Radical Chlorinations of Triglycerides

Philip E. Sonnet* and Stanley Osman
USDA, ARS, ERRC, Philadelphia, Pennsylvania 19118

ABSTRACT: Several triglycerides were synthesized with an iodoaroyl group. Intramolecular radical chain transfer chlorinations were conducted that resulted in the associated pair of fatty acids of the triglyceride becoming chlorinated. The distribution of monochlorinated species was similar to that obtained by direct radical chlorination of the relevant fatty acid methyl esters. Functionalization was, as expected, away from the carboxylate group but gave no indication that either alignment of chains or the constraints of an intramolecular process could limit the manifold of products of the reaction. To gauge the effect on halogenation of a structure, bearing more than one electron-withdrawing group, methyl oleate was converted to the *bis* trifluoroacetate of methyl 9,10-dihydroxystearate. No products of chlorination on carbons 2–8 were observed.
JAOCS 72, 369–374 (1995)

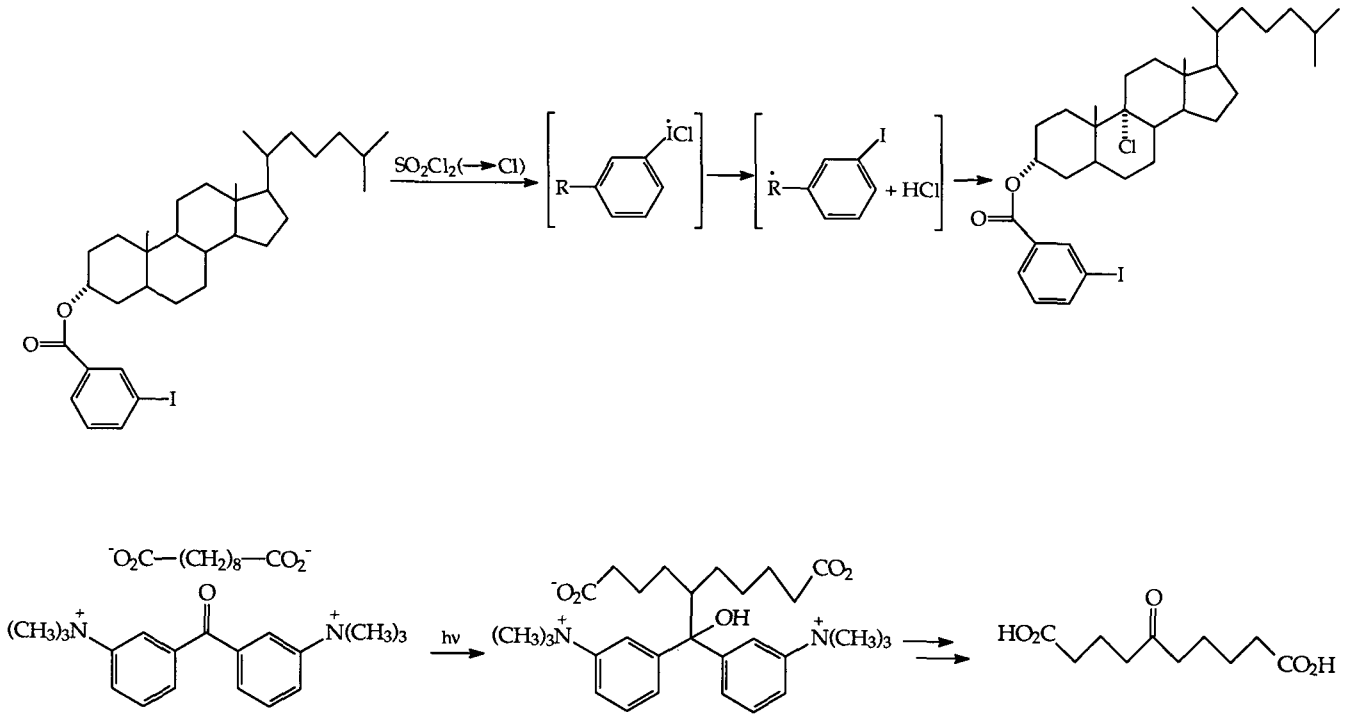
KEY WORDS: Biomimicry, functionalization, radical, triglyceride.

