Polarisation by Cation Formation: a Method for Influencing the Selectivity of Radical Chlorination

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Polarisation by cation formation (e.g., by protonation or by oxocarbonium ion formation) exerts a distinct and systematic effect on the selectivity of radical chlorination of aliphatic acids, amines, and alcohols. A gualitative correlation is demonstrated between the magnitude of deshielding of a given proton (as expressed by the downfield shift in the ¹H n.m.r. spectrum) and its " deactivation " as indicated by diminished rate of its abstraction by chlorine atoms. A convenient method is described for the preparation of new and known aliphatic mono- and polychloro-amines.

THE object of this work is to establish a new approach in radical chemistry; polarisation by cation formation is suggested as an explanation of the underlying effects.

Radical chlorination is generally considered one of the important types of organic reactions.¹ In synthesis it makes possible the introduction of functional groups in positions which are usually inaccessible by ionic reactions, and its theoretical and practical aspects have been much discussed.² However, the fundamental problem of lack of selectivity is a prominent feature of these reactions. The factors influencing the selectivity of ionic chlorinations are well understood; in contrast, with the singular exception of the solvent effects,³ discovered by G. A. Russell, there is no method known to enhance the selectivity of radical chlorinations. Moreover, several classes of compound undergo rapid (and in some cases destructive) *ionic* chlorination; this can be so rapid that it completely overshadows the radical reaction even under radical-generating conditions. This is the case with alcohols,^{4a} amino-acids,^{4b} and aliphatic amines.^{4c}

In the case of amino-acids,⁵ the (destructive) ionic chlorination was avoided by protonation, and thus radical chlorination became observable. The effect of protonation was tentatively explained by considering its influence on the polarisation state of the substrates.56 Since a direct comparison is not possible in regard to reactivity of amino-acids and their protonated form with radical chlorine, in the present study aliphatic acids were subjected to a similar comparison, under conditions which exclude ionic chlorination. We also studied the reactivity of chlorine atoms with protonated aliphatic amines and alcohols; carbonium ions and protonated alcohols were chlorinated advantageously in liquid hydrogen fluoride, a solvent not previously employed in light-catalysed reactions.

EXPERIMENTAL

The special reactor used for chlorinations in liquid hydrogen fluoride was cylindrical with a volume of ca. 140 ml. It was machined from a KEL-F rod (Commercial Plastics & Supply Corp., Newark 14, New Jersey) and was equipped on the top with a window made of transparent

* This reactor was designed and built with the valuable cooperation of Mr. R. Geiger of our machine shop.

¹ G. Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," Macmillan, New York, 1964, p. 282. ² "Methoden der Organischen Chemie" (Houben-Weyl), ed. E. Muller, 4th edn., vol. V/3, Thieme Verlag, Stuttgart, 1962, p. 564.

KEL-F film, 0.25 mm. thick (Fluorocarbon Co., Pine Brook, New Jersey). Irradiation was by a Hanovia mercury lamp (450 w, type 59-A-36) at the focus of a paraboloid reflector. For heat protection a filter with flowing cold water and equipped with quartz windows was placed between the lamp and the reactor. Inlets for chlorine and nitrogen as well as a device for sampling were also provided.*

Irradiation .--- For chlorination of ethylamines, strong u.v. radiation was necessary on the scale of our experiments (0.3-2 mole of amine). To avoid a protracted chlorination, usually two of the 450 w lamps were used. For chlorination of butyl- and pentyl-amines a 140-w lamp (Hanovia, No. 30620) was sufficient. In general, fused quartz flasks were used in these reactions; in 'Pyrex' flasks longer reaction periods were necessary. In some cases, instead of light-initiation, a 3-5% solution of azobisisobutyronitrile in conc. sulphuric acid was added to the reaction mixture, kept at 80-100°, in small portions during the entire chlorination period. Benzoyl peroxide did not seem to catalyse these reactions.

