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Note

On the formation of deoxy sugars from halogenated carbohydrates by α-hydroxyalkyl radicals: considerations for the optimisation of reaction conditions

ROLF LEMMES AND CLEMENS VON SONNTAG
Max-Planck-Institut für Strahlenchemie, Stiftstraße 34–36, D-4330 Mülheim a.d. Ruhr (West Germany)
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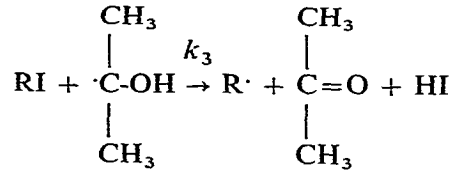
Photolysis of iodinated carbohydrates in primary or secondary alcohols yields the corresponding deoxy compounds[1–5]. Under favourable conditions, the conversion is practically quantitative[5] and the method may be of value in synthesis. It has been suggested that the mechanism of this reaction might involve, in the first step, photolytic cleavage of the C–I bond (reaction *1*, where R is a carbohydrate residue) followed by H-abstraction from the alcohol by the carbohydrate radical (reaction *2*).

$$RI \xrightarrow{h\nu} R^{\cdot} + I^{\cdot} \qquad (1)$$

$$R^{\cdot} + \underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{H\text{-}C\text{-}OH}}}} \xrightarrow{k_2} RH + \underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{{}^{\cdot}C\text{-}OH}}}} \qquad (2)$$

In general, free-radical reactions do not lead to products with such a high chemical purity as observed for the present system, unless the product is formed *via* a chain reaction. That a chain reaction may also be involved in the present system can be deduced from the radiation chemistry of simple alkyl halides[6–9]. We investigated the present system with the aim of identifying conditions for a clean, rapid, and, where desirable, selective dehalogenation (*e.g.*, selectivity of I over Br or I in different stereochemical positions).

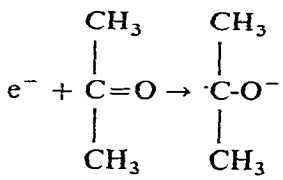
If a chain reaction prevails, the photolytic step (reaction *1*) is only the initiating step and the overall reaction *3* might be of considerable importance.



(3)

One then can start the reaction with any other system which generates α-hydroxyalkyl radicals.

One such system involves the γ-radiolysis of 2-propanol which contains some acetone. Although the γ-radiolysis of 2-propanol[10] is not *a priori* a simple system, it is a very practical one for the present investigation. All reactive radicals ($H^{\cdot}$, $^{\cdot}CH_3$, $^{\cdot}CH_2$-CHOH-CH_3, CH_3-CHO$^{\cdot}$-CH_3) subsequently undergo H-abstractions and generate 2-hydroxypropyl-(2) radicals (*cf.* reaction *2*). The latter radicals are also produced from acetone by scavenging radiolytically formed electrons (reaction *4*). The ketyl product is in equilibrium with its protonated form, the 2-hydroxypropyl-(2) radical (equilibrium *5*). In aqueous solution, the pK value of this system[11] is 12.2.



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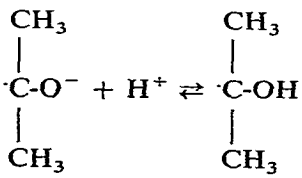
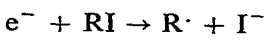


(5)

In the present system, acetone was added in hundred-fold excess over the substrate in order to prevent a reaction of the solvated electrons (for rate constants, see refs. 12 and 13) with the halogenated sugar (reaction *6*).



(6)

The radiation chemical yield of the 2-hydroxypropyl-(2) radicals in this system is not known exactly, but a G value* of ~6 of 2-hydroxypropyl-(2) radicals for 100 eV of absorbed radiation energy is to be expected. There is also a minor contribution (G = 1) of hydroxyethyl radicals[14]. These have properties similar to those of 2-hydroxypropyl-(2) radicals, and they can therefore be considered together. Three compounds were investigated, namely, 3-deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**), 3-deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**), and 3-bromo-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**).