New uses for fatty acids that occur in domestic fats and oils are continuously being sought (1). Ability to transform these compounds, or the natural triglyceride mixtures, to other compounds can create a new reservoir of materials whose properties have not yet been evaluated. We report an initial investigation of selected reactions that were explored for their potential to produce directed chlorinations of fatty acids. The chemistry was selected more for an evaluation of models for functionalization than for immediate utility of the halogenated products, although dehydrohalogenation to olefinic acids and possible subsequent synthetics may indeed be useful. Radicals for chlorination reactions can be generated without ultraviolet light, and the radicals can be complexed to reduce their reactivity and possibly improve selectivity. The triglycerides employed were made from medium-chainlength acids to facilitate analysis of the chlorinated products by gas–liquid chromatography; extension of these results to longer-chain acids would be apparent.

The idea of directing functionalization of a saturated hydrocarbon chain as an act of biomimicry has a long history. The research has led to a greater understanding of mobility in ordered systems (2) but has achieved synthetic success in only specific cases. Generally, radical reactions have been examined because reactions involving C-H bond homolysis in an aliphatic chain are more readily available and amenable to control than are reactions that proceed *via* carbonium ions or carbanions. However, because C-H bonds in chains are of essentially equal energy, a basis for differentiation must be established.

Inducing selectivity in radical reactions of chain compounds has been accomplished historically in one of two ways. If the radical that abstracts a hydrogen atom to generate a carbon radical is electrophilic in nature, then abstraction tends to occur away from an electron-deficient site. Radical chlorinations of fatty acids, esters, and amides, for example, can be accomplished so as to favor the (ω1) position by conducting the reactions in strongly acidic media (3,4). By employing alumina as an adsorbent prior to chlorination, fatty acid carboxyl groups were associated with the support and (ω1) halogenation was favored on steric grounds (5). Alternatively, the abstraction could be caused to occur intramolecularly, and, by using an unreactive and rigid "spacer," functionalize carbons remote from the radical site (2) (Scheme 1). By using such models, Breslow *et al.'s* pioneering research has developed fundamental ideas relevant to aspects of biomimicry (6). A structural feature that can become a free radical was attached to an organic compound by means of a spacer. The initial radical, therefore, was constrained to reacting with a limited number of hydrogen atoms on that organic compound. This idea was quite successful in specifically functionalizing a rigid steroid framework. In complementary work, formally charged groups were employed to limit the mobility of compounds (Scheme 1). Photolysis of salts of benzophenone diammonium salts of dicarboxylic acids produced, after chemical workup, diacids that were principally oxidized in the middle of the chain. Limited flexibility was the basis for the observed selectivity in each of these models. When the target substrate was allowed to retain much of its flexibility, however, reaction occurred at a number of positions. Although the manifold of products often showed a skewed distribution (6,7), use of these schemes for general organic synthesis did not seem likely. Nevertheless, Breslow's ideas could find use in the chemistry of fats and oils be-

*To whom correspondence should be addressed at USDA, ARS, ERRC, 600 East Mermaid Lane, Philadelphia, PA 19118.



SCHEME 1

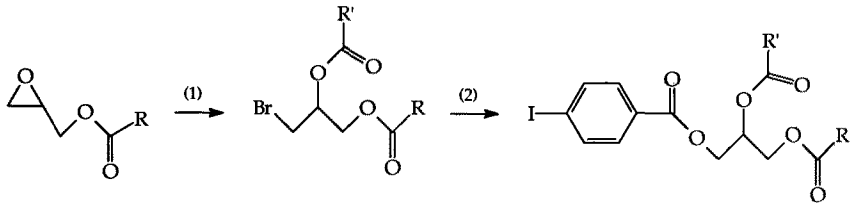
cause the industries that employ these and related materials as feedstock are accustomed to dealing with mixtures.

We report here the preparation of triglycerides in which one of the acid residues is an iodoaryl carboxylic acid that can function to capture a chlorine atom and, as employed in Breslow's work, can abstract a hydrogen atom from one of the two other acid residues to react as part of a radical chain-transfer chlorination (2) (Scheme 2). The iodoaryl acid could potentially be recycled as a partial glyceride by removing the functionalized aliphatic acids lipolytically. We wished to determine whether in this arrangement, and in nonpolar solvents, intramolecular chlorination would lead to a distribution of monochlorinated compounds significantly different from that of direct chlorination of the fatty acid methyl esters themselves. The source of the chlorine atoms that would associate with the iodine was chlorine or sulfuryl chloride. A chlorine adduct was formed from the iodoaroyl triglycerides (i.e., $ArICl_2$) that homolyzed to produce the same initiating radical, ArICl• (6). Initiations of these reactions were either thermal, with benzoyl peroxide as catalyst, or photolytic.