Analytical Procedures .- The chlorination was followed by saponifying degassed samples of the reaction mixture by aqueous sodium hydroxide solution, followed by electrometric titration of the chloride ion. In the case of chloro-acids, a sample was quenched in ice, extracted with benzene, and esterified with an ether solution of diazomethane. The mixture of methyl esters was analysed by gas chromatography. For methyl chloropropionates, a HY-FI Aerograph model 600, with hydrogen flame ionisation detector and a 20% QF-1 on Gas-Chrom P column at 120°, was used, and for methyl chlorobutyrates an Autoprep Aerograph A-700 at 139° with thermal conductivity detector. The area ratios were determined by analysing mixtures prepared from authentic pure methyl esters. Pure chloroacids were esterified and fractionated to provide these standards. Area ratios of methyl 2- and 3-chloropropionates and of methyl 2-, 3-, and 4-chlorobutyrates were close to 1. The composition of artificial mixtures of chloro-acids in 100% sulphuric acid or liquid hydrofluoric acid did not change on irradiation with u.v. light. This

³ (a) G. A. Russell, Tetrahedron, 1960, 8, 101, and previous Papers; (b) see also H. C. Brown in "Vistas in Free Radical Chemistry," ed. W. A. Waters, Pergamon, New York, 1959, p. 207; (c) C. Walling and M. F. Mayahi, J. Amer. Chem. Soc., 1959, 81, 1485; (d) for a recent Review see E. S. Huyser, "Advances in Free Radical Chemistry," ed. G. H. Williams, Academic Press, London, 1965, vol. 1, p. 77.
⁴ (a) Ref. 2, pp. 600, 601; (b) H. Schwanert, Annalen, 1857, 102, 221; (c) C. W. Crane, J. Forrest, O. Stephenson, and W. A. Waters, J. Chem. Soc., 1946, 827; C. C. Price, A. Pohland, and B. H. Velzen, J. Org. Chem., 1947, 12, 308.
⁵ (a) J. Kollonitsch, A. Rosegay, and G. A. Doldouras, J. Amer. Chem. Soc., 1964, 86, 1857; (b) J. Kollonitsch, A. N. Scott, and G. A. Doldouras, *ibid.*, 1966, 88, 3624.

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excludes the possibility that the original composition of the chlorination mixtures became distorted by selective destruction of some of the chlorinated species. The chlorination product obtained from propyl oxocarbonium antimony hexafluoride was quantitatively analysed, with methyl benzoate as internal standard; >98% of the butyryl chloride employed was accounted for.

Chloro-amine mixtures were quantitatively analysed accurately and conveniently by the Spinco-Beckman automatic amino-acid analyser. Using the short column and citrate buffer of pH 5.28, clean separations were achieved. The ninhydrin colour constants were determined by using authentic, pure chloro-amine hydrochlorides. By this new application of the Spinco-Beckman analyser, mixtures of amines and chloro-amines were conveniently and quantitatively analysed.

The mixture of chlorobutanols obtained by chlorination of butanol in liquid hydrogen fluoride was analysed for 4-chlorobutanol by treatment for 16 hr. with aqueous 2N-sodium hydroxide at room temperature, followed by quantitative g.l.c. of the tetrahydrofuran formed; periodic acid oxidation of 2-hydroxybutanol, resulting from 2-chlorobutanol, measured the extent of β -chlorination.

¹H N.m.r. spectra of isolated compounds were recorded with the usual techniques. For the strong-acid systems, to avoid the uncertainty about influencing the spectrum of the standard by the unusual solvents, external tetramethylsilane standard was used. The sample was placed in thin-walled KEL-F inlet tube which was sealed with a hot-air gun and inserted in the usual glass tube.

