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Probing the Mechanism of Sulfoxide-Catalyzed Hemiacetal Activation in Dehydrative Glycosylation

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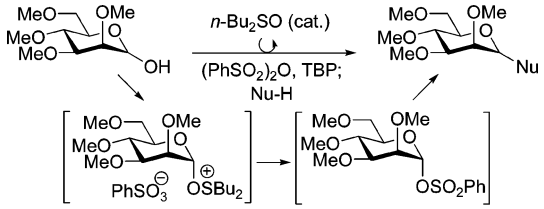

The concept of sulfoxide-covalent catalysis has been established in the context of a versatile hemiacetal hydroxyl activation/substitution reaction for the formation of anomeric linkages. Mechanistic studies focused on the hemiacetal activation process show that this transformation proceeds in the presence of a sulfonic anhydride and an acid scavenger through the intermediacy of a glycosyl sulfonate species (**10**), which serves as a resting state prior to the addition of an external nucleophile and subsequent glycosidic bond formation. Successful determination of the proportion of ^{18}O incorporation in **10** as a function of its formation, via the technique of dynamic monitoring of $^{13}C-^{16/18}O$ isotopic chemical shift perturbations, provides strong evidence that hemiacetal activation proceeds through initial nucleophilic addition of the hemiacetal hydroxyl to the *S*(*IV*)-center of putative sulfonium sulfonate **6**. Further confirmation was obtained through the independent synthesis, structure verification, and ^1H NMR detection of glycosyl oxosulfonium **11** during the sulfoxide-catalyzed conversion of hemiacetal **3** to glycosyl sulfonate **10**.

Introduction

The development of catalytic systems to effect hydroxyl group functionalization has been an area of active interest, with particular recent emphasis on the identification of nonmetallic catalysts. The majority of the work in this field has focused on the discovery of catalysts for hydroxyl group derivatization derived from either nitrogen or phosphorus(III) species to enhance the rates of acylation or alkylation through nucleophilic activation of an appropriate electrophile.[1] Potential alternatives to nitrogen- and phosphorus(III)-based catalyst systems are sulfoxides, nonbasic nucleophiles[2] which are readily available and shelf-stable. Despite these favorable characteristics, the application of sulfoxide catalysis has received only limited attention. Sulfoxides have been used as ligands for metal-centered catalysts[3] and as additives to effect rate acceleration through phase-transfer catalysis,[4] but

(1) (a) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129−161. (b) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358−3359. (c) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492−1493. (d) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169−3170. (e) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629−1630. (f) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813−5814. (g) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412−420. (h) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542−9543. (i) Vedejs, E.; Daugulis, O.; MacKay, J. A.; Rozners, E. *Synlett* **2001**, 1499−1505. (j) Murugan, R.; Scriven, E. F. V. *Aldrichim. Acta* **2003**, *36*, 21−27. (k) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985−3012.

(2) Olavi, P.; Virtanen, I.; Koppela, J. *Suom. Kemistil. B* **1968**, *41*, 326−330.

(3) For the use of sulfoxide ligands in metal-centered catalysis, see: (a) James, B. R.; McMillan, R. S. *Can. J. Chem.* **1977**, *55*, 3927−3932. (b) Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *J. Org. Chem.* **1991**, *56*, 5808−5811. (c) Khiar, N.; Fernández, I.; Alcudia, F. *Tetrahedron Lett.* **1993**, *34*, 123−126. (d) Carreño, M. C.; Ruano, J. L. G.; Maestro, M. C.; Cabrejas, L. M. M. *Tetrahedron*: *Asymmetry* **1993**, *4*, 727−734. (e) Ordoñez, M.; Guerrero-de la Rosa, V.; Labastida, V.; Llera, J. M. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2675−2686. (f) Chelucci, G.; Berta, D.; Saba, A. *Tetrahedron* **1997**, *53*, 3843−3848. (g) Hiroi, K.; Suzuki, Y. *Heterocycles* **1997**, *46*, 77−81. (h) Petra, D. G. I.; Kamer, P. C. J.; Spek, A. L.; Schoemaker, H. E.; van Leeuwen, P. W. N. M. *J. Org. Chem.* **2000**, *65*, 3010−3017. (i) Hiroi, K.; Suzuki, Y.; Abe, I.; Kawagishi, R. *Tetrahedron* **2000**, *56*, 4701−4710. (j) Hiroi, K.; Wantanabe, K.; Abe, I.; Koseki, M. *Tetrahedron Lett.* **2001**, *42*, 7617−7619. (k) Priego, J.; Mancheño, O. G.; Cabrera, S.; Carretero, J. C. *J. Org. Chem.* **2002**, *67*, 1346−1353. (l) Wantanabe, K.; Hirasawa, T.; Hiroi, K. *Chem. Pharm. Bull*. **2002**, *50*, 372−379. (m) Rowlands, G. J. *Synlett* **2003**, 236−240. (n) Ekegren, J. K.; Roth, P.; Källström, K.; Tarnai, T.; Andersson, P. G. *Org. Biomol. Chem.* **2003**, *1*, 358−366. (o) Hiroi, K.; Izawa, I.; Takizawa, T.; Kawai, K. *Tetrahedron* **2004**, *60*, 2155−2162. (p) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346−1347.

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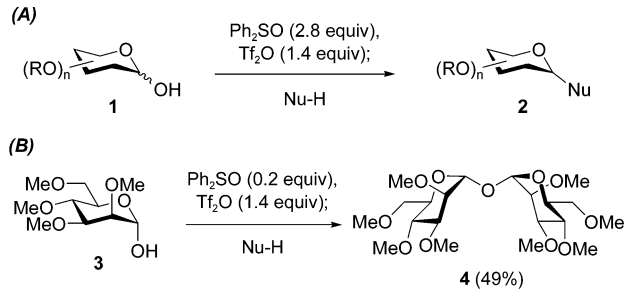
SCHEME 1

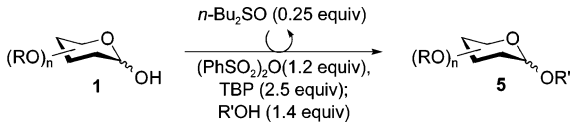


have not been exploited as substoichiometric stand-alone covalent catalysts.[5] Recently, we described an expansion of the available methods for catalytic hydroxyl group functionalization through the use of an alkyl sulfoxide as a stand-alone covalent catalyst for sulfonylation of hemiacetal hydroxyls in the context of dehydrative glycosylation.[6] Herein, we report our further investigations into the mechanism of hemiacetal activation in this unique sulfoxide-catalyzed hemiacetal hydroxyl functionalization.