EXPERIMENTAL PROCEDURES

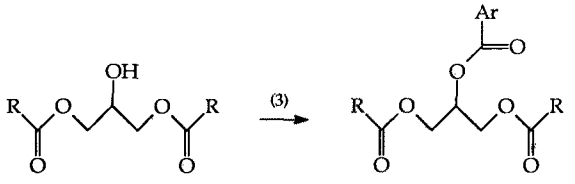
^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained with a Joel JNM-GX 400 FTNMR spectrometer (JEOL, Peabody, MA), deuteriochloroform as the solvent, and tetramethylsilane as the internal standard. Infrared (IR) spectra were obtained on a Perkin-Elmer Model 1310 spectrophotometer (Norwalk, CT) by using 3% solutions in carbon tetrachloride (chlorinated solvents, such as deuteriochloroform and carbon tetrachloride, are potential carcinogens and must be handled with care). Gas–liquid chromatography (GLC) was performed with a Chrompack-Packard Model 438A chromatograph (Whittier, CA) with flame-ionization detection and a Supelcowax column (30 m × 0.25 mm i.d.) (Bellefonte, PA) and operating with helium carrier gas 18 cm/s and a 50:1 split ratio. Thin-layer chromatography (TLC) was accomplished with silica gel plates from Applied Science Labs (Deerfield, IL), with various ratios of ethyl acetate (EA) to hexane (H), and iodine vapor to visualize products. Mass spectrometry was performed on a Hewlett-Packard 59827A mass spectrometer (Sterling, VA) interfaced with a Hewlett-Packard 5890 Series II gas chromatograph. Spectra were obtained in both the electron impact and chemical ionization modes with ammonia as the reagent gas. Reagents were purchased from Aldrich Chemical Company Inc. (Milwaukee, WI) and used directly; solvents were reagent-grade or better and were dried as follows: Tetrahydrofuran (THF) was distilled from lithium aluminum hydride, and benzene and hexamethylphosphoric triamide (HMPT) were dried over 4Å molecular sieves. Photolyses were conducted with a microphotochemical reaction assembly that employed a pen ray lamp (principal emissions at 185 and 254 nm) purchased from Aldrich Chemical Co. and a quartz immersion well with water cooling (15–20°C).

Methyl esters of specific chloroalkanoic acids were prepared by standard methods as follows: 2-Chlorooctanoic and 2-chlorodecanoic acids were prepared by treating the methyl esters of the acids with lithium diisopropylamide and CCl_4 (8). Condensation of methyl chloroacetate and hexanal in the



1 2 3

	R	R'
a	C_7H_{15}	C_9H_{19}
b	C_9H_{19}	C_7H_{15}



4 5

a R = C_7H_{15}
b R = C_9H_{19}

	R	Ar
a	C_7H_{15}	C_6H_4I
b	C_9H_{19}	C_6H_4I
c	C_7H_{15}	C_6H_4—C_6H_4I
d	C_9H_{19}	C_6H_4—C_6H_4I

SCHEME 2

presence of zinc (9) in a sonic bath (10) gave the methyl ester 3-hydroxyoctanoic acid, which was then converted to the 3-chloro derivative with triphenylphosphine dichloride (11). The ω-chloroalkanoic acids were obtained from the ω-chloroalkanols (12) by oxidation with CrO_3-acetone, Jones' reagent (13), and then esterified with BF_3 • methanol. 4-Phenylbenzoic acid was iodinated with iodine and KIO_3 to give 4-(4′-iodophenyl)benzoic acid (14), which was then esterified with BF_3 • methanol. Methyl 2-octenoate was available from an earlier work (15).

