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Specific and Selective Site Reactions of Alkanoate Derivatives. 2. Isomerization and Lactonization of Chloroalkanoic Acids in Strong Acid Media[1]

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(ω – 1)-Monochloro aliphatic acids (and positional isomers) react in a strong acid solvent to give a mixture of γ- and δ-lactones, methyl-branched aliphatic acids, and dimeric acid products. The initial reaction involves rapid and extensive halogen migration along the aliphatic chain with formation of a mixture of isomeric chloro acids. The final products depend on the chain length of the monochloro acids; i.e., lactones are predominantly formed from the 6-chloroheptanoic and 7-chlorooctanoic acids and their positional chloro isomers, whereas methyl-branched aliphatic acids and dimeric acids are the predominant end products from the larger chain chloro acids. These formerly unobserved products from chloro acids in strong acid media explain the poor (ω – 1) positional selectivity of long-chain fatty acids to haloamine halogenation in the intermolecular variation of the Hoffman–Loeffler–Freytag reaction.

Introduction

The intermolecular variation of the Hoffman–Loeffler–Freytag reaction (eq 1)—hereinafter conveniently referred to as IHLF—permits selective (ω – 1) positional halogenation of alkanoate derivatives.[3–8] The reaction was limited

$$CH_3(CH_2)_nCOX + R_2NCl \xrightarrow[Fe^{2+}\text{ or } h\nu]{H^+} CH_3CHCl(CH_2)_{n-1}COX + R_2NH \quad (1)$$

$$X = OH, OCH_3, NR_2$$

scope since (ω – 1) substitution is selective in carboxylate derivatives of intermediate chain length [C_6 (82%)–C_{10} (55%)], whereas selectivity is diminished in longer chain homologues [C_{12} (43%)–C_{18} (14%)].[9]

In our recent study of the parameter of the IHLF reaction[9] we found that the substrate concentration influenced the chloro isomer distribution and we noted that γ- and δ-lactones were formed as coproducts.[9] Other investigators have not previously observed the formation of lactones arising as products of fatty acid halogenation in the IHLF reaction. Although Deno and Pohl[10] observed the disappearance of isomeric chlorooctanoic acids by solvolysis in sulfuric acid, they did not determine the resultant products nor did they provide an understanding of the reaction course. We have therfore examined and report in this paper the details of the acid-catalyzed isomerization and lactonization of chloroalkanoic acids and esters that represent a new reaction of halogeno acids.

Results and Discussion

The series of heptanoic, octanoic, nonanoic, and decanoic acids and esters were chlorinated by the IHLF reaction as previously described.[9] The resultant chloro products were isolated by distillation. In each chlorinated fatty acid mixture, the positional monochloro isomers contained the range of C_5 to terminally substituted products, among which the (ω – 1)-chloro isomer predominated. The chloro isomers were subjected to 96% sulfuric acid (25–30 °C) at 0.5 and 1.0 M substrate concentrations, and the change in product distribution was periodically analyzed by capillary GLC.

Tables I and II record the results of the acid-catalyzed isomerization and lactonization of the chloroheptanoic and chlorooctanoic acids and methyl esters and methyl chloroundecanoate. Lactonization of chloroheptanoic and chlorooctanoic acids and esters in sulfuric acid proceeded more rapidly at 0.5 M than at 1.0 M. All of the chloro

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Table I. Isomerization and Lactonization of Chloroheptanoic and Chlorooctanoic Acids (Esters)[a] in Sulfuric Acid (96%): Effect of Substrate Concentration and Time on Product Distribution