Results and Discussion

Some time ago we disclosed a method for the dehydrative glycosylation of nucleophilic acceptors (Nu-H) with glycosyl hemiacetals (**1**) employing the reagent combination of diphenyl sulfoxide (Ph_2SO) and trifluoromethanesulfonic anhydride (Tf_2O) (Scheme 1A) as the dehydrating agent.[7] This approach was found to be general and applicable to the formation of a wide variety of glycosidic linkages. In this procedure, the sulfoxide species, although necessary for the reaction to proceed, was not consumed in the transformation, suggesting the possibility that the reaction could be extended to employ a substoichiometric amount of sulfoxide. However, subsequent studies demonstrated that when a deficit quantity of sulfoxide (0.2 equiv) is used in a dehydrative glycosylation with 2,3,4,6-tetra-*O*-methyl-D-mannopyranose (**3**, Scheme 1B), only the product of hemiacetal dimerization (**4**) is obtained.[8] The formation of the 1,1′-α,α′-disaccharide **4** in 49% arises from the rapid condensation of a reactive glycosyl electrophile with unactivated hemiacetal (**3**). The failure of sulfoxide turnover in this initial reagent system can be rationalized by the in situ generation of a highly reactive glycosyl triflate intermediate,[8,9] which cannot serve as a stable resting state in the catalytic cycle prior to the addition of an external nucleophilic glycosyl acceptor. Therefore, the key to the successful achievement of sulfoxide turnover is the identification of a sulfoxide and sulfonic anhydride combination that provides the appropriate balance of sulfonate nucleophilicity and glycosyl sulfonate stability and reactivity.

SCHEME 2



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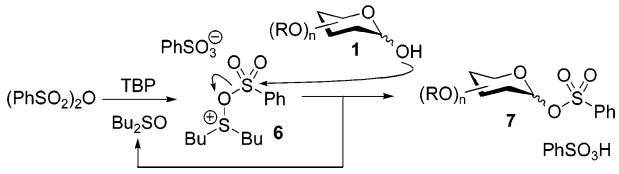

Evaluation of a number of sulfoxide and sulfonic anhydride reagent pairs led to the identification of *n*-butyl sulfoxide (*n*-Bu_2SO) and benzenesulfonic anhydride ($(PhSO_2)_2O$) as a suitable system to effect the formation of new glycosidic linkages with the catalytic turnover of substoichiometric sulfoxide. In this simple procedure, treatment a glycosyl hemiacetal (**1**, Scheme 2) with $(PhSO_2)_2O$ (1.2 equiv), 2,4,6-tri-*tert*-butylpyridine (TBP, 2.5 equiv), and *n*-Bu_2SO catalyst (0.25 equiv) in dichloromethane (0.1 M) at 23 °C, followed by addition of an appropriate nucleophile (1.4 equiv), results in the formation of new anomeric linkage in the glycoside **5**. This method was found to be amenable to the preparation of a variety of different glycosidic linkages,[6] although only limited mechanistic investigations into this novel sulfoxide-catalyzed process have been conducted.

Initial Investigations into the Mode of Catalytic Hemiacetal Activation. A reasonable mechanism for the conversion of hemiacetal **1** to the corresponding glycosyl sulfonate with sulfoxide turnover involves initial electrophilic activation of *n*-Bu_2SO with $(PhSO_2)_2O$ to give the sulfonium sulfonate intermediate (**6**, Scheme 3). Subsequent nucleophilic addition of the hemiacetal **1** into the *S*(*VI*)-center of **6** would result in the generation of glycosyl sulfonate **7** as the resting state with concomitant regeneration of *n*-Bu_2SO. In this mode of hemiacetal activation, sulfoxide serves a dual role, first as a Lewis-basic nucleophilic catalyst to activate $(PhSO_2)_2O$, and then as a leaving group to facilitate the formation of the glycosyl sulfonate. The function of sulfoxide is not unlike that of 4-(dimethylamino)pyridine (DMAP) or phosphine in the catalyzed acylation of nucleophiles.[1]

In an alternative reaction pathway (Scheme 4), sulfonium sulfonate **6** undergoes nucleophilic attack at *S*(*IV*) by the hemiacetal **1** to provide glycosyl oxosulfonium **8**. Subsequent expulsion/regeneration of the sulfoxide catalyst from oxosulfonium **8** by anomeric nucleophilic substitution with $PhSO_3^-$ results in the generation of glycosyl sulfonate **7**. This mechanism is notably distinct from that of traditional nucleophilic catalysis in that the

(4) Select sulfoxides have been employed as phase-transfer catalysts. See: (a) Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A.; Montanari, F.; Cinquini, M. *Tetrahedron Lett.* **1975**, *16*, 3757−3760. (b) Furukawa, N.; Kishimoto, K.; Ogawa, S.; Kawai, T.; Fujihara, H.; Oae, S. *Tetrahedron Lett.* **1981**, *22*, 4409−4412.

(5) For the use of excess chiral sulfoxide for asymmetric allylation of hydrazones and aldehydes through coordinative acceleration see: (a) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610−6611. (b) Massa, A.; Molkov, A. V.; Kočovský, P.; Scettri, A. *Tetrahedron Lett.* **2003**, *44*, 7179−7181 (correction: *Tetrahedron Lett.* **2003**, *44*, 9067). (c) Rowlands, G. J.; Barnes, W. K. *Chem. Commun.* **2003**, 2712−2713.

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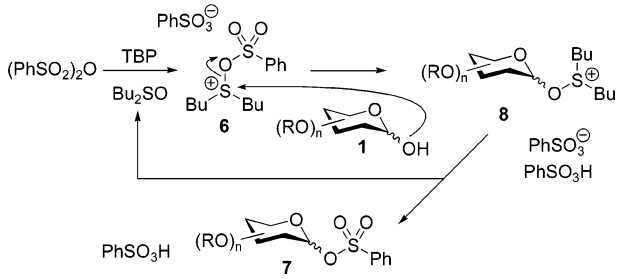
(7) Garcia, B. A.; Poole, J. L.; Gin D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597−7598.