Synthesis of triglycerides, **3a,b**. Glycidyl ester **1a,b** (Scheme 2) (20 mmol) was allowed to react overnight with the appropriate acid anhydride (20.4 mmol) and LiBr (5.2 g, 60 mmol) in 60 mL of dry benzene at ambient temperature. The reaction mixture was diluted with 100 mL of ether and suction-filtered through Celite. The filtrate was washed with H_2O, dried ($MgSO_4$), and concentrated to give crude **2a,b**: IR; 1745 cm^{-1}, ^1H NMR; 5.20 (1H, *m*, HCO), 4.28 (2H, *m*, H_2CO), 3.50 (2H, *m*, H_2CBr), 2.33 (4H, *m*, $CH_2C{=}O$), 1.60 (4H, *bs*, $C\underline{H}_2CH_2C{=}O$), 1.26 (*ca.* 20H, CH_2 env.), 0.87 (6H, *t*, CH_3), ppm; ^{13}C NMR diag. signals; 173.7, 173.2, 70.4, 63.4 ppm; LCMS(CI/NH_3) *m/e* 452 and 454 $(M + NH_4)^+$; TLC (15% EA–H) R_f = 0.48–0.50. The cesium salt of 4-iodobenzoic acid (2.28 g, 6.0 mmol) and **2a,b** (2.17 g, 5.0 mmol) were stirred overnight at 55–60°C under nitrogen in 10 mL of dry 1:1 THF and HMPT. The mixture was diluted with H_2O and extracted with ether. The organic phase was dried and concentrated to give an oil that was purified by flash chromatography with 7.5% EA–H (16). Compounds **3a,b** were obtained: 2.88 g, 96% yield; IR: 1725, 1740 cm^{-1}; ^{13}C NMR diagnostic signals; 173.7, 173.3, 166.0, 138.3, 131.5, 129.5, 101.6 (aryl $\underline{C}$-I), 69.2, 63.6, 62.6 ppm; LCMS ($M + NH_3$) *m/e* 620 $(M + NH_4)^+$; TLC (15% EA–H) R_f = 0.42–0.45.

Synthesis of triglycerides **5a–d**. The 1,3-diglycerides **4a,b** were prepared essentially as described by Jensen and Pitas (17), namely by acylation of solketal followed by boric acid hydrolysis of the acetonide group to give a 1-monoglyceride. This was then esterified, and the product was recrystallized from cold hexane until homogeneous (TLC: R_f = 0.21 with 15% EA–H). The 1,3-diglyceride (15 mmol) was esterified with the iodoaryl acid chloride (20 mmol that had been prepared by heating in $SOCl_2$ under reflux for 5 h) and pyridine (1.7 mL, 21 mmol) in 50 mL of $CHCl_3$ at ambient temperature for 2–3 d. The product was obtained in the usual fashion and purified by flash chromatography with 7% EA–H and produced 60–65% of **5a–d**: IR, 1730, 1745 cm^{-1}; ^{13}C NMR diagnostic signals, 173.2, 165.3, 145.3, 139.8, 138.1, 130.4, 129.5, 127.3, 94.2 (aryl $\underline{C}$-I), 70.4, 62.6 ppm; LCMS(CI/NH_3) *m/e* 648 $(M + NH_4)^+$ for **5a,b**, 724 $(M + NH_4)^+$ for **5c,d**; and TLC (15% ethyl acetate-hexane) R_f = 0.42–0.45.

