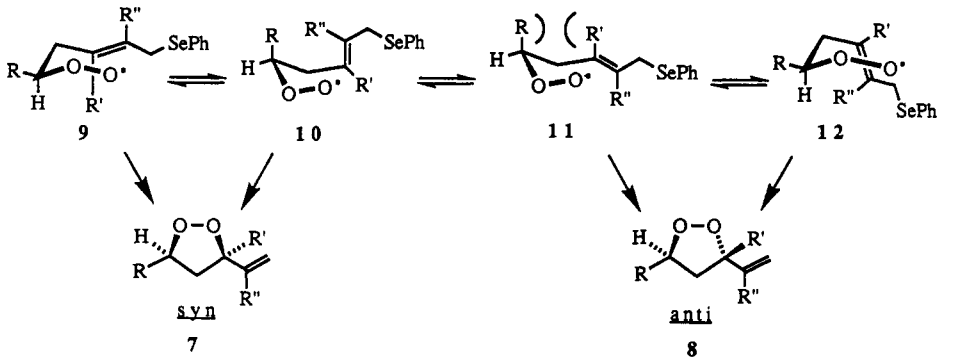
Scheme II



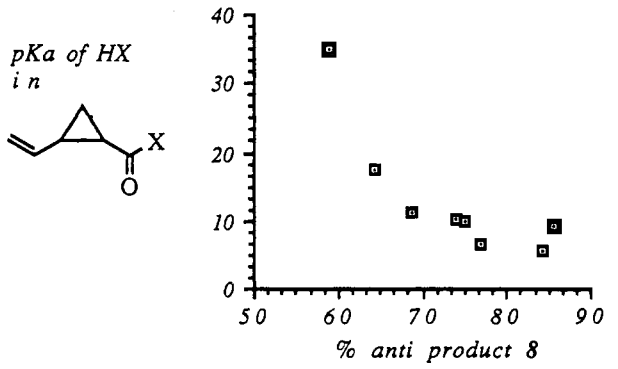


Figure 1.

at −50 °C, while a similar drop in reaction temperature upon oxygenation of the simple ester **1c** only marginally affected the diastereoselectivity (−45 °C, 2.4:1 anti–syn, 29% yield). Further evidence for this significant effect of fluoro substituents on the transition state of cyclization is seen with **1o**. Thus, when R = $CH{=}CHCO_2CH(CF_3)_2$, there is a marked decrease in syn diastereoselectivity relative to the analogous methyl ester case (Table I, compare entries **b** and **o**).

The source of this preference for a pseudoaxial orientation of the ester appendage in the transition state for 5-hexenylperoxy radical cyclization remains a matter of some speculation. Clearly, the electronegativity of the carbonyl moiety is important, as a graph of pK_a (as a measure of electron demand at the carbonyl) of the carbonyl substituent vs % anti dioxolane product formed reveals a striking correlation (Figure 1). Other parameters, such as carbonyl dipole moment[6] or ^{13}C resonance of the carbonyl carbon (see supplementary material), do not show a discernible relationship with anti dioxolane production. At present, we are utilizing computational techniques to probe the manner by which this attribute of the carbonyl functionality is translated into a (electronic?) preference for the axial ester moiety upon cyclization.

In summary, these probes into the mechanistic details of oxygenation lead us to suggest that the transition state preceding anti dioxolane product when R = ester is best represented as a chairlike construct with a *pseudoaxial* ester. Utilizing electron-withdrawing esters affords the otherwise difficultly obtainable anti dioxolane product with excellent stereoselectivity (e.g., Table I, entry **h**), although a precise mechanistic rationale presently eludes us.

Acknowledgment. We thank NIH (GM37681) and NSF (CHE 86-57016) for financial support.

