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Hydroxyl group orientation affects hydrolysis rates of methyl α-septanosides

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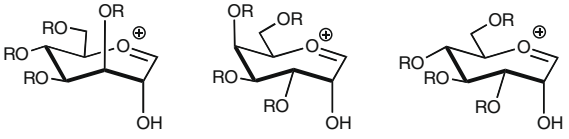
ABSTRACT

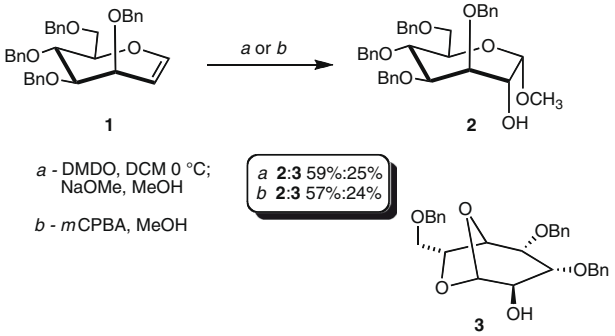
Hydrolysis rates for three related methyl α-septanosides were obtained. The septanosides were synthesized via *m*CPBA epoxidation and methanolysis of D-mannose, D-galactose, and D-glucose-based oxepines. The rate of hydrolysis correlates with the orientation of hydroxyl groups on the septanose ring in a manner analogous to pyranosides.

We recently reported on the unexpected formation of methyl septanoside **2** via DMDO-mediated epoxidation of **1** followed by basic methanolysis (Scheme 1, conditions *a*).[1] A *trans* relationship between the aglycon and C2 hydroxyl group (a *trans*-1,2 glycoside) arising from backside attack on the 1,2-anhydrosugar was anticipated; instead, a *cis*-1,2 glycoside **2** was obtained. Further, a bicyclic product, **3**, accompanied **2**. It was proposed that **2** and **3** arose from the corresponding oxacarbenium ion **4a** even under the basic reaction conditions. Attack on the oxacarbenium by methoxide from the α-face provided **2** while intramolecular attack by the C5 benzyloxy moiety and subsequent loss of a benzylic group provided **3**. Under the same reaction conditions, oxepines[2,3] derived from D-galactose **7** and D-glucose **10** delivered only *trans*-1,2 methyl septanoside products.[4]

We had previously invoked an oxacarbenium ion in the formation of a *cis*-1,2 methyl septanoside from a xylose-based oxepine.[5] Also, *S*-phenyl septanosides, which presumably form reactive oxacarbenium ions upon activation, have been used to prepare a number of septanose glycosides.[3a,6] A formal investigation of oxacarbenium ions related to septanose carbohydrates has not been reported, however. On the other hand, considerable advances have been made recently on the role that substituent effects, stereochemistry, and conformation play in the formation of pyranosyl oxacarbenium ions. The present work aimed to measure the hydrolysis rates of some related methyl α-septanosides in an effort to correlate specific structural features of the molecules with the formation of septanose oxacarbenium ions.



We first endeavored to prepare a group of related methyl septanosides that would serve as substrates of the hydrolysis reactions. Formation of *cis*-1,2 methyl septanosides from oxepines via tandem *m*CPBA epoxidation and methanolysis seemed appropriate because these conditions were presumed to be more conducive to oxacarbenium ion formation. Products and yields for the reaction of oxepines **1**, **7**, and **10** are shown in Schemes 1–3. For mannose-based oxepine **1**, the reaction gave essentially the same result as the DMDO epoxidation followed by methanolysis. The *cis*-1,2 methyl septanoside **2** was the major product (57%) accompanied by the cyclization product **3** (24%). Epoxidation and methanolysis of galactose-based oxepine **7** under the *m*CPBA reaction conditions gave, after C2 acetylation, methyl septanosides **8** (40%) and **9** (45%). Likewise, oxepine **10** delivered **11**–**13** in 29%, 35%, and 18% yields, respectively. In these latter two cases, *cis*-1,2 methyl septanoside products **8** and **12** most likely arose via oxacarbenium ions **5a** and **6a**, respectively. Oxacarbenium ion intermediates are invoked in the formation of **2**, **8**, and **12** because *syn* attack on the 1,2-anydroseptanoses is unlikely.[1,7] Hydrogenolysis of **2** provided **14**. Both **8** and **12** were deprotected by hydrolysis of the C2 acetate under Zemplén conditions followed by hydrogenolysis of the benzyl groups to afford **15** and **16**.



