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RADIATION STUDIES OF ARYL GLYCOSIDES

PART III. THE REACTIVITY OF ARYL GLUCOSIDES TOWARDS HYDROXYL RADICALS AND HYDRATED ELECTRONS

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ABSTRACT

Rate constants for the reactions of hydrated electrons and OH radicals with the aryl aglycon of a series of substituted aryl glycosides have been measured. The results are correlated by using the Hammett relationship $\log(k/k_s) = \rho\sigma$. For hydrated electrons, $\rho = +3.5$, and for OH radicals, $\nu = ca.\ -0.3$, which show that electron-withdrawing groups greatly accelerate e_{aq}^- reactions but exert only a small retarding effect on OH radical reactions; electron-repelling groups exert an opposite effect. Glycosidic scission accompanies these reactions, and there is some similarity in the behaviour of e_{aq}^- with alkaline hydrolysis ($\rho = +2.5$) and of OH radicals with acidic hydrolysis ($\rho = -0.7$) of aryl glucosides. The results show that the sugar ring exerts an electron-attracting influence in relation to the aglycon.

INTRODUCTION

The products of water radiolysis, OH radicals and hydrated electrons (e_{aq}^-), were shown to react with the aryl aglycon of phenyl β-D-glucopyranoside[1]. To obtain further information about the mechanism of reactions of e_{aq}^- and OH radicals with the aromatic moiety, the effect of introducing substituents into the aromatic aglycon will be studied here. The specific reaction rates of a series of aromatic compounds with OH radicals[2] and e_{aq}^-[3] have been determined. It was suggested that e_{aq}^- reacts in the manner of a nucleophile, forming a carbanion as a primary product[3]. The OH radical, on the other hand, resembles an electrophile, and it was concluded that the mechanism of attack of hydroxyl radicals is analogous to an electrophilic aromatic substitution[2]. The aryl glucosides, in our view, offer particular advantages for this type of study, since they are crystalline and can be prepared in a high degree of purity. Moreover, the sugar moiety increases the solubility in water compared with the parent aromatic molecule. Therefore, accurate concentrations can be established and maintained even after rigorous degassing procedures, which would reduce the concentration of certain aromatic solutes of high volatility.

Another objective is to further investigate the electron-attracting influence of the carbohydrate moiety, relative to the aromatic aglycon noted in our previous study[1].

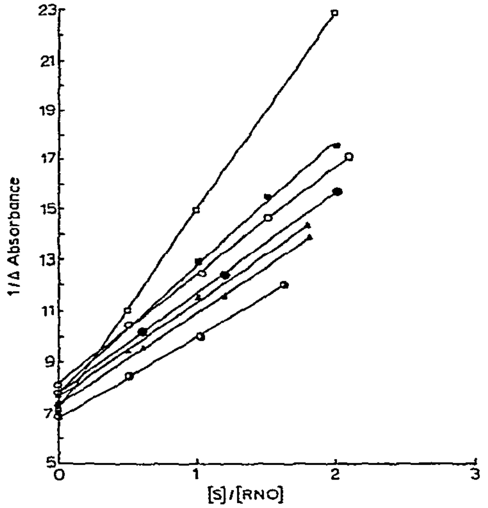
EXPERIMENTAL AND RESULTS

The pulse radiolysis methods were given in the previous paper[1], and the glucosides were prepared as previously described[4].

Hydroxyl radical rates. — For determining the relative rates of reaction of OH with a series of glycosides, *N*,*N*-dimethyl-*p*-nitrosoaniline[5] was used as a competitor[2]. The results of several investigators[6–8] show that care must be exercised if meaningful results are to be obtained with this method. Back reactions and scavenging of secondary radicals observed during pulse radiolysis have cast doubt on the absolute values of the rate constant of OH-radical reactions with the basic form of RNO. Whether *G*(–RNO), measured by the change in the absorbance at λ_{max} 440 nm (ε 34,000 $M^{-1}.cm^{-1}$), is indeed numerically equal to *G*(–RNO) is, at present, in question. To obtain absolute OH rates we have, therefore, used independently determined rate constants as reference values. Phenyl β-D-glucopyranoside was shown to react with OH radicals[1] with a mean value of $k_2 = 4.4 \times 10^9 M^{-1}.sec^{-1}$ by direct measurement of the rate of formation of the OH-radical adduct. Neta and Dorfman[9] used this direct method to avoid the hazards inherent in the various competitive methods. The rate constant $k_{(OH+D\text{-}glucose)} = 1.7 \times 10^8 M^{-1}.sec^{-1}$ was established by Scholes and Willson[10] after normalising to $k_{(OH+thymine)} = 4.3 \pm 1.0 \times 10^9 M^{-1}.sec^{-1}$, which had also been established by direct measurement. In the present investigation, phenyl β-D-glucopyranoside and D-glucose have been used independently in competition with RNO, and the relative rates obtained in this way used to establish the rate constants for the aryl glycosides.