substrate	concn, M	time, h	% chloro acid isomers 8-Cl	7-Cl	6-Cl	5-Cl	% lactones γ	δ
chloroheptanoic[b]		0		10	81	9		
	1.0	1		14 (10)	59 (57)	14 (16)	3 (3)	11 (13)
		2		14 (12)	40 (44)	14 (16)	5 (5)	27 (23)
		4		14 (12)	24 (32)	12 (15)	8 (8)	43 (34)
		6		16 (13)	24 (35)	12 (17)	10 (10)	38 (26)
	0.5	1		12 (11)	42 (41)	13 (14)	4 (5)	27 (27)
		2		12 (12)	23 (25)	10 (13)	7 (8)	46 (41)
		4		13 (14)	7 (7)	5 (7)	13 (14)	59 (56)
		6		14 (12)	2 (2)	3 (3)	17 (16)	62 (64)
chlorooctanoic[b]		0	6	73	16	5		
	1.0	1	10 (7)	38 (38)	20 (22)	7 (8)	7 (8)	19 (18)
		2	10 (8)	25 (23)	14 (14)	5 (6)	14 (15)	33 (34)
		4	10 (8)	10 (14)	6 (9)	3 (5)	25 (22)	47 (42)
		6	11 (9)	4 (11)	3 (7)	2 (4)	29 (28)	51 (39)
	0.5	1	9 (9)	23 (24)	13 (13)	5 (6)	14 (18)	35 (29)
		2	9 (9)	9 (15)	5 (9)	3 (4)	23 (23)	49 (39)
		4	8 (8)	2 (5)	(3)	(2)	34 (34)	56 (48)
		6	8 (6)	2			38 (44)	52 (50)

[a] Values in parentheses are percent chloro isomers derived from the methyl ester isomerizations. [b] No GLC evidence of dimer esters. Hydrocarbon products were <5% of isomerized samples.

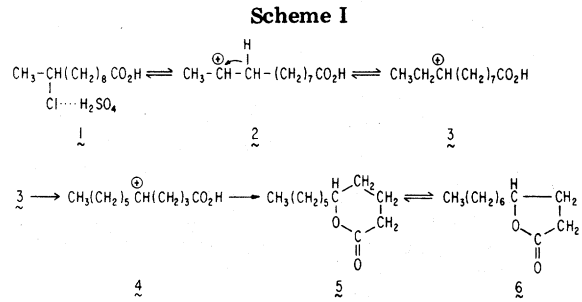
isomers rearranged with the exception of the more stable ω-chloro isomer, which remained unchanged. The chloroalkanoic acids and esters isomerized and lactonized at comparable rates. Chain length also influenced the rate and product distribution, i.e., chloroundecanoates (see below) isomerized faster than chlorooctanoates, which isomerized and cyclized to lactones faster and more completely than the chloroheptanoates. These rate effects were not further studied.

The chloro isomeric mixtures of nonanoic and decanoic acids reacted similarly to the shorter chain homologues over a 2-h period. However, these longer chain chloro acids produced substantial amounts of products having shorter GLC retention times than those of the lactones and chloroalkanoic acids. To acid identification of these short retention time products, we prepared methyl 10-chloroundecanoate as a model compound for isomerization. The chloro ester was prepared by our modification of a reported method.[11] Methyl 10-undecenoate was hydrochloroinated in concentrated HCl containing $FeCl_3$ as the catalyst which gave a mixture of methyl 10-chloroundecanoate (84%), methyl 9-chloroundecanoate (15%), and methyl 8-chloroundecanoate (1%).

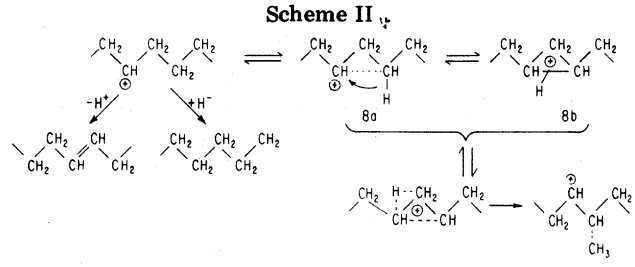
Isomerization of this predominantly (ω − 1)-chloro ester in 96% sulfuric acid was extremely rapid, so that within 1 min a C_5–C_{10} positional chloro isomeric mixture (Table II) was formed. With longer reaction times in the acid medium, subsequent reactions of lactonization, branching, and dimerization predominate. Our-hour contact in acid medium led to a mixture containing 50% short retention time products. These were identified by GLC–MS as methyl-branched methyl decanoate isomers with the methyl branch located at 6-, 7-, 8-, and 9-positions (Table III) and includes the presence of unsaturated esters. Dimeric products, though not identified by conditions used by our GLC, were also obtained and are described later.