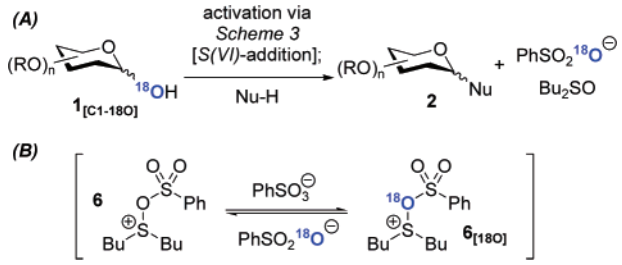
(8) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269−4279.

(9) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

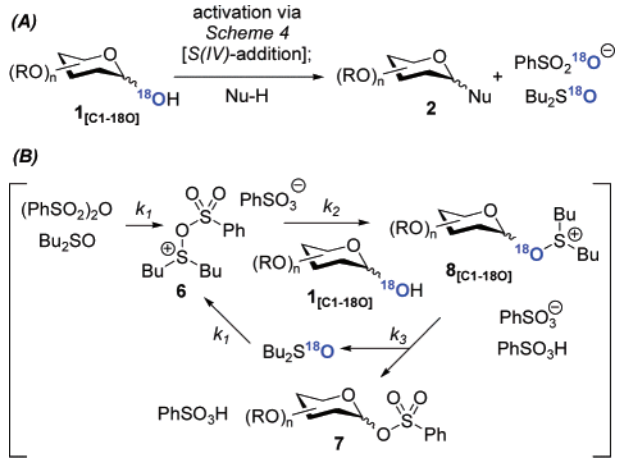
SCHEME 4



SCHEME 5



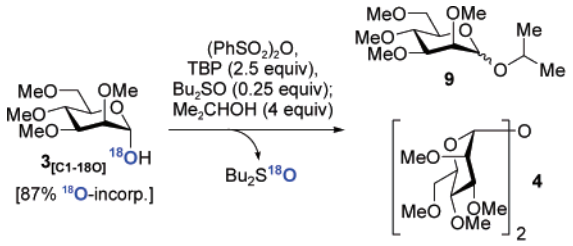
SCHEME 6



sulfoxide catalyst plays a 3-fold role, first as an *O*-nucleophile, then as a *S*(*IV*)-electrophile, and finally as a leaving group to allow for catalyst turnover and glycosyl sulfonate formation.

A straightforward method to gain insight into the pathway for hemiacetal activation is to perform a reaction employing [1-^{18}*O*]-labeled hemiacetal $\mathbf{1}_{[C1-18O]}$ (Schemes 5 and 6). If the *S*(*VI*)-addition pathway is operative (Scheme 5A), nucleophilic addition of hemiacetal ($\mathbf{1}_{[C1-18O]}$) into sulfonium sulfonate **6** would result in immediate transfer of ^{18}O to the sulfonate anion ($PhSO_2{}^{18}O^-$) following the addition of the external nucleophile (Nu-H). However, this mode of hemiacetal activation is not restricted to exclusive transfer of ^{18}O to sulfonate anion, especially if sulfonate exchange on sulfonium sulfonate **6** (Scheme 5B) is rapid during the course of the reaction, which may lead to a small amount of ^{18}O-incorporation in the sulfoxide catalyst. Nevertheless, even if this were the case, the level of ^{18}O-incorporation into sulfoxide by this mechanism should not exceed that of $^1/_6$ of the hemiacetal starting material based solely on the proportion of ^{18}O/^{16}O of all reactive oxygens present in the activation process.

TABLE 1.



Entry	$(PhSO_2)_2O$ (equiv)	**9** (%) (α:β)	**4** (%)	$Bu_2S^{18}O$ (% ^{18}O)
1	1.2	91 (1.2:1)	3	1
2	1.0	88 (1.1:1)	5	65

Conversely, if nucleophilic addition of the [1-^{18}*O*]-labeled hemiacetal $\mathbf{1}_{[C1-18O]}$ into the *S*(*IV*)-center of sulfonium sulfonate **6** is operative, a net transfer of ^{18}O to sulfoxide catalyst as well as the sulfonate anion would be observed (Scheme 6A). However, it is worth noting that the degree of ^{18}O-incorporation into sulfoxide at the conclusion of the reaction can be depleted (Scheme 6B) depending on the relative rates of consumption versus regeneration of *n*-Bu_2SO in the catalytic cycle. If the rate of sulfoxide regeneration (k_3, $\mathbf{8}_{[C1-18O]} \rightarrow \mathbf{7}$, Scheme 6B) is faster than that of initial sulfoxide sulfonylation (k_1, *n*-$Bu_2SO \rightarrow \mathbf{6}$), a mixture of both labeled and unlabeled sulfoxide would accumulate during the course of the reaction, both of which could undergo electrophilic activation with $(PhSO_2)_2O$. Although each successive catalyst turnover would increase the ^{18}O/^{16}O-isotope proportion within *n*-Bu_2SO, there could remain a statistical fraction of the sulfoxide that might undergo zero turnovers and therefore remain unlabeled.

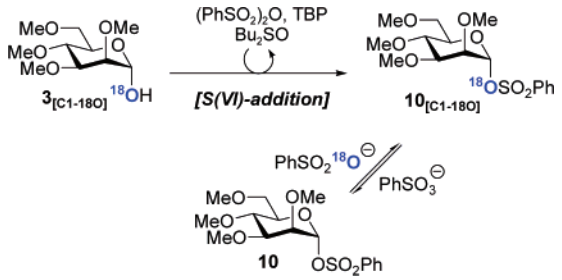
Despite these potential modes of ^{18}O-scrambling (Schemes 5B and 6B), the hemiacetal ^{18}O-transfer experiment was performed (Table 1). [1-^{18}*O*]-Labeled 2,3,4,6-tetra-*O*-methyl-D-mannopyranose ($\mathbf{3}_{[C1-18O]}$, 87% ^{18}O-incorporation)[10] was activated with $(PhSO_2)_2O$ (1.2 equiv) and *n*-Bu_2SO catalyst (0.25 equiv) (Table 1, Entry 1) at 23 °C in CH_2Cl_2, in a reaction procedure mimicking that established for optimal yield of the glycoside product.[6] After 1 h, the reaction was quenched with an excess of 2-propanol to provide 91% isopropyl mannoside **9** (α:β 1.2:1) and 3% 1,1′-α,α′-linked disaccharide **4**.[11] Interestingly, mass spectral analysis of recovered sulfoxide catalyst demonstrated essentially no ^{18}O-incorporation. While this initial result suggests a *S*(*VI*)-addition pathway (Schemes 3 and 5), one must also consider the possibility of artificial late-stage ^{18}O-wash-out from newly labeled sulfoxide due to the ≥0.2 equiv of excess $(PhSO_2)_2O$ present at the end of the process. This could result in sulfonylation of the newly generated ^{18}O-labeled catalyst, leading to some degree of ^{18}O-wash-out from the sulfoxide upon addition of an external unlabeled *O*-nucleophile or hydrolysis at the end of the reaction.[12] Indeed, when the experiment

(10) Prepared through dehydrative glycosylation of $H_2{}^{18}O$ (95% ^{18}O-incorp) to 2,3,4,6-tetra-*O*-methyl-D-mannopyranose.

