Irradiation-Induced De-esterification

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Received June 24, 1963

Solutions of benzyl esters in various solvents are efficiently de-esterified by high-energy electron irradiation. Dose rate and intensity effects are examined and a schematic mechanism proposed. In addition to synthetic applications, the efficient generation of acid can be used as an organic radiation dosimeter.

In connection with a study of solute effects on electron irradiation of cyclohexane and other solvents,[1] a novel and synthetically useful method of de-esterification has been discovered. Previous work on solute reaction in solvents subjected to irradiation led to the discovery that benzyl-type compounds ($C_6H_5CH_2X$, where X = Cl, Br, OH, $OCOCH_3$) had a high reactivity in proportion to their concentration. Furthermore, it was shown previously by iodine-scavenging methods that normal free-radical attack on the solute, thus accounting for its loss, could not explain the high *G* obtained.[1]

Additional insight into this reaction was desired, and, for this reason, a search for the reaction products containing the substituent X was initiated. Benzyl acetate was chosen as the solute to be examined, and acetic acid was considered likely as one of the products of the reaction of the fragment X, if it became dissociated from the parent molecule. The unexpectedly high yield of acetic acid found, indicating a high proportion of C–X cleavage, prompted the detailed investigation reported in this paper. The possibility that the reaction is general for benzyl esters is investigated. Some of the parameters that affect the efficiency and extent of this reaction also are examined.

Results

Benzyl acetate converts with a variable efficiency to acetic acid, as shown in Table I and Fig. 1 and 2. Solvents have a strong effect, and, for benzyl acetate, ethanol yields an almost quantitative amount of acetic acid. Radiation intensity was varied by a factor of ten and had no effect on the *G* (acid), as shown in Table II.

Figure 1 demonstrates that the concentration of ester definitely has an effect on the efficiency of acid production. However, excellent linearity of acid production is obtained when conversions of ester are less than 50% and when the initial concentration is 0.2 *M* (Fig. 2).

Dibenzyl succinate was investigated in some detail. If the irradiation is carried out in cyclohexane, succinic acid precipitates, owing to its lack of solubility. There exists the possibility that both benzyl groups come off simultaneously. The data given in Table III demonstrate that the *G* is low and is a strong function of starting ester concentration. This behavior is consistent with a two-step de-esterification.

Table IV lists the *G* (acid) yields for a series of benzyl or benzyl-type esters, and, by comparison with Table V, it is obvious that the benzyl structure is necessary for the efficient acid production.

Benzyl ethyl succinate presents an interesting example of the specificity of the reaction. Only β-carbethoxy propionic acid is formed, showing that only the benzylated ester is affected.

Discussion

The results given in Tables I–V demonstrate that benzyl esters cleave to acids under the influence of high-energy radiation. The reaction appears quite general and offers a method of de-esterification under conditions of environment that are not possible with other methods. Recent publications have appeared where photolytic methods have been used to convert esters to acids.[2,3] Interestingly, the esters that appear to photo de-esterify most efficiently are those which form stable free radicals.

Some deductions pertaining to the mechanism may be made from the data. If direct photolysis were involved, it would seem reasonable to propose a photodissociation either leading directly to acid, as shown in reaction 2, or to acid through the intermediate carboxyl radical (reactions 3 and 4).

$$\mathrm{RCOOBz} + h\nu \longrightarrow \mathrm{RCOOBz}^* \tag{1}$$

$$\mathrm{RCOOBz}^* + \mathrm{R'H} \longrightarrow \mathrm{RCOOH} + \text{products} \tag{2}$$

$$\mathrm{RCOOBz}^* \longrightarrow \mathrm{RCOO}\cdot + \mathrm{Bz}\cdot \tag{3}$$

$$\mathrm{RCOO}\cdot + \mathrm{R'H} \longrightarrow \mathrm{RCOOH} + \mathrm{R'}\cdot \tag{4}$$

In this work, high-energy radiation introduces a further set of reactions that have to be considered. Most of the energy is initially absorbed by the solvent, and yet the high *G* for ester disappearance calls for a mechanism of transferring the energy to the ester.[1] Two general types of reactions suggest themselves: one an energy transfer process (reaction 6), and the other a free radical derived from the solvent attacking the ester to produce acid as the major product (reactions 7 and 8).

