# A Kinetic Isotope Effect Study on the Hydrolysis Reactions of Methyl Xylopyranosides and Methyl 5-Thioxylopyranosides: Oxygen versus Sulfur Stabilization of Carbenium Ions

**Deepani Indurugalla[†] and Andrew J. Bennet***

*Contribution from the Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, British Columbia V5A 1S6, Canada*

*Received May 18, 2001*

**Abstract:** The following kinetic isotope effects, KIEs ($k_{light}/k_{heavy}$), have been measured for the hydrolyses of methyl α- and β-xylopyranosides, respectively, in aqueous $HClO_4$ ($\mu$ = 1.0 M, $NaClO_4$) at 80 °C: α-D, 1.128 ± 0.004, 1.098 ± 0.005; β-D, 1.088 ± 0.008, 1.042 ± 0.004; γ-$D_2$, (C5) 0.986 ± 0.001, 0.967 ± 0.003; leaving-group $^{18}O$, 1.023 ± 0.002, 1.023 ± 0.003; ring $^{18}O$, 0.983 ± 0.001, 0.978 ± 0.001; anomeric $^{13}C$, 1.006 ± 0.001, 1.006 ± 0.003; and solvent, 0.434 ± 0.017, 0.446 ± 0.012. In conjunction with the reported (*J. Am. Chem. Soc.* **1986**, *108*, 7287−7294) KIEs for the acid-catalyzed hydrolysis of methyl α- and β-glucopyranosides, it is possible to conclude that at the transition state for xylopyranoside hydrolysis resonance stabilization of the developing carbenium ion by the ring oxygen atom is coupled to exocyclic C−O bond cleavage, and the corresponding methyl glucopyranosides hydrolyze via transition states in which charge delocalization lags behind aglycon departure. In the analogous hydrolysis reactions of methyl 5-thioxylopyranosides, the measured KIEs in aqueous $HClO_4$ ($\mu$ = 1.0 M, $NaClO_4$) at 80 °C for the α- and β-anomers were, respectively, α-D, 1.142 ± 0.010, 1.094 ± 0.002; β-D 1.061 ± 0.003, $1.018_5$ ± 0.001; γ-$D_2$, (C5) 0.999 ± 0.001, 0.986 ± 0.002; leaving-group $^{18}O$, 1.027 ± 0.001, 1.035 ± 0.001; anomeric $^{13}C$, 1.031 ± 0.002, 1.028 ± 0.002; solvent, 0.423 ± 0.015, 0.380 ± 0.014. The acid-catalyzed hydrolyses of methyl 5-thio-α- and β-xylopyranosides, which occur faster than methyl α- and β-xylopyranosides by factors of 13.6 and 18.5, respectively, proceed via reversibly formed O-protonated conjugate acids that undergo slow, rate-determining exocyclic C−O bond cleavage. These hydrolysis reactions do not have a nucleophilic solvent component as a feature of the thiacarbenium ion-like transition states.

## Introduction

It has been recognized for a long time that electron lone pairs on heteroatoms are effective stabilizers of adjacent electron-deficient centers, such as carbocations.[1] In the particular case of the acid-catalyzed hydrolysis of glycopyranosides, the general mechanistic features have been recognized for about 30 years[2] and are (a) hydrolysis occurs via specific catalysis,[2] although exceptions occur when the leaving group has a low basicity[3] or the oxacarbenium ion intermediate (**1**) is especially stable;[4] (b) the rate-limiting step involves exocyclic C−O bond cleavage;[5,6] and (c) nucleophilic solvent participation (NSP)[7] does not occur at the hydrolytic transition state (Scheme 1).[6,8] More recently, it has been concluded that aldopyranosides containing neutral leaving groups, such as pyridine, hydrolyze via short-lived nonsolvent-equilibrated oxacarbenium ions ($D_N$ * $A_N$),[8] and that nucleophilic attack occurs prior to complete dissociation of the intermediate ion:molecule pair.[8] Such reactivities are a consequence of the short lifetime of the glucosyl oxacarbenium ion, which has been estimated to be on the order of $1-3 \times 10^{-12}$ s.[8,9]

In contrast to the situation with glycopyranosides, such as **2a** and **2b**, few kinetic studies have been performed on 5-thioglycopyranosides. For instance, Whistler and Van Es noted that methyl 5-thio-α-D-xylopyranoside (**4a**) hydrolyses approximately 10 times faster than methyl α-D-xylopyranoside (**3a**) and that methyl 5-thio-β-D-xylopyranoside (**4b**) hydrolyses approximately fourteen times faster than methyl β-D-xylopyranoside (**3b**).[10] Given that thioglycosides and their derivatives are potential glycosidase inhibitors[11] it is important to delineate the factors which control reactivity in this class of compounds. In a wider context, however, the relative capabilities of sulfur and oxygen atoms to stabilize an adjacent carbenium ion center

* To whom correspondence should be addressed. Phone: (604)-291−3532. Fax: (604)-291−3765. E-mail: Bennet@sfu.ca.

[†] Current address: Department of Chemistry, University of Ruhuna, Matara, Sri Lanka.

(1) For example: (a) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; Wiley-Interscience: New York, 1992; pp 165−174. (b) Lowry, T. H., Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; p 391.

(2) Reviews: (a) Cordes, E. H. *Prog. Phys. Org. Chem.* **1967**, *4*, 1−44. (b) Capon, B. *Chem. Rev.* **1969**, *69*, 407−498. (c) Sinnott, M. L. In *The Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984; pp 389−431.

(3) (a) Bennet, A. J.; Davis, A. J.; Hosie, L.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. 2* **1987**, 581−584. (b) Banait, N. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 7958−7963.

(4) Fife, T. H.; Brod, L. H. *J. Am. Chem. Soc.* **1970**, *92*, 1681−1684.

(5) Banks, B. E. C.; Meinwald, Y.; Rhind-Tutt, A. J.; Sheft, I.; Vernon, C. A. *J. Chem. Soc.* **1961**, 3240−3246.

(6) Bennet, A. J.; Sinnott, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 7287−7294.

(7) Richard, J. P.; Toteva, M. M.; Amyes, T. L. *Org. Lett.* **2001**, *3*, 2225−2228.

(8) (a) Huang, X.; Surry, C.; Hiebert, T.; Bennet, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 10614−10621. (b) Zhu, J.; Bennet, A. J. *J. Am. Chem. Soc.* **1998**, *120*, 3887−3893.

(9) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888−7900.

(10) Whistler, R. L.; Van Es, T. *J. Org. Chem.* **1963**, *28*, 2303−2304.

10.1021/ja011232g CCC: $20.00 
Published on Web 10/10/2001

**Scheme 1**

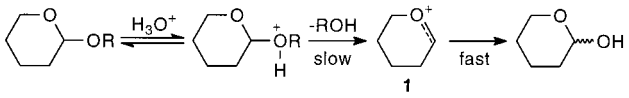



**Chart 1**

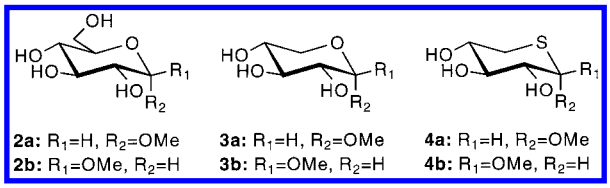
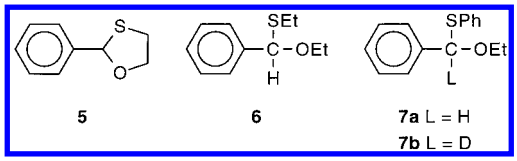
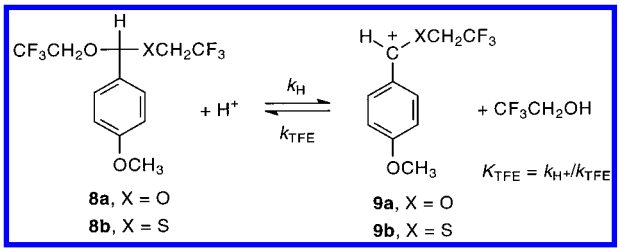



**Chart 2**




has been a controversial subject.[12] For instance, De and Fedor[13] and Fife and Jao[14] proposed radically different mechanisms for the acid-catalyzed hydrolysis of 2-aryl-1,3-oxathiolane derivatives (**5**). Specifically, Fife and Jao[14] suggested that the reaction involved specific acid-catalyzed protonation on sulfur followed by rate-limiting C−S bond cleavage, whereas De and Fedor favored an $S_N2$-like mechanism involving rate-determining C−O bond cleavage.[13] In a separate study, Jensen and Jencks monitored the acid-catalyzed hydrolysis of various acyclic monothioacetals, and they concluded that modification of the structure from **6** to **7a** results in a mechanistic change from initial C−O to initial C−S bond cleavage.[15] In 1979, Modena et al. studied the hydrolysis reactions of methoxymethyl and methylthiomethyl derivatives, and these authors concluded that it was not possible to assess the relative stabilities of thia- and oxacarbenium ions based on hydrolytic rate constants.[16] In other words, one cannot assume a link between the rate of reaction and the thermodynamic stability of the first-formed cationic intermediate. That such a breakdown in a rate-equilibrium relationship occurs during the hydrolyses of acetals and monothioacetals was shown by Jagannadham et al.[17] These authors reported kinetic and thermodynamic data for the formation of the homologous carbocations **9a** (oxacarbenium) and **9b** (thiacarbenium).[17,18] Jagannadham et al. demonstrated that the thiacarbenium ion **9b** ($K_{TFE} = 2.3 \times 10^{-5}$) is more stable relative to its ground state than is the oxacarbenium ion **9a** ($K_{TFE} = 1.0 \times 10^{-6}$), and they argued that this difference reflects ground-state energetics, where stabilizing geminal interactions are stronger for **8a** than for **8b** (Scheme 2).[17]

**Scheme 2**




The second-order rate constant for acid-catalyzed formation of **8a** ($k_{H^+} = 0.23\ M^{-1}\ s^{-1}$) is, however, much greater than that for **8b** ($k_{H^+} = 5.4 \times 10^{-3}\ M^{-1}\ s^{-1}$).[17] Thus, these authors concluded that "The observation that the thermodynamically less stable α-oxygen-stabilized carbocation is formed more rapidly shows that previous attempts to infer the relative stabilities of α-oxygen- and α-sulfur-stabilized carbocations from the relative rate constants for their formation in solvolyses are invalid".[17]

Over the years, many theoretical studies regarding the relative stabilities of oxa- and thiacarbenium ions have been published.[21] In 1996, Buckley and Oppenheimer reported semiempirical computations in which the kinetic and thermodynamic stabilities of linear and cyclic oxa- and thiacarbenium ions were assessed relative to various starting materials, for example, xylopyranosyl pyridinium ions[22] and protonated methyl glucopyranosides.[23] In their computational studies, Buckley and Oppenheimer analyzed the dissociative reactions for analogues of exocyclic O-protonated methyl 5-thioxylopyranoside and methyl xylopyranoside, and they reported that the sulfur homologues underwent spontaneous cleavage to give a thiacarbenium ion intermediate.[23] Thus, if the same mechanism pertains to aqueous solution, these hydrolysis reactions should be general-acid-catalyzed, that is, the exocyclic C−O bond starts to break prior to complete installation of the proton.

