The Ratio Between Endocyclic and Exocyclic Cleavage of Pyranoside Acetals Is Dependent Upon the Anomer, the Temperature, the Aglycon Group, and the Solvent
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1) In the introduction section, previous approaches to analyzing the extent of endocyclic and exocyclic cleavage using linear free energy analysis are briefly described. Based on this and your knowledge of the topic, explain how linear free energy analysis was likely used to differentiate these two pathways. Be sure to describe how these experiments were likely set up, including any changes to the reactants that are necessary and how different results from the experiment would support different reaction pathways. (8 points)

2) Also in the introduction, it is stated that the theory of stereoelectronic control predicts that $\sigma$-anomers should preferentially undergo exocyclic cleavage, while cleavage of $\beta$-anomers would be more likely to occur through an endocyclic pathway. Provide a detailed explanation for both these predictions. (10 points)

3) Provide a detailed explanation as to how probes $\beta$-1 and $\alpha$-1 were employed to differentiate between endocyclic and exocyclic cleavage. In your explanation, be sure to discuss how the results of studies can be used to determine the extent of each pathway that is occurring. (10 points)

4) Draw a reasonable arrow-pushing mechanism for the conversion of compound 5 to 6. In your mechanism, show the full structure for the reagent tBDMSOtf. For all mechanisms, be sure to show all intermediates with appropriate charges and resonance structures (7 points)

5) Draw a reasonable arrow-pushing mechanism for the conversion of compound 8 to 4. In your mechanism, show the full structure for the reagents OsO$_4$ and NaIO$_4$. What are the names of these chemicals? (8 points)

6) Draw a reasonable arrow-pushing mechanism for the conversion of compound 4 to 9. (7 points)

7) Draw a reasonable arrow-pushing mechanism for the conversion of compound 9 to 10a. Briefly describe what Amberlite IR-120(H$^+$) is. (8 points)

8) Draw reasonable arrow-pushing mechanisms for the conversion of compound 15 to 16, 17 and 18. (8 points)

9) Predict which of the following reactions of an intermediate you expect to be faster: the reaction of 2 to form $\beta$-11 and $\alpha$-11, or the reaction of 3 to form 20 and 21. Explain your reasoning. (7 points)
10) Explain the concept of effective concentration and why it is important to the experimental studies described in this paper. (6 points)

11) NMR analysis was used to probe experimental results. Assign the $^1$H NMR peaks shown in Figure 4A and Figure 4D. To do so, do your best to recreate these spectra and label each peak (a,b,c,d...) to correspond with a drawing of the appropriate structure(s) with labeled hydrogens. (10 points)

12) What difference in the product mixture and reaction pathway would you expect if the isopropyl group of $\beta$-1 were changed to a chloride group? (5 points)

13) Which pathway, exocyclic or endocyclic, is more entropically favorable and why? (6 points)
1. In an LFER, we vary the electronics of the system by adding substituents ranging from electron donating groups (EDGs) to electron withdrawing groups (EWGs). We then analyze how this affects the rate by examining the ratio of the reaction rate with a particular substituent \( (k_R) \) to the rate with hydrogen at that position \( (k_H) \). It is important to add substituents in such a way that different results are obtained for each possible mechanism. The most likely LFER approach to the analysis of exocyclic vs. endocyclic cleavage, and the one taken in the cited papers, involves the use of a series of substituted phenyl groups attached to the anomeric carbon as shown below. If exocyclic cleavage is occurring, an EWG speeds up the reaction by creating a better leaving group. If endocyclic cleavage is occurring, an EDG makes the phenolic group a better donor, enhancing the rate. So, the mechanism can be judged in the LFER results as shown. The only concern is that the modification of the substrate can always affect the rate. For instance, the addition of the phenyl group favors exocyclic cleavage as it is a better leaving group and less effective donor than a typical alkoxy group.

![Diagram of LFER with exocyclic and endocyclic cleavage](Image)

2. This is essentially the anomeric effect. In the \( \alpha \)-anomer, a lone pair of the oxygen in the ring is aligned to donate into the adjacent C-O antibonding orbital, which enhances exocyclic cleavage. Inspection of the same orbitals in the \( \beta \)-anomer shows that they are no longer aligned for donation. However, a lone pair of the oxygen outside the ring can align with the neighboring C-O antibonding orbital, which instead promotes endocyclic cleavage.

![Diagram of anomeric effect](Image)
3. Probe β-1 contains an internal appended nucleophile that is designed to selectively trap the endocyclic oxocarbenium ion to yield a product mixture that is different than that from exocyclic cleavage. Specifically, exocyclic cleavage yields an oxocarbenium ion (2) that cannot be trapped by the appended nucleophile, while endocyclic cleavage yields 3, which can be trapped. Deuteration of the appended hydroxymethyl group provides an asymmetric intermediate that facilitates product identification. Product quantitation can then be used to determine the extent of each pathway. Here, it is important to realize that the endocyclic pathways leads to the formation of all 4 possible products, α-11, β-11 (the same products as from exocyclic cleavage) as well as 20 and 21. This is because the 2 hydroxyl groups of 3 are essentially equivalent and should attack the oxocarbenium ion to an equal extent. As a result, the amount of endocyclic cleavage can be calculated as (% of 20/21)x2.

4. There are a few acceptable mechanisms here, one of which is shown below.
5. This mechanism is aided if you remember the results of each transformation, i.e., osmium tetroxide converts an alkene to a 1,2-diol and sodium periodate cleaves a 1,2-diol and results in carbonyls where the hydroxyl groups were.

6.
7. Amberlite IR-120(H+) is an acidic resin. It is used here as an acid catalyst that is easily removed by filtration when the reaction is complete.

8. First, we must understand the reagent boron trifluoride diethyletherate. This is simply a stabilized form of the Lewis acid boron trifluoride (the active species) in which a lone pair on ether is complexed to boron. Methanol that is present in the reaction can then add into boron creating a Brønsted acid.

Each of the reactions are catalyzed by an acid of some sort. It is acceptable to show this as either being the Lewis or Brønsted acid, but one must show where these species come from. I’ll go ahead and use Boron just for fun.

A.

B.
9. Reaction of the oxocarbenium ion of 3 should be faster than that of 2 because it occurs via an intramolecular reaction forming a six-membered ring. Such reactions are known to be much faster than the corresponding intermolecular reactions due to the increased effective concentration of the appended nucleophile.

10. Effective concentration, as mentioned above, describes the increased rates of reaction often seen with favorable intramolecular transformations such as the closing of rings of the appropriate size. This is defined as the enhancement in the rate of an intramolecular reaction compared to the corresponding intermolecular version. The same effect also applies to multivalent binding interactions, in which binding to two appended ligands, such as carbohydrates, by a protein with multiple binding domains leads to much higher affinity than individual analogs. In this paper, effective concentration is important as it enforces the ring-closing reaction of 3 to form 20-22 rather than any number of other reactions involving attacks on the oxocarbenium ion.