Supplementary Material Available: Characterization data and NMR spectra of **7f–o** and **8f–o** (30 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(6) Dipole moments of model compounds. CH_3CO_2-t-Bu 1.93 (22 °C, PhH); Donle, H. L. *Z. Physik Chem.* **1931**, *B14*, 362. CH_3CO_2NHt-Bu 3.90 (30 °C, dioxane): Kumler, W. D.; Porter, C. W. *J. Am. Chem. Soc.* **1934**, *56*, 2549. n-$C_{17}H_{35}COSCH_3$ 1.37 (30 °C, PhH): Hirabayashi, Y. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 175. n-Bu(Et)$CHCO_2CH_2(CF_2)_8H$ 2.8 (20 °C, PhH): Romans, J. B.; Callinan, T. D. *J. Electrochem. Soc.* **1957**, *104*, 357.

(7) pK_a's, except for the amine from **1n**, are found in: Sergeant, E. P.; Dempsey B. *Ionisation Constants of Organic Acids in Aqueous Solution*; Pergamon Press: Oxford, 1979. The pK_a of Et_2NH is used as a model for the amine in **1n** and can be found in: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 2nd ed.; Plenum Press: New York, 1977p p 3.

Face Selectivity of the Protonation of Glycals

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Summary: The proton-catalyzed addition of alcohols to glycals is shown not to be a trans diaxial addition.

We wish to describe our preliminary studies on the stereochemistry of protonation of glycals, the only important reaction of glycals which has not hitherto undergone detailed stereochemical scrutiny.[1] Very recently, Bollitt, Mioskowski, Lee, and Falck (BMLF) disclosed that triphenylphosphine hydrobromide (TPP–HBr) was the

(1) (a) Ferrier, R. J. *The Carbohydrates*, 2nd ed.; Pigman, W., Horton, D., Wander, J., Eds.; Academic Press: New York, 1980; Vol. 1B, pp 843–875. (b) Grewal, G. Ph.D. dissertation, CUNY 1991, Chapter 2, to be published.

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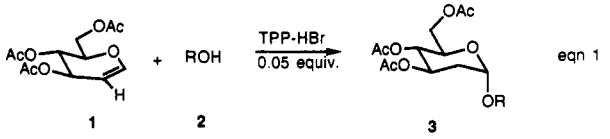
Table I. Sugar Stereochemistry at C-1 and C-2 Resulting from Protonation of Glycals

entry	glycal	R (equiv)	anomer ratio α/β	equatorial D/axial D
1	**7a**	CH_3 (1.5)	70/30	87/13[a,b]
2	**7a**	CH_3CO (1.5)	90/10	92/8[a,b]
3	**7b**	CH_3CH_2 (3)	75/25	67/33[a-c]
4	**7c**	CH_3 (1.5)	77/23	33/67[a,d]
5	**7d**	CH_3 (3)	88/12	87/13[a,d]
6	**7d**	Ph (2)	98/2	85/15[a,d]
7	**7e**	CH_3 (1.5)	21/79	<5/>95[e]

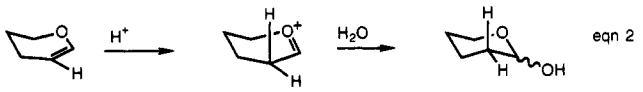
[a] Since the NMR peaks for axial and equatorial D did not give base-line resolution, the peak areas were determined by a visual curve-fitting program; hence, the disparities in the e/a ratios in entries 1–2 and 5–6 indicate the imprecision of the curve-fitting. [b] The ratios were identical in both α and β anomers, hence, the ^2H spectra are of α,β mixtures. [c] The ratio was determined after deacetylation and rebenzylation. [d] The ratio was determined for α anomer only. [e] The ratio was determined for the β anomer only.

catalyst of choice for mild and high-yield protonation and subsequent glycosidation of glycals (eq 1).[2] They observed



1 2 3

mainly α-glycoside products in their examples using glycals with all equatorial substituents. Danishefsky, in the allal series, has obtained a β-glycoside with the BMLF protocol.[3] Earlier, careful physical organic studies had shown that the hydration of enol ethers occurs via an Ad_E2 (addition–electrophilic–bimolecular) mechanism, i.e., a first step of protonation to form a carbonium ion followed by a second step of nucleophilic addition (eq 2).[4] In the pro-