$$\mathrm{R'H}\ (\text{solvent}) + \epsilon \longrightarrow \mathrm{R'H}^* \tag{5}$$

$$\mathrm{R'H}^* + \mathrm{RCOOBz} \longrightarrow \mathrm{R'H} + \mathrm{RCOOBz}^* \tag{6}$$

$$\mathrm{R'H}^* \longrightarrow \mathrm{H}\cdot + \mathrm{R'}\cdot \tag{7}$$

$$\mathrm{R'}\cdot \text{ and/or } \mathrm{H}\cdot + \mathrm{RCOOBz} \longrightarrow \mathrm{RCOOH} + \text{products} \tag{8}$$

A possible means of separating the parts of the debenzylation reaction is by adding free-radical scavengers. If free-radical attack on the ester is the major source of its reaction, then scavengers should prevent the reaction of the ester, and no acid will be produced. Irradiation of 0.1 *M* benzyl acetate in cyclohexane saturated with iodine (0.05 *M*) yielded $-G$ (ester) = 2.3, and *G* (acetic acid) = 1.4, as compared to the values

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(1) A. MacLachlan, *J. Am. Chem. Soc.*, **82**, 3309 (1960).

(2) (a) D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *Tetrahedron Letters*, 1055 (1962); (b) J. A. Barltrop and P. Schofield, *ibid.*, 697 (1962).

(3) (a) H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **83**, 4486 (1961); (b) H. E. Zimmerman and V. R. Sandel, *ibid.*, **85**, 915 (1963).

TABLE I

Ester	Concn., M	Solvent	Dose, $\frac{\text{e.v.}}{\text{ml.}} \times 10^{-21}$	$-G$ (ester)	G (acid)	% yield, acid
Benzyl acetate	0.1	Cyclohexane	1.08	2.7	1.8	67
Benzyl acetate	0.1	Ethanol[a]	1.00	1.6	1.6	100
Benzyl acetate	0.1	Methanol	0.98	1.6	0.85	53
Benzyl butyrate	0.1	Cyclohexane	0.98	2.8	1.4	50
Benzyl butyrate	0.1	Ethanol	0.98	1.8	1.3	72
Benzyl isobutyrate	0.1	Cyclohexane	0.53	2.5	1.7	68

[a] Ethanol was irradiated in the absence of benzyl acetate, and no acetic acid was detected.

TABLE II

RADIATION INTENSITY EFFECT ON G (ACID) FOR BENZYL ACETATE IN CYCLOHEXANE

Beam current,[a] ma.	G (acid)
0.5	2.25
1.0	2.05
2.0	2.05
3.0	2.15
5.0	2.25

[a] Conversions were all adjusted for about 30% reaction of the benzyl acetate.

TABLE III

Initial concn. of dibenzyl succinate, M	G (succinic acid)[a]
0.10	0.047
0.067	0.065
0.020	0.14
0.005	0.10

[a] Same total amount of energy into each sample. Solvent is cyclohexane.

TABLE IV

ACID YIELDS FOR BENZYL-TYPE ESTERS[a]

Ester	Dose, megarads	G (acid)	Acid formed
Benzyl benzoate	11.5	1.08	Benzoic
Benzyl cholate	9.5	1.8	Cholic
α-(Naphthyl)methyl acetate	12.5	1.3	Acetic
Benzyl ethyl succinate	17.2	2.4	β-Carbethoxy propionic

[a] All esters were 0.1 M in cyclohexene except benzyl cholate which was 0.1 M in cyclohexene.

TABLE V

ACID YIELDS FOR NONBENZYL ESTERS[a]

Ester	Dose, e.v./ml. × 10^{-20}	G (acid)
β-Phenylethyl acetate	6.9	0.084
γ-Phenylpropyl acetate	6.7	0.16
Cyclohexyl acetate	6.9	0.23
Cyclohexylmethyl acetate	5.8	0.19
Phenyl acetate	5.7	0.37
Phenyl benzoate	6.2	0.87
Ethyl benzoate	1.6	0.02[b]

[a] All esters 0.1 M in cyclohexane. [b] G.l.c. analysis for loss of ethyl benzoate indicated no detectable reaction.

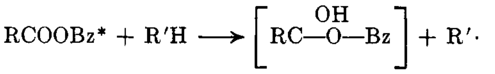
of 2.7 and 1.8 in the absence of scavengers. While both yields are reduced slightly, it would seem most reasonable to eliminate the free-radical attack mechanism.

If acetoxy radicals are produced by dissociation of excited ester, then one would expect either decarboxylation or a capture by the iodine.[4-6]

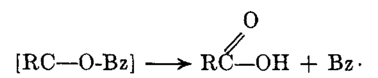
Ethyl benzoate yielded negligible amounts of acid (Table V) and at the same time was not detectably reacted at a dose that would have destroyed 50% of the benzyl acetate (0.1 M). This lack of reactivity demonstrates that the aromatic ring is not the major point of attack for any solvent-derived free radicals. Again, this supports a nonradical path for the acid formation.