11. The first important thing to recognize is that the whole spectrum is not shown and thus all the Hs in the molecule are not represented. Since the spectrum is cropped between 3-5 ppm, only electron deficient Hs show, which are those directly adjacent to electronegative atoms. Spectrum A is indicated to be a mixture of α-starting material (α-11) with a little of the α-product (20) obtained from isotope scrambling due to some endocyclic cleavage. Looking at these structures, the peak that is furthest downfield should be the H on the anomeric carbon, as this is bonded to 2 different oxygens. The only other carbon with Hs next to an oxygen yields different signals for the equatorial and axial Hs due to the constraints of the bicyclic system, accounting for the 2 other major peaks. The smaller peaks in the spectra correspond to the hydroxymethyl group in 20 formed via a small amount of endocyclic cleavage. The hydrogens now come out closer together as they are not constrained within the ring.
The spectra for the β-isopropyl compound in D, which in this case is pure, looks similar except the C-H of the isopropyl group makes an appearance and the other peaks move around a little as would be expected.

12. The paper clearly states that a better leaving group yields more exocyclic cleavage. We can look at the mechanism to rationalize this. In exocyclic cleavage, the chlorine acts as a leaving group that ends up negatively charged. In endocyclic cleavage, it instead acts as an electron donor and ends up positively charged. Since chlorine is electronegative (stabilizes negative charge, definition of a good leaving group), the exocyclic path would be even more preferable. Plus, it makes sense that using a better leaving group would favor the reaction that uses that group as a leaving group.

**Exocyclic cleavage**

\[
\begin{align*}
\text{O} & \quad \text{Cl} \\
\xrightarrow{\text{O}} & \\
\text{Cl}^{-} & \quad \text{O}
\end{align*}
\]

**Endocyclic cleavage**

\[
\begin{align*}
\text{O} & \quad \text{Cl} \\
\xrightarrow{\text{O}} & \\
\text{Cl}^{-} & \quad \text{O}
\end{align*}
\]

13. The paper reports that the exocyclic pathway is more entropically favorable. The simple explanation is that one molecule reacts to form two, which creates more disorder and is entropically favorable. This is fine, although we should always keep in mind that entropy is often more complicated than we think.
The Ratio between Endocyclic and Exocyclic Cleavage of Pyranoside Acetals Is Dependent upon the Anomer, the Temperature, the Aglycon Group, and the Solvent

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Abstract: Several cis-fused decalin pyranosides with intramolecular nucleophiles of high effective molarity were studied to determine the ratio between endocyclic and exocyclic cleavage in specific-acid-catalyzed solvolysis reactions. The molecular design that allows a differentiation between endo- or exocyclic cleavage is the symmetry and asymmetry of the respective oxocarbenium ion intermediates. The synthesis of the molecular probes involves eight steps from a known compound, and proceeds via a key intermediate functionalized with three different oxidation states. A crystal structure confirmed the relative stereochemistry of the probes. A quantifiable percentage of endocyclic cleavage for β-pyranosides was found for all reaction conditions, whereas α-pyranosides show exclusively exocyclic cleavage. The percent of endocyclic cleavage for β-pyranosides is dependent upon the temperature, the aglycon group, and the solvent. At lower temperatures endocyclic cleavage increases. The ΔH and ΔS for endocyclic and exocyclic cleavage were determined to be 19.2 ± 1.4 kcal/mol and −12.6 ± 6.1 eu, and 22.8 ± 1.1 kcal/mol and 3.7 ± 3.8 eu in methanol, respectively. These values support the theory of stereoelectronic control in the cleavage of pyranoside acetics. Pyranosides with phenyl aglycon groups exhibit significantly lower percentages of endocyclic cleavage than pyranosides with alkly aglycon groups. Although an exact percentage of endocyclic cleavage of pyranosides in water could not be determined, it appears to be approximately the same or greater than that which occurs in methanol. The addition of non-hydrogen-bonding/non-nucleophilic solvents increased the percent of endocyclic cleavage. The results are interpreted to support some extent of nucleophilic assistance in the endocyclic solvolysis of pyranosides, stereoelectronic control on the site of cleavage, and the possibility of endocyclic cleavage at the active site of glycosyl transfer enzymes.

Introduction

Pyranoside acetals have two potential cleavage sites during solvolysis reactions, referred to as exocyclic and endocyclic. The exocyclic pathway forms a cyclic oxocarbenium ion, whereas the endocyclic pathway forms an acyclic oxocarbenium ion (Figure 1). Both of these mechanisms were recognized as potential pathways as early as 1955. Since then, the exocyclic pathway has come to be the well-accepted mechanism and is that which is commonly taught in fundamental organic chemistry classes. The evidence in the literature supporting exocyclic cleavage derives primarily from isotope effect studies and linear free energy relationships, some of which were performed using more activated phenyl aglycon leaving groups. Recently, the endocyclic vs exocyclic question was addressed employing alkyl glucopyranosides, and the results were also interpreted to support an exocyclic pathway. Isotope effects, when small or inverse as with many of these studies, are direct evidence for supporting or refuting mechanisms, but are also often subject to multiple interpretations.

The site of cleavage of pyranosides is a classic test of the theory of stereoelectronic control. This theory predicts that α-anomers should proceed via an exocyclic pathway, whereas β-anomers should proceed via an endocyclic pathway. The theory of least motion predicts that both anomers should utilize an exocyclic pathway. The general acceptance of the exocyclic pathway, even for β-anomers, has led proponents of the theory of stereoelectronic control to postulate conformational changes of the pyranoside rings in the exocyclic pathway. For example, a twist boat or flattened chair conformation can lead to stereoelectronically allowed exocyclic cleavage of a β-anomer. However, with the exception of a crystal structure of a puckered pyranoside at the active site of the enzyme lysozyme, there exists little direct evidence for reaction via high-energy conformations. Direct methods for probing reaction intermediates are those of product analysis, scrambling of stereochemistry, and scrambling of α- and β-anomers with α- and β-ano...
bbling of atomic positions with solvent. Such studies are hallmarks of physical organic chemistry which allowed the deciphering of substitution mechanisms, as well as phosphorous and acyl transfer mechanisms. With respect to pyranoside acetals, one would expect scrambling of \( \alpha \) - and \( \beta \) - anomers if endocyclic cleavage were a significant pathway. This is not typically observed, thus supporting exocyclic cleavage. However, in one instance anomerization has been found to be faster than water \( ^{18} \) O incorporation. If the lifetimes of the oxocarbenium ions are shorter than the lifetime of bond rotamers, anomerization might not be observed. Indeed, oxocarbenium ion lifetimes are predicted to be about \( 2.5 \times 10^{-12} \) s in nucleophilic solvents such as alcohols and water, much shorter than the lifetime of typical C–C bond rotamers.