This report addresses several critical questions concerning the relative stabilities and kinetic accessibility of six-membered-ring thia- and oxacarbenium ions. Specifically, do the acid-catalyzed hydrolysis reactions of methyl 5-thioxylopyranosides involve C−O or C−S bond cleavage? Do these reactions proceed with general-acid or specific-acid catalysis? Are the reactions of the ring substituted thiosugars associative ($S_N2$) or dissociative ($S_N1$) in nature? Does replacing the hydroxymethyl group of methyl glucopyranosides (**2a** and **2b**) with a hydrogen atom give rise to any significant change in the hydrolysis mechanism?

## Experimental Section

**General Methods.** Melting points were determined on a Gallankamp melting-point apparatus and are not corrected. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker AMX-400 NMR spectrometer at

(11) For example see (a) Yuasa, H.; Hindsgaul, O.; Palcic, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 5891−5892. (b) Mehta, S.; Andrews, J. S.; Johnston, B. D.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 9783−9790. (c) Weimar, T.; Stoffer, B.; Svensson, B.; Pinto, B. M. *Biochemistry* **2000**, *39*, 300−306. (d) Yuasa, H.; Hashimoto, H. *Trends Glycosci. Glycotech.* **2001**, *13*, 31−55.

(12) Review of acetals and monothioacetal hydrolyses: Satchell, D. P. N.; Satchell, R. S. *Chem. Soc. Rev.* **1990**, *19*, 55−81.

(13) De, N. C.; Fedor, L. R. *J. Am. Chem. Soc.* **1968**, *92*, 7266−7271.

(14) Fife, T. H.; Jao, L. K. *J. Am. Chem. Soc.* **1969**, *91*, 4217−4220.

(15) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476−1488.

(16) Modena, G.; Scorrano, G.; Venturello, P. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1−6.

(17) Jagannadham, V.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 8465−8466.

(18) For carbohydrates, IUPAC nomenclature for the replacement of an oxygen atom by a sulfur is designated by use of thio, that is, 5-thioglucose, reference 19; whereas, in standard IUPAC nomenclature the replacement of a saturated $CH_2$ group by either an oxygen or sulfur atom are designated oxa and thia, respectively, reference 20.

(19) McNaught, A. D. *Pure Appl. Chem.* **1996**, *68*, 1919−2008.

(20) Rigaudy, J.; Klesney, S. P. *Nomenclature of Organic Chemistry*; Sections A−F, and H; Pergamon Press: Oxford, 1979; pp 53−76.

(21) For example: (a) Price, C. C.; Oae, S. *Sulfur Bonding*; Ronald Press: New York, 1962. (b) Bernardi, F.; Csizmadia, I. G.; Schlegel, H. B.; Wolfe, S. *Can. J. Chem.* **1975**, *53*, 1144−1153. (c) Bernardi, F.; Csizmadia, I. G.; Epiotis, N. D. *Tetrahedron*, **1975**, *31*, 3085−3088. (d) Bernardi, F.; Mangini, A.; Epiotis, N. D.; Larson, J. R.; Shaik, S. *J. Am. Chem. Soc.* **1977**, *99*, 7465−7470. (e) Bernardi, F.; Bottoni, A.; Venturini, A. *J. Am. Chem. Soc.* **1986**, *108*, 5395−5400. (f) Apeloig, Y.; Karni, M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 625−636. (g) Wolfe, S.; Shi, Z. *Isr. J. Chem.* **2000**, *40*, 343−355.

(22) Buckley, N.; Oppenheimer, N. J. *J. Org. Chem.* **1996**, *61*, 8039−8047.

(23) Buckley, N.; Oppenheimer, N. J. *J. Org. Chem.* **1996**, *61*, 8048−8062.

400.13 and 100.6 MHz, respectively. Chemical ionization mass spectra were measured using a Hewlett-Packard 5985 mass spectrometer. Tetrahydrofuran was dried by distillation from sodium/benzophenone under a nitrogen atmosphere, $CH_2Cl_2$ and pyridine were distilled from $CaH_2$, and DMSO was dried over molecular sieves (4 Å) and then distilled.

All solutions used in the kinetic experiments were made with Milli-Q water (18.2 MΩ $cm^{-1}$) containing the appropriate volume of AnalaR 60% (w/w) perchloric acid and amount of $NaClO_4$ such that the ionic strength was maintained at $\mu = 1.0$. The acid concentration of all solutions was measured by titration against standardized 0.100 M NaOH solution (Fluka). Perchloric acid-*d* (99+ at. % D) was purchased from Sigma, and deuterium oxide (99+ at. % D) was purchased from Isotec. Sodium ($^{18}O_2$)acetate[24] and ($^{18}O$)methanol[26] were prepared according to literature procedures using ($^{18}O$)water (Isotec, 98.5 atom-% $^{18}O$) as the starting material.

**Synthesis of Labeled Xylosides. (i) General.** Fischer glycosylation was used to make all methyl xylopyranosides except both anomers containing a (1-$^{18}O$)-label. Most of the β-anomer (mp 156−157 °C) was readily separated from the anomeric mixture produced by Fischer glycosylation (α-anomer, mp 89−90 °C) by crystallization from 2-propanol. Subsequent evaporation of the mother liqueur followed by benzoylation (benzoyl chloride in pyridine) gave a mixture, highly enriched in the α-anomer, of the two anomeric 2,3,4,6-tetra-*O*-benzoyl derivatives that could be separated by flash chromatography (silica gel; eluent 1:6 v/v EtOAc:hexane). Zemplén debenzoylation[27] of the purified 2,3,4,6-tetra-*O*-benzoyl precursors, α-anomer (mp 92−93 °C), and β-anomer (mp 109−111 °C) gave the desired glycosides, α-anomer (EtOH/$Et_2O$) and β-anomer (2-propanol), that were carefully recrystallized. Methyl α- and β-L-xylopyranosides were made from commercially available L-xylose by Fischer glycosylation as described above. All methyl xylopyranosides, both labeled and unlabeled, gave elemental analyses (C and H) that were within acceptable error limits (± 0.4% C, ± 0.3% H), and all had melting point ranges of 1 °C or less. In addition, all α- and β-anomers had uncorrected melting points in the range 88−91 °C and 154−157 °C, respectively.

**(ii) Deuterium at C1 and C5.** Treatment of the required 1,2-*O*-isopropylidene-α-D-xylofuranose (Supporting Information) with 1% (w/v) HCl in methanol at reflux temperature overnight gave a mixture of the anomeric methyl xylopyranosides. These mixtures were separated and purified as described above.

**(iii) Deuterium at C2 and $^{13}C$ at the Anomeric Center.** These isotopomers were made by the standard glycosylation/benzoylation procedure using either D-(2-$^2H$)xylose (Omicron Biochemicals, 97.5 atom-% $^2H$) or D-(1-$^{13}C$)xylose (Omicron Biochemicals, 99 atom-% $^{13}C$) as the starting material.

**(iv) $^{18}O$ in the Leaving Group.** Addition of ($^{18}O$)methanol (1.6 mL) to a solution of 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose (6.0 g) and $BF_3$·$Et_2O$ (13 mL) in dry $CH_2Cl_2$ (50 mL) was performed at −78 °C under an atmosphere of dry $N_2$ gas. The resulting solution was stirred overnight, during which time the temperature was allowed to reach ambient temperature. The reaction was quenched by the addition of a saturated $NaHCO_3$ solution (25 mL), and stirring was continued for another 0.5 h. After the organic layer was separated, it was washed with $H_2O$ (50 mL) and saturated NaCl (50 mL), and then it was dried over anhydrous $Na_2SO_4$. After filtration, the solution was evaporated under vacuum. The resulting syrup was purified by flash chromatography (1:4 v/v EtOAc:hexane) to give pure α-anomer (0.75 g, 14%), mp 82−84 °C (lit.[28] 85−86 °C), and the β-anomer contaminated with ∼15% 1,2,3,4-tetra-*O*-acetyl-α-D-xylopyranose (1.1 g, 24%). Recrystallization of the β-anomer from ether:hexane gave pure material, mp 111−113 °C (lit.[29] 114−115 °C). Subsequent Zemplén deacetylation of the purified methyl 2,3,4-tri-*O*-acetyl xylosides gave the desired methyl xylopyranosides, α-anomer (EtOH/$Et_2O$) and β-anomer (2-propanol), which were carefully recrystallized.

**(v) $^{18}O$ at C5.** Sodium ($^{18}O_2$)acetate (2.0 g) was added to a solution of 1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-xylofuranose[30] (8.0 g) in dry DMSO (200 mL). The resulting solution was heated at 85 °C for 24 h. After cooling the reaction mixture to room temperature, $H_2O$ (50 mL) was added, and the resultant solution was extracted with ether (3 × 100 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered, and evaporated under vacuum. The resulting syrup was purified by flash chromatography (silica gel, 1:2 v/v ethyl acetate:toluene) to give 1,2-*O*-isopropylidene-5-*O*-($^{18}O$)acetyl-α-D-(5-$^{18}O$)xylofuranose (2.5 g, 43%), mp 97−98 °C (lit.[30] 100.0−100.5 °C). Treatment of the labeled 1,2-*O*-isopropylidene-5-*O*-acetyl α-D-xylofuranose with 1% (w/v) HCl in methanol at reflux temperature overnight gave a mixture of the two anomeric methyl xylopyranosides that were separated and purified as detailed above.

