Specific and Selective Site Reactions in Alkanoate Derivatives. 1. Factors Affecting ω-1 Chlorinations by *N*-Chloroamines[1]

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Minisci et al.[3] reported the first *intermolecular* variation of the Hoffman–Loeffler–Freytag (HLF) reaction for chlorination of methyl esters of short-chain fatty acids (C_4–C_7) with *N*-chlorodialkylamines. Mainly monochlorinated esters were formed which were functionalized preferentially at the penultimate (ω-1) position[3] (72–92%). These results were interpreted on the basis of a charge repulsion between the amino cation radical generated in the presence of a catalyst and the protonated carboxylic acid group of the substrate as shown in eq 1.[4] Subsequent investigations have determined the kinetics of the reaction,[5] enlarged the scope of the substrates derivatized,[6] and examined the effect of medium acidity[4–6] and the steric structure of the *N*-chloroamines[7,8] on the reaction's selectivity. In view of the need in fatty acid chemistry for reactions that permit selective targeting of substituents in saturated chains, we have chosen the intermolecular HLF chlorinations for a systematic examination of its parameters and a determination of its utility when applied to longer chain fatty acids.

Table I. Variation of Substrate Chain Length

substrate[a]	% convrsn[b]	% selectivity for end positions		
		ω	ω-1	ω-2
hexanoate	98	15	82	3
octanoate	90	7	73	15
decanoate	80	4	55	20
dodecanoate	70	3	43	16
tetradecanoate	65	3	27	11
hexadecanoate	55	2	20	8
octadecanoate	40	1	14	5

[a] Methyl esters, 2 M in H_2SO_4 (97%), 1:1 amine/ester, 10% Fe^{2+}. [b] Determined by GLC.

$$CH_3CH_2(CH_2)_xC(=\overset{+}{O}H)OR' + R_2\overset{+}{N}H\cdot \rightarrow CH_3\dot{C}H(CH_2)_xC(=\overset{+}{O}H)OR' + R_2\overset{+}{N}H_2 \quad (1)$$

Results and Discussion

We chose methyl decanoate as the model chain for study since ω-1 selectivity was appreciable for this chain length and all of the isomeric chloro products were fully resolvable by capillary GLC. In some instances, other acids, amides, and esters were employed to derive additional details. The factors evaluated were the medium acidity,[9] the ratio of *N*-haloamine to substrate,[9] the initiator concentration,[9] the substrate concentration,[10] the functionality of the substrate,[10] chain length, and *N*-chloroamine structure.

Our results on the first three factors above generally agree with those of previous investigators.[9] However, the substrate concentration, a factor not examined by others, is a crucial parameter, since we found that it affects conversion,[10] selectivity,[10] and the nature of the product. In fact, the nature of the product is altered at low substrate concentrations; for example, in the chlorination of methyl octanoate (1 M), the resultant chloro products isomerize by migration of chlorine, leading to subsequent formation of γ- and δ-lactones. These lactones have not previously

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(3) F. Minisci, R. Galli, A. Galli, and R. Bernardi, *Tetrahedron Lett.*, 2207 (1967).
(4) F. Minisci, *Synthesis*, 1 (1973).
(5) J. Spanswick and K. V. Ingold, *Can. J. Chem.*, **48**, 5461 (1970).
(6) N. C. Deno, W. E. Billups, R. Fishbein, C. Pierson, R. Whalen, and J. C. Wyckoff, *J. Am. Chem. Soc.*, **93**, 438 (1971).
(7) R. Bernardi, R. Galli, and F. Minisci, *J. Chem. Soc. B*, 324 (1968).
(8) N. C. Deno, R. Fishbein, and J. Wyckoff, *J. Am. Chem. Soc.*, **93**, 2065 (1971).
(9) Data for medium acidity, ratio of *N*-haloamines to substrate, and initiator concentration are available as supplementary material in Table III.
(10) Data for the substrate concentrations and end-group functionalities are available as supplementary material in Table IV.