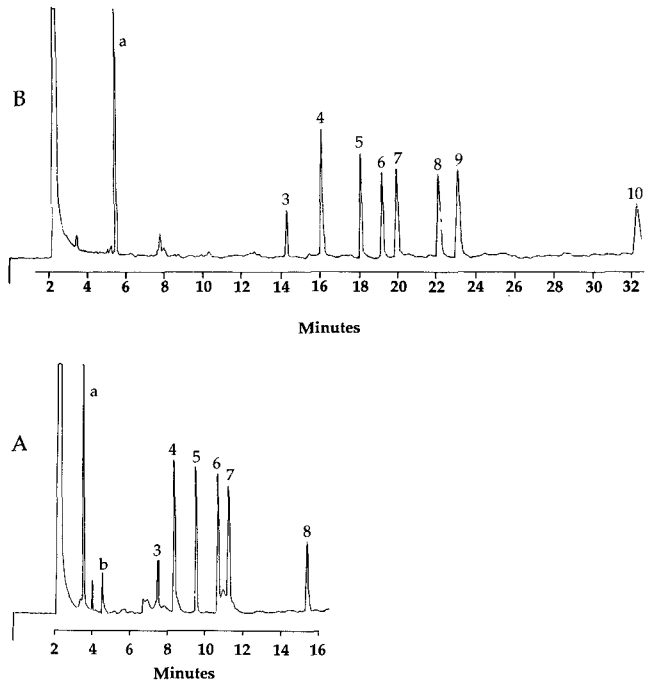


FIG. 1. Gas–liquid chromatography: Supelcowax (30 m × 0.25 mm i.d.; Supelco, Bellefonte, PA) at 140°C; baseline is in minutes. (A) Gas chromatograph of thermal radical chlorination of methyl octanoate with a = methyl octanoate, b = methyl 2-octenoate, and numbers indicate the position isomer of the monochlorinated products. (B) Gas chromatograph of chlorination products from methyl decanoate, and a = methyl decanoate.

Radical chlorinations and analysis. Thermal reactions were conducted by heating the substrate (0.01–0.04 M) in CCl_4 under reflux for 24–48 h with one or more equiv. of SO_2Cl_2 and 10 mol% of benzoyl peroxide. Reaction mixtures were worked up by removing the solvent and transesterifying in methanol with a trace of NaOMe (1 h, ambient temperature). The resulting methyl esters were analyzed by GLC. All of the monochlorinated methyl esters of octanoic and decanoic acids were separated (Fig. 1). Product distribution was assessed by using uncorrected peak areas. The tabulated values are ±2%. Photochemical reaction mixtures were 10-mL volumes of solution (benzene, CCl_4, or acetic acid) with substrate concentrations of 0.001–0.002 M and one or more equiv. of SO_2Cl_2. Photolysis times were 0.25–0.5 h, and reaction products were characterized as described above. Chlorine adducts were prepared by passing Cl_2 through concentrated H_2SO_4 into a $CHCl_3$ solution of the substrate at –20°C for 0.25 h. The yellow solution was concentrated at 30°C and transferred to the microphotochemical glassware. Photolyses were then conducted as already described, but without SO_2Cl_2.

The following control experiments were conducted with a mixture of the methyl monochlorooctanoates: NaOMe–methanol (ambient temperature, 1 h), slight loss of 3-Cl to form 2-octenoate; same mixture heated to reflux (1.5 h), 3-Cl gone and 2-octenoate increased, but there were no other changes in product distribution; treatment with BF_3–methanol (50°C, 5 h) or (reflux, 0.25 h), no changes; passage through Florisil with hexane also did not alter ratios of materials.

Preparation of methyl 9,10-dihydroxyoctadecanoic acid ditrifluoroacetate and its chlorination. A solution of peroxytrifluoroacetic acid was prepared by adding trifluoroacetic anhydride (10 mL, 70 mmol) dropwise to 30% H_2O_2 (1.0 g, 8.8 mmol peroxide) at 0–5°C. Methyl oleate (1.0 g, 3.3 mmol) was added dropwise as a solution in 20 mL of CH_2Cl_2, and the resulting solution was stirred overnight at ambient temperature, whereupon it became homogeneous. The mixture was washed with H_2O and dried ($MgSO_4$). The solvent was removed and the crude product was purified by flash chromatography (5% EA–H) to give **7** in about 90% yield: IR, 1740 and 1790 cm^{-1}. Photolysis was conducted in benzene with 2.5 and 5.0 equiv. of SO_2Cl_2; thermal chlorination was conducted in CCl_4 at reflux with 5.0 equiv. SO_2Cl_2. The reaction mixture was washed with H_2O, dried ($MgSO_4$), and concentrated. The resulting oil was transesterified with NaOMe in methanol as described above to remove the trifluoroacetate groups, then treated with $NaIO_4$ (1 mmol/mmol substrate) in 1:1 H_2O/methanol for 1 h at ambient temperature. The crude aldehydes were worked up and treated with Jones' reagent in acetone (ice bath) until the color of the dichromate persisted. The crude acids were then extracted from an aqueous dilution of the reaction mixture and were treated with diazomethane for GLC analysis.

