ester.

times (4 hr.) produced a dicarboxylic acid mixture with 77% of the diacids in the C-10 to C-15 range. With increasing reaction times, shorter chain dibasic acids in the range C-4 to C-9 appeared via more extensive oxidation of both palmitic acid and the larger dibasic acids. The short chain diacids arose by oxidation of sites remote from both carboxylic ends, i.e., the central carbons, which are least affected by the electronegative groups, are most susceptible to subsequent oxidation (Table VII).

Mid-chain selectivity in ω, ω'-dicarboxylic acids offered the opportunity to introduce a functionality at such a position (49). The concept was tested for chlorination with R<sub>2</sub>NHCl, which indeed provided monochlorodicarboxylic acids with center chain selection of 72-97% (Table VIII).

*Electrochemical acetamidation.* Electrochemical generation of ω-1 radicals from esters was obtained in a solvent that also participated as the reactant (50). Methyl and ethyl esters (Table IX) were potentiostatically acetamidated in

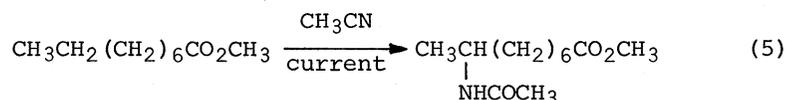
TABLE IX

Anodic Products from Esters<sup>a,b</sup>

Substrate	Faraday/ mol <sup>c</sup>	Product	% Yield <sup>c</sup>
None	4	Succinonitrile, chlorine dioxide	
Ethyl butanoate	2	Ethyl 3-acetamido-	21
	3	butanoate	55
	4		70
Methyl hexanoate	4	Methyl 5-acetamido-	42
		hexanoate	
Methyl nonanoate	4	Methyl 4-acetamido-	11
		hexanoate	
Methyl nonanoate	4	Methyl 8-acetamido-	(25) <sup>d</sup>
		nonanoate	
Ethyl 3-methyl- butanoate	3	Ethyl 3-acetamido-3- methylbutanoate	70

<sup>a</sup>Taken from Miller and Ramachandran (50). <sup>b</sup>Oxidations at 2.74V vs. Ag/AgNO<sub>3</sub> using lithium perchlorate. <sup>c</sup>Faraday/mol and % yields based on added ester. <sup>d</sup> $\omega$ -2 and  $\omega$ -3 isomeric amides were also indicated to be present as major products by glc.

acetonitrile (eq. 5). Lithium perchlorate (at 2.74V) was a more effective electrolyte than tetraethyl fluoroborate (at



3.10V) for the anodic reaction. The mechanism was rationalized to involve alkyl carbonium ions analogous to Ritter type reactions (51). As the alkyl chain length increased from C-4 to C-9,  $\omega$ -1 selectivity declined and  $\omega$ -2 and  $\omega$ -3 substitutions became the major products.

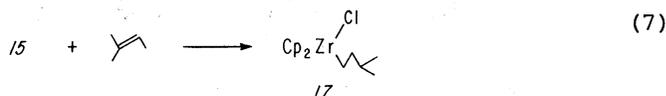
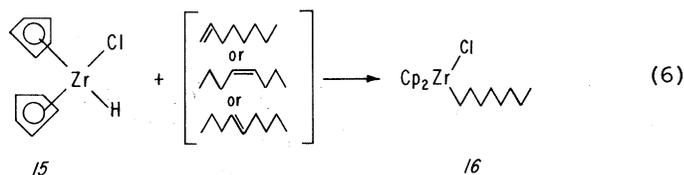
#### $\omega$ -SUBSTITUTION

Although the methyl group's resistance to substitution in competition with methylene has been the rule, Wilson's (30,31) chain extension of fatty acids by small alkyl radicals and Deno's (36) halogenations established the feasibility of  $\omega$ -selection under special conditions. The following two types of reactions enlarge upon this feasibility.

*Deuteration.* An intriguing development for the activation of C-H bonds in hydrocarbons has been carried out with

transition metal complexes (52). Deuterium exchange of hydrogen provided evidence of this activation. The exchange was extended to simple aliphatic carboxylic acids such as nonanoic acid in the presence of potassium tetrachloroplatinate (III) in a deuterium oxide-acetic acid solvent (53). Catalysis of the exchange by perchloric acid with pyrene to inhibit disproportionation incorporated up to 10 deuterium atoms per nonanoic acid molecule (34% deuterium content). Deuterium concentrated at the nonpolar end with extensive replacement of the methyl hydrogens. The success of this exchange is highly encouraging for an investigation of transition metal complexes as a vehicle to control specific or selective substitutions.