4 5 6

tonation step in a polar medium, no strong bridging of the proton can occur. Thus, there was no good reason to expect direct trans addition in cases where stereochemistry was observable. In order to completely determine the stereochemistry of nonenzymic protonation of glycals, we used the BMLF procedure in deuterated media. Thus, the glycals listed in Table I were treated with a catalytic amount of TPP–HBr in the presence of nucleophiles having O–D functions. The stereochemistry and yield of the products were determined by both ^1H and ^2H NMR.[5] A representative set of spectra are shown in Figure 1. It is clear that, except for the case of 3-deoxyglucal **7c** and allal **7e**, deuteron delivery is largely from below the plane to afford what becomes the equatorial ligand at C-2. Hence, the stereochemistry at the anomeric center of the product glycoside is not due to trans addition. The predominant axial stereochemistry at C-1 probably arises from

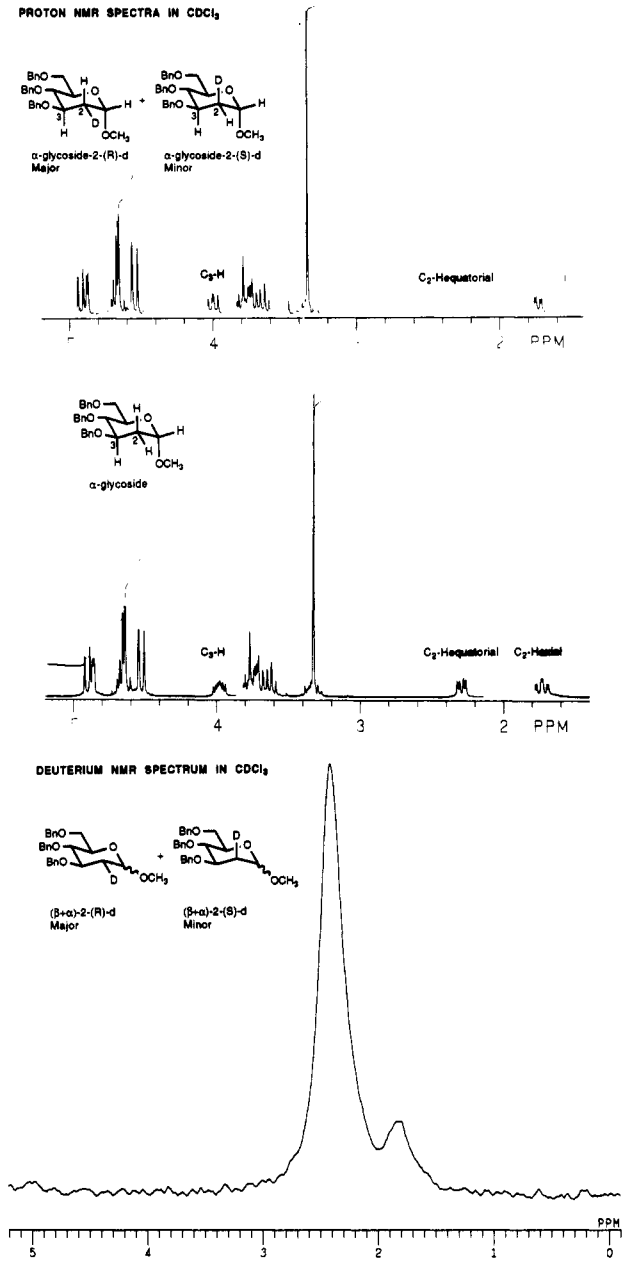
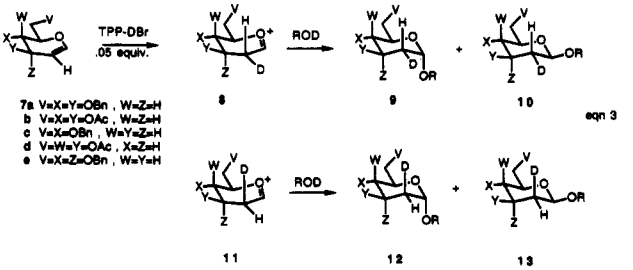