Zimmerman and co-workers[3] have found photo-induced heterolysis reactions of substituted benzyl compounds in polar solvents. The heterolysis mechanism would not appear to be applicable in this work since de-esterification to form acid occurs with unsubstituted benzyl compounds even in cyclohexane. However, if heterolysis in nonpolar solvents of simple benzyl esters requires higher excited states than that obtained by photolysis or perhaps even ionized molecules, ionizing radiation certainly has this capability.

In summary, the data obtained indicate that some type of energy transfer process other than a free-radical reaction is responsible for the efficient excitation of the ester by electron irradiation. Furthermore, a direct dissociation of excited ester into carboxyl radicals and benzyl radicals does not seem reasonable because of the high acid yields obtainable.[4-6] It is suggested that the reaction sequence for excited ester decomposition (reactions 9 and 10) best fits the experimental facts.



$$\mathrm{RCOOBz^* + R'H \longrightarrow \left[RC\overset{\displaystyle OH}{—O}—Bz \right] + R'\cdot} \qquad (9)$$



$$\mathrm{[RC—O\text{-}Bz] \longrightarrow R\overset{\displaystyle O}{\overset{\|}{C}}—OH + Bz\cdot} \qquad (10)$$

Iodine might effect the reaction by reacting directly with the excited ester, but this could be much less efficient than its reaction with radicals.

A similar intermediate has been suggested as contributing to the photodecomposition of alkyl esters.[7] Excited carbonyl-abstracting hydrogen atoms are, of course, well known in ketone photolysis.[8-13]

In addition to the obvious synthetic applications of this reaction as an additional means of de-esterification, it has the possibility of being a simple and convenient organic dosimeter. The dose rate and total dose effects investigated, in Fig. 1 and 2 and Table II, indicate that there are large regions of linearity of acid production; and, therefore, its use as a dosimeter seems ideal. A discussion of the needs for a chemical dosimeter that

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(7) P. Ausloos, *ibid.*, **80**, 1310 (1958).
(8) J. A. Bell and H. Linschitz, *ibid.*, **85**, 528 (1963).
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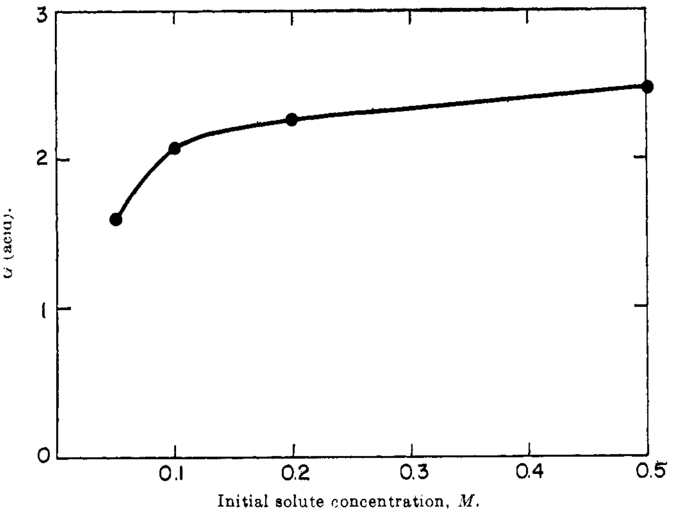

Fig. 1.—Effect of benzyl acetate concentration on G (acid) in cyclohexane. Dose for each irradiation was 5 × 10^{20} e.v./ml.

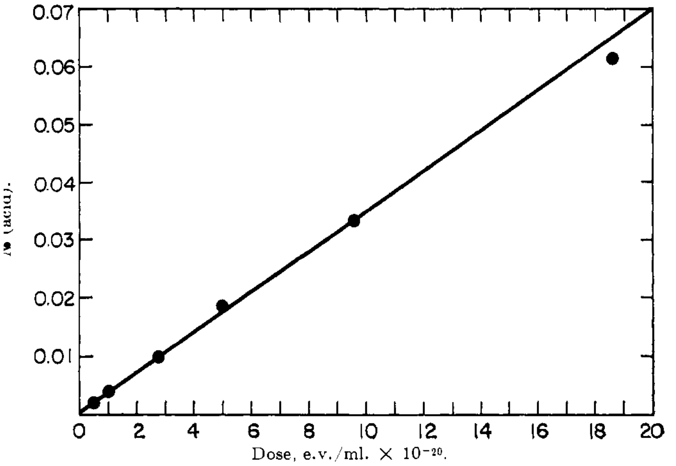

Fig. 2.—N (acid) *vs.* total irradiation dose for 0.2 M benzyl acetate in cyclohexane.