**Synthesis of Labeled 5-Thioxylosides. (i) General.** All labeled and unlabeled methyl 5-thioxylopyranosides, except for the two (1-$^{18}O$)-labeled anomers, were made from the corresponding 1,2-*O*-isopropylidene-α-D-xylofuranose by the following general procedures. 1,2-*O*-Isopropylidene-α-D-xylofuranose was monotosylated using the method of Levene and Raymond[30] to give 1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-xylofuranose in a yield of 80%. Subsequent nucleophilic displacement of the tosylate by sodium benzylthiolate gave 1,2-*O*-isopropylidene-5-thiobenzyl-α-D-xylofuranose (80%).[31] Lithium−liquid ammonia reduction of the thioether gave an 85% yield of 1,2-*O*-isopropylidene-5-thio-α-D-xylofuranose.[31] Methyl 5-thio-α-D-xylopyranoside was made from 1,2-*O*-isopropylidene-5-thio-α-D-xylofuranose via standard Fischer glycosylation conditions (1% HCl in methanol).[31] Hydrolysis of 1,2-*O*-isopropylidene-5-thio-α-D-xylofuranose (0.2 N $H_2SO_4$, 65 °C for 4 h) gave 5-thioxylose, which was transformed into methyl 5-thio-β-D-xylopyranoside in four steps according to the method of Whistler and Van Es.[10] 1,2-*O*-Isopropylidene-α-L-xylofuranose was made from commercially available L-xylose.

All α-anomeric isotopomers had melting points within the range 109−111 °C (lit.[32] 112−113 °C) and satisfactory elemental analyses (C ± 0.4%, H ± 0.3%). For the unlabeled D-sugar $[\alpha]^{25}_D = +321.8°$ (c 1.01, $H_2O$) (lit.[33] +332°) and for the unlabeled L-sugar $[\alpha]^{25}_D = -325.7°$ (c 1.01, $H_2O$). All β-anomeric isotopomers had melting points within the range 159−161 °C (lit.[10] 162 °C) and satisfactory elemental analyses (C ± 0.4%, H ± 0.3%). For the unlabeled D-sugar, $[\alpha]^{25}_D = -66.0°$ (c 1.01, $H_2O$) (lit.[10] −66.3°), and for the unlabeled L-sugar, $[\alpha]^{25}_D = +66.0°$ (c 1.00, $H_2O$).

**(ii) Deuterium at C1, C2, and C5, and $^{13}C$ at the Anomeric Center.** Treatment of the requisite labeled 1,2-*O*-isopropylidene-α-D-xylofuranose (Supporting Information), as described above, gave both anomers of the labeled methyl 5-thio-D-xylopyranoside.

**(iii) $^{18}O$ in the Leaving Group.** A solution of 1,2,3,4-tetra-*O*-acetyl-5-thio-α,β-D-xylopyranose (11.2 g, 33.4 mmol)[34] and $NH_2NH_2$·AcOH (4.0 g, 43.5 mmol) in DMF (250 mL) was stirred for 4 h at room temperature under a $N_2$ atmosphere. The reaction mixture was then diluted with $CH_2Cl_2$ (250 mL), washed with 5% NaCl, and dried over anhydrous $Na_2SO_4$. The filtered solution was evaporated under reduced pressure to obtain a syrup. This syrup was purified using flash chromatography (silica gel, 2:1 v/v ethyl acetate:hexane) to give 2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranose (7.1 g, 72%) and a mixture of the α- and β-anomers (0.7 g, 7%). Characterization for the α-anomer, mp 118−119 °C, $^1H$ NMR ($CDCl_3$) δ 5.54 (t, 1H, $J_{3,2} + J_{3,4} = 20.0$, H-3), 5.14 (ddd, 1H, $J_{2,1} = 2.8$, $J_{2,OH} = 1.0$, H-2), 5.10 (m, 1H, H-1), 4.09

(24) In our hands, synthesis of sodium ($^{18}O_2$)acetate using the method of Hutchinson and Mabuni (reference 25) yielded material with a lower atom % $^{18}O$ than the reagent ($^{18}O$)water (presumably because of the presence of adventitious water).

(25) Hutchinson, C. R.; Mabuni, C. T. *J. Labelled Compd. Radiopharm.* **1977**, *13*, 571−574.
(26) Sawyer, C. B. *J. Org. Chem.* **1972**, *37*, 4225−4226.
(27) Thompson, A.; Wolfrom, M. L. *Methods Carbohydr. Chem.* **1963**, *2*, 215−220.
(28) McEwan, T.; McInnes, A. G.; Smith, D. G. *Carbohydr. Res.* **1982**, *104*, 161−168.
(29) Schroeder, L. R.; Counts, K. M.; Haigh, F. C. *Carbohydr. Res.* **1974**, *37*, 368−372.
(30) Levene, P. A.; Raymond, A. L. *J. Biol. Chem.* **1933**, *102*, 317−330.
(31) Ingles, D. L.; Whistler, R. L. *J. Org. Chem.* **1962**, *27*, 3896−3898.
(32) Hughes, N. A.; Munkombwe, N. M. *Carbohydr. Res.* **1985**, *136*, 411−418.
(33) Whistler, R. L.; Feather, M. S.; Ingles, D. L. *J. Am. Chem. Soc.* **1962**, *84*, 122.
(34) Al-Masoudi, N. A.; Pfleiderer, W. *Tetrahedron*, **1993**, *49*, 7579−7592.

(ddd, 1H, $J_{4,5a} = 11.3$, $J_{4,5e} = 4.5$, H-4), 3.10 (dd, 1H, $J_{5a,5e} = 13.0$, H-5a), 2.72 (ddd, 1H, $J_{1,5e} = 1.4$, H-5e), 2.26 (dd, 1H, $J_{1,OH} = 2.4$, OH), 2.07 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.3, 170.2, 170.1, 75.7 (C-2), 73.3 (C-4), 71.8 (C-1), 70.3 (C-3), 25.1 (C-5), 21.0, 20.9, 20.8.

**2,3,4-Tri-*O*-acetyl-5-thio-α-D-xylopyranosyl Trichloroacetimidate.** Trichloroacetonitrile (24 mL, 240 mmol) and $K_2CO_3$ (33 g, 240 mmol) were added to a stirred solution of 2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranose (7.0 g, 24 mmol) in $CH_2Cl_2$ (75 mL) maintained under an inert atmosphere. After stirring overnight, the reaction mixture was filtered through a bed of Celite, which was subsequently washed with $CH_2Cl_2$ (100 mL). The combined organic layers were concentrated under reduced pressure to obtain a syrup that was purified using flash chromatography (silica gel, 1:2 v/v ethyl acetate:hexane) to give 2,3,4-tri-*O*-acetyl-5-thio-α-D-5-xylopyranosyl trichloroacetimidate as a white solid (6 g, 57%), a mixture of the α- and β-anomers (1.8 g, 17%), and the β-anomer (0.4 g, 4%).[35] Characterization for the α-anomer: mp 104−105 °C, $^1H$ NMR ($CDCl_3$) $\delta$ 6.28 (dd, 1H, $J_{1,2} = 3.0$, $J_{1,5e} = 1.2$, H-1), 5.57 (t, 1H, $J_{3,2} + J_{3,4} = 20.0$, H-3), 5.26 (dd, 1H, H-2), 5.15 (ddd, 1H, $J_{4,5a} = 11.3$, $J_{4,5e} = 4.5$, H-4), 3.06 (dd, 1H, $J_{5a,5e} = 13.2$, H-5a), 2.80 (ddd, 1H, H-5e), 2.11 (s, 3H, $CH_3$), 2.05 (s, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 169.7, 169.7, 169.5, 160.9, 90.8, 76.2 (C-1), 73.8 (C-2), 72.5 (C-4), 70.1 (C-3), 26.3 (C-5), 20.7, 20.5, 20.4.

**Methyl 5-Thio-α- and β-D-(1-$^{18}$O)xylopyranosides.** ($^{18}$O)Methanol (1.1 mL, 27 mmol) was added, with stirring, to a cold solution (−78 °C) of 2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranosyl trichloroacetimidate (5.5 g, 13 mmol) and trimethylsilyl triflate (0.5 mL, 3 mmol) in dry $CH_2Cl_2$ (35 mL) maintained under a $N_2$ atmosphere. The resulting mixture was stirred for 13 h at −78 °C and then allowed to warm to room temperature. After addition of $Et_3N$ (~3 mL) the resultant solution was concentrated to a dark syrup. The syrup was purified using flash chromatography (silica gel, 1:4 v/v ethyl acetate:hexane) to give analytically pure samples of methyl 2,3,4-tri-*O*-acetyl-5-thio-α-D-(1-$^{18}$O)xylopyranoside (0.98 g, 25%) and methyl 2,3,4-tri-*O*-acetyl-5-thio-β-D-(1-$^{18}$O)xylopyranoside (1.02 g, 26%). Standard Zemplén deacetylation of the protected (1-$^{18}$O)-labeled sugars gave the desired methyl 5-thio-(1-$^{18}$O)xylopyranosides, which were carefully recrystallized.

**Rate Constant Measurements.** Pseudo-first-order rate constants ($k_{obs}$) for the acid-catalyzed hydrolyses of methyl α-D-xylopyranoside and methyl β-D-xylopyranoside were obtained by measuring the change in optical rotation with time for a solution (α-anomer 0.5 mg/mL, $\lambda$ = 240 nm; β-anomer 1.0 mg/mL, $\lambda$ = 275 nm) in a 10-cm-path-length jacketed cell located in a JASCO J-710 spectropolarimeter. Thermostated water (Neslab RTE-110 water bath) was passed through the cell jacket such that the measured temperature of water exiting the cell was 80.0 ± 0.5 °C. Pseudo-first-order rate constants ($k_{obs}$) were calculated by performing nonlinear least-squares fits of the rotation versus time data to a standard first-order rate equation. In a similar fashion, the acid-catalyzed hydrolyses of methyl 5-thio-α- and β-D-xylopyranoside (0.5 mg/mL) were monitored at 350 nm.