*The G value is defined as the number of molecules formed per 100 eV of absorbed radiation energy.

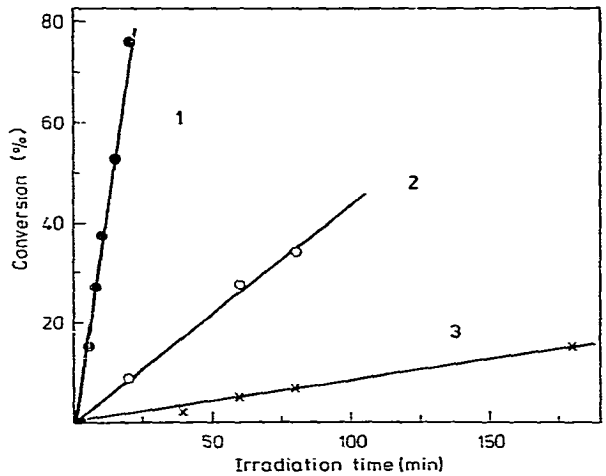


Fig. 1. Release of halide ion from compounds **1**–**3**.

In agreement with the photolytic study[5], 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**4**) was the only detectable product and the reaction could be carried to completion, as shown by h.p.l.c. For the kinetic studies, it was easier to measure the progress of the reaction by determining the release of halide ion.

Fig. 1 shows the results of experiments at practically neutral conditions. Solid sodium hydrogencarbonate was added[5] to scavenge the liberated hydrogen halides. Under these conditions, there is a large difference in the rates of formation of halide ions, which follow the sequence **1** ≫ **2** > **3**. There is an activation energy involved in the dehalogenation process, as shown by the temperature dependence of the rate of dehalogenation of **2** (Table I).

As expected for a chain reaction, there is a strong dose-rate effect. At a dose of 5.7×10^{18} eV.g^{-1} and a dose rate of 6×10^{19} eV.g^{-1}.h^{-1}, only 40% of the *allo*-iodide (**2**) was converted into **4**, whereas at the same dose, but with the lower dose-rate of 2.5×10^{18} eV.g^{-1}.h^{-1}, the conversion was 90%.

TABLE I

DEHALOGENATION OF HALOGENATED SUGARS BY 2-HYDROXYPROPYL-(2) RADICALS

Compound[a]	*G (Halide ions) in the γ-radiolysis of acetone containing 2-propanol*			
	Solid hydrogencarbonate			*10⁻²M KOH*
	0°	*20°*	*60°*	*20°*
gluco-Iodide (**1**)		130		660
allo-Iodide (**2**)	14	15,36[b]	19	270
gluco-Bromide (**3**)		3		270

[a] 10^{-3}M Solutions. [b] 10^{-2}M.

If the dehalogenation was carried out in basic medium (10^{-2}M KOH), under conditions where alkali-induced dehalogenation does not occur in the time scale of the experiments, there was a much faster dehalogenation and the rate sequence **1** $\gg$ **2** $\approx$ **3** was observed. The marked difference between the hydrogencarbonate-buffered and the alkaline conditions is due to the much stronger reducing-power of the radical anion as compared to the neutral species. At pH $\sim$12, $\sim$50% of the 2-hydroxypropyl-(2) radicals are dissociated (equilibrium *5*). However, from the large difference in the rate of dehalogenation in alkaline medium as compared with hydrogencarbonate-buffered conditions, it is clear that the chemistry in alkaline medium is largely governed by the reactions of radical anions (reaction *7*).

$$RX + \cdot C(CH_3)_2-O^- \xrightarrow{k_7} R^\cdot + X^- + C(CH_3)_2=O \qquad (7)$$

It was not possible to study the reaction at higher pH and higher temperatures, because thermal dehalogenation then becomes significant.