For γ-irradiation, doses of not more than 4×10^{17} eV.ml^{-1} were employed. We have confirmed that $G(\text{–RNO})_{440\ nm}$ was unchanged at 1.1 over a dose rate of 5–14 × 10^{16} eV.ml^{-1}.min^{-1} and RNO concentrations of 10–50 μm. In the competition studies ratios of $[S]/[RNO] \ngtr 2.5$ were used. No significant reaction of the carbohydrate radicals with alkaline RNO under the oxygenated conditions of our experiments was found. Fig. 1 shows typical competition plots of monosubstituted aryl glucosides, using the RNO method. Each point is the mean of two separate runs. Di- and trisubstituted aryl glycosides were similarly examined. The results are given in Table I. For comparison, in selected instances, we have also employed the pulse radiolysis method[11], using CNS^- as a competitor. Despite the evidence that this reaction is more complex than was at one time envisaged, its value in giving good relative values, particularly for a related series of compounds, has been emphasised[12].

Hydrated electron rates. — By using the rate of disappearance of e_{aq}^- in aqueous solutions of aryl glucoside measured by pulse radiolysis, the pseudo-first-order rate



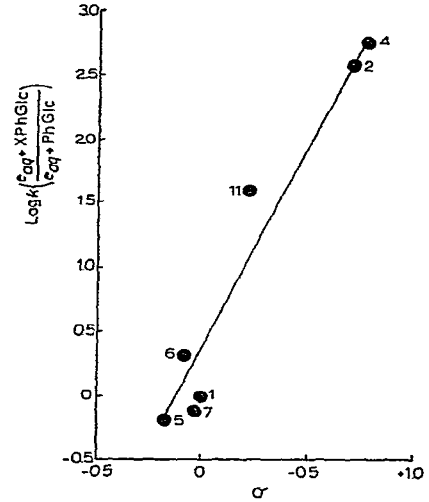


Fig. 1. Typical competition plots for the reactions of OH radicals with monosubstituted ary glycosides by using the RNO method[5]: aryl β-D-glucopyranosides; □ *p*-methoxylphenyl; ■ phenyl; ○ *m*-nitrophenyl; ● *p*-chlorophenyl; ▲ *p*-cresyl; △ *m*-bromophenyl; ◑ *p*-nitrophenyl.

Fig. 2. Correlation of rates of reaction of e_{aq}^- by using the Hammett equation; the numbers refer to glycosides listed in Table I.

TABLE I

SECOND-ORDER RATE CONSTANTS FOR THE REACTIONS OF HYDRATED ELECTRONS AND HYDROXYL RADICALS WITH SUBSTITUTED ARYL GLUCOSIDES

β-D-*Glucopyranoside*	$10^7 \times k_2(e_{aq}^- + glycoside)$ ($M^{-1}.sec^{-1}$)	$10^9 \times k_2(OH + glycoside)$ ($M^{-1}.sec^{-1}$)	
		RNO method	*CNS⁻ method*
1 Phenyl	6.5	4.4	3 5
2 *o*-Nitrophenyl	2540	3.0	2.9
3 *m*-Nitrophenyl	—	3.4	—
4 *p*-Nitrophenyl	3890	2.8	2.6
5 *o*-Cresyl	4.1	3.4	3.2
6 *m*-Cresyl	14	3 0	3.7
7 *p*-Cresyl	6.1	2.7	2.2
8 *p*-Methoxyphenyl	—	7 0	6.9
9 *p*-Hydroxylphenyl	—	2.7	—
10 *m*-Chlorophenyl	—	3.2	—
11 *p*-Chlorophenyl	257	3.4	3.4
12 *p*-Cyanophenyl	—	3.5	—
13 *m*-Bromophenyl	—	3.2	—
14 2,4-Dimethylphenyl	5.0	—	2.7
15 2,4,6-Trimethylphenyl	—	3.2	—
16 3,4-Dimethylphenyl	—	3.6	—
17 2,4,6-Trichlorophenyl	—	1.9	—

constant can be found. When there is reaction with the glucoside, an estimate of the second-order rate constant can, therefore, be obtained. The results are given in Table I.

