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# The 5-Thioglucopyranosyl Carbenium Ion Is a Solvent-Equilibrated Cation

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We report that the 5-thioglucopyranosyl carbenium ion is formed about 800 times faster than the parent glucopyranosyl carbenium ion in the hydrolyses of the corresponding glycopyranosyl fluorides, yet the sulfur-stabilized carbenium ion, which is formed faster, has at least a 360-fold longer lifetime in aqueous solution. This profound breakdown of rate equilibrium relationships reflects the larger intrinsic barrier for reaction of sulfur-relative to oxygen-stabilized carbenium ions.[1,2] Both experiment[1] and theory[3] suggest that an adjacent sulfur atom stabilizes a carbenium ion to a greater extent than does an adjacent oxygen atom.

Acetals are one of the most important biological functional groups.[4] The sulfur congeners, such as 5-thioglycopyranosides and related analogues, have been investigated by several research groups as potential glycosidase inhibitors.[5] Although it has been known for nearly 40 years that both methyl 5-thioxylopyranosides (**1b** and **2b**) undergo acid-catalyzed hydrolysis faster than the corresponding oxygen congeners (**1a** and **2a**),[6] only recently was it established, using kinetic isotope effect (KIE) measurements, that specific acid-catalyzed hydrolysis of methyl 5-thioxylopyranoside proceeds via exocyclic C−O bond cleavage such that positive charge at the transition state is stabilized by the ring sulfur atom.[7]
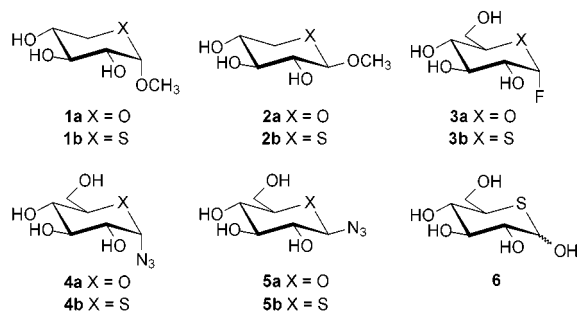


Of note, glucopyranosyl fluoride (**3a**) reacts with azide ion, to give **5a**,[8] and water[9] via "exploded" (weakly associative) $A_N D_N$

(S_N2) transition states. However, glycopyranosides that contain neutral leaving groups react via short-lived, nonsolvent-equilibrated oxacarbenium ions ($D_N * A_N$; $S_N1$).[10] In these cases, nucleophilic attack occurs prior to the complete dissociation of the intermediate ion:molecule pair.[10]

It seemed clear that a comparison of the lifetimes for carbohydrate-based oxa- and thiacarbenium ions in aqueous solution was warranted. Thus, this report addresses critical questions concerning the relative stabilities and kinetic accessibilities of six-membered ring thiacarbenium ions. In particular, do the substitution reactions of 5-thioglucopyranosyl fluoride (**3b**) occur via an associative ($S_N2$) or a dissociative ($S_N1$) mechanism?

Two previous syntheses of **3b** have been reported.[11] However, in neither case was a detailed mechanistic study undertaken, although it was reported in a footnote that "in contrast to the behaviour of *glucosyl fluoride*, 5-thio-α-D-glucopyranosyl fluoride was spontaneously hydrolysed ... in the absence of enzyme".[11b] Details for the synthesis and characterization of compound **3b** and both anomers of the azide substitution product (**4b** and **5b**) are included in the Supporting Information.

The hydrolysis reactions of **3b** were performed in aqueous solutions containing various concentrations of added anions and were followed by monitoring the protonation of a phenolate indicator using UV−visible spectroscopy.[12,13] Notably, the hydrolytic rate constant for **3b** ($I = 2.0$ M, NaClO$_4$) is independent of the indicator used (Tables S1 and S2, Supporting Information). Thus, the observed pseudo-first-order rate constant ($k_{hyd}$) is constant over at least 2.5 pH units (kinetic solutions are buffered by either phenol, p$K_a$ = 9.98, or 4-nitrophenol, p$K_a$ = 7.15),[14] and therefore, the reaction being monitored is neither acid- nor base-catalyzed.[15]

Compound **3b** reacts about 800-fold faster at 30 °C than **3a** ([NaClO$_4$] = 2.0 M).[8] Presumably, the enhanced reactivity of **3b** results, in part, from ground-state destabilization that is caused by a smaller anomeric effect in the S−C−F system compared to the O−C−F system.[16]

Reactions of **3b** in the presence of added anionic nucleophiles were performed at the same ionic strength ($\mu = 2.0$, NaClO$_4$) and temperature (30 °C) used for the study of the reactions of **3a**.[8] The observed first-order rate constants ($k_{obs}$) for the hydrolysis of **3b** as a function of anion concentration are essentially invariant (listed in Table S2, Supporting Information). A plot of the rate constant data for the substitution reactions of **3b** is given in Figure S1.