Figure 1. Deuterium (61.4 MHz) and proton (300 MHz) NMR spectra for methyl glycosides obtained from **7a**.

the kinetic anomeric effect (KAE) expected for trapping the intermediate oxonium ions 8 and 11 (eq 3).[6] Hence,



8 9 10

11 12 13

the differing α/β ratios are due to differing magnitudes of the KAE inherent in the developing C-1–nucleophile

(2) Bollitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812–5813.

(3) Danishefsky, S. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **1991**, *113*, 5080–5082.

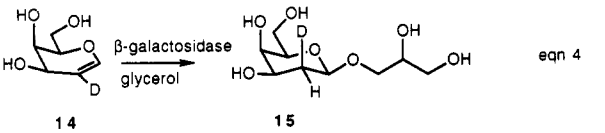
(4) (a) Salomaa, P.; Kankaanpena, A.; Lajunen, M. *Acta Chem. Scand.* **1966**, *20*, 1790–1801. (b) Kresge, A. J.; Chiang, Y. *J. Chem. Soc. B*, **1967**, 53–57 and 58–61.

(5) Lemieux has reported the syntheses of 2-deuterioglycosides by Pd-catalyzed deuterogenolysis of 2-iodosaccharides and has reported their 60-MHz proton spectra which are in good agreement with our data. Lemieux, R. U.; Levin, S. *Can. J. Chem.* **1964**, *42*, 1473–1480.

(6) (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectron Effects at Oxygen*; Springer Verlag: New York, 1983. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983.

bonding. One can interpret the observation of a β-glycoside in the allal series simply as the result of the steric repulsion of the 3-axial substituent overriding the KAE. Our results are consistent with the Ad_E2 mechanism with a kinetically (sterically?) controlled protonation followed by glycosyl transfer directed by the KAE. They are only surprising to the extent that the intuition of many practicing organic chemists assumes that trans diaxial addition of electrophilic reagents to alkenes is the common behavior. Our results confirm a related experiment with similar mild conditions where Michalska et al. added deuterated thiophosphoric acid to glucal to afford cleanly a 2-deoxypyranose thiophosphate product resulting from cis addition from the α-face.[7] In a control experiment for enzyme studies (vide infra) using rather unusual conditions, Lehmann treated the triacetate of galactal-2-*d* (**14**) with a melt of phenol and p-TosH at 60 °C to afford largely α-glycoside with no stereoselectivity in the proton delivery.[8]

It is interesting to compare our acid-catalyzed results with those of enzyme-catalyzed additions. Lehmann[8] and Hehre,[9] in a pioneering series of experiments that anticipated recent work applying enzymology to preparative glycoside chemistry,[10,11] demonstrated that glycals could be stereospecifically converted to 2-deoxyglycosides using glycosidase enzymes. For example, the galactal-2-*d* (**14**) was cleanly transferred to glycerol using a β-galactosidase, affording glyceryl 2-deoxy-β-galactoside (**15**) (eq 4). De-



