Tetrahedron. Vol. 34, pp. 947 to 950. Pergamon Press 1978. Printed in Great Britain

PHOTOCHEMICAL CHLORINATION OF ALKANOIC ACIDS ANCHORED TO A POLYMERIC SUPPORT†

P. BOSCH, J. FONT,* A. MORAL and F. SÁNCHEZ-FERRANDO
Departamento de Química Orgánica, Universidad Autónoma de Barcelona, Bellaterra, Spain.

(*Received in UK* 2 *August* 1977; *Accepted for publication* 3 *October* 1977)

Abstract—The synthesis of 2-(poly-*p*-styryl)ethyl esters of hexanoic, heptanoic, octanoic, nonanoic and decanoic acids as well as (poly-*p*-styryl)methyl octanoate and poly-2-(nitro-*p*-styryl)ethyl octanoate are described and their photochlorination are studied and compared with the monomeric (conventional) photochlorination of the methyl, benzyl and 2-phenylethyl esters of these acids. Hypotheses are advanced to explain the results on monochlorination products.

The use of insoluble polymers as supports for reagents and/or substrates in organic chemistry has received considerable attention in recent years, since it can solve a series of problems that by way of conventional methods cannot be undertaken.[1] Besides a major application in the stepwise synthesis of macromolecules,–i.e. Merrifield's solid-phase peptide synthesis[2]–several other uses of this technique have been devised in the present decade, based on some advantages or properties of the method, mainly: (i) dilution or separation of reactants,[3] (ii) simple filtration of the polymeric reagent -or reacted mixture[4]-, (iii) three-phase tests,[5] (iv) introduction of environments with different polar and/or steric requirements, for a given reaction, relative to its solution analog.[6]

The last property, which we believe has great potential, e.g. in remote functionalization, has not been fully exploited. Two approaches can be suggested to accomplish remote functionalization in solid phase: (i) both reagent and substrate are bound on the polymer (e.g. cross-linked polystyrene) in which case only those positions of the substrate close to the reagent—proximity depending on steric and conformational factors—would be functionalized (Fig. 1), (ii) only the reagent (or the substrate) is bound on the polymer and now functionalization will be imposed by steric hindrance towards the substrate (or reagent) approaching from the solution. In the second case (Fig. 2), selective functionalization on anchored substrate units will be clearly favoured by their close proximity—using a highly loaded polymer—and by the size of the reagent.

In the present paper we wish to report our work, based on the latter approach, on the reaction between solution-photolytically generated chlorine radicals (as reagent) and several alkanoic acids (as substrate) anchored on different insoluble supports derived from cross-linked polystyrene.

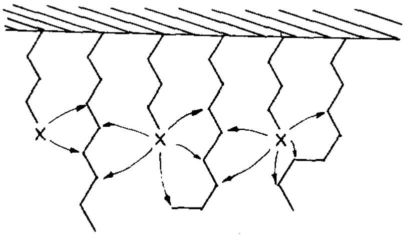

Fig. 1.

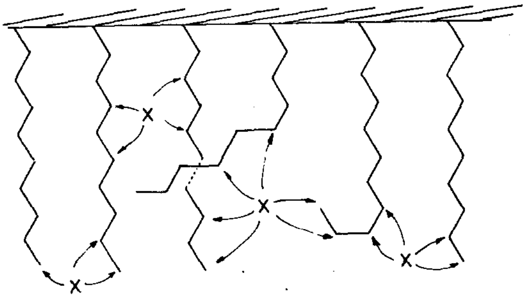

Fig. 2.

Very few reagents have been previously employed to carry out radical remote functionalization: the triplet state of benzophenone[7] and some aryldichloroiodine compounds[8] on steroid substrates, and chromium trioxide[9] and four types of radicals (Cl·, Br·, RO· and $R_3N^{\ddagger}$)[10] that efficiently abstract hydrogen atoms from alkanes.