Table II. Structural Variations of Substrate and Chlorinating Agent

substrate	N-Cl reagent	% convrsn	% isomer distribn 2-Cl	3-Cl	4-Cl	5-Cl	6-Cl	7-Cl	8-Cl	9-Cl	10-Cl	11-Cl	12-Cl
methyl nonanoate	NCDA[a]	42[b]			tr	3	10	20	62	5			
nonanoamide	NCDA[a]	40[b]			2	3	9	21	58	6			
$C_8H_{17}CON(CH_3)CH_2CH_2OH$	NCDA[a]	41[b]				2	9	19	63	5			
$C_8H_{17}CON(CH_2CH_2OH)_2$	NCDA[a]	91				2	10	20	63	5			
$C_8H_{17}CONH(CH_2CH_2OCH_2CH_2OH)$	NCDA[a]	91				2	10	20	62	5			
$C_{11}H_{23}CON(CH_2CH_2OCH_2CH_3)_2$	NCDA[a]	88				1	6	8	14	15	15	39	2
methyl dodecanoate	$ClN(CH_2CH_2OCH_2CH_3)_2$	24		2	5	7	9	11	12	13	16	17	9
methyl decanoate	4-$N(CH_3)$Cl-3,5-Cl_2-1-$COCH_3C_6H_2$	20[b]			4	6	10	21	30	22	6		
	$CH_3CON(CH_3)Cl$	8[b]	3	6	10	12	12	13	15	17	11		
	NCTs[c]	35			2	6	13	18	23	36	2		
	TCIA[d]	35		3	9	13	14	13	15	19	14		
	TCM[e]	11		2	10	14	15	15	16	16	12		
	TSCA[f]	24	3	3	7	11	12	14	16	22	12		

[a] N-Chlorodiisopropylamine. [b] Ratio of substrate to chlorinating agent is 2:1. [c] N-Chloro-N-methyl-p-toluenesulfonamide. [d] Trichloroisocyanuric acid. [e] Trichloromelamine. [f] Bis(trimethylsilyl)chloroamine.[14,16]

been reported as products of the intermolecular HLF reaction. This isomerization is currently under further investigation.

The influence of end-group functionality (acid, ester, or amide) on selectivity was also determined.[10] We observed no important differences in conversion (70–80%) or ω-1 selectivity (55%) between decanoic acid, decanoamide, and methyl decanoate. These results were unexpected on the basis of previously published data by Deno,[6] who observed a 50% decrease in ω-1 substitutions for octanoamide compared to ω-1 substitutions for octanoic acid. Complete experimental details regarding substrate concentration were not given by Deno;[6] therefore an exact comparison with our results cannot be made.

The first five factors from our data[9,10] thus provided the optimum set of conditions (97% H_2SO_4, 2 M substrate concentration, 1:1 ester to amine ratio, 10 mol % of ferrous sulfate) for determining the effect of substrate chain length on selectivity and conversion. Most investigators have found that the chain length of the substrate is one determinant that influences site selectivity.[4,11] In fact, Deno[12] finds no substitution at the ω-1 position beyond the C_{12} chain length. His results, however, were derived by a multistep degradation of chloro products followed by GLC analysis of methyl esters of the resultant fragments. Such degradative methods of analysis destroy unsuspected coproducts, like the lactones, thus preventing their detection. We, therefore, used capillary GLC to obtain direct analysis of the chloro product mixture to examine the even-membered homologous series of methyl esters from hexanoate to octadecanoate. All of the isomeric products were resolvable up to and including the C_{12} chain; for longer chain lengths up to and including C_{18}, the ω, ω-1, ω-2, and ω-3 isomers were resolved from the mid-chain isomers. Using the optimum conditions established for ω-1 chlorinations, we found substitution at the ω-1 position for all the homologues, although the ω-1 selectivity decreased in a steady manner from 82% (C_6) to 14% (C_{18}) (Table I).

Some investigators have suggested that modification of the substrate and of the N-chloroamine to increase steric bulk[13] and electrostatic repulsion[14] may cause enhanced ω-1 selectivity. To study these effects, we first extended the reaction to mono- and diethanolamide derivatives of nonanoic acid, which were expected to develop a greater electronic field and steric bulk at the carboxylate group. No difference in ω-1 selectivity between the simple methyl ester and the highly substituted amides was found (Table II). We next attempted to increase both the steric bulk and electronic charge on the aminium radical by using a variety of N-chloro compounds in reactions with methyl decanoate. In all cases, not only was the specificity for ω-1 substitution lessened but the product mixture approached a random distribution, and conversion to chloro products was low (Table II). Presumably, the introduction of large functional groups into the N-chloroamine either inhibited the formation of the radical cation intermediate or introduced excessive steric repulsions leading to free-radical chlorination.

Conclusions

From the above discussion it is seen that the only parameters which affect ω-1 selectivity in the intermolecular HLF reactions are the acidity of the medium, the substrate concentration, and the substrate chain length. Optimum reaction conditions were established to demonstrate ω-1 substitution in long-chain fatty acids and esters, although selectivity decreased in the series from 82% (C_6) to 14% (C_{18}). Therefore, on the basis of chlorination as a model reaction, the chemical solution method would appear to have little value for specific ω-1 derivatizations of saturated substrates beyond the C_{10} chain length.