**Isotopic Compositions.** From the absence of a signal in the $^1H$ NMR spectrum, it was estimated that all deuterium-labeled compounds contained >95 atom % $^2H$. The isotopic composition of $^{13}C$-labeled materials was assumed to be identical (99 atom %) to that of the purchased starting material D-(1-$^{13}$C)xylose or D-(1-$^{13}$C)glucose (Omicron Biochemicals). The atom percentages of $^{18}O$ in methyl α- and β-D-(5-$^{18}$O)xylopyranosides (56.0%), methyl α- and β-D-(1-$^{18}$O)-xylopyranosides (90.5%), and methyl 5-thio-α- and β-D-(1-$^{18}$O)-xylopyranosides (94.0%) were calculated by using the least-squares method of Brauman[36] on the isotopic peak distribution of either the M + 1 ion (xylosides) or the M − 17 ion (thioxylosides) measured in the CI mass spectrum.

**KIE Measurements.** The change in optical rotation of a solution (1 mL) containing equal amounts (≈10 mg each) of the labeled D-sugar and the unlabeled L-sugar was monitored at either 404.6 or 436 nm using a Perkin-Elmer 241MC polarimeter. Thermostated water (Lauda RM 6 water bath, bath temperature 80.0 ± 0.5 °C) was circulated through the cell jacket. The experimental time courses were fit to eq 1 using a standard nonlinear least squares algorithm.

$$\alpha = Ae^{-kt} + Be^{-kt/C} + \alpha_\infty \quad (1)$$

The optical rotation change for the complete reaction for the light isomer ($A = \alpha_{t=0} - \alpha_{t=\infty}$) was measured in a separate experiment. The optical rotation for the heavy isotopomer ($B$), the KIE ($C$), the rate constant for the light isotopomer ($k$), and the optical rotation at infinite time ($\alpha_\infty$) were treated as variables in the nonlinear fit of the optical rotation vs time data to eq 1. For each kinetic run, it was checked that $B \sim -A$ and that $k$ is identical (within experimental error) to the value obtained in a separate experiment. For some small KIEs, $k$ could not be treated as an unrestricted variable (see Tables 1−3), and in these cases, the value of $k$ was constrained to ±10% of that measured in a separate experiment. The ring oxygen and the leaving-group $^{18}O$ kinetic isotope effects were corrected to account for incomplete labeling using the method of Bergson et al.[37]

**Table 1.** Kinetic Isotope Effects for the Acid-Catalyzed Hydrolysis of Methyl α-Xylopyranoside and Methyl α-Glucopyranoside at 80 °C

| site of isotopic substitution | methyl α-xylopyranoside KIE | methyl α-xylopyranoside ave | methyl α-glucopyranoside ave[a] |
|---|---|---|---|
| α-D | 1.1329 | 1.128 (4) | 1.137 (7) |
| | 1.1258 | | |
| | 1.1251 | | |
| β-D | 1.0826 | 1.088 (8) | 1.073 (3) |
| | 1.0838 | | |
| | 1.0977 | | |
| γ-$D_2$ or γ-D[b] | 0.9855 | 0.986 (1)[c] | 0.987 (2) |
| | 0.9854 | | |
| | 0.9866 | | |
| leaving-group $^{18}O$ | 1.0218 | 1.023 (2)[c] | 1.026 (1) |
| | 1.0246 | | |
| | 1.0214 | | |
| rings $^{18}O$ | 0.9829 | 0.983 (1)[c] | $0.996_5$ (1) |
| | 0.9841 | | |
| | 0.9826 | | |
| anomeric $^{13}C$ | 1.0075 | 1.006 ($1_4$)[c] | 1.007 (1) |
| | 1.0048 | | |
| | 1.0058 | | |
| solvent ($k_{D_3O^+}/k_{H_3O^+}$) | | 2.31 (9) | 1.8[d] |

[a] Data taken from ref 6. [b] Data for xylopyranoside is for [5-$D_2$]; for glucopyranoside, is for [5-$D_1$]. [c] Constrained fit. [d] Ref 41.

**Solvent Kinetic Isotope Effects.** Second-order rate constants ($k_{D_3O^+}$) for the acid-catalyzed hydrolysis of methyl α- and β-D-xylopyranoside, and methyl 5-thio-α- and β-D-xylopyranoside were calculated from the measured pseudo-first-order rate constants ($k_{obs}$) acquired at a single $D_3O^+$ concentration (see Supporting Information).

**Product Studies.** Methyl α-D-xylopyranoside (50 mg) was dissolved in 10 mL of $HClO_4$ (0.50 M; $\mu$ = 1.0, $NaClO_4$), and the resulting solution was heated at 80 °C for 4 h (~3−4 half-lives). After neutralization by the addition of NaOH (1 M), the solution was evaporated to dryness. The $^{13}C$ NMR spectrum of the resulting residue was identical to that of D-xylose (plus some methyl α-D-xylopyranoside) acquired under identical conditions. Identical experiment with methyl β-D-xylopyranoside (0.50 M $HClO_4$) and methyl 5-thio-α- and β-D-xylopyranoside (0.10 and 0.05 M $HClO_4$, respectively) gave equivalent results.

## Results

Figure 1 presents the observed rate constants ($k_{obs}$) obtained as a function of [$H_3O^+$] for the hydrolyses of methyl α- and β-xylopyranosides (**3a** and **3b**) at 80 °C to give xylose as the sole carbohydrate product. Individual rate constants are given in Table S1 of Supporting Information. The calculated second-order rate constants ($k_{H_3O^+}$) for the acid-catalyzed hydrolysis of

(35) Metha, S. Ph.D. Thesis, Simon Fraser University, April 1994.
(36) Brauman, J. I. *Anal. Chem.* **1966**, *38*, 607−610.
(37) Bergson, G.; Matsson, O.; Sjöberg, S. *Chem Scr*. **1977**, *11*, 25−31.

**Table 2.** Kinetic Isotope Effects for the Acid-Catalyzed Hydrolysis of Methyl β-Xylopyranoside and Methyl β-Glucopyranoside at 80 °C

| site of isotopic substitution | methyl β-xylopyranoside KIE | methyl β-xylopyranoside ave | methyl β-glucopyranoside ave[a] |
|---|---|---|---|
| α-D | 1.0953 | 1.098 (5) | 1.089 (6) |
| | 1.1040 | | |
| | 1.0941 | | |
| β-D | 1.0428 | 1.042 (4) | 1.045 (4) |
| | 1.0378 | | |
| | 1.0461 | | |
| γ-$D_2$ or γ-D[b] | 0.9684 | 0.967 (3) | 0.971 (3) |
| | 0.9635 | | |
| | 0.9680 | | |
| leaving-group $^{18}O$ | 1.0247 | 1.023 (3)[c] | 1.024 (1) |
| | 1.0194 | | |
| | 1.0240 | | |
| ring $^{18}O$ | 0.9776 | 0.978 (1) | 0.991 (2) |
| | 0.9787 | | |
| | 0.9787 | | |
| anomeric $^{13}C$ | 1.0090 | 1.006 (3)[c] | 1.011 (2) |
| | 1.0076 | | |
| | 1.0069 | | |
| | 1.0018 | | |
| | 1.0025 | | |
| solvent ($k_{D_3O^+}/k_{H_3O^+}$) | | 2.24 (1) | |

[a] Data taken from ref 6. [b] Data for xylopyranoside is for [5-$D_2$]; for glucopyranoside, is for [5-$D_1$]. [c] Constrained fit.

**Table 3.** Kinetic Isotope Effects for the Acid-Catalyzed Hydrolysis of Methyl 5-Thio-α- and β-xylopyranoside at 80 °C[a]

| site of isotopic substitution | methyl 5-thio-α-xylopyranoside KIE | methyl 5-thio-α-xylopyranoside ave | methyl 5-thio-β-xylopyranoside KIE | methyl 5-thio-β-xylopyranoside ave |
|---|---|---|---|---|
| α-D | 1.1429 | 1.142 ± 0.010 | 1.0960 | 1.094 ± 0.002 |
| | 1.1308 | | 1.0942 | |
| | 1.1511 | | 1.0928 | |
| β-D | 1.0613 | 1.061 ± 0.003[b] | 1.0181 | $1.018_5$ ± 0.001[c] |
| | 1.0615 | | 1.0174 | |
| | 1.0613 | | 1.0200 | |
| γ-$D_2$ | 0.9988 | 0.999 ± 0.001[c] | 0.9851 | 0.986 ± 0.002 |
| | 0.9994 | | 0.9841 | |
| | 1.0001 | | 0.9882 | |
| leaving-group $^{18}O$ | 1.0273 | 1.027 ± 0.001 | 1.0364 | 1.035 ± 0.001 |
| | 1.0256 | | 1.0339 | |
| | 1.0278 | | 1.0348 | |
| anomeric $^{13}C$ | 1.0325 | 1.031 ± 0.002 | 1.0299 | 1.028 ± 0.002 |
| | 1.0316 | | 1.0286 | |
| | 1.0289 | | 1.0253 | |
| | 1.0306 | | | |
| solvent ($k_{D_3O^+}/k_{H_3O^+}$) | | 2.37 ± 0.08 | | 2.63 ± 0.09 |

[a] Quoted values are the average (mean) of the individual runs, and the quoted errors are the $\sigma_{n-1}$ values. [b] Standard error associated with the data fitting for each individual run. [c] Constrained fit.

methyl α- and β-xylopyranosides at 80 °C ($\mu$ = 1.0, $NaClO_4$) are (2.42 ± 0.07) × $10^{-4}$ $M^{-1}$ $s^{-1}$ and (5.24 ± 0.10) × $10^{-4}$ $M^{-1}$ $s^{-1}$, respectively. Thus, under similar conditions the hydrolyses of xylopyranosides are approximately 7-fold faster than the corresponding glucopyranosides ($\mu$ = 2.0, $HClO_4$),[6] and this value compares favorably with reported values of approximately 5 that were measured under identical conditions.[2b]