In an attempt to trap the short-lived oxocarbenium ions, thereby allowing product analyses which would support either endocyclic or exocyclic cleavage, Franck studied a system with an intramolecular enamine nucleophile in methanol with acidic ion exchange resin, and Reid studied the reaction of acylammonium ions and a methyl \( \beta \)-glucoside in acetic anhydride. Both of these studies support the existence of endocyclic cleavage. Therefore, the endocyclic cleavage pathway for pyranoside acetals in protic solvents such as methanol and low dielectric solvents is substantiated, but is certainly not well documented with many examples. Until very recently, evidence for endocyclic cleavage in water was completely lacking. Other studies supporting endocyclic cleavage include Lewis acid induced cleavage of pyranosides in low dielectric media, which has been proposed to proceed in certain cases by exclusively an endocyclic pathway, and the observation that furanoside acetals are known to hydrolyze partially by endocyclic cleavage.

To elucidate the balance between endocyclic and exocyclic cleavage in furanosides, early work focused on changing the aglycon group and the sugar structure. With \( \beta \)-d-xylofuranosides, endocyclic cleavage was found for alkyl and electropositive aglycon groups, but upon making this group more electronegative the mechanism switched to exocyclic. The entropies of activation for the sugars which underwent endocyclic cleavage were negative, supporting the participation of water as a nucleophile in the transition state. Further, when examining other sugars, \( \beta \)-ribofuranosides were similar to the \( \beta \)-xylofuranosides; however, \( \alpha \)-arabinofuranosides and \( \alpha \)-lyxofuranosides were found to predominantly undergo exocyclic cleavage. Hence, when the CH₂OH group of the furanoside is cis or trans to the aglycon group, endo- or exocyclic cleavage was observed, respectively. Given these results for furanosides, one might expect that certain pyranosides, with the appropriate sugar structure and aglycon group, would also show some endocyclic cleavage.

Renewed interest in the question of endocyclic and exocyclic cleavage of pyranosides was sparked by a molecular dynamics calculation by Post and Karplus. Their calculations suggest that endocyclic cleavage is operating at the active site of the enzyme lysozyme. If endocyclic cleavage is indeed the mechanism for this enzyme but exocyclic cleavage is the pathway in solution, nature has evolved a catalyst for a hydrolysis mechanism that is higher in energy than the alternative solution mechanism. Therefore, it is imperative to probe if endocyclic cleavage is a viable mechanism in aqueous media.

We have been interested in the endo/exocyclic cleavage controversy due to a desire to produce a synthetic glycosylase, and reasoned that knowledge of the correct pathway to target was paramount to catalyst design. Therefore, probes \( \alpha \)-1 and \( \beta \)-1 were designed to distinguish exo- and endocyclic cleavage in protic media. Herein, we discuss the subtle details in the design of these probes, evidence supporting endocyclic cleavage in water, as well as our results that quantify exo- and endocyclic cleavage in methanol as a function of different aglycon groups, temperature, and solvent polarity. We discuss the relevance of the results to the theory of stereoelectronic control, nucleophilic assistance, and the mechanism for lysozyme.

Results and Discussion

A. Probe Design. To detect endocyclic cleavage in methanol and in water, probe 1 was designed for subjecting to mild acid-catalyzed solvolysis. The design incorporated an appended intramolecular nucleophile to selectively trap one of the two differing oxocarbenium ion intermediates from either exocyclic (2) or endocyclic (3) cleavage pathways (Figure 2). We reasoned that, to compete for a very short lived oxocarbenium ion, an intermediate with a high effective molarity nucleophile would be required. Therefore, we incorporated a nucleophile with essentially identical molarity to that of the endocyclic leaving group. This resulted in the design of a probe which forms a symmetric intermediate upon endocyclic cleavage, and an asymmetric intermediate from exocyclic cleavage. The symmetry of intermediate 3 is broken solely by isotopic labeling. Compound 2 cannot undergo intramolecular closure due to insufficient length of the appendage whereas 3 may be trapped by either the deuterium-labeled or unlabeled appendage. Although 1 is not a saccharide, it is a good mimic thereof. The ring fusion and the appendage keep the pyranoside ring from flipping (see below), and since Franck and Reid have found endocyclic cleavage for actual saccharides, one does not require the presence or absence of neighboring hydroxyl groups.

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(23) Since synthetic receptors for sugars are now prevalent (see the following reference), one can imagine the development of synthetic glycosidases: Aoyama, Y. Comprehensive Supramolecular Chemistry, Pergamon Press: New York, 1996; Vol. 2, Chapter 9.
However, the neighboring hydroxyls may influence the ratio between endo- and exocyclic cleavage.

In order to study a particular anomer and to mimic the rigid ring systems of saccharides, the tetrahydropyran ring was fused to a second ring. Since the solvolysis of equatorial anomers of rigid tetrahydropyranyl acetals could proceed through a higher energy twist boat conformation in a stereoelectronically favored pathway, the cis stereochemical configuration in 1 was chosen as it is less conducive to any such boat conformations (eq 1).

In contrast to other typical pyranosides, partial ring flip of 1 leads to a significant steric interaction between the aglycon group and perihydrogens. Later, we will present experimental evidence that such a ring flip would give different results than those obtained (see section H).

The cis ring fusion in 1 does allow the decalin system to undergo interconversion as shown in eq 2. Molecular mechanics, however, suggested that the ring flip of the cis-fused skeleton is unfavorable due to severe steric interactions with the appended nucleophile. For the energy minimized structures, obtained using the MM2 force field, the ring flipped conformation was found to be 6–8 kcal/mol greater in energy. Although the Curtin–Hammett principle would predict that a pathway involving the ring flip form is still possible since the 6–8 kcal/mol is lower than the activation energy for the reaction, we will present experimental evidence that this ring flip does not lead to any observable products (see section E).

B. Synthesis. The challenges for the synthesis of the probe were matters of symmetry and oxidation states. The synthesis of a molecule designed to generate an intermediate which is symmetrical except with respect to the position of the deuterium atoms precluded the obvious dissection of the molecule into a symmetrical 1,3-carbinol cyclohexane. Another restriction placed upon the synthesis was the incorporation of the deuterium label via an ester reduction at a late step. These criteria mandated the manipulation of a molecule containing three different functional groups each with a different oxidation state (4, Scheme 1): that of an alcohol (endocyclic leaving group), aldehyde (acetal), and ester (site for deuterium incorporation). Compound 4 was envisioned to be produced from the previously synthesized undeacaneone carboxylate 5.