Experimental Section

Materials. Commercially available fatty acids and esters were used without purification. Concentrated sulfuric acid and ferrous sulfate were Baker[15] analyzed reagents. N-Chlorodiisopropylamine was prepared from N-chlorosuccinimide and diisopropylamine in ether at 25 °C as previously described.[6,7] Bis(trimethyl-

(11) N. C. Deno, *Methods Free-Radical Chem.*, **3**, Chapter 3 (1972).
(12) N. C. Deno and E. Jedziniak, *Tetrahedron Lett.*, 1259 (1976).
(13) F. Minisci, R. Galli, M. Perchinunno, and R. Bernardi, *Chim. Ind. (Milan)*, **50**, 453 (1968).

(14) A recent article by Roberts and Wilson (*J. Chem. Soc., Chem. Commun.*, 752 (1978)) suggested that bis(trimethylsilyl)haloamines would be more effective than dialkylhalogenoamines in the HLF reaction because of the increase in electrophilicity and reactivity of the aminyl radicals. We investigated the N-chloro derivative in this reaction and observed only random chlorination (Table II).

(15) 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.

silyl)chloroamine was prepared by the method of Wiberg and Raschig.[16]

Analytical Procedures. Conversions of carboxylic esters to their chloro derivatives were determined by GLC analysis on an HP 5830 gas chromatograph with SCOT columns (50 ft Carbowax or 50 ft DEGS). Complete separation of isomers was accomplished for the chloro esters up to dodecanoate and appeared in order from the 5 to the 12 isomer. For longer chain lengths (C_{14}–C_{18}), ω, ω-1, ω-2, and ω-3 isomers were completely separated from the mid-chain isomers.

Chlorinations. In a three-necked flask equipped with a thermometer and a mechanical stirrer and containing concentrated sulfuric acid (10 mL) was added the methyl ester (20 mmol) while the temperature was maintained below 5 °C via an ice–alcohol bath. The *N*-chlorodiisopropylamine (22 mmol) was then carefully added dropwise. The ferrous sulfate heptahydrate (2 mmol) was added, and the mixture was vigorously stirred. The ice bath was removed and the temperature rose to 34 °C within 2–5 min. After being stirred for 1 h, the mixture was poured over ice and extracted three times with methylene chloride (75 mL). The combined extracts were washed with water and dried over sodium sulfate, and the solvent was removed via a rotary evaporator at ambient temperature. Any free carboxylic acid present was esterified by diazomethane, and the crude product was analyzed by GLC. When amides were used as substrates, they were hydrolyzed and reesterified by refluxing with HCl/MeOH for 18 h.