The rate constants for the reactions of **3b** in the presence of azide in D$_2$O solution were also monitored by UV−visible spectroscopy (Table S3, Supporting Information). In addition, the products for the substitution reactions in D$_2$O were monitored by $^1$H NMR spectroscopy and are listed in Table 1.

In D$_2$O, as the concentration of N$_3^-$ is changed from 0.0 to 1.0 M ($\mu = 2.0$, NaClO$_4$), a marginal increase of 1.19-fold in

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(12) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7900.

(13) The hydrolysis of **3b** in the presence of added nucleophiles was followed at 287 nm using a phenol indicator solution (0.9 mM, ≈82% phenolate anion; $I$ = 2.0, NaClO$_4$); see Supporting Information.

(14) Serjeant, E. P.; Dempsey, B. *Ionisation Constants of Organic Acids in Aqueous Solution*; Pergamon Press: Oxford, 1979.

(15) The rate constants for the spontaneous hydrolysis of **3a** and **3b** increase as ionic strength is varied from 0 to 2 M (NaClO$_4$) by factors of ∼1.7, (ref 8) and 1.62 (Tables S1, Supporting Information), respectively.

(16) (a) Wolfe, S.; Pinto, B. M.; Varma, V.; Leung, R. Y. N. *Can. J. Chem.* **1990**, *68*, 1051. (b) Scott, C.; Grein, F. *Can. J. Chem.* **1996**, *74*, 1221.

**Table 1.** Product Percentages Formed in the Substitution Reactions of **3b** as a Function of [$N_3^-$] in $D_2O$ ($\mu$ = 2.0 M, $NaClO_4$) at 30 °C[a]

| [$N_3^-$] (M) | 6[b] | 4b[b] | 5b[b] | 5b/4b |
|---|---|---|---|---|
| 0.276 | 58.4 | 16.5 | 25.1 | 1.52 |
| 0.467 | 43.4 | 20.7 | 35.9 | 1.73 |
| 0.667 | 32.9 | 22.5 | 44.6 | 1.98 |
| 1.000 | 24.3 | 24.1 | 51.6 | 2.14 |

[a] Estimated errors in product percentages ±5%. [b] The observed H-1 chemical shifts ($\delta$) for the products are: **4b** (5.23), **5b** (4.89), $\alpha$-**6** (5.27), and $\beta$-**6** (5.01).
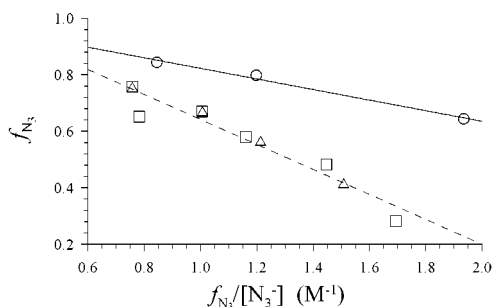


**Figure 1.** Plot of $f_{az}$ versus $f_{az}/[N_3^-]$ for the reactions of 5-thio-$\alpha$-D-glucopyranosyl fluoride ($\mu$ = 2.0 M, $NaClO_4$) $D_2O$ ($\triangle$ data from product studies, $\square$ data from kinetic experiments) $H_2O$ ($\bigcirc$). The lines are the best linear fits to the data.

**Scheme 1**
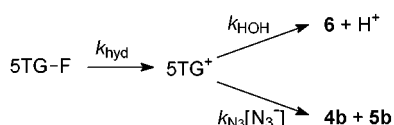


rate constant for the reaction of **3b** is associated with the formation of over 75% of the substitution products (**4b** and **5b**). These observations are consistent with a scheme in which 5-thio-$\alpha$-D-glucopyranosyl fluoride (5TG-F) undergoes an $S_N1$ reaction (Scheme 1).

The solvent KIE of 1.24 ± 0.11 suggests that the rate-limiting departure of fluoride ion occurs with some electrophilic assistance originating from H-bonding to water.