Scheme 2 shows the complete synthetic pathway. The silyl enol ether 6 was formed as both a means of protecting the ketone during the subsequent reduction and also to establish the site for the oxidation to 4. The ester moiety of 6 was reduced to an alcohol (7) with diisobutylaluminum hydride and protected with a tert-butyldimethylsilyl group (8). The oxidation of the silyl enol ether with osmium tetroxide was sensitive to both scale and purity of reagents. Furthermore, it could not be accomplished with the alcohol of 7 in an unprotected form, nor could the oxidation be cleanly effected with ozone. Thus, oxidation of 8 afforded an acylal moiety (4). Compound 4 was not routinely purified due to decomposition. It was instead submitted directly to the next step affording the acetal 9 in a yield of 58% from 7. This step involved the treatment of crude 4 with acidic methanol, which accomplished the deprotection of the alcohol, cyclization and formation of the methyl acetal, and the esterification of the carboxylic acid. At this stage the methyl acetal can be converted to any desired acetal, utilizing the corresponding alcohol and amberlite acidic resin. An aldehyde (acetal), and ester (site for deuterium incorporation). Compound 4 was envisioned to be produced from the previously synthesized undeacaneone carboxylate 5.

Scheme 2. Synthesis of 1

(a) tBDMSOTf, Et3N, CH2Cl2; (b) DIBAL, THF; (c) tBDMSOTf, Et3N, THF; (d) OsO4, NaIO4, THF/H2O; (e) MeOH, HCl; (f) iPrOH, Amberlite IR-120(H+); (g) [1,5-HD]-RhCl2, THS, H2 (150 psi), pH 7.6, EtOAc; (h) LiAlD4, THF.

Conditions: (a) tBDMSOTf, Et3N, CH2Cl2; (b) DIBAL, THF; (c) tBDMSOTf, Et3N, THF; (d) OsO4, NaIO4, THF/H2O; (e) MeOH, HCl; (f) iPrOH, Amberlite IR-120(H+); (g) [1,5-HD]-RhCl2, THS, H2 (150 psi), pH 7.6, EtOAc; (h) LiAlD4, THF.

Scheme 3. Synthesis of 14

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6 \(\rightarrow\) 15

\(\alpha\)-methyl group

16 \(\rightarrow\) 17 \(\rightarrow\) 18

\(\beta\)-methyl group

16 \(\rightarrow\) 19 \(\rightarrow\) 14
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"Conditions: (a) OsO\(_4\), NaIO\(_4\), THF/H\(_2\)O; (b) MeOH, BF\(_3\)OEt\(_2\); (c) [1,5-HDRhCl\(_2\)]\(_2\), THS, H\(_2\) (150 psi), pH 7.6, EtOAc; (d) LiAlH\(_4\), THF."

isopropyl group (10a) was used with 1, but a methyl acetal version of the probe (11) was also synthesized as independent structural proof of the products resulting from methanolation. In addition, 3,4-di-tert-butylphenyl (10c) as an aglycon group was also prepared to test the effect of leaving group ability on the percent endocyclic cleavage (12; see section I). The tert-butyl groups in 10c were included solely to prevent reduction of this aromatic group in the next step of the synthesis. After introduction of the desired aglycon group, compound 10 was hydrogenated with [di-\(\mu\)-chlororh(1,2,5,6-\(\eta\))1,5-hexadienyl]-dirhodium ([1,5-HDRhCl\(_2\)]\(_2\)) by employing a phase transfer catalyst in a biphasal system of ethyl acetate and tertiary sodium phosphate buffer, affording two diastereomers (13). Finally, the ester was reduced with lithium aluminum deuteride, and the \(\alpha\)- and \(\beta\)-anomers of 1 (or 11 and 12) were separated by preparative HPLC.

As will be discussed in section G, an acyclic version of 1 (14, Scheme 3) was needed to test a mechanistic postulate. Therefore, compound 6 was submitted to oxidation by osmium tetroxide, and the resulting acylal (15) was opened to the acyclic dimethyl acetal (16) with the Lewis acid BF\(_3\). This later reaction was exceedingly slow, taking approximately four weeks, but at higher temperatures, the major product (17) stemmed from elimination. Also observed was the methyl acylal intermediate (18). This acyclic intermediate (16) was hydrogenated (19), and the esters were subsequently reduced with lithium aluminum hydride as in the synthesis of 1.

C. Structural Determination. As discussed in the Design Criteria, a symmetrical intermediate (3) was required for this experiment. Therefore, it was crucial to determine the relative stereochemistry of the stereogenic centers of the probes that had been imparted during the hydrogenation. This was accomplished by several methods. Analysis of the \(J_{HH}\) coupling constants, comparison of the C-13 resonances with stereoisomers of 2,9-dimethyldecalin, and difference NOE experiments (Supporting Information) gave evidence of only cis stereochiristry. This was later confirmed with an X-ray crystal structure (Figure 3) of the \(\alpha\)-methyl probe (\(\alpha\)-11).

D. Experimental Design. Endocyclic or exocyclic cleavage was delineated from analysis of the products of the solvolysis experiments. Specifically, for the solvolysis of 1 the asymmetric oxocarbenium ion from exocyclic cleavage 2 cannot be intramolecularly trapped. Therefore, only the corresponding \(\alpha\)- and \(\beta\)-methyl acetal (11) can be formed (Figure 2). However, the symmetric oxocarbenium ion 3 generated from endocyclic cleavage yields not only \(\alpha\)-11 and \(\beta\)-11, but also the deuterium-scrambled counterparts 20 and 21. Furthermore, by reversal of the endocyclic ring opening, deuterium can be incorporated into the pyran ring of the starting material (22). Therefore, exocyclic cleavage yields no deuterium scrambling, but endocyclic cleavage results in formation of deuterium-scrambled products and starting material.

Endocyclic cleavage was evidenced by the presence of a \(^1\)H NMR resonance for the methylene protons of the appendage (CH\(_2\)OH). The resonance for these protons (3.5 ppm) were integrated to determine the percentage endocyclic cleavage. To accurately determine this percentage the area for the appendage protons was divided by the sum of the area for the corresponding ring methylene protons (3.8 and 3.6 ppm) and the appendage. The ratio was multiplied by 2 to account for the chance of labeled appendage trapping. The accuracy of this technique suffers as the area of the resonance of the CH\(_2\)OH becomes a small percentage of the total area for this resonance plus that of the corresponding ring protons. Therefore, a control experiment was performed to determine the detection limits for the method.

Spectra with a controlled percentage of protoi appendage were generated through the incremental addition of perproteo probe (\(\beta\)-1(H\(_2\))) to a solution of \(\beta\)-1. The amount for each aliquot was controlled so that each addition would result in the same incremental increase in percent area. The curve generated was linear for NMR integrations corresponding to greater than 6% endocyclic cleavage (Supporting Information). This represents the minimum detection limit for accurate quantitation, although lower percentages could be detected by visual inspection of the \(^1\)H NMR spectra.

Unlike the methanolysis reactions, the detection of endocyclic cleavage in the hydrolysis reaction is complicated by the fact that the products are hemiacetals not acetals. Hemiacetals scramble the position of the deuterium by mutarotation at a rate faster than the hydrolysis. Therefore, endocyclic cleavage was instead detected solely by analysis of the reisolated starting material.