Preferential functionalization on alkanoic acids derivatives has been observed in a few instances. Money *et al.*[9] studied the reaction between long chain methyl alkanoates and chromium trioxide and found enhanced reactivity at some of the chain positions. Examples of selective chlorination are also known; Deno *et al.* reported selective photochlorination at the terminal Me group of alkanoic acids adsorbed on alumina[11] and on the other hand butyric, hexanoic and octanoic acids are selectively photochlorinated at C_4 and C_ω by conducting the reaction in 90% sulfuric acid;[12] finally, Deno[13] and Schäfer[14] have also reported regioselective chlorination of several substrates (1-hexanol, hexanoic acid, dicarboxylic acids, etc.) when treated with N-chlorodiisopropylamine in sulfuric acid.

EXPERIMENTAL

The following esters (**1a**, **1b**, **1c**, **1d**, **1e**, **1f** and **1g**) were photochlorinated in homogeneous phase: Photochlorinations were carried out in a small conventional photochemical reactor vessel with a Pyrex immersion well and a mercury lamp Phillips HPK-125, during 10 min, on 1 g of ester dissolved in 10 ml CCl_4, to which 8 ml of a soln of Cl_2 in CCl_4 (0.029 g Cl_2/ml) was added. In this way conversions of *ca* 28% on monochloroalkanoates were achieved, while little or no di- or poly-chloroalkanoates were observed.

Gc analysis of the monochloroesters was effected on a Perkin–

---

†This work was presented, in part, at the VIII Int. Conf. Photochemistry, Edmonton, Canada (Aug. 1975).

Elmer F-21 instrument using a flame detector and a 2 m × 2.5 mm, 5% DEGS on Chromosorb W-AW-DMCS 60/80 mesh column. The seven isomeric methyl monochlorooctanoates were identified by mixed injection with independently prepared[15] authentic samples. Their retention times increase in the order 2-chloro, 3-chloro, 4-chloro, etc. in the octanoate series, and the same order was assumed for the other series studied; in fact, Deno has observed the same trend for the three methyl chlorobutyrates.[11] Peaks for 6-chloro/7-chloro and 8-chloro/9-chloro in the decanoate series were not resolved and each pair integrated as a whole.

The following polymeric esters were photochlorinated: poly(*p*-styryl)methyl octanoate (a "polymeric" benzyl octanoate) **2**, poly-2-(*p*-styryl)ethyl hexanoate **3a**, poly-2-(*p*-styryl)ethyl heptanoate **3b**, poly-2-(*p*-styryl)ethyl octanoate **3c**, poly-2-(*p*-styryl)ethyl nonanoate **3d**, poly-2-(*p*-styryl)ethyl decanoate **3e** and poly-2-(nitro-*p*-styryl)ethyl octanoate **3f**. Two kinds of polymer **2** were used: "diluted" **2** (sample **2a**) prepared by treatment of commercial Merrifield resin (chloromethylated styrene-2% DVB copolymer, 1.1–1.4 meq Cl/g) with octanoic acid and triethylamine, and "concentrated" **2** (sample **2b**) prepared by stoichiometric chloromethylation[2a] of 2% cross-linked polystyrene, 2.1 meq Cl/g, followed by octanoic acid-triethylamine treatment.

The preparation of **3a–e** was conducted essentially as previously described[3] for *p*-(2-hydroxyethyl)polystyrene: treatment of a slurry of 2% cross-linked polystyrene in CCl_4 with Br_2 (stoichiometrically) in the presence of thallium(III) acetate gave *p*-bromopolystyrene (3.2 meq Br/g); this was converted to the Li-derivative by n-BuLi in toluene, then reacted with ethylene oxide followed by hydrolysis with aq. HCl-dioxane (the resulting polymer contained 2.9 meq OH/g) and final acylation with the corresponding acid chloride. Nitration of **3c** by fuming nitric acid[2a] furnished **3f**.

After each synthetic step as well as before analysis or utilization, the polymers were thoroughly washed with several solvents and dried under vacuum at 80° over P_2O_5 "Solid phase" photochlorination of **2a–b** and **3a–f** was effected as follows: to a slurry of the polymeric ester (1 g) in CCl_4 (15 ml) a soln (3–4 ml) of Cl_2 in CCl_4 (29 mg Cl_2/ml) was added and the mixture was irradiated under stirring for 10 min. The polymer was then filtered, washed and transesterified by refluxing with HCl-MeOH-dioxane. Removal of the polymer by filtration yielded the mixture of unreacted and chlorinated alkanoic acids in the form of methyl esters, ready for gc analysis. No scrambling of Cl takes place during transesterification, since a sample of photochlorinated methyl octanoate maintained its composition, as shown by gc, after refluxing with methanolic HCl. Preferential transesterification of the chlorinated products was not observed in a time-coarse study of this step, in which gc analysis revealed that the mixtures of chloroesters liberated from a photochlorinated polymer (**3c**) during transesterification at times varying from 1 hr to 2 days had the same compositions. In these "solid phase" photochlorinations the photoconversion to monochlorinated alkanoic acids was 25–35%.