In addition, hydrolysis of the two anomeric 5-thioxylopyranosides (**4a** and **4b**) yields 5-thioxylose as the sole carbohydrate product, and the derived pseudo-first-order rate constants at several different perchloric acid concentrations are organized in Table S2 (Supporting Information). A plot of the observed rate constants ($k_{obs}$) for hydrolysis of **4a** and **4b** as a function of $-\log[H_3O^+]$ is shown in Figure 2. The data listed in Table S2 were used to calculate second-order rate constants ($k_{H+}$) for

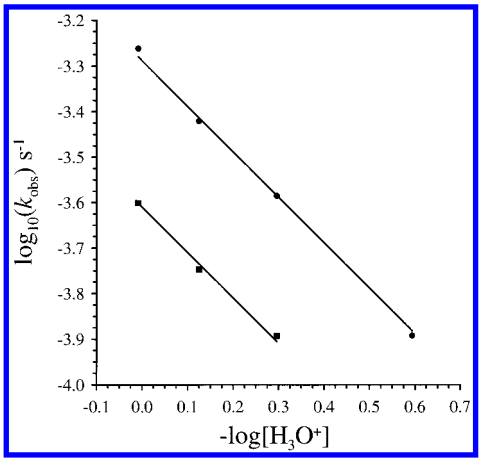



**Figure 1.** Plot of $\log(k_{obs})$ against $-\log[H_3O^+]$ for the hydrolysis of methyl α- (■) and β- (●) D-xylopyranosides at 80 °C ($\mu$ = 1.0; $NaClO_4$). The given lines are the best linear fits to the data.

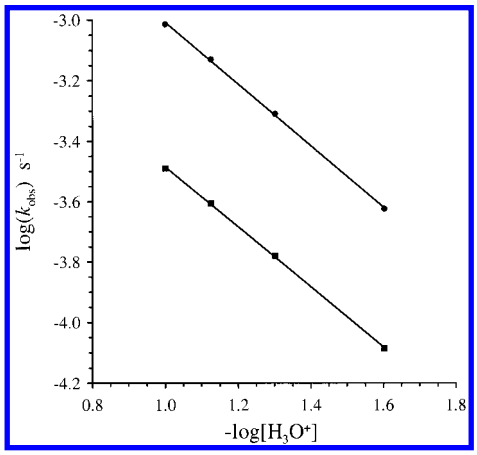



**Figure 2.** Plot of $\log(k_{obs})$ against $-\log[H_3O^+]$ for the hydrolysis of methyl 5-thio-α- (■) and β- (●) D-xylopyranosides at 80 °C ($\mu$ = 1.0; $NaClO_4$). The given lines are the best linear fits to the data.

the hydrolysis of methyl 5-thio-α- and β-D-xylopyranoside, and these values are (3.29 ± 0.04) × $10^{-3}$ $M^{-1}$ $s^{-1}$ and (9.73 ± 0.17) × $10^{-3}$ $M^{-1}$ $s^{-1}$, respectively. In comparison to methyl α- and β-xylopyranosides, the two ring-sulfur homologues hydrolyze faster by factors of approximately 13.6 and 18.5 for the α- and β-anomers, respectively. These rate ratios are in reasonable agreement with the corresponding values of 10.1 and 14.5 reported by Whistler and Van Es (0.5 N HCl, 75 °C).[10]

All heavy-atom and secondary deuterium kinetic isotope effects (SDKIEs) were measured using the "quasi-racemate" methodology.[37,38] In these experiments, approximately equal amounts of a labeled D-sugar and an unlabeled L-sugar are mixed, and the change in optical rotation is followed as a function of time. Shown in Figures 3 and 4 are typical observed changes in rotation versus time; also shown are the calculated best nonlinear fits to the data. Tables 1 and 2 summarize the measured heavy-atom, secondary deuterium, and solvent deuterium KIEs for the acid-catalyzed hydrolysis of methyl α- and β-xylopyranosides, respectively. Also included in Tables 1 and 2 are the reported KIEs for the hydrolysis of methyl α- and β-glucopyranosides.[6] The calculated heavy-atom and secondary deuterium KIEs for the acid-catalyzed hydrolysis of methyl 5-thio-α- and β-xylopyranosides are listed in Table 3. The measured solvent kinetic isotope effect values, which were

(38) Nadvi, N. S.; Robinson, M. J. T. *Abstracts, 4th International Symposium on Physical Organic Chemisty*; The Chemical Society: London, 1978; C1, p 141.

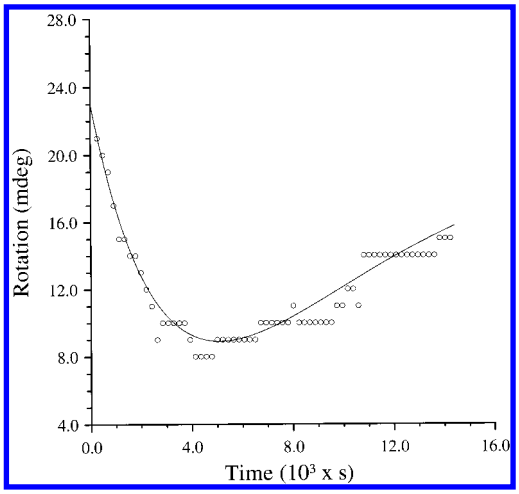



**Figure 3.** Plot of observed rotation versus time for the hydrolysis of the quasi-racemate containing 10 mg of both methyl $\beta$-D-(1-$^{18}$O)-xylopyranoside and methyl $\beta$-L-xylopyranoside at 80 °C. For clarity, only every fourth data point is shown. The given line is the best nonlinear fit to the data.

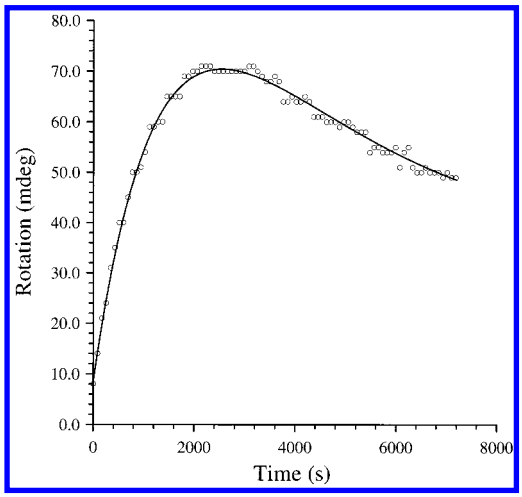


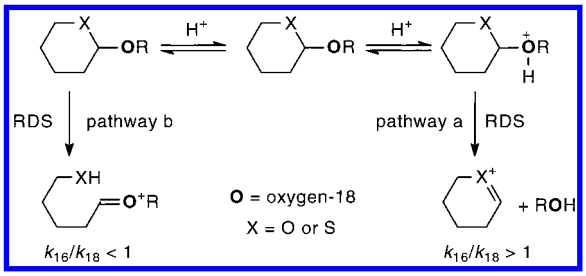

**Figure 4.** Plot of observed rotation versus time for the hydrolysis of the quasi-racemate containing 10 mg of both methyl 5-thio-α-D-(1-$^{13}$C)xylopyranoside and methyl 5-thio-α-L-xylopyranoside at 80 °C. For clarity, only every fourth data point is shown. The given line is the best nonlinear fit to the data.

obtained by direct comparison of derived second-order rate constants, are also included in Tables 1−3.

## Discussion

**Hydrolysis of Methyl Xylopyranosides: Solvent KIEs.** The measured solvent deuterium KIEs ($k_{D_3O^+}/k_{H_3O^+}$), of greater than 2 (Tables 1 and 2), for the hydrolyses of methyl α- and $\beta$-xylopyranosides can be interpreted using the principles of isotopic fractionation factor analysis (equation 2),[39] where eq 2 expresses the relationship between the rate constants observed in $D_2O$ and $H_2O$ and the fractionation factors ($\phi_i^{TS}$ and $\phi_j^{R}$) for the exchangeable protons undergoing change in their bonding at the transition and reactant states, respectively.[39] Two simplifying approximations used ion this analysis are (1) $D_3O^+$ is a stronger acid in $D_2O$ than is $H_3O^+$ in $H_2O$ ($\phi = 0.69$), and (2) hydrogens being transferred or "in flight" between oxygen

**Scheme 3**




atoms as part of the rate-limiting step possess a fractionation factor ($\phi$) of ∼0.3−0.5. In addition, hydrogen atoms involved in H-bonds where the overall bonding is loose have fractionation factors <1, and these secondary KIEs can contribute significantly to the overall effect. If the hydrolytic transition state is close to the protonated glycoside, then $k_{D_3O^+}/k_{H_3O^+}$ should approximately be equal to $(0.69)/(0.69)^3$ (≈ 2.1); whereas, a transition state that is close in structure to the oxacarbenium ion (**1**, Scheme 1) should generate a solvent KIE of $\sim 1/(0.69)^3$ (≈ 3.0). Therefore, it can be concluded, on the basis of the measured solvent KIEs (Tables 1 and 2) that the hydrolysis reactions of both methyl xylopyranosides involve equilibrium protonation, that is, specific-acid catalysis, followed by a rate-limiting C−O bond cleavage step, and this event must involve the departure of a neutral leaving group.

$$k_{D_2O}/k_{H_2O} = \prod_i^n \phi_i^{TS} / \prod_j^n \phi_j^{R} \qquad (2)$$

**Ring and Leaving Group $^{18}$O KIEs.** The ring $^{18}$O KIE and the leaving group $^{18}$O KIE are useful probes for determining whether endocyclic or exocyclic C−O bond cleavage occurs during these hydrolysis reactions (Scheme 3, X = O).[40] Specifically, rate-limiting exocyclic C−O bond cleavage generates a normal KIE ($k_{16}/k_{18} > 1$) for the (1-$^{18}$O)-isotopomer, but an inverse KIE ($k_{16}/k_{18} < 1$) is indicative of rate-limiting step endocyclic C−O bond cleavage.[40] The measured leaving group $^{18}$O and ring $^{18}$O KIEs for methyl α-xylopyranoside are 1.023 ± 0.002 and 0.983 ± 0.001, respectively (Table 1), and the corresponding KIEs for the $\beta$-anomer are 1.023 ± 0.003 and 0.978 ± 0.001, respectively (Table 2). These observed $^{18}$O KIEs are similar to the EIEs calculated, at the HF/4.31G level of theory, for the acid-catalyzed formation of an oxacarbenium ion from methanediol (ring $^{18}$O ≈ 0.977 and leaving group $^{18}$O ≈ 1.020).[42] Although the calculations were performed on the smallest possible model compound, it is clear that significant exocyclic C−O bond cleavage and endocyclic C−O bond strengthening are two critical attributes of the two anomeric xylopyranosyl hydrolysis transition states.