E. Product Analysis Studies. The initial mechanistic studies were product analysis experiments to determine the site of cleavage. Probe \(\beta\)-1 was solvolyzed in methanol-\(d_4\) with deuterium chloride as the catalyst. The reaction was monitored by gas chromatography and quenched after 30% of the starting material had been consumed to minimize secondary solvolysis of the methyl acetal products. The starting material, as well as the \(\alpha\)-methyl and \(\beta\)-methyl acetal products were separated by HPLC, and their \(^1\)H NMR spectra were obtained.

The resulting spectra from the methanolysis reaction at \(-20^\circ\)C are shown in Figure 4. Several temperatures were explored (see section J). At \(-20^\circ\)C the ratio of \(\alpha\)-methyl acetal product
At the mixture of the rate constant for solvolysis of than the methyl acetals were detected in the 1 H NMR, and the equilibrated and the reaction proceeds with less nucleophilic hydrolysis mechanism. It may also signify that the oxocarbe- may indicate that more endocyclic cleavage is operative in the higher percentage of scrambling of starting material in water reisolated starting material in the methanolysis reactions, the endocyclic cleavage was detected in the products than the exhibited less scrambling (Figure 5). Since significantly more from a similar methanolysis experiment after 90% completion lower limit as the amount of endocyclic cleavage proceeding endocyclic cleavage is estimated for the hydrolysis. This is a Figure 5. From this graph a lower limit of approximately 12% endocyclic cleavage as a function of completion is shown in Figure 4. 1 H NMR (500 MHz) spectra of a typical methanolysis experiment. (A) α-Methyl acetal product from β-1. Resonances between 3.4 and 3.6 ppm indicate isotopic scrambling and hence endocyclic cleavage. (B) β-Methyl acetal product from β-1. (C) Reisolated starting material (β-1). (D) β-1 prior to the experiment. In spectra B, C, and D, the resonances at 3.5 ppm indicate isotopic scrambling.

(α-11) to β-methyl acetal product (β-11) was temperature was approximately 85: 15. At −20 °C the rate constant for solvolysis of β-1 to form the mixture of α- and β-11 was 8.96 × 10−7 s−1, almost identical to the rate constant for solvolysis of α-1, 9.49 × 10−7 s−1 (discussed in section H). At this same temperature, 27% endocyclic cleavage was observed in the α-methyl product (Figure 4A), while a greater amount, 60%, was found in the β-methyl product (Figure 4B). Analysis of the reisolated starting material indicated only a small amount of scrambling, visually evident but below our minimum level for quantitation (Figure 4C). No epimerization of β-1 to α-1 was observed.

The detection of endocyclic cleavage at ambient temperature in the hydrolysis of β-1 was accomplished using deuterium chloride as the acid catalyst in deuterium oxide containing 10% acetonitrile-d3 for solubility purposes. The reaction was allowed to proceed to 17, 55, 70, and 90% completion. The starting material was reisolated and analyzed by 1 H NMR. A plot of endocyclic cleavage as a function of completion is shown in Figure 5. From this graph a lower limit of approximately 12% endocyclic cleavage is estimated for the hydrolysis. This is a lower limit as the amount of endocyclic cleavage proceeding on to products cannot be detected. Starting material reisolated from a similar methanolysis experiment after 90% completion exhibited less scrambling (Figure 5). Since significantly more endocyclic cleavage was detected in the products than the reisolated starting material in the methanolysis reactions, the higher percentage of scrambling of starting material in water may indicate that more endocyclic cleavage is operative in the hydrolysis mechanism. It may also signify that the oxocarbenium intermediates in the hydrolysis reaction are more solvent equilibrated and the reaction proceeds with less nucleophilic participation than for the methanolysis (see section G).

The solvolysis reactions were very clean. No products other than the methyl acetals were detected in the 1 H NMR, and the mass balance for the isolated products indicated close to 100% yield. This is good evidence that none of the reaction proceeds via a ring flipped form of β-1 as shown in eq 2. If a significant percentage of the reaction proceeded via such an intermediate compound, 23 (eq 2) would be expected to accumulate since such tricyclic acetals are known to be quite resistant to solvolysis relative to a pyranoside acetal.28 Furthermore, we attempted to influence the reaction to proceed via a ring flipped form of β-1, again without any indication of 23. When using HCl in benzene to effect an acid catalyzed cleavage of β-1 there is no nucleophilic solvent to attack, and thus if ring flipped β-1 was accessible, we would expect to isolate 23. However, only dimers of 1 were isolated under these conditions. Thus, we conclude that none of the reaction proceeds as indicated in eq 2.

Franck has also examined the possibility of endocyclic cleavage in methanol, with acidic ion exchange resin at 25 °C, by using a saccharide with an intramolecularly attached enamine nucleophile. He reports approximately 50% endocyclic cleavage of β-anomers, whereas we found only about 14% or less in the α-anomer product from β-1 with HCl at 25 °C.29 Therefore, β-1 was subjected to acid catalyzed methanolysis with the same resin (Dowex 50 × 8−200) at 25 °C. Indeed, the percent endocyclic cleavage does increase with the resin; 21% endocyclic cleavage was found in the α-anomer product. Since the interior of an ion exchange resin inherently has less solvent present and is more ionic than bulk solution, we were prompted to test how solvents with different dielectric constants, lower methanol concentrations, or increases in salt would affect the percent endocyclic cleavage.

F. Solvent/Salt Effects. While the rate of the reaction increased approximately 2-fold in the presence of added LiClO4, the percent endocyclic cleavage remained constant with or without this salt in pure methanol. The effect of dielectric constant was probed in two experiments where cosolvents of different polarity were mixed with methanol. At 25 °C endocyclic cleavage in a 1:1 mixture of benzene and methanol was determined to be 35% and 62% in the α- and β-methyl products, respectively. Similar results (36% and 54%) were obtained for the reaction conducted in a 1:1 mixture of dimethyl sulfoxide and methanol. These percentages of endocyclic cleavage are significantly higher than what would be predicted for pure methanol at 25 °C (see section J and Table 1).

(29) In our original communication describing the experimental design using I, we reported 14% endocyclic cleavage at 25 °C. As can be seen by analysis of Table 1, 10% endocyclic cleavage would be predicted from extrapolation to 25 °C.
Table 1. Percent Endocyclic Cleavage of 1 in Acid Catalyzed Methanolysis as a Function of Temperature

<table>
<thead>
<tr>
<th>Temperature</th>
<th>10 °C</th>
<th>0 °C</th>
<th>−10 °C</th>
<th>−20 °C</th>
<th>−30 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>percent endocyclic cleavage</td>
<td>13</td>
<td>19</td>
<td>22</td>
<td>27</td>
<td>31</td>
</tr>
</tbody>
</table>

The error in these numbers is at most ±2%.

Figure 6. Acidic methanolysis of 14 leads almost exclusively to a β-anomer.

Figure 7. Newman projections of 14. A and B lead to β-products, whereas C leads to α-products.

benzene lowers the dielectric constant of the solution whereas DMSO increases the dielectric compared to pure methanol, these results indicate that the dielectric constant is not a significant factor in the percent endocyclic cleavage, similar to that of added salt. The common factor between these solvent studies and the resin study is the lower concentration of the nucleophile methanol, therefore indicating a differing role for the methanol in the rate determining steps along the endo- and exocyclic cleavage pathways.