Scheme 1. Epoxidation and methanolysis of oxepine **1**.

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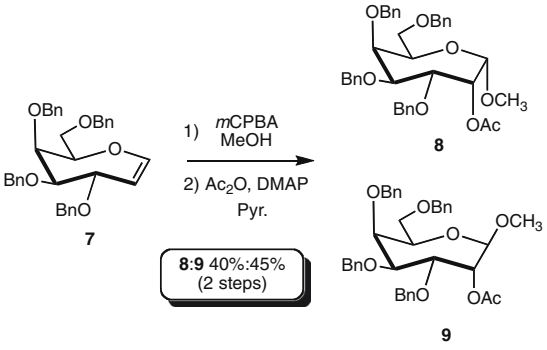
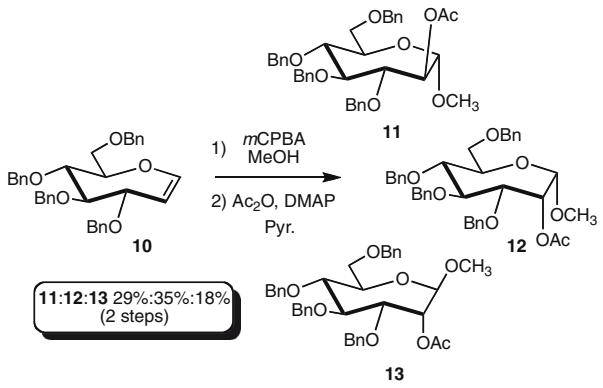
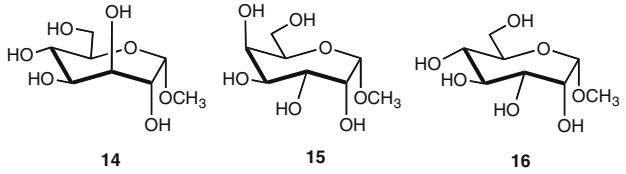


Scheme 2. *m*CPBA epoxidation and methanolysis of oxepine **7**.

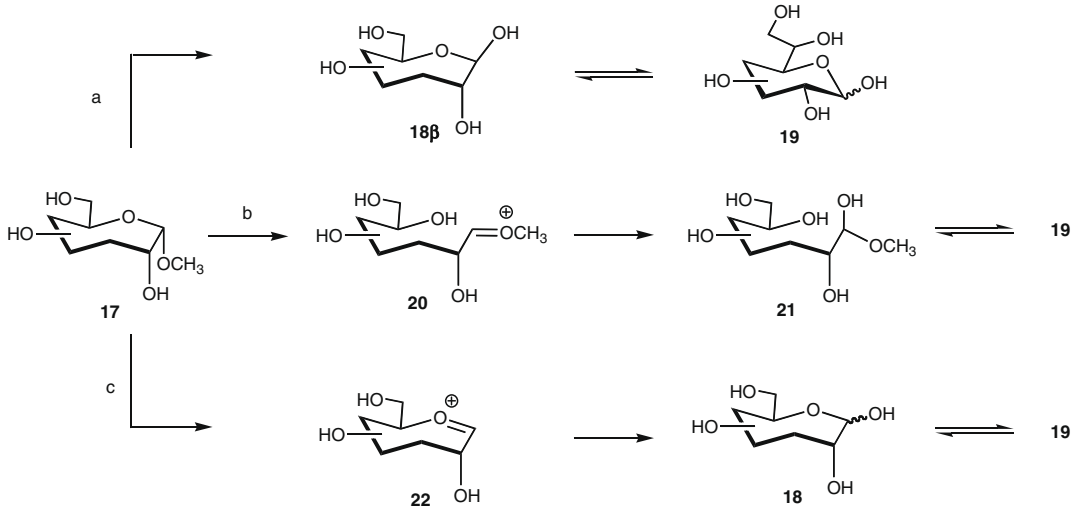


Scheme 3. *m*CPBA epoxidation and methanolysis of oxepine **10**.