(11) Product ratios determined by ^{1}H NMR.

(12) Additional ^{18}O-wash-out can arise as a consequence of 1,1′-α,α′-linked disaccharide (**4**) formation, which provides for an even greater excess of unconsumed sulfonic anhydride at the conclusion of the process.

SCHEME 7

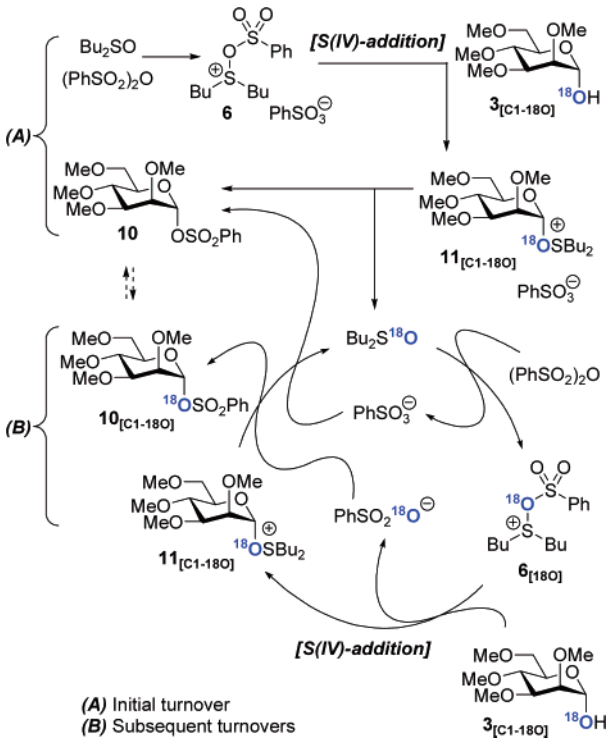


is performed under modified conditions with only 1.0 equiv of $(PhSO_2)_2O$ (Table 1, entry 2), mass spectral analysis of the regenerated sulfoxide catalyst revealed 65% ^{18}O-incorporation, a significant yet nonquantitative level of ^{18}O-transfer from hemiacetal to sulfoxide.[13] These apparently disparate results highlight the dramatic sensitivity of this type of ^{18}O-transfer experiment, based solely on product analysis, to trace quantities of excess $(PhSO_2)_2O$. Thus, a novel strategy was envisioned to provide an unambiguous distinction between the two hemiacetal activation pathways via the dynamic monitoring of ^{18}O-incorporation into the glycosyl sulfonate intermediate **7**.

Unambiguous Determination of the Mode of Hemiacetal Activation. Previous ^{18}O-tracer experiments (Table 1), based solely on analysis of regenerated sulfoxide catalyst, were complicated by factors such as sulfoxide turnover, competitive hemiacetal self-condensation, and excess quantities of $(PhSO_2)_2O$. This precluded the acquisition of accurate ^{18}O-transfer data for mechanistic evaluation under conditions typically used in the catalytic dehydrative glycosylation process,[6] which employ a small excess of $(PhSO_2)_2O$ (1.2 equiv) to minimize self-condensation of the hemiacetal donor.

However, the course of hemiacetal activation, be it through *S*(*VI*)-addition or *S*(*IV*)-addition, also has a direct consequence on the proportion of anomeric ^{18}O-incorporation in the glycosyl sulfonate as the activation proceeds. For example, if the activation of $\mathbf{3}_{[C1-18O]}$ proceeds through hemiacetal addition at the *S*(*VI*)-center of sulfonium sulfonate **6** (Scheme 7), the initial product formed would be the ^{18}O-labeled glycosyl sulfonate ($\mathbf{10}_{[C1-18O]}$) whose $^{18}O/^{16}O$ isotope ratio would directly reflect that of the hemiacetal ($\mathbf{3}_{[C1-18O]}$) starting material. In the (unlikely) event that no anomeric exchange of sulfonate in $\mathbf{10}_{[C1-18O]}$ occurs, this $^{18}O/^{16}O$ ratio would remain at this initial level throughout the course of glycosyl sulfonate formation. Alternatively, if intramolecular or intermolecular exchange of the anomeric sulfonate oxygens on mannosyl sulfonate $\mathbf{10}_{[C1-18O]}$ is active, then the observed $^{18}O/^{16}O$ isotope ratio of $\mathbf{10}_{[C1-18O]}$ would either be constant

SCHEME 8



at approximately $^1/_3$ or $^1/_6$ that of the [1-^{18}O]-labeled hemiacetal $\mathbf{3}_{[C1-18O]}$ (rapid intramolecular or intermolecular sulfonate exchange, respectively) or decrease to those values during the reaction (slow intramolecular or intermolecular sulfonate exchange, respectively).

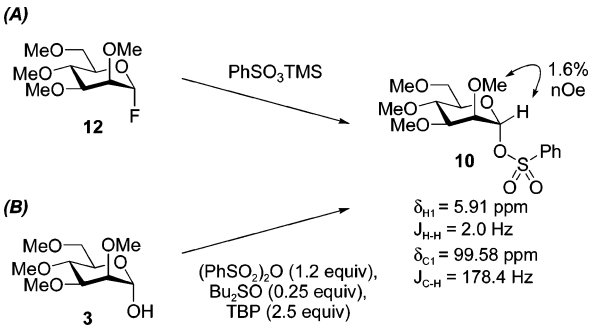
In contrast, consideration of the pathway of hemiacetal addition to the *S*(*IV*)-center of sulfonium sulfonate **6** would provide a different profile for the $^{18}O/^{16}O$ isotope ratio as a function of conversion to glycosyl sulfonate. In this scenario (Scheme 8), there can be no ^{18}O-transfer to the anomeric position of the glycosyl sulfonate **10** until after the first turnover of sulfoxide (i.e., Scheme 8A, $Bu_2SO \rightarrow \mathbf{6} \rightarrow \mathbf{11}_{[C1-18O]} \rightarrow \mathbf{10}$). At that point, each successive sulfonylation of newly generated *n*-$Bu_2S^{18}O$ with $(PhSO_2)_2O$ would result in the increase of the $^{18}O/^{16}O$ isotope ratio of anionic sulfonate in solution, which ultimately serves as a nucleophile to effect additional sulfoxide turnover (i.e., Scheme 8B, $Bu_2S^{18}O \rightarrow \mathbf{6}_{[18O]} \rightarrow \mathbf{11}_{[C1-18O]} \rightarrow \mathbf{10}_{[C1-18O]}$). A direct consequence would be an increase in the $^{18}O/^{16}O$ isotope ratio in the glycosyl sulfonate **10** as it is being formed, reaching a maximum level corresponding to the final statistical $^{18}O/^{16}O$ ratio in the sulfonate anion.