*Olefin and acetylene migration.* A unique approach to terminal substitution is offered by double bond isomerization in an unsaturated hydrocarbon. Schwartz and coworkers (54,55) transformed terminal and internal olefins to terminally substituted alkanes by hydrozirconation. Alkyl zirconium (IV) complexes of the type  $[\eta^5-(C_5H_5)_2Zr(Cl)R]$  were derived by addition of  $[\eta^5-(C_5H_5)_2Zr(Cl)H]$  15 to the olefin. The complexes from internal olefins transformed to terminal complexes by rapid rearrangement through Zr-H elimination and readdition (eq. 6, 7 and Table X for selected reactions; Cp =  $\eta^5-C_5H_5$ ). The zippering of zirconium along the chain ceases at the less



hindered position. The organozirconium intermediate is functionalized by reaction with electrophiles (Table X). Oxidation to alcohols is accomplished with a variety of oxidants ( $H_2O_2/NaOH(aq)$ ;  $t-C_4H_9OOH$ ; peroxyacid;  $O_2/H_3O^+$ ) (56). Halogenated reagents ( $Br_2$ ,  $I_2$ , or  $C_6H_5ICl$ ) regenerate a  $Cp_2Zr(Cl)X$  species which is recoverable and recyclable to  $Cp_2Zr(Cl)H$ . Carbonylation of 16 produced an aldehyde, acid, or ester on protonolysis of the acyl zirconium (IV) complex depending on the cleaving reagent used (eq. 8a-8c) (55).

Zirconium complex 16 acylates with acyl halides slowly and in good yield if steric congestion is low but does not add to the carbonyl group of ketenes or aldehydes or to alkylating

TABLE X<sup>a</sup>

## Hydrozirconation of Olefins: Products of Electrophilic Reactions

Olefin	Electrophile	Product	% Yield
1-Octene or 4-octene	H <sup>+</sup>	Octane	100
	Br <sub>2</sub>	1-Bromooctane	96
	I <sub>2</sub>	1-Iodooctane	91
	C <sub>6</sub> H <sub>5</sub> ICl <sub>2</sub>	1-Chlorooctane	65
	CH <sub>3</sub> C(O)Cl	2-Decanone	80
	H <sub>2</sub> O <sub>2</sub> /NaOH (aq.)	1-Octanol	69
1-Hexene or 3-hexene	dil HCl	n-Heptanal	99
	Br <sub>2</sub> /CH <sub>3</sub> OH	Methyl n-heptanoate	51
	NaOH/H <sub>2</sub> O <sub>2</sub>	n-Heptanoic acid	77
2-Methyl-2-butene	Br <sub>2</sub>	1-Bromo-3-methylbutane	100
	CH <sub>3</sub> C(O)Cl	5-Methyl-2-hexanone	72
	dil HCl	4-Methylpentanal	71
	Br <sub>2</sub> /CH <sub>3</sub> OH	Methyl 4-methyl pentanoate	50
	NaOH/H <sub>2</sub> O <sub>2</sub>	4-Methylpentanoic acid	26
	O <sub>2</sub> /H <sub>3</sub> O <sup>+</sup>	3-Methyl-1-butanol	70
Cyclohexene	Br <sub>2</sub>	Bromocyclohexane	95
	dil HCl	Cyclohexane carboxyaldehyde	97
	O <sub>2</sub> /H <sub>3</sub> O <sup>+</sup>	Cyclohexanol	76

<sup>a</sup>Ref. 47, 48, and 49.



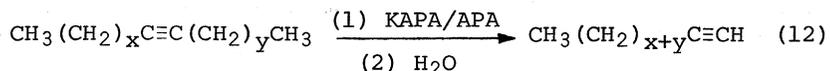
TABLE XI

Distribution of Oxidized Positions (%)<sup>a</sup>

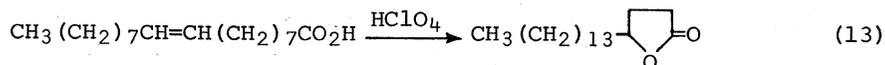
Alcohol moiety	Oxidation site											
	9	10	11	12	13	14	15	16	17	18	19	20
Dodecanol	6	28	65	0								
Tetradecanol	1	3	11	49	22	0						
Hexadecanol	1	8	10	8	3	66	10	0				
Octadecanol	tr	8	17	21	18	12	5	13	6	0		
Eicosanol	<2	5	15	20	19	19	13	8	1	0	0	0

<sup>a</sup>Taken from Breslow (1,62).