Registry No. Methyl hexanoate, 106-70-7; methyl octanoate, 111-11-5; methyl decanoate, 110-42-9; methyl dodecanoate, 111-82-0; methyl tetradecanoate, 124-10-7; methyl hexadecanoate, 112-39-0; methyl octadecanoate, 112-61-8; methyl 6-chlorohexanoate, 14273-89-3; methyl 5-chlorohexanoate, 35783-67-6; methyl 4-chlorohexanoate, 71194-26-8; methyl 8-chlorooctanoate, 16195-75-8; methyl 7-chlorooctanoate, 67963-60-4; methyl 6-chlorooctanoate, 67963-59-1; methyl 10-chlorodecanoate, 71194-27-9; methyl 9-chlorodecanoate, 71194-28-0; methyl 8-chlorodecanoate, 71194-29-1; methyl 12-chlorododecanoate, 71194-30-4; methyl 11-chlorododecanoate, 71194-31-5; methyl 10-chlorododecanoate, 71194-32-6; methyl 14-chlorotetradecanoate, 71194-33-7; methyl 13-chlorotetradecanoate, 71194-34-8; methyl 12-chlorotetradecanoate, 71194-35-9; methyl 16-chlorohexadecanoate, 71194-36-0; methyl 15-chlorohexadecanoate, 71194-37-1; methyl 14-chlorohexadecanoate, 71194-38-2; methyl 18-chlorooctadecanoate, 71194-39-3; methyl 17-chlorooctadecanoate, 71194-40-6; methyl 16-chlorooctadecanoate, 71215-21-9; methyl nonanoate, 1731-84-6; nonanoamide, 1120-07-6; *N*-hydroxyethyl-*N*-methylnonanamide, 35627-81-7; *N,N*-bis(hydroxyethyl)nonanamide, 3077-37-0; *N*-[2-(2-hydroxyethoxy)ethyl]nonanamide, 32368-60-8; *N,N*-bis(2-ethoxyethyl)dodecanamide, 71194-41-7; NCDA, 24948-81-0; *N*-chloro-2-ethoxy-*N*-(2-ethoxyethyl)ethanamine, 71194-42-8; methyl 4-(chloromethylamino)-3,5-dichlorobenzoate, 71194-43-9; *N*-chloro-*N*-methylacetamide, 5014-39-1; NCTs, 2350-10-9; TCIA, 87-90-1; TCM, 7673-09-8; TSCA, 4148-01-0; methyl 5-chlorononanoate, 71194-44-0; methyl 6-chlorononanoate, 71194-45-1; methyl 7-chlorononanoate, 71194-46-2; methyl 8-chlorononanoate, 63318-22-9; methyl 9-chlorononanoate, 22457-33-6; 4-chlorononanamide, 71194-47-3; 5-chlorononanamide, 71194-48-4; 6-chlorononanamide, 71194-49-5; 7-chlorononanamide, 71194-50-8; 8-chlorononanamide, 71194-51-9; 9-chlorononanamide, 71194-52-0; 5-chloro-*N*-(2-hydroxyethyl)-*N*-methylnonanamide, 71194-53-1; 6-chloro-*N*-(2-hydroxyethyl)-*N*-methylnonanamide, 71194-54-2; 7-chloro-*N*-(2-hydroxyethyl)-*N*-methylnonanamide, 71194-55-3; 8-chloro-*N*-(2-hydroxyethyl)-*N*-methylnonanamide, 71194-56-4; 9-chloro-*N*-(2-hydroxyethyl)-*N*-methylnonanamide, 71194-57-5; 5-chloro-*N,N*-bis(2-hydroxyethyl)nonanamide, 71194-58-6; 6-chloro-*N,N*-bis(2-hydroxyethyl)nonanamide, 71194-59-7; 7-chloro-*N,N*-bis(2-hydroxyethyl)nonanamide, 71194-60-0; 8-chloro-*N,N*-bis(2-hydroxyethyl)-nonanamide, 71194-61-1; 9-chloro-*N,N*-bis(2-hydroxyethyl)nonanamide, 71194-62-2; 5-chloro-*N*-[2-(2-hydroxyethoxy)ethyl]nonanamide, 71194-63-3; 6-chloro-*N*-[2-(2-hydroxyethoxy)ethyl]nonanamide, 71194-64-4; 7-chloro-*N*-[2-(2-hydroxyethoxy)ethyl]nonanamide, 71194-65-5; 8-chloro-*N*-[2-(2-hydroxyethoxy)ethyl]nonanamide, 71194-66-6; 9-chloro-*N*-[2-(2-hydroxyethoxy)ethyl]nonanamide, 71194-67-7; 5-chloro-*N,N*-bis(2-ethoxyethyl)dodecanamide, 71194-68-8; 6-chloro-*N,N*-bis(2-ethoxyethyl)dodecanamide, 71194-69-9; 7-chloro-*N,N*-bis(2-ethoxyethyl)dodecanamide, 71194-70-2; 8-chloro-*N,N*-bis(2-ethoxyethyl)dodecanamide, 71194-71-3; 9-chloro-*N,N*-bis(2-ethoxyethyl)dodecanamide, 71194-72-4; 10-chloro-*N,N*-bis(2-ethoxyethyl)dodecanamide, 71194-73-5; 11-chloro-*N,N*-bis(2-ethoxyethyl)dodecanamide, 71194-74-6; 12-chloro-*N,N*-bis(2-ethoxyethyl)dodecanamide, 71194-75-7; methyl 3-chlorododecanoate, 71194-76-8; methyl 4-chlorododecanoate, 71194-77-9; methyl 5-chlorododecanoate, 71194-78-0; methyl 6-chlorododecanoate, 71194-79-1; methyl 7-chlorododecanoate, 71194-80-4; methyl 8-chlorododecanoate, 71194-81-5; methyl 9-chlorododecanoate, 71194-82-6; methyl 4-chlorodecanoate, 71194-83-7; methyl 5-chlorodecanoate, 71194-84-8; methyl 6-chlorodecanoate, 71194-85-9; methyl 7-chlorodecanoate, 71194-86-0; methyl 2-chlorodecanoate, 20589-84-8; methyl 3-chlorodecanoate, 71194-87-1; methyl 5-chlorooctanoate, 67963-58-0; decanoic acid, 334-48-5; 5-chlorodecanoic acid, 71194-88-2; 6-chlorodecanoic acid, 71194-89-3; 7-chlorodecanoic acid, 71194-90-6; 8-chlorodecanoic acid, 71194-91-7; 9-chlorodecanoic acid, 71194-92-8; 10-chlorodecanoic acid, 37027-56-8; decanoamide, 2319-29-1; 5-chlorodecanoamide, 71194-93-9; 6-chlorodecanoamide, 71215-22-0; 7-chlorodecanoamide, 71194-94-0; 8-chlorodecanoamide, 71194-95-1; 9-chlorodecanoamide, 71194-96-2; 10-chlorodecanoamide, 71194-97-3.

(16) N. Wiberg and F. Raschig, *J. Organomet. Chem.*, **10**, 15 (1967).

Supplementary Material Available: Table III (variables on chlorination of methyl decanoate) and Table IV (variation of substrates and molar concentration) (2 pages). Ordering information is given on any current masthead page.