Details of the reduction process *3* are not yet fully understood. For the dehalogenation of CCl_4, it has been shown[15] that the kinetic parameters do not entirely fulfil the requirements of the Marcus theory of electron transfer, although this theory explains some electron-transfer reactions quite adequately. An adduct [$HOC(CH_3)_2$-İ-R], a 9-I-2 intermediate[16], might even be considered as a short-lived intermediate (*cf.* ref. 17). The present study cannot prove or disprove the formation of such an intermediate; however, trivalent iodine is known, as well as halide ions complexed with radicals, and similar complexes in sulfur free-radical chemistry are well documented[18,19].

There is a large difference in the reactivity between the *gluco*-iodide (**1**) and the *allo*-iodide (**2**). The most likely reason is steric hindrance in **2**. The isopropylidene groups would hinder the approach of the 2-hydroxypropyl-(2) radical to the *allo*-compound **2** similarly to their hindrance of overall S_N2 attack on the *gluco*-compound **1** (*cf.* ref. 20). If an attack from the front is not possible, an electron transfer may also occur from the rear side (*cf.* ref. 21), possibly with some lower rates.

In basic medium, the rate of reaction is considerably increased. The reactivity of the various compounds is now very similar, although the *gluco*-iodide **1** still reacts twice as fast as the other two compounds. There is no longer a difference between the rates for the *allo*-iodide **2** and the *gluco*-bromide **3**. From the difference in rates for **1** and **2**, it appears that steric hinderance persists for the reaction of the radical anion.

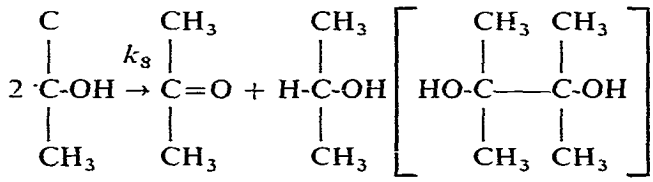
Under neutral conditions, the reactivity of the bromide **3** is considerably less than that of the stereochemically equivalent iodide **1**. Under basic conditions, the reactivity of **3** is much enhanced ($\sim$100-fold) with respect to the quasi-neutral conditions, but it does not attain the reactivity of **1**. The lower reactivity of the

bromo compound compared to the iodo compound could result from the difference in the C–X bond energies[22].

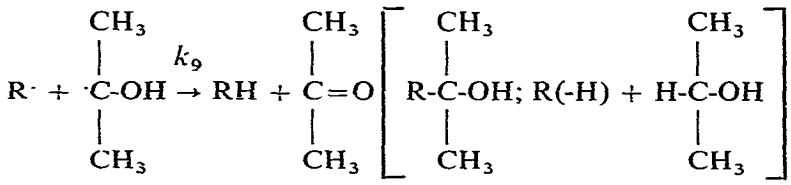
The chain reaction is strongly inhibited by O_2, and at least two mol of 2-hydroxypropyl-(2) radicals are consumed by one mol of oxygen[23].

The rate constant of reaction *2* is the same for all three systems studied, because the radical R· has the tendency to become planar and readily inverts. Thus, there will be no difference in the structure of R· whether the precursor is a *gluco-* or *allo-*compound.

There are three possible termination reactions, namely, self-termination of the initiating radicals (reaction *8*), and cross-termination (reaction *9*) and self-termination of the sugar radicals (reaction *10*). The self-termination of the α-hydroxypropyl-(2) radicals largely occurs *via* a disproportionation process, and combination to give pinacol is of minor importance[24]. Because of this preference to disproportionate in the self-termination reaction, it is also likely that the 2-hydroxypropyl-(2) radical does so in the cross-termination (reaction *9*). This may be one reason why 2-propanol is such a suitable substrate. The self-termination of the sugar radicals (reaction *10*) can lead to dimeric material (R–R, see below).