2,2,2-Trichloroethylamine.-This experiment illustrates the preparative methods. Ethylamine gas (99 g., 2.2 moles) was added with cooling to 100% sulphuric acid (504 g., 5.15 moles), and, under u.v. irradiation by two 450-w lamps and with vigorous stirring, chlorine was passed for 23 hr. at 80-100°. Assay by the amino-acid analyser indicated a 76% yield of the trichloro-amine. After degassing, the mixture was quenched in ice; the sparingly soluble trichloroamine sulphate, which crystallised, was filtered off and slurried in water, ammonium hydroxide (150 c.c.) was added with cooling, and the liberated base extracted with ether. After drying $(MgSO_4)$, the trichloro-amine hydrochloride was precipitated (194 g., 48%) by introduction of hydrogen chloride; m. p. $>230^{\circ}$ (subl.) (Found: C, 12.8; H, 2.9; Cl, 76·4; N, 7·7. Calc. for $C_2H_5Cl_4N$: C, 13·0; H, 2·75; Cl, 76.7; N, 7.6%). The ¹H n.m.r. spectrum supports the assigned structure.6

2,2-Dichloroethylamine.—Chlorination of ethylamine as described above, but interrupted after the uptake of 1.2 atom of chlorine, gives a mixture of 2-chloro- and 2,2-dichloro-ethylamine; the latter was obtained pure by distillation in vacuo, b. p. $52^{\circ}/45$ mm. (Found: C, 15.7; H, 4.3; Cl, 70.4; N, 9.6. C₂H₆Cl₃N requires C, 15.9; H, 4.0; Cl, 70.7; N, 9.3%). The ¹H n.m.r. spectrum supports the assigned structure. Hydrochloride, m. p. 167—168° (decomp.).

RESULTS AND DISCUSSION

We suggest that the most important factor behind the selectivity shifts (Table 1) is the polarisation of the substrates by the positive charge introduced:

$$\begin{array}{c} \mathsf{R}-\mathsf{C} \swarrow \mathsf{OH} \ (\mathrm{I}) & \mathsf{R} = \mathsf{Et} \ (\mathrm{II}) \\ & \mathsf{OH} \ (\mathrm{III}) & \mathsf{R} = \mathsf{Pr} \ (\mathrm{IV}) \end{array} \\ \end{array} \\ \begin{array}{c} \mathsf{R}-\mathsf{CO}^+ \ \mathsf{SbF_6}^- \end{array}$$

TABLE 1

Influence of cation formation on the radical chlorination of carboxylic acids

	Parts of chloro-acid, ^a and relative selectivity		
	2-Chloro	3-Chloro	4-Chloro
CH ₃ ·CH ₂ ·CO ₂ H ^b	1 (0.68)	$2 \cdot 22$ (1)	
,, + liq. HF	1 (0.15)	10 (1)	
$\begin{array}{c} (15 \text{ mol.}) \\ + 100\% \text{ H}_2\text{SO}_4 \\ (8 \text{ mol.}) \end{array}$	1 (0.04)	40 (1)	
CH3•CH3•CH3•CO3H	1(0.30)	6.7 (1.98)	5.1(1)
,, + liq. HF	1 (0.09)	16 (1.5)	16 (1)
$,, +\frac{100\%}{(8 \text{ mol.})} \text{H}_2\text{SO}_4$	1 (0.06)	18 (1.12)	24 (1)
$CH_3 \cdot CH_2 \cdot CH_2 \cdot CO^+ SbF_6^-$ in liq.	1 (0.002)	70 (0.17)	600 (1)

^a Conversion 20—40%; usual reaction time 20—60 min. at 5—10°. ^b M. S. Kharasch and H. C. Brown, J. Amer. Chem. Soc., 1940, **62**, 926; J. Wautier and A. Bruylants, Bull. Soc. chim. belges, 1963, **72**, 222 ^c Prepared by addition of SbF_5 to solution of acid chloride in liq. HF (G. A. Olah, W. S. Tolgyesi, S. J. Kuhn, M. E. Moffatt, I. J. Bastien, and E. B. Baker, J. Amer. Chem. Soc., 1963, **85**, 1328).

The presence of positive charge is reflected in the strong deshielding of the protons of the α - and β -methylene groups as compared with the acids themselves; the ¹H n.m.r. spectra displayed strong downfield shifts in solutions of (I)—(IV). There is a qualitative correlation between the magnitude of this downfield shift and the change of the ratio of the relative selectivities (" deactivation factor") of the corresponding sites (see Table 2).