DISCUSSION

Substitution of e_{aq}^-, unlike the widely studied, nucleophilic and electrophilic substitution reactions[13], does not involve the usual bond making and breaking processes or atom transfer. Nevertheless, the reactions of e_{aq}^- show some similarity with those of classical nucleophiles in attacking localized centres in an aromatic nucleus[3]. To a first approximation, this reaction may be regarded as a simple, charge-transfer process involving incorporation of the electron into one of the orbitals of the aromatic group. Since the charge distribution in an aromatic nucleus is profoundly redistributed by the introduction of substituents, it is to be expected that the reaction of e_{aq}^- at these centres should vary correspondingly. Indeed, in a general fashion, it has been found that groups which withdraw electrons from the ring increase the rate of reaction with e_{aq}^-, and those which donate electrons decrease the rate[14].

Our observations illustrate this behaviour in a clear-cut fashion. The second-order rate constants vary over three orders of magnitude from 6.5×10^7 $\text{M}^{-1}.\text{sec}^{-1}$ for phenyl β-D-glucopyranoside to $>10^{10}$ when nitro groups are introduced. Introduction of methyl groups promotes the opposite effect; the e_{aq}^- rate changes from 6.5×10^7 (phenyl) to 4.1×10^7 (*o*-cresyl) and 6.1×10^7 $\text{M}^{-1}.\text{sec}^{-1}$ (*p*-cresyl). The *m*-cresyl group is anomalous, and although the difficulty of relaying electronic effects from the meta position is apparent during aromatic substitution, it is important to note that this group actually enchances the e_{aq}^- rate ($k = 13.6 \times 10^7$ $\text{M}^{-1}.\text{sec}^{-1}$). Effectively, due to the presence of the sugar ring, the aromatic nucleus is disubstituted in the aryl glucosides. Anbar and Hart[3] found for *m*- and *p*-disubstituted benzenes a similar increase in e_{aq}^- reactivity when the substituents were meta. Considering the electron density, for example, in fluorophenol for which $k_{\text{meta}} > k_{\text{para}}$, it is clear that position 5 (OH at C-1) would be particularly electron-deficient and so would present a favourable site for e_{aq}^- attack. From our results, the glucosyl group exerts an electron-withdrawing influence on the nucleus and provides, therefore, a direct parallel, since the CH_3, like O^-, repels electrons. This specific enhancement of rate is, therefore, additional evidence that the attack of e_{aq}^- is highly localised.

Where comparison is possible, the reaction rate with the glucoside is greater than with phenol or benzene substituted with the same group (Table II). The glucosyl residue, therefore, exerts a definite electron-withdrawing effect on the aromatic aglycon. Previously, there has been no demonstration of the electron-withdrawal property of the sugar ring.

The effect of a para chlorine atom is to greatly increase the e_{aq}^- rate, and the predominant effect is clearly the $-$I effect of the chlorine atom. This behaviour is quite different from the effect of this group in aromatic substitution, when slow *o*- and *p*- substitution is found following the tautomeric release of electrons at the demand of the reagent in opposition to the $-\mathrm{I}$ effect. Such an enhanced e_{aq}^- rate is also found when chlorine is introduced into aromatic molecules (Table II).

TABLE II

COMPARISON OF e_{aq}^- RATE CONSTANTS OF SUBSTITUTED ARYL D-GLUCOSIDES AND THE CORRESPONDING BENZENE AND PHENOL DERIVATIVES

X	*X-Phenyl* D-*glucopyranosides*	*HO–PhX* $10^7 k_2(\mathrm{M}^{-1}.\mathrm{sec}^{-1})$	*PhX*
H	6.5	0.4	1.4
Cl	257	64	50
NO_2	3890	2500	3000

As for other aromatic solutes, the reaction of OH radicals with phenyl β-D-glucopyranoside is at the aryl aglycon, forming a hydroxycyclohexadienyl-type radical. Factors which would lead to stabilization of this radical would be expected to increase the OH reaction rate. Thus, electron-repelling groups should promote reaction by making available positions of high electron density where the OH radical could add to form a bond. Although not as definitive as for e_{aq}^- reactions, the results show certain indications that electron-attracting groups decrease (*e.g.* NO_2) and electron-releasing groups increase the reactivity (*e.g.* OCH_3) of OH radicals. However, since OH radicals are uncharged, the large variations in rate found with e_{aq}^- would not be expected, and are not, in fact, found. The rate constants obtained from the RNO method, based on the D-glucose and phenyl β-D-glucopyranoside rate constants, correlate well, which indicates that reliable, relative rates for the series of substituted glycosides are given in Table I. Although not always identical, the relative rates obtained by the CNS^- method show a similar trend, and provide additional support that the values obtained by the RNO method are reliable. Consequently, it is the results from the RNO method which have been used in the following correlation. Nevertheless, it is only prudent to point out that, until the detailed mechanism of the RNO reactions following irradiation is fully elucidated, it is unwise to place absolute faith in the values obtained.