RESULTS AND DISCUSSION

The results of the homogeneous photochlorination of **1a–e** and "solid phase" photochlorination of **3a–e** are given in Table 1. The conventional results for **1a–e** agree with the scarcely reported data found in the literature for the photohalogenation of alkanoic esters.[16] Thus, the methylene hydrogens at C_2 are strongly deactivated due to the inductive effect of the methoxycarbonyl group and this effect is still apparent, at least in part, for C_3. On the other hand, the hydrogens at C_ω are less reactive than other methylene hydrogens, while maximum reactivity is found at $C_{\omega-1}$, probably due to the greater inductive effect of the Me group and/or hyperconjugation.

A comparison between both series of values in Table 1 immediately shows a diminished reactivity for C_ω in "solid phase", contrary to what could be expected (Fig. 2 and relevant text in the Introduction). However, this fact can be explained by recalling Russell's results[19] on radical chlorination of hydrocarbons in π-electron rich aromatic solvents: under these conditions the rate determining step, H-atom abstraction from the hydrocarbon, is effected by a π-complex between the electrophyllic chlorine radical and the aromatic nucleus, and accordingly the reactivity of the reagent decreases while its selectivity increases. Although our photochlorinations were conducted in carbon tetrachloride, the alkanoate moieties anchored to the polymer are surrounded by benzene rings, which might form π-complexes with the Cl atoms, thus increasing their selectivity. Figures 3 and 4 represent two possible ways of Cl atom delivery from such π-complexes, "intramonomeric" and "intrapolymeric" respectively.

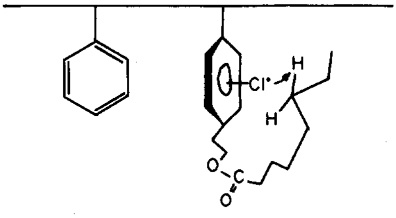

Fig. 3.

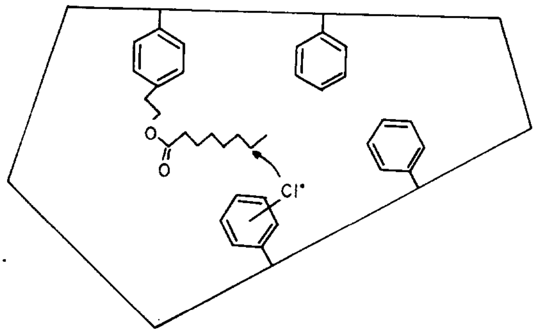

Fig. 4.

Data from Table 2, in which photochlorination results are given for all tested derivatives of octanoic acid, can be of great value in assessing this possibility. If this data are considered together with data in Table 1, some general conclusions can be established.

Relative reactivities from Tables 1 and 2 show a quite general and gradual increase in reactivity from C_2 to $C_{\omega-1}$ in all cases. The immediately apparent explanation based on transmission of the electron deficiency (due to the inductive effect of the methoxycarbonyl group) along the chain is untenable at such long distances as three or more σ bonds.

Comparison between columns **1c** and **1h** in Table 2 shows that $C_6H_6Cl\cdot$ is a much milder reagent than $Cl\cdot$, since the former has a strong discrimination against the hydrogen atoms attached to C_2 and to the terminal Me group. Relative reactivities from compounds **1f**, **1g**, **2a**, **2b** and **3c** (Table 2) are found to have values intermediate between those of the first and last columns. This is a

Table 1. Photochlorination of alkanoic acids as methyl esters and as poly-2-(*p*-styryl)ethyl esters[a,b] in CCl_4