The next objective was to characterize the hydrolysis rates of *cis*-1,2 methyl septanosides **14**–**16**.[8,9] The *cis*-1,2 methyl septanosides were chosen because they share the same stereochemistry at C1 and C2, and because they vary by just one other stereocenter on the septanoside ring. These structural similarities would allow the direct comparison of the hydrolysis rates to specific stereochemical features. Preliminary experiments explored the details of the hydrolysis reactions. The fact that a hydrolysis reaction had indeed occurred was confirmed by MS analysis of the product materials after the NMR kinetics experiments.[10] Potential mechanistic pathways for the hydrolysis of the methyl glycosides (e.g., **17**) were next considered (Scheme 4). Pathway *a* depicts an A2 mechanism where protonation of the exocyclic *O*-methyl oxygen would be followed by S_N2 attack by water to give **18β**. Based on the literature estimates of the relative stabilities of septanoses versus pyranoses, **18β** could be expected to equilibrate to the substituted pyranose **19**.[11] Pathways *b* and *c* represent alternative A1 mechanisms that differ in which anomeric C–O bond is broken en route to the respective oxacarbenium ions; in *b*, the endocyclic oxygen would be protonated followed by C–O bond breakage to form **20**.[12] Alternatively, in *c* the exocyclic oxygen would be protonated and C–O bond breakage would form **22**. Addition of water to either of the oxacarbenium species would give rise to intermediate **21** or **18** that would then equilibrate to **19**. Pathway *c* was considered the most likely route of hydrolysis based on the following observations. First, oxacarbeniums were invoked in the formation of *cis*-1,2 methyl septanosides **2**, **8**, and **12** from their corresponding 1,2-anhydroseptanoses as previously discussed. Second, oxacarbenium **6b** was directly observed by MS. Although this was a gas-phase experiment, the result indicated that the exocyclic C–O bond breakage was preferred under the reaction conditions. Further, qualitative correspondence between the gas-phase observation of oxacarbenium ions and rate of hydrolysis has been demonstrated.[13,14]

A ^{1}H NMR integration assay was used to measure the hydrolysis kinetics of **14**–**16**. Preliminary experiments using **16** as a test substrate (1–2 mM) varied the reaction temperature and DCl concentration. Conditions of 50 °C and 0.5 M DCl seemed well suited to observe hydrolysis based on these experiments. Integration values for the protons associated with the methyl group of the aglycon were collected at regular intervals for each compound **14**–**16** (Fig. 1) and were used to calculate the concentration of the starting methyl α-septanoside that remained in the solution. Curve fitting gave k_{obs} values of $5.97 \times 10^{-4}\ s^{-1}$, $8.91 \times 10^{-4}\ s^{-1}$, and $1.14 \times 10^{-4}\ s^{-1}$, respectively. The apparent concentration for the methyl glycoside peak of **14** does not approach zero in the same way that **15** and **16** do; this is due to coincidental overlap of the methyl glycoside peak with a signal arising from the product pyranose.



Scheme 4. Mechanistic pathways for methyl septanoside hydrolysis.

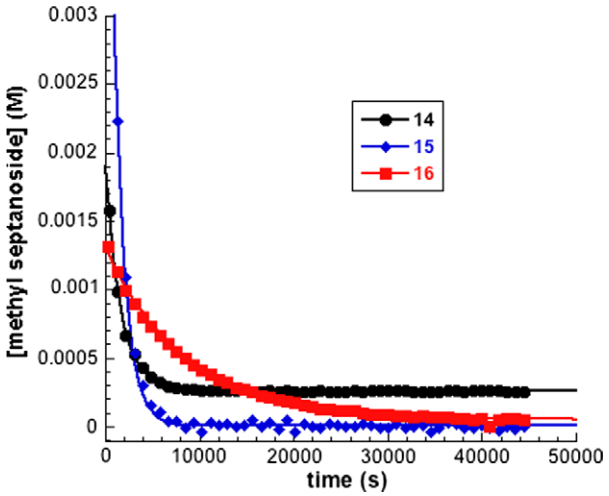


Figure 1. Methyl α-septanoside hydrolysis curves. The plot shows concentration of methyl septanoside versus time over the course of the reaction.

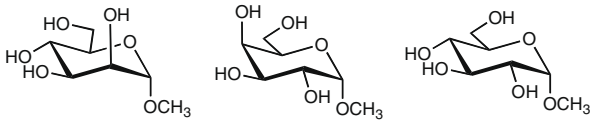
Table 1
Rate constants for glycoside hydrolysis by ^{1}H NMR integration assay at 50 °C in 0.5 M DCl

	Glycoside CH_3	CH_3OH	Avg.	Lit. value[a]
	$10^4\ k_{obs}\ (s^{-1})$			
14	5.97 ± 0.60	7.54 ± 0.56	6.76	
15	8.91 ± 0.14	7.95 ± 0.28	8.43	
16	1.14 ± 0.17	0.97 ± 0.24	1.01	
23				0.209
24				0.355
25				0.071

[a] Hydrolysis of **23**–**25** was at 60 °C in 2 M HCl. See Ref. 8b.