**Anomeric $^{13}$C KIEs.** In principle, the rate-limiting exocyclic C−O bond cleavage can occur via either a dissociative ($S_N1$) or a weakly associative ($S_N2$) mechanism. For glucopyranosides that hydrolyze to give a neutral leaving group, the reaction generates ion:molecule pairs that react with solvent before reaching equilibrium,[8] that is, via a $D_N$ * $A_N$ mechanism. Reaction center $^{13}$C KIEs ($k_{12}/k_{13}$) have been used as a diagnostic tool to distinguish between associative (1.03−1.08) and dis-

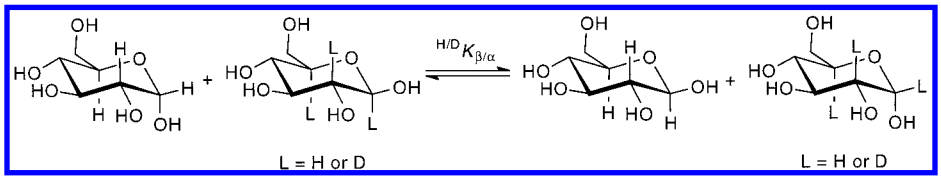
(39) (a) Alvarez, F. J.; Schowen, R. L. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, pp 1−60. (b) Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, pp 177−273.

(40) Bennet, A. J.; Sinnott, M. L.; Wijesundera, W. S. S. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1233−1236.

(41) Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429−3440.

(42) Barnes, J. A.; Williams, I. H. In *Organic Reactivity: Physical and Biological Aspects*; Golding, B. T., Griffin, R. J., Maskill, H., Eds.; Royal Society of Chemistry: Cambridge, 1995; pp 437−443.

**Scheme 4**




sociative (1.00−1.01) substitution mechanisms.[43] For example, on the basis of the anomeric $^{13}C$ KIEs for these reactions of 1.085 ± 0.008 and 1.032 ± 0.003, respectively,[44] Zhang et al. concluded that the reactions of α-D-glucopyranosyl fluoride (anionic leaving group) with azide and water occur via $S_N2$ mechanisms. In contrast, the anomeric $^{13}C$ KIE for the spontaneous hydrolysis of α-D-glucopyranosyl 4′-bromoisoquinolinium bromide is 1.005 ± 0.002, a value that is consistent with a dissociative mechanism.[45]

The measured values for the $^{13}C$ KIEs on the acid-catalyzed hydrolysis of methyl α- and β-D-xylopyranosides are 1.006 ± 0.001 and 1.006 ± 0.003, respectively (Tables 1 and 2). Thus, it can be concluded that, as in the case of methyl glucopyranoside hydrolysis,[6] no nucleophilic solvent participation is occurring at the methyl xylopyranoside reaction transition states.

**α-Secondary Deuterium Kinetic Isotope Effects (α-SDKIEs).** The measured α-SDKIEs for the acid-catalyzed hydrolysis of methyl α- and β-xylopyranosides are 1.128 ± 0.004 and 1.098 ± 0.005, respectively (Tables 1 and 2), and the corresponding values for methyl α- and β-glucopyranosides are 1.137 ± 0.007 and 1.089 ± 0.006, respectively.[6]

The origin of an α-SDKIEs is considered to arise mainly from the weakening of an out of plane $C_\alpha$-H(D) bending vibration as hybridization at the reaction center changes from $sp^3$ to $sp^2$.[43] Hybridization changes from $sp^3$ to $sp^2$ that occur during these reactions trigger bonding changes other than weakening of the out of plane $C_\alpha$-H(D) bending vibrations. For example, the reaction center C−H(D) stretching force constant increases, which results in a shortening of the bond and an associated attenuation of the measured α-SDKIE. Such offsetting changes in bending and stretching vibrations complicate the analysis of α-SDKIE values, as demonstrated by the recent vigorous debate regarding the interpretation of α-SDKIE values for gas-phase $S_N2$ reactions.[46] Therefore, it appears that the equivalence, within experimental error, of the measured α-SDKIEs for each anomer of methyl glucoside and methyl xyloside probably results from a coincidental canceling of minor changes in the transition state's bending and stretching force constants. This fortuitous cancellation occurs despite the inequality in xylosyl and glucosyl transition state charge delocalization (vide infra).

In addition, ground-state force constant differences are present between the two anomeric glycosides, as revealed by the existence of a conformational equilibrium isotope effect (CEIE; i.e., $^{H/D}K_{\beta/\alpha}$) for the mutarotation of glucose between its α- and β-anomers of 1.043 ± 0.004 (Scheme 4; $L_1$ = D, $L_2 = L_5$ = H).[47]

In their study, Lewis and Schramm calculated, using various levels of theory up to RHF/6-31G**, which also included an Onsager dipole model correction ($e$ = 78.8), that the α-CEIE arises from a hyperconjugative interaction between the ring oxygen $n_p$ lone pair and the $\sigma^*$ orbital of the anomeric C−H bond, resulting in a specific loosening of the axial C−H bond in the β-anomer.[47] A consequence of the CEIE is that anomeric differences between measured α-SDKIE are probably dominated by ground-state effects, and thus, delineation of transition state structural information that is contained in these isotope effects becomes challenging.[45]

***β*-SDKIEs.** The magnitude of a β-SDKIE measured on a dissociative reaction ($S_N1$) is influenced by transition state geometry,[48] and thus, these isotope effects contain transition-state structural information. For instance, the size of a β-SDKIE increases with decreasing carbenium ion stability, and it reaches a maximal value when the hyperconjugative overlap of the β-C−H(D) bond and the nascent p orbital are aligned in the transition state.[48] A complicating factor, however, in the analysis of β-SDKIEs on reactions of glycosides is the existence of a ground-state β-CEIE ($^{H/D}K_{\beta/\alpha}$), which for glucose is 1.027 ± 0.005 (Scheme 4; $L_2$ = D, $L_1 = L_5$ = H).[47] Lewis and Schramm proposed that the β-CEIE originates from differences in $n_p$(O2) → $\sigma^*$(C2−H) orbital overlap between the two anomers that result from variations in the preferred H−C2−O−H torsional angle.[47] Clearly, the strength of the $n_p$(O2) → $\sigma^*$(C2−H) orbital interaction will be mediated by solvent, and thus, the influence of this interaction on the magnitude of the measured β-SDKIEs will be modulated by solvent reorganization along the reaction coordinate.

At the hydrolytic transition states for both anomeric glucopyranosides, however, the C1 carbon has a greater positive charge accumulation than in the corresponding transition states for hydrolysis of the analogous xylopyranoside; thus, it is likely that a less optimal alignment of the $\sigma$(C2−H) and $\rho$(C1) orbitals is occurring at the xylopyranosyl transition states, although the exact degree of this alignment difference is difficult to gauge, because it is not obvious how transition-state charge distribution affects solvent reorganization in the vicinity of the C2 hydroxyl group.

**Remote Deuterium KIEs.** The γ-SDKIEs associated with labeling at C-5 can, in principle, arise from three different phenomena, namely (1) deuterium conformational isotope effects, (2) steric isotope effects, or (3) inductive effects.

First, the conformational deuterium isotope effect arises from the observed equatorial preference of deuteron relative to proton in cyclohexane ring systems. Specifically, Aydin and Günther[49] determined a CEIE of 1.06 at −88 °C using NMR spectroscopy, but Williams[50] calculated a CEIE value of 1.039 for the same equilibrium at −88 °C. More recently, measurements by Anet and Kopelevich[51] have lowered the estimated free energy for

(43) Melander, L.; Saunders: W. H. *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: New York, Chichester, Brisbane, Toronto, 1980; pp 235−248.
(44) Zhang, Y.; Bommuswamy, J.; Sinnott, M. L. *J. Am. Chem. Soc.* **1994**, *116*, 7557−7563.
(45) Huang, X.; Tanaka, K. S. E.; Bennet, A. J. *J. Am. Chem. Soc.* **1997**, *119*, 11147−11154.
(46) (a) Wolfe, S.; Kim, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 8056−8061. (b) Poirier, R. A.; Wang, Y.; Westaway, K. C. *J. Am. Chem. Soc.* **1994**, *116*, 2526−2533. (c) Moliner, V.; Williams, I. H. *J. Am. Chem. Soc.* **2000**, *122*, 10895−10902.
(47) Lewis, B. E.; Schramm, V. L. *J. Am. Chem. Soc.* **2001**, *123*, 1327−1336.
(48) Reference 43; pp 174−180.
(49) Aydin, R.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 985−986.
(50) Williams, I. H. *J. Chem. Soc., Chem. Commun.* **1986**, 627−628.
(51) Anet, F. A. L.; Kopelevich, M. *J. Am. Chem. Soc.* **1986**, *108*, 1355−1356.

the equatorial preference of deuterium in cyclohexane to 6.3 ± 1.5 cal mol$^{-1}$ at 25 °C, that is, a CEIE of 1.011 at this temperature. In addition, Anet and Kopelevich have reported that deuterium in 5,5-dimethyl-1,3-dioxane-2-$^2$H prefers to occupy the equatorial position by 49 ± 3 cal mol$^{-1}$ (CEIE = 1.086 at 25 °C).[52] Thus, the C5-equatorial deuteron in xylosides should generate a smaller $\gamma$-SDKIE than does the axial deuteron. This presumably is a consequence of a larger ground-state interaction of the $n_p$(O5) orbital with the $\sigma^*$(C5−$H_{axial}$) orbital.