Position \ Substrate	$MeOCOC_5H_{11}$ 1a	Ⓟ$CH_2CH_2OCOC_5H_{11}$ 3a	$MeOCOC_6H_{13}$ 1b	Ⓟ$CH_2CH_2OCOC_6H_{13}$ 3b	$MeOCOC_7H_{15}$ 1c	Ⓟ$CH_2CH_2OCOC_7H_{15}$ 3c	$MeOCOC_8H_{17}$ 1d	Ⓟ$CH_2CH_2OCOC_8H_{17}$ 3d	Me $OCOC_9H_{19}$ 1e	Ⓟ$CH_2CH_2OCOC_9H_{19}$ 3e
2	2.0(0.15)	7.1(0.6)	1.0(0.07)	1.3(0.16)	0.9(0.09)	1.3(0.2)	1.9(0.2)	2.1(0.4)	1.2(0.1)	0.5(0.2)
3	15.0(1.0)	13.2(1.2)	12.7(0.93)	7.1(0.8)	9.5(0.93)	4.6(0.7)	10.4(1.2)	5.0(1.0)	9.5(1.0)	4.4(1.0)
4	29.6(2.0)	30.1(2.76)	16.8(1.23)	17.3(1.95)	13.6(1.4)	11.3(1.73)	12.1(1.4)	13.8(2.8)	11.7(1.3)	8.7(2.0)
5	31.4(2.1)	33.3(3.06)	23.1(1.7)	30.4(3.42)	13.2(1.3)	15.4(2.36)	10.4(1.2)	12.8(2.59)	10.0(1.1)	10.0(2.3)
6	22.0(1.0)	16.3(1.0)	25.9(1.9)	30.6(3.45)	21.3(2.1)	30.0(4.6)	11.3(1.3)	16.2(3.28)	22.0[c](1.2)[d]	33.8[c](3.9)[d]
7			20.5(1.0)	13.3(1.0)	26.1(2.5)	27.6(4.22)	18.1(2.1)	21.1(4.27)		
8					15.4(1.0)	9.8(1.0)	22.5(2.5)	21.6(4.38)	31.8[c](1.8)[d]	36.6[c](4.2)[d]
9							13.3(1.0)	7.4(1.0)		
10									13.8(1.0)	6.5(1.0)

a) Figures are normalized per cent contents in monochloroderivatives (after transesterification where appropriate) assuming equal response factors in the FID of the gc for all the isomeric methyl monochloroalkanoates.

b) Figures into brackets are relative reactivities per H atom within the same molecule (methyl groups of different substrate do not have to react at the same rate

c) Addition of two values, since two peaks were unresolved by gc.

d) Mean value for two consecutive positions unresolved by gc.

Table 2. Photochlorination of several octanoic acid esters[a,b].

Substrate / Position	$MeOCOC_7H_{15}$ 1c	$PhCH_2OCOC_7H_{15}$ 1f	$PhCH_2CH_2OCOC_7H_{15}$ 1g	Ⓟ$CH_2OCOC_7H_{15}$ "diluted" 2a	Ⓟ$CH_2OCOC_7H_{15}$ "conc." 2b	Ⓟ$CH_2CH_2OCOC_7H_{15}$ 3c	Ⓟ$(NO_2)CH_2CH_2OCOC_7H_{15}$ 3f	$MeOCOC_7H_{15}$ in benzene[c] 1h
2	0.9(0.09)	0.74(0.11)	1.61(0.3)	0.98(0.26)	0.62(0.16)	1.3(0.2)	13.53(0.8)	0.0(0.0)
3	9.5(0.93)	7.5(1.16)	6.3(1.2)	4.7 (1.26)	4.6(1.19)	4.6(0.7)	3.26(0.2)	3.0(1.5)
4	13.6(1.4)	13.3(2.0)	22.0(4.4)	12.8(3.43)	14.1(3.65)	11.3(1.7)	14.7(0.9)	14.0(7.0)
5	13.2(1.3)	16.5(2.55)	18.8(3.7)	20.4(5.47)	21.2(5.48)	15.4(2.4)	10.5(0.6)	24.0(12.0)
6	21.3(2.1)	28.7(4.44)	20.0(4.0)	27.6(7.4)	27.5(7.11)	30.0(4.6)	12.24(0.7)	30.0(15.0)
7	26.1(2.5)	23.5(3.63)	23.7(4.7)	27.8(7.45)	26.1(6.75)	27.6(4.2)	21.33(1.3)	26.0(13.0)
8	15.4(1.0)	9.7(1.0)	7.5(1.0)	5.6(1.0)	5.8(1.0)	9.8(1.0)	24.5(1.0)	3.0(1.0)