Furthermore, as product formation occurs after the rate-limiting step, the pseudo-first-order rate constant ($k_{HOH}$) for the reaction of the thiacarbenium ion with water can be calculated using eq 1, where $f_{az}$ is the fraction of azide product, and $k_{N_3}$ is the diffusional rate constant for reaction of the carbenium ion with azide ($\sim$5 × 10$^9$ M$^{-1}$ s$^{-1}$).[17]

$$f_{az} = 1 - \frac{k_{HOH}}{k_{N_3}} \times \frac{f_{az}}{[N_3^-]} \qquad (1)$$

Figure 1 displays the results from the product study in $D_2O$ (Table 1) and the kinetic data in both $H_2O$ and $D_2O$ (Tables S2 and S3) plotted according to eq 1.[18]

The intercepts for the two correlations of 1.01 ± 0.02 ($H_2O$) and 1.09 ± 0.05 ($D_2O$) are equal to 1 (at the 95% confidence level). The derived values for $k_{HOH}/k_{N_3}$ and $k_{DOD}/k_{N_3}$ are 0.184 ± 0.016 M, 0.45 ± 0.05 M, respectively. A nonlinear fit of the $D_2O$ data to a standard saturation curve gives a value of 0.36 ± 0.01 M for $k_{DOD}/k_{N_3}$.[19] Therefore, the estimated lifetime for the 5-thioglucopyranosyl cation in water (1/$k_{HOH}$, $\tau_{HOH}$) is 1.1 × 10$^{-9}$

**Scheme 2**
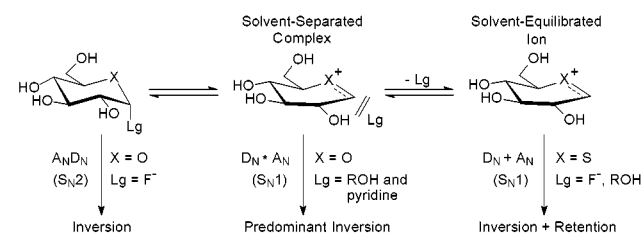


s, a lifetime that is sufficient for the intermediate to become solvent-equilibrated.[2] According to the Stokes–Einstein and Smoluchowski equations the rate of diffusion is inversely proportional to the viscosity ($\eta$).[20] Given that $\eta(D_2O)/\eta(H_2O) \approx$ 1.23, the calculated lifetime (1/$k_{DOD}$, $\tau_{DOD}$) in deuterium oxide is 0.68 × 10$^{-9}$ s.[21] Thus, $k_{DOD}/k_{HOH}$ = 1.6, suggesting that trapping of **5TG$^+$** is faster in $D_2O$, provided that the reaction with azide ion is diffusion-controlled.

In contrast, the estimated lifetime for the glucopyranosyl cation is around (1–3) × 10$^{-12}$ s.[10,22] Thus, the substitution of the ring oxygen by a sulfur atom increases the lifetime of the cyclic carbenium ion by at least 360-fold. The formation of more $\beta$-azide product in the reactions of 5-thioglucopyranosyl fluoride suggests that the transition state for capture on the $\beta$-face is lower in energy than that for capture on the $\alpha$-face. This behavior is opposite to that observed with glycopyranosyl-based intermediates.[10]

As a final point of interest, we comment on the changes in the product ratio **5b**/**4b** with azide ion concentration (Table 1). The pseudo-first-order rate constant for capture of the thiacarbenium ion **5TG$^+$** ($k_{DOD}$ + $k_{N_3}$[$N_3^-$]),[23] is probably of the same order as that for conformational interconversion of the various half-chair and boat conformations. In other words, the observed changes in the product ratio reflect reactions from different conformational ensembles of the cation.

In summary, the collective evidence to date suggests the mechanisms for nucleophilic substitution in glucopyranosides and 5-thioglucopyranosides shown in Scheme 2.

**Supporting Information Available:** Experimental procedures for the preparation of **3b**, **4b**, and **5b**, their characterization, and the $^1H$ and $^{13}C$ NMR spectra for compound **3b**; protocols for acquisition of the kinetic data and the tables of observed pseudo-first-order rate constants and a plot of $k_{obs}$ versus anion concentration for the reactions of 5-thio-$\alpha$-D-glucopyranosyl fluoride (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Assuming $f_{az}$ = 1 − $f_{acid}$, (fraction of acid produced).

(19) Both *x*- and *y*-axes in Figure 1 contain terms in $f_{az}$; therefore, errors in $f_{az}$ values result in a correlation between *x*- and *y*- values. Thus, the $D_2O$ data points were also fit to the equation $f_{az}$ = ($k_{N_3}$[$N_3^-$]/$k_{DOD}$)/(1 + ($k_{N_3}$[$N_3^-$]/$k_{DOD}$)).

(20) Logan, S. R. *Fundamentals of Chemical Kinetics*; Longman: Harlow, 1996; p 78.

(21) $k_{DOD}$ = 0.36 × (5 × 10$^9$)/1.23 = 1.46 × 10$^9$ s$^{-1}$.

(22) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888.

(23) The average times before reaction of **5TG$^+$** in $D_2O$ are 0.68 and 0.18 ns, at azide ion concentrations of 0.0 and 1.0 M, respectively.[24]

(24) Wilkinson, F. *Chemical Kinetics and Reaction Mechanisms*; Van Nostrand Reinhold: New York, 1980; p 17.