R' = alkyl. The reaction provides the preparation of tri-substituted olefins, e.g., 19(a & b) in reaction with N-bromo-succinimide produces dialkyl vinyl bromide. Subsequent reaction of the latter product in tandem with lithium dialkyl copper (59a,b) is a potential synthesis of trialkyl olefins from dialkyl acetylene (59a). Subsequent hydrozirconation of trialkyl olefins should afford branched chain derivatives with a terminal (primary) functionality. An "acetylene zipper" for inducing migration of an internal acetylene to the terminus (eq. 12) was accomplished by a superbases, potassium 3-aminopropylamide (KAPA; KNH(CH<sub>2</sub>)<sub>3</sub>NH<sub>2</sub>) in 3-aminopropylamine (APA) (60).

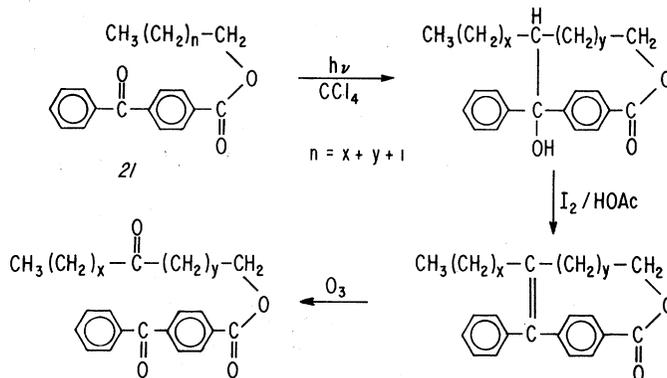


Whether these facile isomerizations of olefins and acetylenes are extensible to unsaturated fatty acids in preparation of terminally substituted derivatives is still to be determined, but their applicability will depend upon the influence of the polar group on the direction of migration. It has been shown in an acid-catalyzed isomerization of oleic acid (61) that migration proceeds toward the carboxyl end and terminates at C-4 in formation of  $\gamma$ -lactone (eq. 13). The latter isomerization offers entry to specific  $\gamma$ -functionalizations.



## PHOTOCHEMICAL MID-CHAIN FUNCTIONALIZATION

An innovative intramolecular photochemical functionalization of a long chain compound was derived by Breslow and Winnik (62).  $\rho$ -Benzoylbenzoic acid 20, as photosensitizer, was attached to the polar end of the substrate molecule, e.g., by esterification of 1-hexadecanol. Because of the approximate



Scheme 6

equivalence in length of sensitizer and alkane, the ketone chromophore was capable of overlapping target C-H bonds at mid and extended regions of the captive chain (21 in Scheme 6). Irradiation of the hexadecyl ester followed in sequence by dehydration, ozonolysis and hydrolysis resulted in a distribution of ketonic hexadecanols in which hydrogen was abstracted beyond C-10 (Table XI). In 1-dodecanol, (1),  $\omega$ -1 (C-11) abstraction was predominant whereas 1-tetradecanol (62) and 1-hexadecanol (63) provided  $\omega$ -2 (C-12 and C-14, respectively) predominance. Less selectivity was introduced owing to increased flexibility of longer chains in the alcohol moiety. 1-Octadecanol and 1-eicosanol oxidized in the range C-10 to C-16.

The above intramolecular orientations required molecular bonding of the sensitizer. If a special intermolecular interaction between substrate and reagent were to lower the transition state by a few kcal/mol, a preferential orientation permitting attack at a specific site would have a higher probability and favorable energy over other arrangements (63). Breslow chose the hydrogen bond dimerization of carboxylic acids as an example of the intermolecular association that would lead to the expectation of selective reactions among equivalently unactivated carbons (eq. 14). Backbending in alignment of the alkane chain with the chromophore would not require additional activation energy for scission of the covalent bond. Dimerization between benzophenone-4-carboxylic acid and 1-hexadecanol hemisuccinate represented the relevant interactive dimer 23. Equilibria among symmetric dimers from 20 and 22 are irrelevant as symmetric dimers disproportionate with eventual cross-dimerization to relevant species 24 consumed in the process. Overall yield of the keto-hexadecanol mixture was 24% with 94% of the ketone functionality distributed in the C-9 to C-15 range.



Since fats are ubiquitous in nature and originate in general metabolic processes by novel biosynthetic reactions, the enzymes responsible for these conversions could be effectively utilized for specific transformations. The enzyme approach is a fertile, unexplored area currently in need of study and development. Supported enzyme systems would thus provide efficient processes for the modification of fats.