It is well known that lifetimes of cationic intermediates are critically dependent on the solvent. The lifetimes increase when the solvent becomes less nucleophilic. Analogously, a less nucleophilic solvent system would increase the lifetimes of the oxocarbenium ions in the solvolysis of pyranoside acetals. We find this also leads to an increased reaction via the endocyclic pathway.

G. Nucleophilic Participation. In support of a role for methanol in the solvolysis rate determining steps, nucleophilic participation has been previously reported in the hydrolysis of acetals. Such participation is consistent with all the results of the investigations described herein. As one example, if the symmetrical oxocarbenium ion 3 is solvent equilibrated, the two intramolecular nucleophiles each with an effective molarity of 30000–50000 M\(^{-1}\) should scramble the position of the deuterium in the starting material to a much greater extent than in the products. This is not observed, suggesting that the nucleophile is preassociated with the developing oxocarbenium ion. Since the appendage in 1 is too short, it cannot be the preassociated nucleophile; therefore, the solvent must act in the nucleophilic assistance.

If nucleophilic assistance is prevalent for endocyclic cleavage, it would afford an acyclic acetal intermediate (24; see section K). This compound, however, was not detected in the methanolysis experiments. Yet, if the subsequent methanolysis of this intermediate was much faster than the initial solvolysis of probe β-1, the intermediate would not accumulate and could not be detected. This may be expected since the solvolysis of 24 with nucleophilic assistance would benefit from the high effective molarity of both appended nucleophiles.

The possible existence of an acyclic intermediate such as 24 was explored by methanolysis studies of an acyclic probe (14, Figure 6). The rate constant determined at −20 °C was nearly 300 times greater than for the solvolysis of β-1. Therefore, 24 is a kinetically feasible intermediate.


Interestingly, the predominant product from the methanolysis of 14 was the β-methyl acetal; very little α-methyl acetal was detected (less than 10%). Assuming that a large fraction of endocyclic cleavage proceeds through compound 24, the product distribution from 14 provides an explanation for the increased amount of endocyclic cleavage detected in the β-methyl product from β-1 (see section E). Since endocyclic cleavage proceeding through an acyclic acetal affords primarily β-anomer products, the isolated β-products indicate larger percentages of endocyclic cleavage. α-Products from structures such as 24 are minor, and therefore lower percentages of endocyclic cleavage are found in the α-products.

Examination of Newman projections of the C–C bond adjacent to the acetal linkage of 14 provides a rationale for the dominant stereoselectivity of this ring closure (Figure 7). For the two lowest energy conformations of the three possible, attack of the nucleophile from the least hindered face affords the β-anomer. The α-anomer results from the highest energy conformation.

Nucleophilic assistance has been invoked previously to explain the solvolysis reactions of acetals. For example, a reaction with full $S_2$ character would consistently result in inversion of configuration of the acetal carbon, and this is observed with β-acetals since the kinetic product is an α-acetal. In the studies described herein, the dominate product is α since the majority of the pathway is exocyclic (see section E). In contrast, according to our results, endocyclic cleavage of a β-anomer results in predominantly β-products. Importantly, the β-products from β-1 are not 100% deuterium scrambled. Therefore, some β-product results from β-1 via another pathway (see section K). These results are consistent with a previous postulate that nucleophilic assistance can occur from both the same and opposite faces of the oxocarbenium ion from which the leaving group departed.

H. Stereoelectronic Control. These experiments that determine the site of cleavage of pyranosides provide a new system in which to test the principles of the theory of stereoelectronic control. According to this theory, the α-anomer would be predicted to proceed smoothly with exocyclic cleavage since the lone pair of the pyran oxygen is antiperiplanar to the exocyclic C–O bond. The β-anomers cannot attain the proper geometry for exocyclic cleavage, but endocyclic cleavage is stereoelectronically enhanced by the lone pair of the exocyclic oxygen. The most recent evidence suggests that β-anomers may follow a syn-periplanar route. In order to assess the impor-

tance of this theory for the hydrolysis of pyranoside acetals, we examined the solvolysis of the axial anomer of the probe (\(\alpha\)-1).

A change in mechanism for the different anomers that reconfirms the importance of the principles of stereoelectronic control was found for the \(\alpha\)- and \(\beta\)-anomers of 1. The results of a methanolysis experiment conducted at 25 °C indicated that no endocyclic cleavage had occurred (Figure 8A). Examination of the reisolated starting material from a hydrolysis experiment confirmed that this pathway was also inoperative in water (Figure 8A). The theory of stereoelectronic control therefore correctly predicts the \(\alpha\)-anomer reactivity, but seemingly is not correct for \(\beta\)-acetals, since for \(\beta\)-acetals endocyclic cleavage is not the dominant pathway.

This experiment sheds light on the possibility of a high-energy sofa or twist-boat conformation of \(\beta\)-1 (eq 1). Since we find that axial aglycon groups proceed solely via an exocyclic cleavage mechanism, any high-energy conformations of \(\beta\)-1 with the aglycon group in a pseudooxial position should also use an exocyclic pathway. Yet, endocyclic cleavage is evident with \(\beta\)-1. Therefore, a partial ring flipped form of \(\beta\)-1 cannot lead to all the solvolysis products found.

To further test the importance of stereoelectronic control in the reactivity of \(\beta\)-acetals, we examined different aglycon groups which would be expected to influence the orbital interactions. Better exocyclic leaving groups should counteract stereoelectronic considerations and enhance exocyclic cleavage. In addition, we examined temperature effects, which would be expected to reveal the differences in activation entropies and enthalpies for endo- and exocyclic cleavage.

I. A Phenyl Aglycon Group. A change in mechanism is known to occur when the leaving group is an activated leaving group such as aryl.\(^{34}\) The mechanism switches from specific acid catalysis with alkoxy tetrahydropyran acetals to general acid catalysis as the leaving group changes to aryloxy. To assess whether the site of cleavage in aryloxy pyranosides also changes, the methanolysis of the aryloxy probe \(\beta\)-12 was conducted at 0 °C. At 30% completion, the methanolysis of \(\beta\)-12 was terminated and endocyclic cleavage was detectable but below our limit for quantitation. Even when allowed to proceed to 55% completion, the \(\alpha\)-methyl products indicated only 9% endocyclic cleavage, significantly lower than that found at 0 °C for \(\beta\)-1 (see the next Section).

The lower percent endocyclic cleavage with the better aglycon leaving group is indicative of a weakening of the exocyclic C–O bond, just as was found for furanosides.\(^{20,21}\) Therefore even better leaving groups such as halide or \(p\)-nitrophenyloxy would be expected to react even more completely via an exocyclic pathway. This experiment confirms the studies using such good leaving groups that indicate exocyclic cleavage,\(^3\) but it also casts doubt on conclusions of the exocyclic cleavage mechanism for alkoxy aglycon groups that are formed based upon these better aglycon leaving groups.