In order to account for the products of isomerization and rearrangement we propose the carbenium ion mechanism in Schemes I (isomerization–lactonization), II (branching and desaturation), and III (unsaturation–dimerization) illustrated by 10-chloroundecanoic acid. The driving force for the reaction arises from the initial hydrogen bonding of sulfuric acid to the chlorine atom in structure 1. The

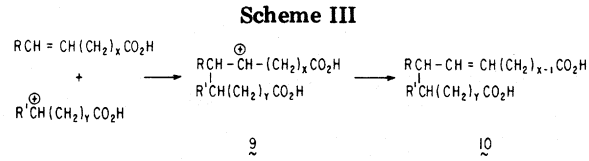
Scheme I



Scheme II



Scheme III



carbenium ion 2 (Scheme I) generated from substrate 1 by halogen abstraction migrates along the chain and terminates at C_5 (4) by carboxyl oxygen entrapment to give the δ-lactone 5. γ-Lactone 6 is derived from δ-lactone 5 in an equilibrium[12] that thermodynamically favors the former but which is kinetically slow at room temperature. This equilibrium accounts for the predominant formation of δ-lactone in room temperature reactions. The δ-lactone has also been observed in the sulfuric acid catalyzed treatment of unsaturated acids[13] as we have confirmed with 10-undecenoic acid, whereas γ-lactone was almost exclusively formed at elevated temperatures.[14,15] The scheme

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Table II. Isomerization and Lactonization of Methyl 10-Chloroundecanoate (1 M) in Sulfuric Acid (96%): Product Distribution in the Absence and Presence of Bromide Ion

time, min	% chloro isomer distribution[a]						% lactones	% branched-chain isomers[b]
	10	9	8	7	6	5		
0	84	15	1					
1	37	26	16	13	6	1		2
5	31	25	17	14	8	1		5
10	28	23	16	13	7	2	1	8
20	25	20	14	12	8	2	2	16
30	22	18	12	10	8	2	3	24
45	16	12	9	8	7	3	6	39
60[c]	9	7	5	5	6	3	11	49
			In the Presence of Br^-[d]					
20	15 (10)	10 (10)	8 (6)	9 (5)	9 (3)	2 (2)	3	6

[a] Percent bromo isomer in the mixture in parentheses. [b] Comprised of iso and ante isoundecanoates and 6- and 7-methyl decanoates, which were short retention time methyl esters in GLC (values uncorrected for detector response). See Table III for MS analysis. [c] Sample consisted of 90% of this distribution and about 10% diester. [d] Complete material balance for other products was not made.

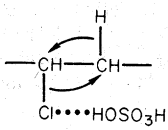
Table III. Methyl-Substituted Methyl Decanoates:[a] Mass Spectral Patterns of GLC Fractions

methyl site	m/e of ion forms					
	12	13	14	15	16	other
6	115	143	111	116	117	124[b]
7	129	157[c]	125	130	131	
8	143	171[d]	139	144	145	
9	157	185[e]	153	158	159	135[f]

[a] Mol wt = 200 amμ. [b] 6-Methyl substitution gives rise to an M − 76 peak (m/e 124). [c] Represents 7-methyl position. [d] Represents 8-methyl position. [e] m/e 185 is not observed. This would represent the fragment of a terminal CH_3 which is not a generally expected fragment in MS. [f] Methyl group at (ω − 1)-position generates an M − 65 peak (m/e 135).

is analogous to the lactonization mechanism of unsaturated (or hydroxy) acids,[14,15] indicating their relationship.

The positional chloro isomers arise in carbenium ion migration **2** → **3** by chloride entrapment in carbenium ion–halide ion pairs. Chloride anion is readily exchanged in the ion pair as evidenced by reaction of the methyl 10-chloroundecanoate in the presence of sodium bromide (Table II). Interchange between bromide and chloride ions produced all of the corresponding C_5–C_{10} positional chloro and bromo isomers. This precludes an alternative interchange mechanism (**7**) via simultaneous intramolecular hydride–chloride shifts that would give only chloro isomers.