TABLE 2

Correlation of extent of polarisation (deshielding in ¹H n.m.r.) with deactivation in radical chlorination

	Downfield shifts ^a of pro- tons on C-2 and C-3; deactivation factors ^b in parentheses		
	C-2	C-3	
$\dot{C}H_3 \cdot \dot{C}H_2 \cdot \dot{C}O_2H + \text{liq. HF (15 mol.)} + 100\% H_2SO_4 (8 \text{ mol.})$	$\begin{array}{c} 0{\cdot}23 \ (4{\cdot}5) \\ 0{\cdot}52 \ (17{\cdot}0) \end{array}$		
CH ₃ ·CH ₂ ·CO+ SbF ₆ ⁻ in liq. HF	1.85 (> 100)	0.97 (>100)	
$CH_3 \cdot CH_2 \cdot CH_2 \cdot CO_2H + \lim_{mail} HF (10)$	0.22 (3.3)	0 (1.32)	
,, $+100\% H_2SO_4$ (8 mol.)	0.48 (5.0)	0.32 (1.76)	

CH₃·CH₂·CH₂·CO+SbF₆⁻ in liq. HF 1.72 (150.0) 0.72 (11.6) ^a In p.p.m., relative to (non-polarised) substrate; Me₄Si as external standard. ^b RS of a given proton in substrate/RS of the same proton in the polarised form.

(The observed paramagnetic shifts are in good agreement with those in H_2SO_4 -SO₃ systems.⁷)

We believe that this deactivation is due mainly to the electron-withdrawing effect of the positive charge introduced, and its magnitude is expected to be inversely proportional to distance, thus explaining the preferential attack by the chlorine atoms (which are electrophilic)

⁶ A. N. Nesmeyanov, L. I. Zakharkin, and R. Kh. Freidlina, Izvest. Akad. Nauk S.S.S.R., 1958, 841 (Chem. Abs., 1959, 53, 1111).

1111). ⁷ N. E. Deno, C. U. Pittman, jun., and M. J. Wisotsky, J. Amer. Chem. Soc., 1964, **86**, 4370. on the protons farthest from the positive pole. The electrostatic repulsion between this positive pole and the chlorine atoms accentuates the effect.^{3a,8}

Table 2 also illustrates that the deactivation caused by oxocarbonium-ion formation is powerful enough to inhibit chlorination of the α - and β -protons as well, whereas the effect caused by protonation is much weaker on the β -proton.

Liquid hydrogen fluoride was especially advantageous in some of these reactions. For example, chlorination of propyl oxocarbonium ion, prepared in sulphuric acid– sulphur trioxide,⁷ resulted in a complex mixture, probably by decomposition of the primarily formed chloroacids by free sulphur trioxide.

It is more difficult to evaluate the influence of induced polarisation on the radical chlorination of amines. In protonated amines the protons of the carbon bearing the amino-group became completely unreactive (Table 3) while the reactivity of the β -, γ -, and δ -protons is influenced to a decreasing extent. Thus, the chlorination pattern of acids and protonated amines is similar, but in the absence of radical catalysis acids are completely unreactive with chlorine (under the conditions here employed) even in their non-protonated form, whereas amines as free bases are extremely reactive with chlorine under non-radical conditions too.^{4c} Ionic (degradative) chlorination is the only observable reaction in this case; therefore, a direct comparison is not possible for reactivity of amines and polarised (protonated) amines with chlorine atoms. Thus, Amundsen and Pitts,

TABLE 3

Radical chlorination of amine salts; where not indicated otherwise, catalysis was by u.v. irradiation (see Experimental section); in the absence of radical catalysis, no reaction takes place in these systems with chlorine.