J. Temperature Effects. The observation of both endo- and exocyclic cleavage pathways for the solvolysis reactions of \(\beta\)-1 suggests that there was only a small difference in their activation energies. To fully delineate the thermodynamic parameters, thereby revealing any enthalpy differences between the two pathways as predicted by the theory of stereoelectronic control, the solvolyses were conducted at several temperatures. The products of these experiments were analyzed for a change in the percentage of endocyclic cleavage. Using the method described in section C, the percent endo- and exocyclic cleavage was determined at 10, 0, −10, −20, and −30 °C in methanol. Multiplying the methanolysis rate constants obtained at these temperatures by the fraction of endo- or exocyclic cleavage determined at each temperature gave the rate constants for endo- and exocyclic cleavage. At most a 10% deviation in rate constants was found and a 2% deviation on the percent endocyclic cleavage. These rate constants were used to calculate the enthalpy and entropy of activation for each pathway via Eyring plots. The results are summarized in Table 1 and Figures 9 and 10.

The enthalpic and entropic activation terms for endocyclic cleavage were found to be 19.2 ± 1.4 kcal/mol and −12.6 ± 6.1 eu, while the corresponding parameters for exocyclic cleavage were 22.8 ± 1.1 kcal/mol and 3.7 ± 3.8 eu. The errors on these activation parameters were calculated with the errors given in rate constants and endocyclic cleavage that were discussed above. The greater enthalpy required for exocyclic cleavage is attributable to a stronger exocyclic bond. This is predicted by the theory of stereoelectronic control since the endocyclic C–O bond of \(\beta\)-pyranosides is destabilized by the donation of the exocyclic oxygen’s lone pair of electrons into its antibonding orbital. The greater positive entropy of activa-

tion for exocyclic cleavage stems from the generation of two molecules in the transition state. This is the same reasoning as discussed with regards to the negative entropy of activation of endocyclic cleavage of furanosides. Therefore, β-pyranosides have two conflicting influences on their reactivity. One is a stereoelectronic effect (enthalpic) which favors endocyclic cleavage, and the other is entropy which favors exocyclic cleavage. The balance of these two factors near ambient temperature results in predominantly exocyclic cleavage. With α-acetals, both stereoelectronic control and entropy reinforce one another, resulting in solely exocyclic cleavage.

Further analysis of the entropies of activation for the two pathways gives even more insight into the reaction mechanism. As discussed in section G, because of their fleeting lifetimes, oxocarbenium ions 2 and 3 may more resemble transition states than intermediates in methanol and water. Thus, nucleophilic participation is likely, and is reflected by the negative or near zero values for ΔS. A small part of the negative entropy of activation for endocyclic cleavage of β-anomers is also likely due to freezing of the conformation of the exocyclic C=O bond that would be required for the stereoelectronically allowed cleavage. However, since freezing of a bond rotation is thought to cost only about 4.5 eu, this is not enough to explain the full −12 eu found. Therefore, we again find evidence in support of nucleophilic participation.

There is some evidence that nucleophilic participation should be greater in endocyclic than exocyclic cleavage. Bennett has stated that the glucosylcarbenium ion has a lifetime greater than 2.5 × 10−12 s in water. This is greater than the lifetimes for acyclic analogs found by Amyes and Jencks, and slightly greater than that estimated by these same researchers for the glucosylcarbenium ion. We therefore postulate that acyclic oxocarbenium ions in methanol may also have shorter lifetimes than cyclic analogs and therefore require more nucleophilic assistance.

K. How Symmetric Is the Symmetric Intermediate? Data have been presented to this point which are consistent with the notion of nucleophilic participation in the solvolysis reactions. Although such participation is not definite, nor does it effect the conclusion of endocyclic cleavage, it does have an influence on the symmetry of the intermediate formed from endocyclic cleavage and therefore the percent of endocyclic cleavage reported. As pictured in Figure 2, the intermediate from endocyclic cleavage is completely symmetrical except for the isotopic labeling. However, if a full fledged oxocarbenium ion is not produced and the solvent is partially bonding in the transition state, then the intermediates formed are 24A and 24B.

![Figure 10](image-url)  
**Figure 10.** Eyring plot of endo- and exocyclic cleavage of β-1.

as well as their enantiomers (see below). These compounds are chiral and therefore are not symmetric. The diastereomers A and B are formed depending upon whether the nucleophilic assistance is backside or frontside, respectively. A 1:1 ratio of formation of these adducts is equivalent to a solvent equilibrated oxocarbenium ion. Since it is unclear the extent to which nucleophilic participation is involved, and the relative fractions of backside and frontside attack of the nucleophile are unknown, it is impossible to state which of the diastereomers is dominant. However, to whatever extent the backside and frontside attacks are not 1:1, the factor of 2 applied to the analysis of endocyclic cleavage, based on the assumption of symmetry of the intermediate (discussed in section C), should be depressed, thereby lowering the percent of endocyclic cleavage below that reported herein.

This analysis can be extended even further to show that backside nucleophilic assistance is not enough to explain all the data, and that frontside attack is also likely occurring. If the nucleophilic assistance in the endocyclic cleavage of β-1 is predominantly backside, the first formed acetal intermediate would be 24A, which has two more rotamers around the acetal bond, 24C and 24D (Figure 11). Only 24A can go back to starting material, and hence no deuterium scrambling would occur in the starting material. Indeed, we find very little scrambling in the starting material. However, rotamer 24A can only produce a β-methyl acetal product (β-11) with 100% deuterium in the ring. We find about 30% in the ring, thereby giving a calculated percent of endocyclic cleavage at −20 °C of 60% (see section E). Moreover, rotamer 24C will only produce an α-methyl acetal product with 0% deuterium in the ring, and yet we find 13−14%, thereby giving 27% endocyclic cleavage for this product. Finally, rotamer 24D can only produce α-1 with 100% deuterium in the ring, and yet we find none of α-1 with or without deuterium scrambling. If α-1 forms, since we run the reaction to only 30% completion and the α-1 solvolyzes at essentially the same rate as β-1 (see section F), we should find significant amounts of α-1. All these results taken together are good evidence that there must be an additional endocyclic route to forming products besides that shown in Figure 11, and that there must be an additional route to forming β-products. The best explanations are that frontside nucleophilic assistance is also occurring (which would give essentially the opposite deuterium incorporation in the products to that discussed above) and that some β-product arises from exocyclic cleavage.