It is important to note that for the *S*(*VI*)-addition pathway (Scheme 7), there is no scenario that would afford an increase in the anomeric $^{18}O/^{16}O$ ratio of the glycosyl sulfonate **10** as a function of its extent of formation, unlike that which is expected in the *S*(*IV*)-addition pathway (Scheme 8).[14] This would hold true irrespective of the relative rates of the various sulfonate anion exchange processes in the activation process.

(13) Lowering the amount of $(PhSO_2)_2O$ from 1.2 to 1.0 equiv in entry 2 also led to the formation of the 1,1′-α,α-linked disaccharide **4** in marginally enhanced yield (5%). This in turn would contribute to incomplete consumption of $(PhSO_2)_2O$ and account for some degree of ^{18}O-wash-out from newly generated ^{18}O-sulfoxide This is in contrast to the near-quantitative ^{18}O-transfer observed when 2,3,4,6-tetra-*O*-methyl-D-glucopyranose was employed as the hemiacetal donor using a deficit quantity (0.95 equiv) of $(PhSO_2)_2O$ (ref 6). In a further modification of the glycosylation procedure, treatment of 2 equiv of $\mathbf{3}_{[C1-18O]}$ (2.2 equiv, 87% ^{18}O-incorporation) with $(PhSO_2)_2O$ (1.0 equiv) and *n*-Bu_2SO (0.25 equiv) leads to the formation of the 1,1′-α,α-linked disaccharide **4** (91%) and recovered sulfoxide catalyst with 84% ^{18}O-incorporation.

(14) Small perturbations arising from $C-^{16/18}O$ equilibrium isotope effects are likely to be negligible and should not significantly influence the trends to be observed in the ^{18}O-incorporation into **11** as a function of its formation. See: Rishavy, M. A.; Cleland, W. W. *Can. J. Chem.* **1999**, *77*, 967−977.

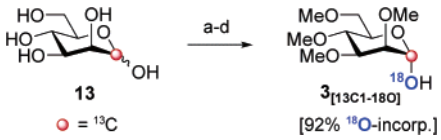
SCHEME 9



Measurement of the changes in the $^{18}O/^{16}O$ isotope ratio of mannosyl sulfonate **10** during the course of its formation can be achieved through the use of ^{13}C NMR spectroscopy as it is known that ^{13}C NMR resonances experience a small but significant upfield chemical shift perturbation (~0.01−0.05 ppm) when directly bound to ^{18}O relative to that of ^{16}O.[15] This would provide a means by which carbons bound to ^{16}O and ^{18}O could be differentiated and their relative amounts quantified via ^{13}C NMR integration.[16,17]

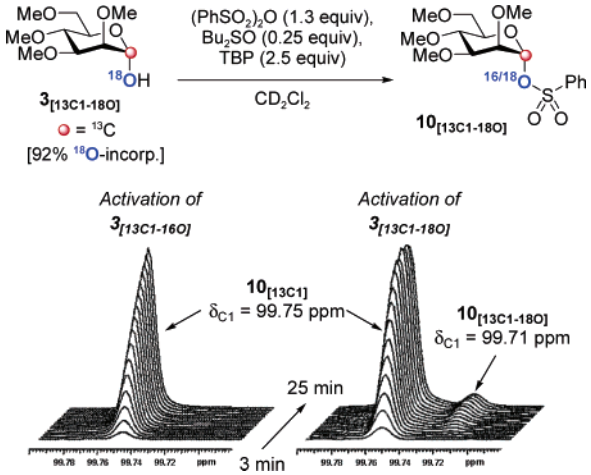
To conduct this experiment, the mannosyl sulfonate **10** first was independently synthesized and characterized (Scheme 9A) so that its presence could be unambiguously identified in the sulfoxide-catalyzed activation process. The synthesis of mannosyl sulfonate **10** is relatively straightforward (Scheme 9A), analogous to our previous protocol in the generation of glycosyl triflates.[8,9,18] Treatment of mannosyl fluoride **12**[19] with trimethylsilyl benzenesulfonate ($PhSO_3TMS$)[20] in CD_2Cl_2 provided mannosyl sulfonate **10** (85% conversion) after 4 h at 0 °C. The structure of the α-glycosyl sulfonate **10** was verified by a battery of NMR techniques (^1H, ^{13}C, J_{C1H1}, HMQC, nOe). For comparison (Scheme 9B), a solution of **3**, $(PhSO_2)_2O$, and TBP in CD_2Cl_2 was treated with *n*-Bu_2SO at 20 °C. After 35 min, ^1H NMR analysis revealed >95% conversion of hemiacetal **3** to a species with ^1H NMR resonances identical to that of the previously synthesized α-mannosyl sulfonate **10**.

SCHEME 10[a]



[a] Reagents and conditions: (a) Dowex-50W, MeOH, 65 °C; (b) 50% NaOH, DMSO; MeI, 0 to 23 °C; (c) 8 N HCl, 60 °C; (d) Ph_2SO, Tf_2O, TBP, −78 to −45 °C; 1% $H_2{}^{18}O$ in THF, −78 to 22 °C.