RESULTS AND DISCUSSION

The desired triglycerides were synthesized by standard procedures (17,18) (Scheme 2). Glycidyl octanoate, **1**, for example, was converted to a 3-bromo-1,2-propanediol diester, **2a**, by treatment with decanoic anhydride and lithium bromide in benzene at room temperature. Reaction of **2a** with the cesium salt of 4-iodobenzoic acid gave the triglyceride **3a**. The 1,3-diglycerides, **4**, were prepared as described (17), recrystallized to homogeneity (TLC), and then allowed to react in chloroform with the appropriate iodobenzoyl chloride to produce the corresponding triglycerides, **5**. These were oils that were purified by flash chromatography (16).

Direct chlorination of methyl octanoate and methyl decanoate in carbon tetrachloride with sulfuryl chloride under reflux gave monochlorinated products in yields that depended on the amount of chlorinating agent used (Fig. 1). Yields were not specifically an issue at this point, though, with a 2:1 ratio of the halogenating agent to the substrate, the apparent yield of monochlorinated materials was about 80% by GLC. However, to test the inherent selectivity of a particular substrate, it was necessary to keep the degree of conversion to monochlorinated products low. A greater degree of halogenation would likely be accomplished in conjunction with altered ratios of the monohalogenated products. Identities of methyl 2-, 3-, and 8-chlorooctanoates, methyl 2-octenoate, and methyl 2- and 10-chlorodecanoates were made with synthesized materi-

TABLE 1
Thermal Chlorination with Sulfuryl Chloride[a]

	Position of chlorine								
	2	3	4	5	6	7	8	9	10
Methyl octanoate	—	5	16	19	21	25	14[b]	—	—
Methyl octanoate[c]	—	6	15	18	23	25	13[b]	—	—
Trioctanoin	—	—	18	22	23	22	15	—	—
Methyl decanoate	—	5	14	12	13	12	14	17	13[b]
Methyl decanoate[c]	—	5	12	13	14	14	17	18	8[b]

[a]Reactions were conducted at substrate concentrations of 0.01 M with benzoyl peroxide as catalyst in carbon tetrachloride under reflux. Reactions at 0.02 and 0.04 M in substrate gave essentially the same results.
[b]Photolysis with sulfuryl chloride in benzene at 15–20°C produced only trace amounts of the ω-product.
[c]Reaction conducted with one equivalent of methyl 4-iodobenzoate present.

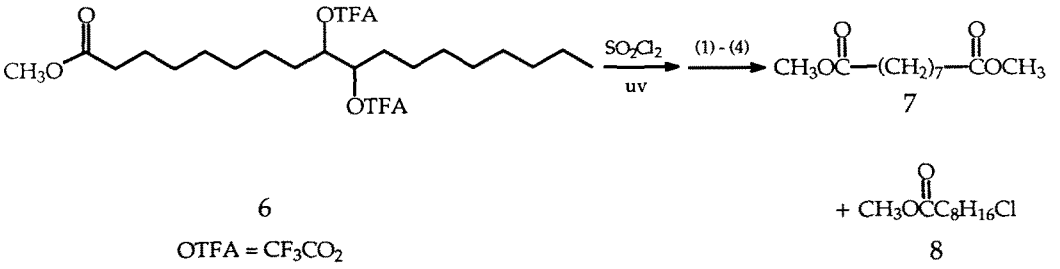
TABLE 2
Photolytic Chlorination with SO_2Cl_2 in CCl_4[a]

		Position of chlorine							
		3[b]	4	5	6	7	8	9	10
Trioctanoin		6	12	19	30	23	11	—	—
2a:	C_8 products	6	13	16	25	26	13	—	—
	C_{10} products	—	5	10	12	25	29	20	—
2b:	C_8 products	3	6	16	31	38	6	—	—
	C_{10} products	—	7	9	21	21	23	30	—
5a		4	8	18	22	37	11	—	—
5b		—	10	17	13	20	20	21	—
5c		—	14	23	25	27	10	—	—
5d		—	4	14	10	22	24	18	7

[a]Reactions were 0.001–0.002 M in substrate at T = 15–20°C. Thermal reactions and reactions of chlorine adducts (ultraviolet) gave very similar results.
[b]The value is the sum of 3-Cl and 2-octenoate esters.