L. Relevance to Lysozyme and Other Glycosidases. As discussed in the Introduction, endocyclic cleavage has recently been proposed for hydrolysis of oligosaccharides at the active site of the enzyme lysozyme. Part of the impetus for these studies was the determination if endocyclic cleavage of saccharides in aqueous or other protic solvents was a viable pathway. Since both Franck and Reid have found endocyclic pathways for actual saccharides, we herein report endocyclic cleavage using a pyranoside probe under several experimental conditions, we conclude that endocyclic cleavage is a perfectly viable mechanism for β-pyranoside hydrolysis and solvolysis. The percent of endocyclic cleavage is a delicate balance of three factors: the leaving group ability, the nucleophilicity of the solvent, and the temperature.

activation prefers exocyclic cleavage with both \( \beta \)- and \( \alpha \)-acets. The conflicting activation parameters result in mostly exocyclic cleavage of \( \beta \)-pyranosides at ambient temperature. This enthalpy preference for endocyclic cleavage can be overcome by using a better leaving group such as an aryl aglycon. To explain the lack of scrambling in the starting material as well as the negative or close to zero activation entropies, nucleophilic assistance is likely. Further, the more negative activation entropy compared to exocyclic cleavage supports less nucleophilic assistance in the exocyclic pathway. Hence, both nucleophilic participation and stereoelectronic control seem to play roles in the solvolysis reactions; neither alone are enough to explain the data. Therefore, our results are most consistent with a transition state structure similar to 25 for the endocyclic cleavage of \( \beta \)-acets. The transition state involves both the solvent oxygen lone pairs (frontside and backside) and the exocyclic oxygen lone pairs stabilizing the developing positive charge on carbon. Similar transition states have also been previously proposed for exocyclic cleavage.30

**Experimental Section**

A. General Considerations. Instrumentation. \(^1\)H and \(^1\)C NMR spectra were obtained using a General Electric QE-300 spectrometer. Integrations for the analysis of endocyclic cleavage were performed on a General Electric GN-500. GC studies were conducted on a Hewlett-Packard 5890 Series II gas chromatograph. Reactant and product separation was accomplished with a HP-1 Crosslinked Methyl Silicon Gum column (25 m × 0.2 mm × 0.33 mm film thickness). Split injection using a split liner containing column packing material was used to prevent column contamination by nonvolatile components of the sample. A column head pressure of 25 psi provided a column flow of 1.0 mL/min helium carrier gas.

B. Analytical Studies. a. General Procedure for the Product Analysis Studies. The solvents for the \(^1\)H NMR experiments were purchased from Isotech, Inc. The deuterium chloride was obtained from Cryogenic Rare Gases. The acidic methanol and deuterium oxide solutions, prepared by bubbling deuterium chloride into methanol-\( d_4 \), and \( D_2 O \) were titrated with a sodium hydroxide solution that was standardized with potassium hydrogen phthalate. The Dowex resin was treated with a dilute solution of deuterium chloride in methanol-\( d_4 \), filtered, and dried in vacuo. One specific example of methanolysis or hydrolysis is given below.

b. Methanolysis. Either probe \( \alpha \) - or \( \beta \)-1 (0.033 g, 0.14 mmol) was dissolved in methanol-\( d_4 \) (0.494 mL) and placed in an NMR tube. To this was added methylene chloride (1 \( \mu \)L) as an internal standard. Prior to the addition of a standardized solution of deuterium chloride in methanol-\( d_4 \), and \( D_2 O \) were titrated with a sodium hydroxide solution that was standardized with potassium hydrogen phthalate. The Dowex resin was treated with a dilute solution of deuterium chloride in methanol-\( d_4 \), filtered, and dried in vacuo. One specific example of methanolysis or hydrolysis is given below.

c. Hydrolysis. The probes (0.033 g, 0.14 mmol) were dissolved in acetonitrile-\( d_3 \) (75.0 \( \mu \)L) and deuterium oxide (675 \( \mu \)L), and placed in an NMR tube. For the experiments which were quenched at 70 and 90% completion, greater amounts of starting material were hydrolyzed.
in a reaction flask. To the reaction was added dimethyl sulfoxide (1 µL) as an internal standard. An initial spectrum of the reaction mixture was obtained before the addition of a standardized solution of deuterium chloride in deuterium oxide (54 µL, 161 mM). 1H NMR spectra were obtained periodically until the reaction was quenched with triethylamine (10 µL) at the appropriate completion percentage. The reaction mixture was concentrated and a final spectrum in chloroform-d was obtained to confirm the percent completion. This mixture was purified by flash chromatography (hexanes/ethyl acetate, 2:1). The 1H NMR spectra of the purified starting material (5 mg) were obtained to determine the percentage endocyclic cleavage.

d. Kinetic Studies. GC conditions for the programmed run consisted of an initial time of 0.5 min at 200 °C followed by a ramp of 15 °C/min to 250 °C and a final time of 2.0 min at 250 °C. The total run time was 5.83 min. The injector and detector temperature was maintained at 250 °C. The components were detected with a flame ionization detector (FID). Aliquots of the reaction solution (2 µL) were taken periodically and quenched with a solution (20 µL) of triethylamine and dichloromethane (1:1). Retention times for α-methyl, β-methyl, and starting material were 3.4, 3.5, and 3.9 min, respectively. A specific example is described below.

A solution of β-1 (0.006 g, 0.03 mmol) in methanol-d4 (167 µL) was placed in an NMR tube. The tube was placed in a constant temperature bath at −20 °C. An initial aliquot was obtained prior to addition of a solution of deuterium chloride in methanol-d4 (3 µL, 0.77 M). Progress of the reaction was followed by removing aliquots at regular intervals for the initial 10 percent of the solvolysis.

Rate constants were calculated from a plot of the first 10% of the reaction versus time. Peak areas of GC chromatograms obtained from aliquots of the first 10% of the reaction were integrated. The peak area of the products was divided by the total peak area for all of the reaction components. An internal standard of trans-decaline was used to monitor peak areas. It was assumed that the response to the FID detector for the starting material and products are identical due to their similar structures. The average values from quadruple injections of each aliquot were plotted versus time. The slope of the resulting line afforded the rate constant by the method of initial rates. Errors on the rate constants were at most 10%.

e. Variable Temperature Solvolyses. Naphthalene (4 mg) was placed in an NMR tube as an internal standard. To this was added a solution of β-1 (0.030 g, 0.13 mmol) and lithium perchlorate (0.137 g) in methanol-d4 (167 µL). The tube was placed in a constant temperature bath at the appropriate temperature. An initial aliquot was obtained prior to addition of a solution of deuterium chloride in methanol-d4 (13 µL, 0.528 M). Progress of the reaction was followed by GC for only the first 10% of reaction. Rate constants were calculated as described above. After 30% completion the reaction was terminated by the addition of triethylamine (10 µL), and the endo- to exocyclic cleavage ratio determined as described above. Using a 10% error on the rate constants, as well as 2% error on the percent endocyclic cleavage, errors on the ΔS° and ΔH° were calculated.

f. Variable Solvent Analyses. The variable solvent experiments were conducted as described above with β-1 (0.030 g, 0.13 mmol) in methanol-d4 (248 µL) at 0 °C, except that benzene or dimethyl sulfoxide (247 µL) was also added.