SCHEME 11



The successful characterization of mannosyl sulfonate **10** therefore set the stage for the tracking of its ^{18}O-incorporation profile during the hemiacetal activation process. In the interest of obtaining accurate ^{13}C NMR integral data with the substrate concentrations typical for hemiacetal activation, a doubly labeled $^{13}C1$-labeled hemiacetal donor with an anomeric ^{18}OH group was prepared (Scheme 10). [1-^{13}C,^{18}O]-Labeled 2,3,4,6-tetra-*O*-methyl-D-mannopyranose (**3**$_{[13C1-18O]}$, >99% ^{13}C-incorporation, 92% ^{18}O-incorporation) was synthesized in a four-step sequence starting from [1-^{13}C]-labeled D-mannose (**13**). Fischer glycosylation of methanol with **13**, followed by permethylation, anomeric deprotection, and C1-hydroxy exchange with $H_2{}^{18}O$ (95% ^{18}O-incorporation) provides **3**$_{[13C1-18O]}$.

Sulfoxide-catalyzed hemiacetal activation was then performed on [1-^{13}C,^{18}O]-labeled mannose hemiacetal **3**$_{[13C1-18O]}$ (Scheme 11). A solution of **3**$_{[13C1-18O]}$, $(PhSO_2)_2O$, and TBP in CD_2Cl_2 was treated with *n*-Bu_2SO at 20 °C and monitored by ^{13}C NMR.[21−23] Examination of the $^{13}C1$ resonance of the mannosyl sulfonate **10** (δ_{C1} 99.75)[24] revealed the emergence of a minor ^{13}C resonance (δ_{C1}

(15) See, inter alia: (a) Jameson, C. J. *J. Chem. Phys.* **1977**, *66*, 4983−4988. (b) Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252−253. (c) Darensbourg, D. J. *J. Organomet. Chem.* **1979**, *174*, C70−C76. (d) Vederas, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 374−376. (e) Vederas, J. C. *Can. J. Chem.* **1982**, *60*, 1637−1642. (f) Risley, J. M.; Van Etten, R. L. In *NMR: Basic Principles and Progress*; Gunther, H., Ed.; Springer-Verlag: Berlin, Germany, 1990; Vol. 22, pp 81−168.

(16) Measurement of the changes in $^{16}O/^{18}O$-incorporation over time by ^{13}C NMR has been used to study the mechanism of sulfonate exchange. See: (a) Fujio, M.; Sanematsu, F.; Tsuno, Y.; Sawada, M.; Takai, Y. *Tetrahedron Lett.* **1988**, *29*, 93−96. (b) Tsuji, Y.; Kim, S. H.; Saeki, Y.; Yatsugi, K.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* **1995**, *36*, 1465−1468. (c) Tsuji, Y.; Toteva, M. M.; Amyes, T. L.; Richard, J. P. *Org. Lett.* **2004**, *6*, 3633−3636.

(17) This method has also been used to monitor positional isotope exchange in carbohydrates. See: (a) Mega, T. L.; Cortes, S.; Van Etten, R. L. *J. Org. Chem.* **1990**, *55*, 522−528. (b) Barlow, J. N.; Girvin, M. E.; Blanchard, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 6968−6969.

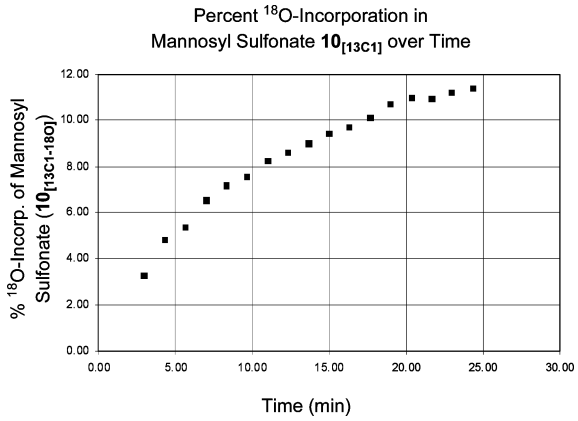
(18) Callam, C. S.; Gadikota, R. R.; Krein, D. M.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 13112−13119.

(19) Prepared from the treatment of 2,3,4,6-tetra-*O*-methyl-D-mannopyranose with excess hydrogen fluoride−pyridine complex, following a known procedure for the conversion of glycosyl hemiacetals to glycosyl fluorides. See: Szarek, W. A.; Grynkiewicz, G.; Doboszewski, B.; Hay, G. W. *Chem. Lett.* **1984**, 1751−1754.

(20) Prepared from the treatment of benzene with trimethylsilyl chlorosulfonate following a known procedure. See: Hofman, K.; Simchen, G. *Liebigs Ann. Chem.* **1982**, 282−297.

(21) In the interest of maximizing signal to noise, individual spectra were acquired without waiting for complete relaxation between pulses. However, it was anticipated that this would not present a problem in the determination of accurate $^{13}C-^{16}O/^{13}C-^{18}O$ ratios as the substitution of an ^{16}O with an ^{18}O (neither of which is NMR active) should not result in a significant change in the rate of longitudinal relaxation of the attached ^{13}C atom. Indeed, measurement of the longitudinal relaxation time (T_1) of both [1-^{13}C,^{16}O]-labeled mannosyl sulfonate (**10**$_{[13C1]}$, Scheme 11) and [1-^{13}C,^{18}O]-labeled mannosyl sulfonate (**10**$_{[13C1-18O]}$) at the conclusion of hemiacetal **3**$_{[13C1-18O]}$ activation by the inversion recovery method demonstrated T_1 values within 5% of one another (1.64 ± 0.03 and 1.72 ± 0.04 s, respectively). For an excellent review of ^{13}C-relaxation mechanisms, see: Levy, G. C.; Lichter, R. L.; Nelson, G. L. Introduction, Theory and Methods. In *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; John Wiley & Sons: New York, 1980; pp 1−28.