(*8*)



(*9*)

(*10*)

A full, kinetic evaluation of the reaction scheme is not possible with the present system, partly because the RX concentration can be varied over only a narrow range, the lower limit being set by the analytical procedure, and the upper limit by competition involving reaction *6*. However, the expected increase in the rate of dehalogenation with increasing concentration of **2** in the hydrogencarbonate-containing system is clearly observed (Table I). From the data in Table I, the order of magnitude of k_2 can be estimated. This is possible if reaction *7* is very much faster than reaction *2*, and if termination occurs only by reaction *10*. In alkaline solutions with **1** as substrate, such conditions seem to prevail. Using the known initiation rate and assuming diffusion-controlled termination [$k_{10} = (1–2) \times 10^9 M^{-1}.s^{-1}$], k_2 is then estimated as $\sim 25–50 M^{-1}.s^{-1}$. This value compares well with the value of $53 M^{-1}.s^{-1}$ determined for the reaction of the 2-hydroxypropyl-(1) radical with 2-propanol[25,26]. Being a

primary alkyl radical, the 2-hydroxypropyl-(1) radical is expected to be somewhat more reactive than the secondary alkyl radical derived from **1–3**.

For compounds **2** and **3**, a similar estimate can be made for k_3 at neutral conditions. There, k_3 tends to be rate-determining, and termination is largely by reaction *8*. It can then be estimated that k_3(**3**) is $\sim 300 M^{-1}.s^{-1}$, and that k_3(**2**) is a factor of 4 or 5 higher [k_3(**1**) should be even higher, but a proper estimate is difficult to obtain from the present data].

The present data show that chain reactions play a considerable role in the radical-induced dehalogenation of iodo and bromo sugars. In order to obtain products of high purity, conditions should be chosen to favour such chain reactions. For this reason, low initiation rates, high concentrations of sugar halide, and, if possible, alkaline conditions are advantageous. On starting the reaction photolytically with iodides as substrates, it might be favourable[2] to filter out a considerable part of the light in order to achieve sufficiently low rates of initiation. The filtering out of high-energy photons can have a marked effect because, in solution, halogen compounds tend to undergo cleavage of the C–X bond at high photon-energies with substantially higher quantum yields (*e.g.*, ref. 27).

We therefore suggest that the high yield of dimeric material (R–R) observed[2] at high initiation rates (unfiltered light) is due to a combination of the carbohydrate-derived radicals (reaction *10*) formed in reaction *1*. The alternative mechanism[2] ($R^{\cdot} + RX \rightarrow R\text{–}R + X^{\cdot}$) does not explain the results[2], because it does not involve the postulated wavelength-dependence of reaction *1* (alternative reaction paths at shorter wavelengths).

EXPERIMENTAL

3-Deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) and the corresponding *allo*-compound (**2**) were prepared according to Binkley and Hehemann[28]. 3-Bromo-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**) was prepared by the same triflate-displacement method[28], using tetrabutylammonium bromide as bromine source. All of the above materials were purified by column chromatography on silica gel with toluene–acetone (99:1).

Solutions of **1–3** (10^{-3}M unless otherwise stated) in 2-propanol containing acetone and solid sodium hydrogencarbonate (both in 100-fold excess to RX) or 10^{-2}M KOH were freed from oxygen by purging with Ar for 30 min or by several freeze–pump cycles. The samples were irradiated in a Nuclear Engineering Ltd. panorama 60-Co-γ source at a dose rate of 1.2×10^{18} eV.g^{-1}.h^{-1}, with doses ranging from 10^{16}–3.6×10^{18} eV.g^{-1}. Halide ions were titrated potentiometrically with 0.01M $AgNO_3$. With hydrogencarbonate-containing samples (10^{-3}M **2**, 10^{-1}M acetone), it was confirmed (*cf.* ref. 5) by h.p.l.c. (Li-chromosorb, A-100, toluene–acetone 95:5) that 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**4**) was the only detectable carbohydrate product and that quantitative conversions are possible.

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