Substrate	Main product	Yield ^a (%)
MeNH,	No reaction	
EtNH,	Cl ₂ CH·CH ₂ ·NH ₂ ^b	78
EtNH ₂	Cl ₃ C·CH ₂ ·NH ₂	76
Et ₃ N	CICH ₂ ·CH ₂ ·NEt ₂ ^c	61 °
BuNH ₂	CICH ₂ ·CH ₂ ·CH ₂ ·CH ₂ ·NH ₂ ^d	40
so-C ₅ H ₁₁ ·NH ₂	ClCH ₂ ·CHMe·CH ₂ ·CH ₂ NH ₂	36
ClCH ₂ ·CH ₂ ·NMe ₂	Cl ₂ CH·CH ₂ ·NMe ₂ ^f	56 g

^a Assay by Spinco-Beckman automatic amino-acid analyser. ^b Chlorination in 100% H_2SO_4 (2·5 mol.). ^c Chlorination in 100% H_2SO_4 (3 mol.), with azobisisobutyronitrile catalyst (0·04 mol. added in 10 portions in 2 hr.); isolation as hydrochloride, via base. ^d Chlorination in CF₃·CO₂H (6 mol.); assayed as pyrrolidine, after ring-closure with OH⁻. ^e Chlorination in CF₃·CO₂H (6 mol.); assayed as 3-methylpyrrolidine after ring-closure with OH⁻. ^f Chlorination in 100% H_2SO_4 (4 mol.); isolation as hydrochloride (m. p. 199–200°), via the base, b. p. 65–67°/53 mm. ^e Isolated yield.

describing the photochlorination of a tertiary amine hydrochloride in chloroform solution,⁹ discuss the in-

⁸ (a) For an incisive discussion of radical chemistry, see J. M. Tedder, *Quart. Rev.*, 1960, 336; (b) for a systematic study of radical substitution of aliphatic compounds, see J. M. Tedder and his co-workers, *J. Chem. Soc.* (B), 1966, 605, and preceding Papers.

fluence of the NHR_2^+ group on the reactivity of the attached hydrocarbon moiety but do not deduce anything regarding the comparative reactivity of amines and their salts. Nevertheless, from our results with acids, it can be inferred that the influence of induced polarisation is analogous in the two cases. In Table 3 only the main reaction products are indicated; e.g., from butylamine, besides the main product, smaller amounts of the β - and γ -chloro-amines are also formed. The strong deactivation by the amine moiety is indicated by the preferred formation of the δ -chloro-product from butylamine. For the hypothetical hydrocarbon -CH₂·CH₂·CH₂·CH₃, considering the usual relative selectivities of primary and secondary protons (1:3.7), 13% of δ -chlorination is expected, whereas 40% was observed. In general, the selectivities are similar to those found for amino-acids.5a,b This method gives ready access to many mono- and poly-chloro-amines, some of which are very useful in synthesis. It thus complements the Hofmann-Loffler-Freytag (H.L.F.) reaction which is applicable only on secondary amines and it leads invariably to δ -chloro-amines.¹⁰ The arguments by which we excluded a H.L.F. mechanism for the chlorination of amino-acids ⁵ are applicable here too.

Protonation of aliphatic alcohols also exerts a protective influence against ionic chlorination. Radical chlorination of aliphatic alcohols, polarised by dissolution in liquid hydrogen fluoride (10-15 mol.) provided the first synthesis of chloro-alcohols from alcohols. Liquid hydrogen fluoride is a uniquely suitable solvent for the study of radical chlorination of alcohols, since other strong acids esterify or dehydrate most alcohols. n-Butanol with this method gave a mixture of 4-, 3-, and 2chlorobutanol in the ratio 2:3:2; the 4-chloro-compound was the main product obtained from isopentyl alcohol. These results are attributed to the polarisation caused by the presence of a positive pole in the protonated species, ROH_2^+ F⁻. This polarisation was reflected in the ¹H n.m.r. spectra, which indicated strong downfield shifts of the CH protons, to an extent which decreased with growing distance from the protonated site.

Since polarisation, by protonation or by other means, of several classes of organic compound is feasible, the approach discussed above promises to be of general importance in radical reactions. Our studies are continuing.

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⁹ L. H. Amundsen and L. S. Pitts, J. Amer. Chem. Soc., 1951, 73, 1494.

¹⁰ E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.*, 1960, **82**, 1957; P. G. Gassman and D. C. Heckert, *Tetrahedron*, 1965, **21**, 2725.