CHART 1



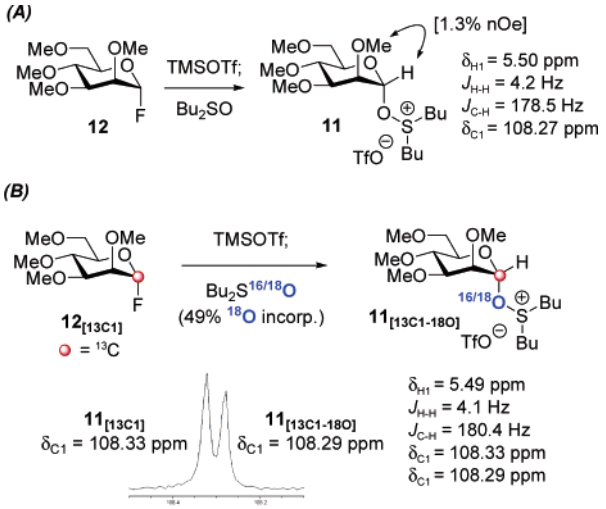
99.71) during the course of the reaction, characteristic of the upfield chemical shift perturbation of $^{13}C-^{18}O$ vs $^{13}C-^{16}O$. Careful integration of the relative proportion of these peaks as a function of time revealed an increase in the percent ^{18}O-incorporation of the glycosyl sulfonate **10** during the course of its formation (Chart 1) approaching a limit at ~12%. In comparison with the predicted trends for both the *S*(*VI*)- versus *S*(*IV*)-pathways (Schemes 7 vs 8), this result clearly reinforces initial hemiacetal nucleophilic addition at *S*(*IV*) of **6** (Schemes 4 and 8) as the activation pathway, even when probed under typical reaction conditions involving excess $(PhSO_2)_2O$ dehydrating agent.[25] Indeed, hemiacetal addition into the *S*(*IV*)-center of **6** is consistent with the previously demonstrated proclivity for sulfonium sulfonates to accept oxygen nucleophiles at *S*(*IV*).[26]

Detection and Analysis of Mannosyl Oxosulfonium 11. The evidence in support of hemiacetal activation through the *S*(*IV*)-pathway implies that the glycosyl oxosulfonium species **11** (Scheme 8) must be a transient intermediate in the hemiacetal activation process. If this species is of sufficient stability to be detected, one would expect it to be initially formed via the *S*(*IV*)-addition pathway in a substoichiometric quantity and eventually diminish as the conversion to the glycosyl sulfonate concludes.

Due to its enhanced reactivity, independent preparation of the putative mannosyl oxosulfonium **11**, for the purpose of initial identification (Scheme 12A), was significantly more challenging than its anomeric sulfonate counterpart **10**. Using an adaptation of a procedure previously developed within our group,[8] mannosyl fluoride **12**[19] was treated with excess TMSOTf (6 equiv) in CD_2Cl_2 at −78 °C to provide the glycosyl triflate intermediate. After 30 min at −45 °C, the reaction was cooled to −78 °C whereupon excess *n*-Bu_2SO (7.0 equiv) was added to give, after warming to 23 °C, the putative mannosyl oxosulfonium **11** (66% conversion). ^1H NMR characterization of **11** revealed the presence of an anomeric doublet at δ 5.50 ppm ($^3J_{HH}$ = 4.2 Hz) which exhibited nOe enhancement upon irradiation of the C(2)−OCH_3 resonance (1.3%). The anomeric carbon at δ 108.27 was unambiguously identified by correlation with the anomeric proton and found to exhibit a $^1J_{CH}$ of 178.5 Hz, indicative of an equatorial anomeric proton. Although these data are consistent with the structure of **11**, the paucity of data for characterization of anomeric oxosulfonium intermediates in the literature necessitated the further structure verification of **11** by confirming its anomeric C−O connectivity (Scheme 12B). Following the previously described procedure for the synthesis of **11**, [1-^{13}C]-labeled mannosyl fluoride $\mathbf{12}_{[13C1]}$ was sequentially treated with TMSOTf and *n*-$Bu_2S^{16/18}O$ (49% ^{18}O-incorporation).[27] The resulting ^{13}C NMR of the product (50% conversion) showed the presence of two anomeric carbon resonances, at δ 108.33 and δ 108.29, with a $\Delta\delta$ of 0.04 ppm. The presence of two C1 resonances is indicative of ^{18}O-induced isotope chemical shift perturbation by the partially labeled sulfoxide, providing clear evidence that the species observed by ^1H and ^{13}C NMR indeed incorporates a C−O linkage between the anomeric carbon and the sulfoxide oxygen, consistent with the structure of mannosyl oxosulfonium **11**.

With the successful preparation of both the mannosyl oxosulfonium **11** and the glycosyl sulfonate **10**, the entire hemiacetal activation process was then monitored by ^1H NMR. Hemiacetal activation was performed on 2,3,4,6-

SCHEME 12



(22) Individual spectra were acquired with an acquisition time of 2.0 s utilizing a 72° pulse. The optimum pulse angle was determined using the Ernst equation, $\cos(\alpha) = e\wedge(-t_r/T_1)$, where α is the pulse angle and t_r is the relaxation time between pulses. See: Ernst, R. R.; Anderson, W. A. *Rev. Sci. Instr.* **1966**, *37*, 93−102.

(23) Subsequent averaging of every 40 spectra provided one data point every 80 s. Baseline resolution between the closely spaced $^{13}C-^{16}O$ and $^{13}C-^{18}O$ resonances was achieved by the application of a resolution enhancement of −0.8 Hz and a Gaussian apodization of 0.5 s. The application of resolution enhancement in FT NMR has been shown to have only a limited effect on the accuracy of integration. See: Kupka, T.; Dzięgielewski, J. O. *Magn. Reson. Chem.* **1988**, *26*, 353−357.

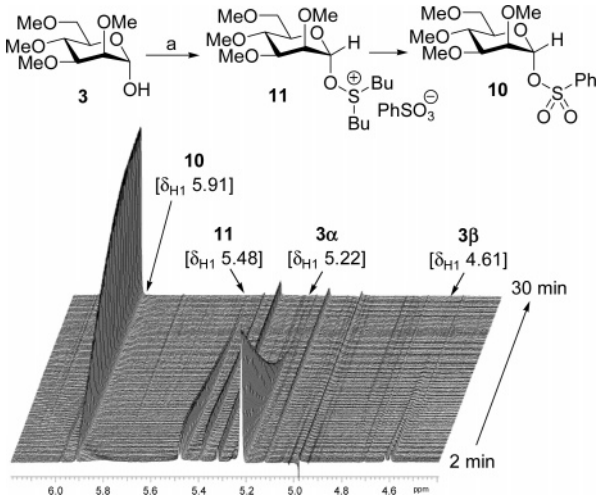
(24) δ_{C1} is shifted slightly downfield (0.17 ppm) from the corresponding resonance measured in the independent synthesis and characterization of **10**. This is likely the result of differing ionic strengths for the two reaction solutions, as the synthesis of **10** from mannosyl fluoride **12** (Scheme 9A) should yield no ionic products whereas the conversion of hemiacetal $\mathbf{3}_{[13C1-18O]}$ to $\mathbf{10}_{[13C1-18O]}$ (Scheme 11) would also generate pyridinium sulfonate as a byproduct.