eqn 4

14 **15**

livery of the proton to C-2 of the galactal took place specifically from the bottom face to afford apparent trans addition. Although it would be simple to explain the observation as a direct trans addition, the accepted interpretation is more complex. Thus, it has been shown that the enzyme delivers the glycerol to the β-face of the galactosyl anomeric carbon in a step subsequent to the initial bonding of an enzymic nucleophile on the α face,[12] ostensibly the microscopic reversal of the enzyme's natural and stereospecific cleavage mechanism.[13] The attachment of a proton at C-2 and the presumed enzymic nucleophile at the intermediate stage must have been via cis addition. We are now able to speculate that the β-galactosidase-promoted addition with an overall trans outcome was really a more stereoselective version of a simple acid-catalyzed cis addition, subject to stereoelectronic control, with the β-enzyme affording below-plane protonation corresponding to our observation. In contrast, the above-plane protonation with the α-glucosidase enzyme is not consistent with the simple acid-catalyzed chemistry of glycals followed by glycosyl transfer. The unanswered question concerning our chemical results and also the larger field of electrophilic addition to glycals is what is the basis for "below-plane" or "equatorial-developing" attack at C-2? One popular explanation, namely pyramidalization of the alkene carbon,[14] is belied by the reported crystal structures for glycals.[15] A rationalization, commonly known as the Cieplak effect,[16] where the more electron-rich bond vicinal and anti-parallel to the forming bond, directs the attack, can explain the outcome only in the 3-deoxyglucal case. Some as yet undefined steric effect of the 3-equatorial substituent and the 4-axial proton may be a part of the explanation in the glucal series while in the galactal and allal cases, a steric repulsion of 4-axial and 3-axial groups, respectively, are probably determinant. More work remains to be done to discover the balance of forces that controls the face-selectivity of electrophilic attack in glycals.[17,18]

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(8) (a) Lehmann, J.; Schroter, E. *Carbohydr. Res.* **1972**, *23*, 359–368. (b) Lehmann, J.; Zieger, B. *Carbohydr. Res.* **1977**, *58*, 73–78 (β-galactosidase, trans "diequatorial").
(9) Hehre, E. J.; Genghof, D. S.; Sternlicht, H.; Brewer, C. F. *Biochemistry* **1977**, *16*, 1780–1787. (α-glucosidase, trans diaxial, and β-glucosidase, trans "diequatorial").
(10) The Lehmann–Hehre discoveries have been applied to the synthesis of disaccharides in the β-2-deoxy series: Petit, J.-M.; Paquet, F.; Beau, J.-M. *Tetrahedron Lett.* **1991**, *32*, 6125–6128.
(11) (a) Berkowitz, D. B.; Danishefsky, S. J. *Tetrahedron Lett.* **1991**, *32*, 5497–5500. (b) Thiem, J.; Wiemann, T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1163–1164. (c) Ichikawa, Y.; Look, G. C.; Wong, C.-H. *Anal. Biochem.* **1992**, *202*, 215–238.
(12) (a) Viratelle, O. M.; Yon, J. *Biochemistry* **1980**, *19*, 4143–4149. (b) Sinnott, M. L. In *Enzyme Mechanisms*; Page, M. I., Williams, M. A., Eds.; Royal Society of Chemistry: London, 1987; p 259.
(13) (a) Sinnott, M. J. *Chem. Rev.* **1990**, *90*, 1171–1202. (b) Franck, R. W. *Bioorganic Chem.* **1992**, *20*, 77–88.
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(17) Presented in part at the American Chemical Society, Fourth Chemical Congress of North America, New York, NY, Aug 25–30, 1991, O-69.
(18) This research was supported by grants from PSC-CUNY, the National Cancer Institute of NIH, and the American Cancer Society. The Hunter NMR facility receives partial support from an NIH-RCMI grant RR-03037.

Substitution Reactions of a Nucleofugal Group in Heptamethine Cyanine Dyes. Synthesis of an Isothiocyanato Derivative for Labeling of Proteins with a Near-Infrared Chromophore

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Summary: The reactions of dye **1** with MeONa, $MeNH_2$, PhONa, PhSNa, PhSH, and 4-H_2NPhSH to yield the corresponding derivatives **2a–e**, hydrodechlorination of **1** to **3** in the presence of EtSNa or PhSNa/Ph_2PH, and synthesis of the SCN-substituted dye **4**, a new reagent for ultratrace detection of proteins, are described.

Currently there is immense interest in the chemistry of polymethinamidinium salts (cyanine dyes) that absorb in the near-infrared (NIR) region. This class of compounds is important as sensitizers for photography and xerography,

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