To obtain some correlation of the results, we have attempted to fit the e_{aq}^- and OH rates to the Hammett relationship[15–21] $\log(k_{C_6H_5X}/k_{C_6H_6}) = \rho\sigma$. Fig. 2 shows a plot of $\log\{k(e_{aq}^- + \text{X-PhGlc})/k(e_{aq}^- + \text{PhGlc})\}$ against σ. The σ-values are those derived[20] by using the ionization of benzoic acids. The values for ortho substituents come by the study of the hydrolysis of substituted acetic acid esters[22]. The corresponding plot for the reactions of OH radicals is given in Fig. 3. For substituents having a deactivating effect, both the σ-meta and σ-para values were used. For substituents which activate the ring, only the σ-para values were used. This procedure was also used by Anbar and Hart[3] in acknowledgment that OH radicals would seek points of high electron density, in the manner of electrophiles.

Whereas a reasonable correlation is found in e_{aq}^- reactions (Fig. 2), there are obvious anomalies which do not fit into the expected relationship for OH reactions

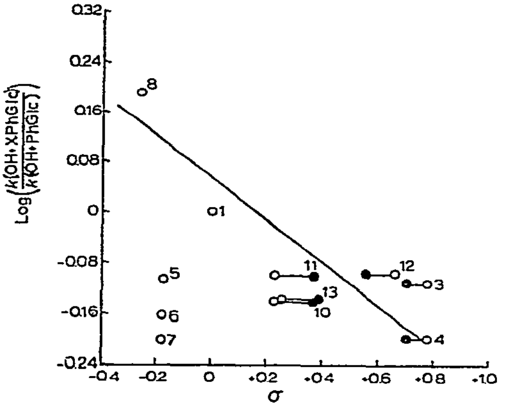


Fig. 3. Correlation of the rates of reaction of OH radicals by using the Hammett equation; the numbers refer to glycosides listed in Table I.

(Fig. 3). The *o*-, *m*-, and *p*-cresyl derivatives, in particular, do not increase the OH-radical reactivity as would be anticipated if the reactivity was influenced only by the electron density of the nucleus. Similar deviations for methyl groups, and generally for groups not containing a lone pair of electrons, were encountered also by Cercek[23]. Introduction of additional substituents into the nucleus exerts little influence on the rate, apart from the 2,4,6-trichloro derivative. Here, the predicted decrease in rate due to the —I effect of these groups is found. However, considerable steric hindrance would also accompany the introduction of these additional groups. Indeed, steric factors appear to over-ride any marginal effects which might accrue from an increase in electron density and lead to a decrease in rate, which thus points to a lack of specific localization in the reactions of OH radicals compared with e_{aq}^-.

Since attack by e_{aq}^- and OH radicals at the aryl aglycon leads to glycosidic scission[1], it is interesting to compare ρ-values obtained in the Hammett relationship for these species with comparable values for the acid- and alkali-catalysed scission of the glycosidic bond for a series of substituted aryl glycosides[24] (Table III). Attack by e_{aq}^- resembles the behaviour of nucleophilic hydroxyl ions, and the ρ-values are similar. The behaviour of OH radicals shows some resemblance to that of the electrophilic H^+, since the ρ-values are negative, indicating acceleration by electron-donating groups. The substituent effects, however, as already noted, are far less-pronounced

TABLE III

ρ-VALUES OBTAINED FROM THE HAMMETT RELATIONSHIP, $\log(k/k_s) = \sigma\rho$, FOR VARIOUS REACTING SPECIES

	e_{aq}^-	*OH*	*H*	H^+	OH^-	NO_2^+
Aryl glycosides	+3.5[a]	*ca.* −0.3[a]	—	−0.7[25]	+2.5[25]	—
Aromatic compounds	+4.8[3]	−0.4[2]	−0.7[25]		+2.4[26]	−7.3[26]

[a] Present investigation.

for OH radicals. Their behaviour is even more marked when comparison is made with electrophilic aromatic substitution, where, for example, $\rho = 7.3$ for NO_2^+.

In conclusion, therefore, there seems reasonable support for regarding e_{aq}^- as a nucleophile in these reactions. For the reactions of OH radicals, on the other hand, whereas there is some justification for the view that the rates are influenced by electron density at the site of reaction, any further analogy with the behaviour of electrophiles in aromatic substitution reactions cannot be justified by the available results. For hydroxyl-radical reactions, the influence of steric factors in the aryl glycosides would appear to be as great as, if not more than, that of electonic factors.

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