als (Experimental Procedures section). Other monochlorinated fatty acids were then presumed on the basis of relative retentions of GLC. The ratios of monochlorinated compounds varied from 5% C-3 to 25% C-7 (ω2); 15% of the mixture was halogenated at C-8 (Table 1). This distribution was little changed by conducting the chlorination in the presence of methyl 4-iodobenzoate. It was expected that the initially generated chlorine atom would associate with the aryl iodide and thereby be reduced in activity. Hydrogen abstraction would still be bimolecular but possibly become more selective—this was not the case. The results for methyl decanoate were essentially the same, though only a trace of the 3-Cl compound was observed. In addition, neither methyl 2-octenoate nor methyl 2-decenoate, which could have arisen by dehydrohalogenation of the 3-Cl compound, was observed. The results indicate generally strong discrimination against the 3-position. Chlorination of trioctanoin in this fashion, followed by transesterification with methanol–sodium methoxide, produced a more complex mixture. Control experiments with chlorinated methyl esters by means of the transesterification procedure showed that the ratios were not disturbed by such exposure, and the 3-Cl compound dehydrohalogenated only slowly. The 3-Cl adduct was present in trace amount (no 2-octenoate), but the distribution of monochlorinated compound was otherwise similar. Chlorinations of triglycerides **3** and **5** were conducted thermally and by photolysis. Because of the similarity of the results, only data from photolysis, conducted at 0.001–0.002 M concentration of substrate with SO_2Cl_2 in CCl_4, are tabulated (Table 2). There was virtually no ω-product in any of the reactions, and substitution was absent or reduced at the 3-position. No significant difference in product distribution in the photolyses of **3a,b** was observed that could be traced to the relative positions of the fatty acid residues to the iodobenzoyl group on the glycerol backbone. Similar observations were made when those triglycerides were photolyzed that carried the 4-iodobenzoyl group in the 2-position, **5a,b**. Triglycerides **5c,d** contain the longer biphenyl spacer that we thought might narrow the product distribution. As the data of Table 2 show, there was no significant difference in the distributions obtained with **5c,d** from those of **5a,b**. The chlorine adducts of **5c,d** were also photolyzed neat without any noteworthy consequences. Clearly, chain flexibility of the fatty acid chains in CCl_4 is too great, even when those fatty acids are incorporated into triglycerides that might be aligned to some extent. Reactions were also conducted in benzene and acetic acid as solvents to note a possible effect of solvent either in improved alignment (benzene) or substrate coiling (acetic acid). Again, the distribution of monochlorinated materials was not significantly altered.

We also examined a substrate for which deterrence to reaction, based upon the chlorine atom's electrophilicity, could lead to more selective reactions. Methyl oleate was converted to the methyl ditrifluoroacetate triester of 9,10-*bis*-dihydroxyoctadecanoic acid, **6**, with peroxytrifluoroacetic acid and trifluoroacetic anhydride (Scheme 3). Photolysis with SO_2Cl_2 was followed by: (i) transesterification with methanol-sodium methoxide; (ii) periodate cleavage; (iii) oxidation with Jones' reagent to carboxylic acids (9); and (iv) esterification with diazomethane. The distribution of monochloro-nonanoates (8) (Scheme 3) indicates halogenation of **6** from C-13 to C-18 in a manner similar to the halogenations of the octanoate and decanoate esters described. This suggests that the trifluoroacetoxy substituent may act like a carbalkoxy group by deterring reaction proximate to the electron-deficient functional group. The other fragment from **6**, dimethyl azelate (7), was not accompanied by products of halogenation. In complementary experiments, dimethyl azelate was subjected to radical chlorination conditions, allowing determination of monohalogenated adducts. Although the product mixture was more complicated, it was clear that the halogenation of **6** had not produced any products of attack upon carbons 2–8. Perhaps, the triester coils in the solvent so as to effectively shield those carbons positioned between the carbomethoxy and trifluoroacetoxy groups. An observation, the basis for which may be the same, was made when 9,10-dibromostearic acid was chlorinated with N-chlorodiisopropylamine in trifluoroacetic acid, giving 87% chlorination in the (ω1) to (ω3) positions (19).



8: C-4(10%), C-5(20%), C-6(24%), C-7(25%), C-8(20%)

SCHEME 3

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[Received March 9, 1994; accepted October 24, 1994]