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The methyl-branched chain isomers originate from chain rearrangements via carbenium ion migration. Four methyl-branched decanoates (6–9-positions) derived from methyl 10-chloroundecanoate are depicted to arise from carbenium ion **2** in a configuration of a cyclopropylium intermediate **8a**[15] (Scheme II) by a carbon bond shift. This rationale had been invoked by Showell and co-workers[15] to explain the branced-chain acids and branched-chain γ-lactones formed by their acid-catalyzed γ-lactonization of oleic acid. Additional support for this mechanism is derived from Kramer's[16] study of haloalkane isomerizations in strong acid solution. He proposed a protonated cyclopropane structure similar to **8b** in Scheme II to account for isoalkane formation. Scheme II depicts formation of saturated normal and branched acids by hydride addition[16,17] and for corresponding unsaturated acids by deprotonation.[15] Presence of these acids was evidenced by mass spectra. (The presence of unsaturated monobasic methyl esters whose formation is shown in Scheme II was suggested by mass spectra, but the compounds were not isolated and characterized.)

An ester mixture was isolated by column chromatography. Mass spectral analysis showed eight of 10 possible parent peaks having m/e 270 through m/e 368 with the peak to peak difference of M − 14. These peaks correspond to an homologous diester series differing sequentially by one CH_2 group. Formation of the diesters (**10**) is accounted for in the generalized Scheme III as arising by carbenium ion addition to the olefinic ester mixture. The carbenium ion addition stage is analogous to Showell's[15] or den Otter's[17,18] mechanism for the acid- or clay-catalyzed isomerization of oleic acid. The dimers in the isomeric series could arise by fragmentation of the carbenium ion species (loss of R^+ in **9**) followed by deprotonation to the olefinic diacid.

Complete positional isomerization of chloro acids resulting in all of the chloro acid isomers from (ω − 1) to C-5 inclusive is a previously unobserved phenomenon. Generally, halogen positional isomerization in aliphatic halides is confined to two to three carbons.[19] In view of the protonated halogen's facility to migrate rapidly and extensively along the chain and the statistical limitations imposed on (ω − 1) selectivity by the multiple-chain methylenes relative to the (ω − 1)-position, it is now evident that the intermolecular IHLF reaction is not applicable for highly selective (ω − 1) functionalization off long-chain fatty acids.

Conclusions

Halogen in halogeno aliphatic acids is readily displaced in a strong acid solvent to give mixtures of chloro isomeric acids, γ- and δ-lactones, methyl branched chain acids, and dimeric olefinic acid products. Halogen migration along

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the aliphatic chain is rapid (within 1 min) and extensive (at least six carbons distant), which would substantially account for diminishing ($\omega - 1$) selectivity in the IHLF reaction of long-chain fatty acids. Although Lewis-acid-induced isomerization of halogeno compounds is an established classical organic reaction, halogen migration in solvolytic displacement reactions at saturated carbon atoms[19] has generally been confined to three-carbon isomerizations. Our results therefore reveal the unexpected ability of halogen to migrate extensively along the chain in halogeno aliphatic acids[20] and to yield lactones in the moderate chain members. In the longer chain acids, nonhalogenated products are predominantly formed by ionic isomerization, rearrangement, and dimerization reactions.

Experimental Section

Materials. Heptanoic, octanoic, nonanoic, and decanoic acids and esters were chlorinated as previously described.[9] Each chloro acid (ester) mixture was distilled to give a product predominant in the ($\omega - 1$) isomer. Methyl 10-undecenoate was Eastman Organic Chemical White label.[21]

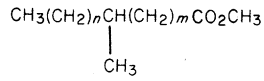
Preparation of Methyl 10-Chloroundecanoate. This compound was prepared by our modification of a reported procedure.[11] In the latter method, hydrogen chloride is added to 10-undecenoic acid at atmospheric pressure and room temperature for a reaction maintained for about 10 weeks. In our following modification, reaction at higher pressure and temperature reduced reaction time to 24 h.