a) Solvent, unless otherwise stated, was carbon tetrachloride. b) See footnotes a and b of Table 1

c) Data from reference 12

clear indication of a mixed mechanism, part of the hydrogens being abstracted by free Cl radicals while another part are abstracted by π-complexed Cl radicals. The relatively high reactivity of C_2 in all polymeric esters (Tables 1 and 2) might, however, indicate the operation of yet another mechanism, which should be ionic and proceed through reaction of Cl molecules with the conjugate acid (or equivalent enol form) of the ester group, formed under the presence of hydrogen chloride.

The very low relative reactivity values for compound **3f** indicate that Cl atoms generated in solution attack preferentially the terminal positions of the anchored octanoyl moiety, possibly because of the reduced ability of the electron-deficient benzene rings of the nitrated polymer to complex electrophyllic Cl atoms and/or low swelling of the nitropolymer by the solvent. However, since values for **3f** are even smaller than for **1c**, a second effect, such as preferential attack at positions nearer to the interface polymer-solution, must be operative. Cl_2 molecules, nevertheless, seem to have a better chance to enter the polymer lattice since C_2, in this case is highly reactive.

The small relative reactivity maxima found for C_6 in **3c**, **1f**, **1h** and for C_4 in **1c**, **1d**, **3d**, **1e**, **3f** and **1g** throw no light on the question of "intramonomeric" vs "intrapolymeric" Cl atom delivery. Contributions from both mechanisms can be operative, but their incidence in reactivity differences must be small, since Table 2 shows little, although appreciable, contribution of the π-complexed radical mechanism.

REFERENCES

[1] For reviews see [i] C. G. Overberger and K. N. Sannes, *Angew. Chem. In. Edit.* **13**, 99 (1974); [ii] C. C. Leznoff, *Chem. Soc. Rev.* 3, 65 (1974); [iii] A. Patchornik and M. A. Kraus, *Pure Appl. Chem.* **43**, 503 (1975).

[2] [i] R. B. Merrifield, *J. Am. Chem. Soc.* **85**, 2149 (1963); [ii] G. R. Marshall and R. B. Merrifield, '*Biochemical Aspects on Reactions on Solid Supports*' (Edited by G. R. Stark). p. 111. Academic Press, New York and London (1971).

[3] F. Camps, J. Castells, M. J. Ferrando and J. Font, *Tetrahedron Letters* 1713 (1971).

[4] F. Camps, J. Castells, J. Font and F. Vela, *Ibid.* 1715 (1971).

[5] J. Rebek, Jr. and F. Gaviña, *J. Am. Chem. Soc.* **97**, 3453 (1975).

[6] C. G. Overberger, M. Marimoto, I. Cho and J. C. Salomone, *Macromolecules* **2**, 553 (1969).

[7] R. Breslow, *Chem. Soc. Rev.* **1**, 553 (1972).

[8] R. Breslow, R. J. Corcoran and B. B. Snider, *J. Am. Chem. Soc.* **96**, 6791-2 (1974).

[9] C. R. Eck, D. J. Hunter and T. Money, *J. Chem. Soc. Chem. Comm.* 865 (1974).

[10] N. C. Deno, D. G. Pohl and H. J. Spinelli, *Bioorganic Chem.* **3**, 66 (1974).

[11] N. C. Deno, R. Fishbein and C. Pierson, *J. Am. Chem. Soc.* **92**, 1451 (1970).

[12] N. C. Deno, R. Fishbein and J. C. Wyckoff, *Ibid.* **92**, 5274 (1970).

[13] N. C. Deno, W. E. Billups, R. Fishbein, C. Pierson, R. Whalen and J. C. Wyckoff, *Ibid.* **93**, 438 (1971).

[14] F. Kämper, H. J. Schäfer and H. Luftmann, *Angew. Chem. In. Edit.* **15**, 306 (1976).

[15] J. Font, A. Moral, F. Sánchez-Ferrando and J. Elguero, *Tetrahedron* (this issue).

[16] W. A. Thaler, *Methods Free-Radical Chem.* **2**, 121 (1969).