can be used in metallic vessels as well as glass vessels is given by Hardwick and Guenther.[14]

Experimental

Irradiation Procedure.—The radiation source used in this work was a General Electric resonant transformer supplying 2-m.e.v. electrons, at beam currents up to 5 ma. Samples were irradiated in the multiple cell sample holder previously described[15] or on a larger scale in a deoxygenating flask. This flask is a flat-bottom beaker, with a ground glass rim. The total volume is 250 ml. with an inside diameter of 9 cm. After placing the solution to be irradiated and a magnetic stirring bar in the vessel, the top is sealed with a sheet of aluminum foil held in place with a clamped aluminum ring. Deoxygenating is accomplished by purging with argon through a side arm for 20 min. before and continuing the flow at a lower rate during irradiation. Temperature is controlled by immersing the entire lower two-thirds of the vessel in a constant temperature bath. Evaporation losses were prevented by presaturation of the argon with the appropriate solvent.

Iodine-scavenging experiments were carried out by maintaining excess solid iodine in the stirred irradiation cell.

Analytical Procedures.—Acid and ester yields were analyzed by g.l.c. analysis whenever possible. Benzyl acetate, butyrate, ethyl benzoate, acetic acid, and butyric acid conveniently were analyzed on a 5-ft. column of 15% stearic acid–15% silicone grease on Chromosorb at 108–150°.

Acid yields also were determined by titration with 0.02 M aqueous sodium hydroxide to the phenolphthalein end point. Aliquots of the irradiated solution were added to an equal volume of distilled water, flushed with argon to remove the carbon dioxide, and then titrated.

β-Carbethoxy propionic acid and cholic acid were isolated from the irradiation of their respective benzyl esters. The irradiated solutions were extracted with 10% aqueous sodium bicarbonate; the extracts were neutralized with dilute hydrochloric acid and extracted with ether. After drying the ether solution over Drierite, the acids were isolated by removing the solvent. Infrared spectral analyses and comparison with authentic samples of the acids served to prove the structures. Blanks were carried through the isolation procedure to be certain no ester hydrolysis occurred.

Materials.—Cyclohexane was Eastman Spectro Grade, ethanol was Pharmco absolute, and methanol was Baker Analyzed reagent.

β-Carbethoxy benzyl propionate was prepared from β-carbethoxy propionyl chloride by the method of Hauser.[16] β-Carbethoxy propionyl chloride was prepared by the method of Riegel and Lillienfield.[17]

Benzyl cholate was synthesized by placing 100 g. (0.24 mole) of cholic acid in 50 ml. of water and neutralizing to the phenolphthalein end point with 20% aqueous sodium hydroxide. Benzyl chloride (45 g., 0.35 mole) was added and the mixture refluxed for 2 hr. After cooling, the mixture was extracted with ether and the ether layer washed with 10% aqueous sodium bicarbonate and dried over Drierite. After evaporation of the ether, the oil was extracted eight times with cyclohexane to remove the residual benzyl chloride. No success was obtained with crystallizing the benzyl cholate, and therefore, it was used directly. After a time, the viscous oil crystallized spontaneously. Infrared spectroscopy was used to verify the ester structure.

α-(1-Naphthyl)methyl acetate (I) was prepared by refluxing 40 g. (0.28 mole) of α-chloromethylnaphthalene with 0.3 M sodium acetate in 250 ml. of glacial acetic acid for 3 hr. The acetic acid was removed by evaporation, and the residue extracted with ether. After evaporating the ether, the oil was distilled to yield I, b.p. 80° (0.5 mm.).

α-Cyclohexylmethyl acetate was prepared from 25 g. (0.18 mole) of cyclohexylcarbinol by reaction with 14.5 g. (0.19 mole) of acetyl chloride in 23 g. (0.2 mole) of dimethylaniline and 50 ml. of ether. The acetyl chloride was added dropwise at a rate necessary to maintain reflux. The residue was extracted with ether. The ether layer was extracted with 10% aqueous hydrochloric acid, then washed with 10% sodium bicarbonate, water, and then dried over Drierite. The ether was removed and the ester was distilled under vacuum, b.p. 105° (56 mm.).

Acknowledgment.—Thanks are due to J. M. White for his assistance in carrying out the experiments.

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