Concentrated hydrochloric acid (100 mL) was added to methyl 10-undecenoate (100 mmol) and ferric chloride hexahydrate (2 mmol) in a 200-mL glass pressure flask equipped with a magnetic stirring bar. The sealed flask was maintained in a silicone oil bath at 60 °C for 24 h. The reaction mixture was poured over ice, extracted with methylene chloride, and dried over sodium sulfate, and the solvent was removed in vacuo. The partially hydrolyzed ester was reesterified in refluxing methanol containing *p*-toluenesulfonic acid catalyst. Vacuum distillation of the crude product gave methyl monochloroundecanoate (16 g, 70% yield) in the isomeric distribution of ($\omega - 1$)- (84%), ($\omega - 2$)- (15%), and ($\omega - 3$)- (1%) chloro substitution.

General Reaction Procedure. Reactions of monochloro aliphatic acids were readily carried out in an open beaker equipped with thermometer and magnetic stirrer. Monochloro acid or ester (5 mmol or 10 mmol) was added to 96% sulfuric acid (10 mL) and the mixture was stirred at room temperature (a slight exotherm was noted). At selected intervals, samples (1–2 mL) were quenched in iced water, extracted with methylene chloride, dried over sodium sulfate, and desolvated in vacuo. The sample was esterified (diazomethane) and analyzed by GLC.

Analytical Procedures. Product mixtures were analyzed on a Hewlett-Parkard HP 5830 gas chromatograph with 50-ft DEGS SCOT column. The monochloro isomers of the alkanoate methyl esters were completely resolved with peaks appearing in positional order from 5-chloro to ω-chloro isomer. The γ-and δ-lactones, which had longer retention times than the chloro isomers, were identified by comparison with authentic samples (courtesy of D. Schwartz). The branched-chain saturated methyl esters, which had lower retention times than the chlorinated alkanoate methyl esters, were identified by GLC–MS as methyl-substituted methyl decanoates with the methyl branch at the 6-, 7-, 8-, and 9-positions.

Methyl-branched methyl esters of long-chain saturated carboxylic acids of the general form



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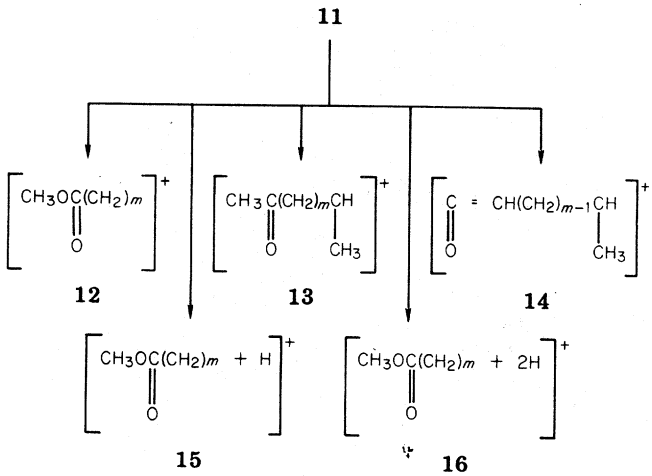
where $m + n = 7$ (mol wt = 200 amμ), fragment to the following mass spectral ion forms:



The presence of these peaks plus peaks normally arising from methyl esters (i.e., m/e 74, 87, M − 29, 31, 43) confirm the structure of the branched-chain monobasic acids. Table III lists the fragmentation pattern in support of the identification of the methyl-branched methyl decanoates substituted at the 6-, 7-, 8-, and 9-positions.

Acknowledgment. We express our gratitude to D. Schwartz for standard samples of γ- and δ-lactones and to E. Piotrowski for mass spectral analyses.

Registry No. 6-Chloroheptanoic acid, 34520-06-4; 7-chloro-octanoic acid, 53431-85-9; methyl 6–chloroheptanoate, 78898-18-7; methyl 7-chlorooctanoate, 67963-60-4; methyl 10-chloroundecanoate, 63318-23-0; methyl 6-methyldecanoate, 51771-68-7; methyl 7-methyldecanoate, 81740-33-2; methyl 8-methyldecanoate, 5129-64-6; methyl 9-methyldecanoate, 5129-55-5; methyl 10-undecenoate, 111-81-9.

(20) A reported halogeno lactonization by bromine addition to a Δ^4-unsaturated acid or ester (R. T. Arnold, M. M. Campos, and K. L. Lindsay, *J. Am. Chem. Soc.*, **75**, 1044 (1953)) is not comparable and does not involve isomerization.

(21) Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.