Investigations in the past 15 years have revealed several interesting regiospecific oxidations of long chain aliphatic compounds in microorganisms, plants, and animals that support the optimism of a potential commercial role. Oxidations of alkanes and fatty acids have been observed at sites of interest to this review, namely the  $\omega$ ,  $\omega-1$ ,  $\omega-2$ , mid-chain at  $C_9$  and  $C_{10}$ , and  $\alpha$ -positions, and in desaturations at  $C_9,_{10}$  and  $\alpha$ ,  $\beta$ , or  $\gamma$ -positions in formation of  $\Delta^9$ ,  $\Delta^2$ , and  $\Delta^3$  acids. Some examples of these functionalizations are illustrated in Table XII. The biochemical approach affords opportunities to achieve desirable alterations in a long chain as is evident even from these few illustrations. A review of the biological production of fatty chemicals is presented elsewhere in our monograph by Wallen (75).

#### OVERVIEW

Halogenations have been the most accessible and simplest reactions to examine in regiospecific substitutions. It is therefore not surprising that the majority of the substitutions have been represented by halogenations, especially with small and moderate size aliphatic compounds. The latter compounds also serve as models for potential extensions to long chain fatty acids. The halogenations have firmly established the  $\omega-1$  position as the primary focus for substitution. Unfortunately, as the chains extend beyond 10 carbon atoms, methylene dilution statistically overrides positional selectivity, and rapid attenuation of the polar effect of the carboxyl group becomes inevitable at the increasing distance. However, appropriate solvents may add variety to these substitutions through formation of micelles of long chain compounds that may advantageously allow substitutions to occur at other regions of the molecule. The few other  $\omega-1$  reactions like oxidation and acetamidation extend the scope of the selectivity, but their present state of development with small chain compounds is exploratory and for long chain fatty acids nonexistent.

Some analytical difficulties have surfaced in this work, particularly in the determination of complex isomeric compositions of products from long chain fatty acids. It is desirable in these analyses to minimize chemical alterations of the

TABLE XII

## Regiospecific Biochemical Oxidations and Desaturations of Fatty Acids

Reaction	Compound	Product	Source	Ref.
$\omega$ -hydroxylation	decanoic	10-OH decanoic sebacic	rat liver	65
$\omega$ -1 hydroxylation	lauric	12-OH lauric	<i>Pseudomonas oleovorans</i>	66,67
	stearic	17-OH stearic	yeast	68,69
	oleic	17-OH oleic	yeast	68,69
$\omega$ -2 hydroxylation	palmitic	14-OH palmitic	<i>Bacillus megaterium</i>	70
$\omega$ -oxo+C <sub>9</sub> (10) hydroxylation	palmitic	16-oxo-9(10)- hydroxy palmitic	<i>Vicia faba</i> leaves	71
$\alpha$ -hydroxylation	palmitic	2-OH palmitic	higher plants	72,73
C <sub>2,3</sub> and C <sub>9,10</sub> desaturation	palmitic	$\Delta^2$ - and $\Delta^9$ - palmitoleic	rat liver	74

crude products. For example, oxidative degradation used in some work for determination of product distributions destroys unsuspected sensitive compounds like lactones that arise from halogenations in prolonged contact with strong acids.

In order to enhance  $\omega$ -1 selectivity in the long aliphatic chains, a means of anchoring the substrate for favorable orientation between a target carbon site and the reagent must be devised. Breslow's approach in his regiospecific photochemical oxidation of a long chain alcohol molecularly attached to the photosensitizer is an interesting example of this concept. Breslow's success is encouraging for extension of the intramolecular concept to include other chemical variations between substrates and reagents.

The terminal methyl group continues to be the most difficult site to substitute regiospecifically. However, the intermediation of organometallic compounds may have promise for entry at this position. This was suggested by two independent studies with organometallics. The nearly complete deuteration of the methyl terminus in saturated fatty acids by means of an organoplatinum compound suggests the possibility of methyl functionalization by other types of organometallics. The elegant contributions of Schwartz and his colleagues using organozirconium complexes for inducing migration of an internal double bond of olefinic hydrocarbons to the terminus provides many terminal derivatives by subsequent reaction with reagents. This approach may open up a new route through an unsaturated center, providing organometallic induced isomerizations are applicable to such functionally substituted alkanes as fatty acids.

The emphasis in this review has been on the biomimetic approach. While chemists will follow their own inclinations to regiospecific substitutions, the biochemists will undoubtedly chart the alternate course through enzymes *per se*. Both approaches are necessary in seeking new techniques and gaining invaluable insights in controlling and diverting chemical transformations. In this review the limited information on introducing substituents at selected or specific positions in long chain compounds brings into focus a challenging area of research on which to build a unique fatty acid chemistry.

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