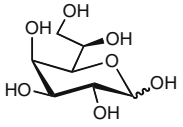
Methanol, the other product in the hydrolysis reaction, was monitored in the same way, however. Analysis of this signal gave similar values of k_{obs} for each of the methyl septanosides (Table 1). The agreement between the rate constants between the different signals provides a measure of their accuracy.[15]

Consideration of the kinetics data suggested parallels between the methyl α-septanosides **14**–**16** reported here and their methyl α-pyranoside counterparts **23**–**25**.[16] The rates of hydrolysis for **14**–**16** are faster compared to those of **23**–**25** (Table 1) despite the milder reaction conditions used on the septanosides. This likely reflects an inherent instability of the seven-membered ring septanosides versus six-membered ring pyranosides.[17] Additionally, the rank ordering of methyl α-septanosides **14**–**16** mirrors that of methyl α-pyranosides **23**–**25**. Methyl α-galactoside **24** is hydrolyzed fastest followed by methyl α-mannoside **23** and then methyl α-glucoside **25**. For the methyl α-septanosides, galactoside analog **15** was the fastest followed by mannoside and glucoside analogs **14** and **16**, respectively. One implication from the parallel between **24** and **15** is that the C5 hydroxyl stabilizes **5b** via through-space electron donation in a fashion akin to the way the C4 hydroxyl stabilizes the galactopyranosyl oxacarbenium ion.[18] Overall, the data for the septanosides here compare well with the results from other groups that have correlated substituent electronics,[19] stereochemistry of hydroxyl groups,[20] and conformation[21] with the rate of oxacarbenium ion formation for pyranosides. Of particular importance to this investigation is the fact that equatorial hydroxyl groups in a pyranoside are known to be more electron withdrawing than are axial hydroxyl groups. Our conformational analyses on α-septanosides[4,22] showed that the preferred conformation for **16** is a $^{3,4}TC_{5,6}$ conformation which is related to the $^4C_1$ conformation of pyranosides. Further, this conformation is highly populated (>90% of the ground state Boltzmann) with the aglycon group in an axial configuration. In the $^{3,4}TC_{5,6}$ conformation, all the hydroxyl groups in **16** except C2 are equatorial and related structures **14** (C3) and **15** (C5) each have one additional axial hydroxyl group. Our data then suggest that equatorial hydroxyl groups are similarly electron-withdrawing in septanosides. Importantly, we interpret the parallel trends in rates of hydrolysis as further evidence for a common oxacarbenium pathway.



23 **24** **25**

The structure of the hydrolysis products remained to be confirmed. As depicted in Scheme 4, addition of water to the oxacarbenium ion should provide a septanose hemi-acetal such as **18**. Septanose hemi-acetals have been observed in aqueous solutions, but only in low concentrations in systems that otherwise block (by deoxygenation or protection of hydroxyls) the formation of the furanose or pyranose hemi-acetals.[11,23,24] We anticipated that a pyranose such as **19** would be the preferred configuration of the hydrolysis product because of the inherent stability of the six-membered ring and the availability of the appropriate hydroxyl groups for it to form. NMR analysis (^{1}H, COSY, and HSQC) of the reaction solution after hydrolysis kinetics that had been obtained for **14** showed that **26** was present as a mixture of α- and β-anomers. The most diagnostic data were the H1 chemical shifts (5.00 ppm for α-**26**, 4.34 ppm for β-**26**) and the associated $^3J_{H1,H2}$ coupling constants (3.4 and 7.9 Hz, respectively).[25]



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In summary, we have provided the first data on the rates of methyl α-septanoside hydrolysis and have compared them to the rates of related methyl α-pyranosides. Importantly, the results demonstrated that hydroxyl group orientation affects the rate of hydrolysis in this group of septanosides. Correlation between hydroxyl group orientation and relative rate reported here mirrors that of methyl α-pyranosides and suggests that, as with pyranosides, equatorial hydroxyl groups are more electron-withdrawing than the axial hydroxyl groups. Investigation of the hydrolysis products showed that the septanose hemi-acetal products equilibrated to the more stable pyranose ring forms. The results have provided insight into the fundamental reactivity of these unnatural carbohydrates.

Acknowledgments

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Supplementary data

Supplementary data (kinetics, characterization and other experimental data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.109.

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