Second, the $\gamma$-CEIE for mutarotation of glucose is 1.036 ± 0.004 (Scheme 4; $L_5$ = D, $L_1$ = $L_2$ = H), and Lewis and Schramm concluded that this effect originates from a steric interaction of the C5−H/D with the C1−OH group in the α-anomer.[47]

Third, a deuteron should behave in a conformationally independent manner as an electron donor when compared to a similarly positioned proton.[53]

Given the uncertainty in the dominant cause of a remote SDKIE and that the associated errors with the $\gamma$-SDKIEs are around 10% of the isotope effect, an extended analysis of the magnitude of the measured $\gamma$-SDKIE values is unwarranted at the present time.

**Comparison to the Acid-Catalyzed Hydrolyses of Methyl Glucopyranosides.** The magnitude of a KIE is governed by bonding changes between the ground state and the transition state. To compare the effects of a hydroxymethyl group on the hydrolytic pathway, it is prudent to compare only the KIEs measured for glycopyranosyl derivatives that react via similar mechanisms. In these specific-acid-catalyzed reactions, the transition state is approached from the conjugate acid of the substrate, although not necessarily from the most stable conformation of this intermediate (Scheme 1).

Both anomers of methyl glucopyranoside[6] and methyl xylopyranoside react via an acid-catalyzed exocyclic C−O bond cleavage pathway, and thus, any extra conformational flexibility in the xylopyranosyl series has no effect on the mode of reactivity, although both a conformationally flexible pyranoside[54] (based on a *cis*-decalin framework) and several alkyl glycofuranosides[40,55,56] undergo hydrolysis via initial endocyclic C−O bond cleavage. Nonetheless, the observed differences between the ring $^{18}$O KIEs (Tables 1 and 2) indicate that stronger $n_p$(O) → $\rho$(C1) interactions are occurring at the hydrolytic transition states for the two anomeric xylopyranosides than those occurring at the corresponding transition states for glucopyranoside hydrolysis. Although positively charged aglycons display different conformational preferences relative to neutral aglycons,[57,58] it is the magnitude of these effects at the hydrolytic transition state, that is, where the aglycon possesses a partial charge, that bring about transition-state conformational differences between glucopyranosides and xylopyranosides, and as a result, different ring $^{18}$O KIEs.

Another notable difference between the hydrolyses of methyl α-glucopyranoside and methyl α-xylopyranoside is the smaller solvent KIE for the former reaction (Table 1). This presumably results from unequal secondary KIE contributions that originate from dissimilar solvation requirements at the respective transition states rather than any involvement of a general-acid-catalyzed pathway.[59]

**Transition State Conformations.** The size of the ring-$^{18}$O and the $\beta$-secondary deuterium KIEs were used as the basis for the proposal that methyl α- and $\beta$-glucopyranoside hydrolyzed via flattened $^1S_3$ skew boat and flattened $^4C_1$ chair transition state conformations, respectively.[6] At the present time, it is clear that deriving conformational information from measured $\beta$-SDKIEs on glycoside hydrolysis reactions is more enigmatic than has previously been assumed. Nonetheless, any perturbing influence exerted by the ground-state $\beta$-CEIE on the magnitude of the measured $\beta$-SDKIE for hydrolysis of methyl α-D-glucopyranoside would require that the H−C2−C1−O1 dihedral angle in the transition state be larger than the previously estimated value of between 31 and 43 °.[6] Therefore, the transition state structure is, if anything, further removed from that of the ground-state $^4C_1$ chair conformation than the proposed flattened $^1S_3$ skew boat.[6] On the other hand, it is likely that the transition state conformations for the acid-catalyzed hydrolysis of methyl α- and $\beta$-xylopyranosides are close to the structure of the oxacarbenium ion itself, which most probably is the $^4H_3$ half-chair conformation.

**Ground-State Effects in 5-Thioglycosides.** In comparison to carbon−oxygen bond lengths and angles, the longer C−S bond and the smaller C−S−C angle force 5-thiopyranosides to adopt puckered ring conformations.[60] This ring puckering is evident in the crystal structures for both anomers of methyl 5-thioribopyranoside.[61] In addition, a larger anomeric effect exists for 5-thiopyranosyl compounds, as compared to their oxygen analogues.[62,63] This enhanced tendency for an electronegative group to adopt an axial orientation is mainly caused by electronic factors.[64] Even though the exo-anomeric effect for 5-thiosugars, which involves delocalization of the exocyclic oxygen's $n_p$ lone pair into the $\sigma^*_{C-S}$ of the C5−S bond, is larger than for the parent ring-oxygen carbohydrates,[21g] it is the total of the endo- and exo-anomeric effects that gives rise to the greater total anomeric effect.[64] The greater exo-anomeric effect in 5-thioxylose manifests itself in the measured anomeric $^1J_{C-H}$ coupling constants, and these values for methyl 5-thio-α-(equatorial C−H) and $\beta$-xylopyranosides (axial C−H) are 156.3 and 158.9 Hz, respectively. The relative magnitude of these values is opposite to the standard Perlin effect[65] observed on the two anomeric methyl xylopyranosides in which the measured $^1J_{C-H}$ values are 170.2 and 161.7 Hz for the α- (equatorial C−H) and the $\beta$-anomer (axial C−H), respectively.

(52) Anet, F. A. L.; Kopelevich, M. *J. Am. Chem. Soc.* **1986**, *108*, 2109−2110.

(53) Reference 43; pp 180−181.

(54) (a) Liras, J. L.; Anslyn, E. V. *J. Am. Chem. Soc.* **1994**, *116*, 2645−2646. (b) Liras, J. L.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **1997**, *119*, 8191−8200.

(55) Capon, B.; Thacker, D. *J. Chem. Soc. B* **1967**, 185−189.

(56) (a) Lönnberg, H.; Kankaanperä, A.; Haapakka, K. *Carbohydr. Res.* **1977**, *56*, 277−287. (b) Lönnberg, H.; Kulonpää, A. *Acta Chem. Scand., Ser. A.* **1977**, *31*, 306−312. (c) Lönnberg, H.; Valtonen, L. *Finn. Chem. Lett.* **1978**, 209−212.

(57) The term "reverse anomeric effect" was originally used to describe this effect; see: Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205−2213.

(58) For recent discussions on the origin of this effect, see: (a) Perrin, C. L.; Armstrong, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 6825−6834. (b) Perrin, C. L.; Fabian, M. A.; Brunckova, J.; Ohta, B. K. *J. Am. Chem. Soc.* **1999**, *121*, 6911−6918. (c) Randell, K. D.; Johnston, B. D.; Green, D. F.; Pinto, B. M. *J. Org. Chem.* **2000**, *65*, 220−226. (d) Vaino, A. R.; Szarek, W. A. *J. Org. Chem.* **2001**, *66*, 1097−1102.

(59) A mechanistic change to general-acid catalysis has been associated with values of $k_{D_3O^+}/k_{H_3O^+}$ closer to 1.0; for example, see reference 3a.

(60) Lambert, J. B.; Wharry, S. M. *Carbohydr. Res.* **1983**, *115*, 33−40.

(61) Girling, R. L.; Jeffrey, G. A. *Acta Crystallogr., Sect. B* **1973**, *29*, 1102−1111.

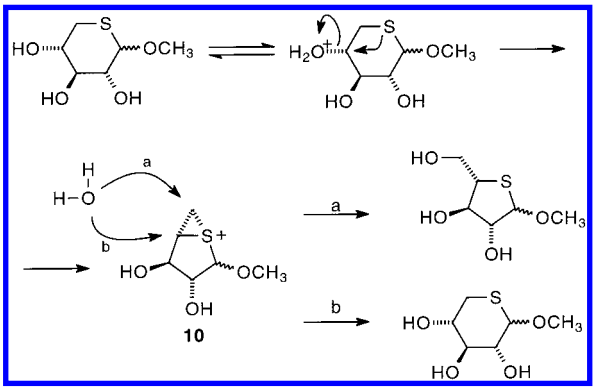
(62) Lambert, J. B.; Wharry, S. M. *J. Org. Chem.* **1981**, *46*, 3193−3196.

(63) Hughes, N. A.; Munkombwe, N. M. *Carbohydr. Res.* **1985**, *136*, 397−409.

(64) Pinto, B. M.; Leung, R. Y. N. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; American Chemical Society: Washington, DC, 1993; pp 126−155.

(65) Wolfe, S.; Pinto, B. M.; Varma, V.; Leung, R. L. N. *Can. J. Chem.* **1990**, *68*, 1051−1062.

**Scheme 5**



In contrast to the situation with glucose,[47] no extensive study on conformational equilibrium isotope effects (CEIE) has been reported for 5-thiosugars, although Anet and Kopelevich have reported that the deuterium atom in 5,5-dimethyl-(2-$^2$H)-1,3-dithiane exhibits no preference to reside in either the equatorial or the axial position (i.e., CEIE = 1).[66]

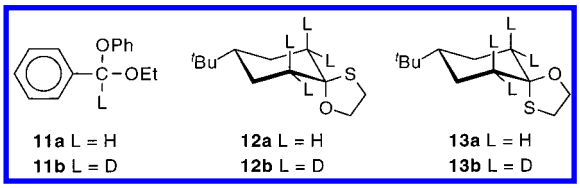
**Acid-Catalyzed Hydrolysis of Methyl 5-Thioxylopyranosides.** The acid-catalyzed hydrolysis of both anomers of methyl 5-thioxylopyranosides yields 5-thioxylose as the sole carbohydrate reaction product. Thus, even though transannular sulfur participation has been shown to occur during the acid-catalyzed methanolysis of 5-thioglucose,[67,68] it is clear that no notable intramolecular sulfur participation occurs during these reactions, because if the thiiranium ion **10** were formed, it would give 4-thio-L-arabinose derivatives by preferential attack on the primary carbon of this intermediate (Scheme 5).

The measured solvent deuterium KIEs ($k_{D_3O^+}/k_{H_3O^+}$) for hydrolysis of methyl 5-thio-α- and β-xylopyranosides are 2.37 ± 0.08 and 2.63 ± 0.09, respectively (Table 3). These KIEs are consistent with specific acid-catalyzed processes in which preequilibrium protonation occurs on the exocyclic oxygen atom, followed by rate-limiting C−O cleavage (also see leaving group $^{18}$O−KIE). Furthermore, the larger solvent KIE ($k_{D_3O^+}/k_{H_3O^+}$) for the hydrolysis of the β-anomer is consistent with a later transition state for C−O bond cleavage. Nevertheless, it is apparent that general-catalyzed processes, such as a nucleophilic attack of water catalyzed by surrounding solvent molecules, are unimportant at the hydrolytic transition states.

**Heavy-Atom Kinetic Isotope Effects.** The measured leaving-group $^{18}$O KIEs for methyl 5-thio-α- and β-xylopyranosides are 1.027 ± 0.001 and 1.035 ± 0.001, respectively (Table 3). Given that these reactions are specific-acid-catalyzed, the magnitude of the $^{18}$O KIEs indicates that both methyl 5-thio-α- and β-xylopyranosides hydrolyze exclusively via rate-limiting exocyclic C−O bond cleavage. In addition, the larger leaving group KIE for the β-anomer, although closer to the values typically found for general-acid-catalyzed reactions of acetals (1.035−1.045),[59,69] is consistent with a stronger ground-state exocyclic C−O bond, a consequence of the larger exo-anomeric effect in 5-thiosugars and a later transition state structure (vide supra).

As mentioned above, measured reaction center $^{13}$C−KIE values have been used to distinguish between $S_N1$ ($k_{12}/k_{13}$ = 1.00−1.01) and $S_N2$ ($k_{12}/k_{13}$ = 1.03−1.08) mechanisms.[43] In the present case, the measured $^{13}$C KIEs for acid-catalyzed

**Chart 3**



**11a** L = H **12a** L = H **13a** L = H
**11b** L = D **12b** L = D **13b** L = D

hydrolysis of methyl 5-thio-α- and β-xylopyranoside are 1.031 ± 0.002 and 1.028 ± 0.002, respectively (Table 3). Two distinct postulates could explain the magnitude of these anomeric $^{13}$C−KIEs. First, the hydrolysis reaction may occur via an "exploded" $S_N2$ mechanism similar to that proposed by Zhang et al. for the hydrolysis of α-D-glucopyranosyl fluoride ($k_{12}/k_{13}$ = 1.032).[44] Second, the observed $^{13}$C KIE might be larger than that expected for an $S_N1$ reaction (1.00−1.01), because force constant changes between the ground-state and the transition state associated with the C−S bond may be smaller than those associated with carbon bonded to second row elements, such as oxygen (acetals) and carbon (alkyls). A piece of evidence that strongly favors the latter interpretation is that 5-thio-α-D-glucopyranosyl fluoride reacts with azide via a dissociative mechanism ($S_N1$),[70] in contrast to the corresponding associative reaction of α-D-glucopyranosyl fluoride with azide ($S_N2$).[71] In other words, the 5-thioglucopyranosyl cation is a reaction intermediate under conditions where the glucopyranosyl cation has no measurable lifetime; therefore by analogy, the 5-thioxylopyranosyl thiacarbenium ion will also have a discrete existence.

In summary, it can be concluded that these hydrolysis reactions proceed via thiacarbenium ion-like transition states with no nucleophilic solvent participation.

**Secondary Deuterium KIEs.** In contrast to the situation with acetals, few SDKIE studies have been performed on the hydrolysis reactions of monothioacetals. In one such study, Ferraz and Cordes reported that the α-SDKIE values ($k_{7a}/k_{7b}$) for the acid-catalyzed and the spontaneous hydrolysis of **7** are 1.04 ± 0.01 and 1.13 ± 0.02, respectively.[72] Unfortunately, comparison of these values with the corresponding α-SDKIEs ($k_{11a}/k_{11b}$) for the hydrolysis of **11**[73] remains problematic, because hydrolysis of **7a** exhibits no measurable general-acid catalysis,[15] but **11a** reacts via a general-acid-catalyzed mechanism.[73]

Nevertheless, the measured α-SDKIE values for the hydrolysis reactions of methyl 5-thio-α- and β-xylopyranosides are 1.142 ± 0.010 and 1.094 ± 0.002, respectively (Table 3), and despite the absence of a significant α-CEIE (vide supra), these values are remarkably similar to those for the corresponding methyl xylopyranosides of 1.128 ± 0.004 and 1.098 ± 0.005, respectively (Tables 1 and 2).

Given that the α-SDKIE for the acid-catalyzed hydrolysis of **7** (1.04) is radically different from that for **4a** or **4b**, it is possible that the magnitude of this KIE might be a convenient criterion for distinguishing between initial C−S (**7**) or C−O (**4a** and **4b**) bond cleavage, although more examples are clearly required in order to test this hypothesis. In 1972, Guinot and Lamaty reported that the acid-catalyzed hydrolyses of compounds **12** and **13** (20% v/v $H_2O$/2-propanol) takes place with β-SDKIEs

(66) Anet, F. A. L.; Kopelevich, M. *J. Chem. Soc., Chem. Commun.* **1987**, 595−597.
(67) Hashimoto, H.; Yuasa, H. *Tetrahedron Lett.* **1988**, *29*, 1939−1942.
(68) Yuasa, H.; Tamura, J.; Hashimoto, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2763−2769.
(69) Rosenberg, S.; Kirsch, J. F. *Biochemistry* **1981**, *20*, 3196−3204.
(70) Johnston, B. D.; Indurugalla, D.; Pinto, B. M.; Bennet A. J. *J. Am. Chem. Soc.*, submitted for publication.
(71) Banait, N. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 7951−7958.
(72) Ferraz, J. P.; Cordes, E. H. *J. Am. Chem. Soc.* **1979**, *101*, 1488−1491.
(73) Lamaty, G.; Menut, C.; Nguyen, M. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 75−77.

($k_{H4}/k_{D4}$) of 1.32 and 1.11, respectively.[74] These spiro monothioketals, however, must have a suboptimal $n_p(S) \rightarrow \rho(C1)$ orbital overlap at their respective hydrolytic transition states, and thus, these reactions would be expected to generate unusually large $\beta$-SDKIEs for ketal derivatives.[75] The measured $\beta$-SDKIEs for methyl 5-thio-α- and $\beta$-xylopyranoside hydrolyses are $1.061 \pm 0.003$ and $1.018_5 \pm 0.001$, respectively (Table 3), and both values are smaller than the corresponding KIEs for hydrolysis of the two anomeric methyl xylopyranosides. The smaller $\beta$-SDKIEs for the hydrolysis of the 5-thioxylosides probably results from a worse hyperconjugative overlap of the C−H(D) bond with the nascent p-type orbital on the anomeric carbon. At the present time, given the uncertainty surrounding solvation of the C2−OH group and the resultant effect on the magnitude of the isotope effect, it is difficult to assess what transition state conformation information is contained in these KIEs.

The measured $\gamma$-SDKIEs for methyl 5-thio-α- and $\beta$-(5−$2H_2$)xylopyranosides are $0.999 \pm 0.001$ and $0.986 \pm 0.002$, respectively. Given the uncertainties concerning the principal cause of these isotope effects, it is apparent that a detailed analysis on the magnitudes of these $\gamma$-SDKIEs is unwarranted at this time.

## Conclusions

Removal of the C5-hydroxymethyl group from methyl glucopyranosides generates a more optimal $n_p(O5) \rightarrow \rho(C1)$ orbital overlap at the hydrolytic transition state. Thus, strengthening of the endocyclic C−O bond is heavily coupled to cleavage of the exocyclic C−O bond at the transition states for the specific-acid-catalyzed hydrolyses of methyl xylopyranosides.

The acid-catalyzed hydrolyses of methyl 5-thioxylopyranosides occur via reversibly formed O-protonated conjugate acids that undergo slow, rate-determining exocyclic C−O bond cleavage. These hydrolysis reactions proceed with no detectable side reactions involving transannular participation of the ring sulfur atom. Moreover, these hydrolysis reactions do not have a solvent nucleophilic component as a feature of the thiacarbenium ion-like transition states.

**Acknowledgment.** The authors gratefully acknowledge the Natural Sciences and Engineering Research Council of Canada for financial support of this work. We also thank Perkin-Elmer for the loan of a printer, Professors Piers and Tanner (University of British Columbia) for allowing us unlimited access to their polarimeter, Professor Horenstein (University of Florida) for valuable discussions, and the three anonymous referees for helpful suggestions.

**Supporting Information Available:** Experimental details for the synthesis of 1,2-*O*-isopropylidene-α-D-(1-$^2$H)xylofuranose, 1,2-*O*-isopropylidene-α-D-(1-$^{13}$C)xylofuranose, 1,2-*O*-isopropylidene-α-D-(5-$^2H_2$)xylofuranose, and 1,2-*O*-isopropylidene-α-D-(2-$^2$H)xylofuranose. Tables of observed rate constants for the hydrolysis reactions of methyl α- and $\beta$-D-xylopyranosides, and methyl 5-thio-α- and $\beta$-D-xylopyranoside as a function of $[H_3O^+]$ at 80.0 °C and an ionic strength of 1 M ($NaClO_4$). This material is available free of charge via the Internet at http://pubs.acs.org.

JA011232G

(74) Guinot, F.; Lamaty, G. *Tetrahedron Lett.* **1972**, 2569−2572.

(75) The $\beta$-SDKIEs per deuterium atom are 1.072 and 1.026 for **12** and **13**, respectively, but the $\beta$-SDKIEs per deuterium atom for hydrolysis of 2,2-diethoxypropane in 50% v/v dioxane/water is 1.017 (reference 76).

(76) Shiner, V. J., Jr.; Cross, S. *J. Am. Chem. Soc.* **1957**, *79*, 3599−3602.