(25) It should be noted that the advent of turnover in sulfoxide during the reaction precludes complete exclusion of the *S*(*VI*)-addition pathway (Scheme 3) from these data alone.

(26) Tidwell, T. T. *Synthesis* **1990**, 857−870.

(27) Partially labeled *n*-$Bu_2S^{18}O$ was prepared by sequential treatment of *n*-Bu_2SO with 0.5 equiv of Tf_2O at −78 °C in CH_2Cl_2 followed by the addition of excess $H_2{}^{18}O$ (95% ^{18}O-incorp) in THF. The percent ^{18}O-incorporation was determined by using field ionization mass spectrometry.

SCHEME 13

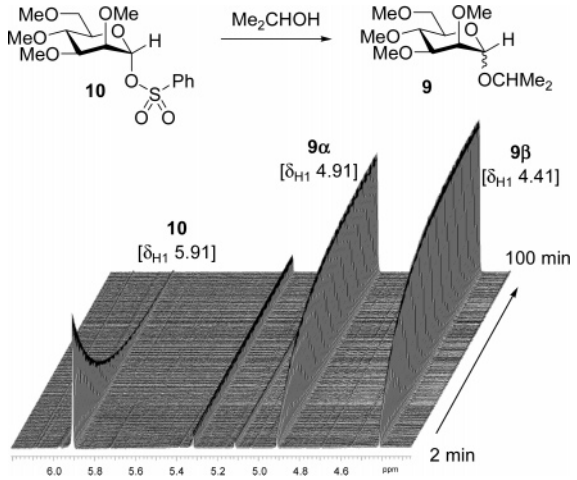


[a] Reagents and conditions: $(PhSO_2)_2O$ (1.2 equiv), TBP (2.5 equiv), CD_2Cl_2 (0.05 M); *n*-Bu_2SO (0.24 equiv).

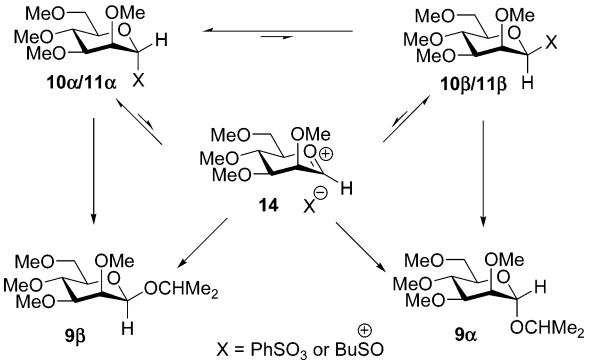
tetra-*O*-methyl-D-mannopyranose (**3**) in CD_2Cl_2 (Scheme 13). A solution of **3** (13:1 α:*β*), $(PhSO_2)_2O$ (1.2 equiv), and TBP (2.5 equiv) in CD_2Cl_2 was treated with *n*-Bu_2SO (0.24 equiv) at 20 °C, leading to complete consumption of both the α-hemiacetal **3**α (*δ* 5.22) and *β*-hemiacetal **3***β* (*δ* 4.61) within 30 min to give >95% of α-mannosyl sulfonate **10** (δ_{H1} 5.91).[28,29] A second species, with a characteristic anomeric resonance at *δ* 5.48 ($^3J_{HH}$ = 3.9 Hz), was assigned as the transient mannosyl oxosulfonium **11**, which exhibited an initial rapid increase in the formation followed by gradual decline over the period of 30 min. It should be noted that this δ_{H1} is shifted slightly upfield (0.02 ppm) from the corresponding resonance measured in the independent synthesis and characterization of **11** (Scheme 12A), although this is likely due to the variability of oxosulfonium counterion in each of the experiments (i.e., TfO^- in Scheme 12, $PhSO_3^-$ in Scheme 13). The observation of this reaction profile of the transient α-mannosyl oxosulfonium **11** during hemiacetal activation is again consistent with hemiacetal activation through the *S*(*IV*)-addition pathway (Scheme 4).[30,31]

^{1}H NMR Analysis of Glycosylation of 2-Propanol. Following the ^{1}H NMR tracking of the hemiacetal activation process, ^{1}H NMR analysis of the subsequent glycosylation stage of the reaction was then monitored. The newly generated α-mannosyl sulfonate **10** (vide supra) was treated with an excess of 2-propanol (4 equiv), and the process of glycosylation was followed via ^{1}H NMR at 20 °C (Scheme 14). Examination of the ^{1}H NMR data revealed near complete conversion of glycosyl sulfonate **10** to isopropyl 2,3,4,6-tetra-*O*-methyl-D-mannopyranoside (**9**) as a 1:1 α:*β* mixture of anomers after 100 min. Inspection of the α- and *β*-mannoside (**9**α*β*) resonances

SCHEME 14



SCHEME 15



(*δ* 4.91 and *δ* 4.41, respectively) over time indicates that the two products are formed at comparable rates and maintain a steady ratio throughout the reaction.

The observed kinetic product ratio of **9** (1:1 α:*β*)[32] in the glycosylation of 2-propanol with the single α-mannosyl sulfonate **10** (Scheme 14) highlights the differing mechanistic pathways by which the glycosides **9** can be formed (Scheme 15). If glycosylation is an S_N2 process (A_ND_N), then the α- and *β*-sulfonates (**10**) (or α- and *β*-oxosulfoniums (**11**)) must be in rapid equilibration, leading to the formation of α-mannoside **9**α at a rate comparable to that of the *β*-mannoside **9***β* through anomeric displacement with inversion. On the other hand, if glycosylation is a dissociative process ($D_N + A_N$ or D_N*A_N),[33] then the active glycosylating species would be glycosyl oxocarbenium **14**, formed through dissociation of the anomeric leaving group. Anomeric substitution to form the α- and *β*-products then occurs at similar rates on **14** to give the observed product ratio (Scheme 15).

(28) ^{1}H NMR spectra were acquired at a rate of one spectrum every 10 s.

(29) The ^{1}H NMR resonances at *δ* 5.32 and *δ* 5.34 are due to the presence of residual $CDHCl_2$ and CH_2Cl_2.

(30) The species corresponding to δ_{H1} 5.14 ppm, formed slowly over the course of the reaction to the extent of 2%, was determined to be 1,1′-α,α-linked disaccharide **4** (Scheme 1).

(31) The minor transient resonance at *δ* 5.40 may correspond to the anomeric proton of the *β*-anomer of mannosyl sulfonate **11**, although its rigorous structural verification has yet to be achieved.

(32) A solution of **9** (1:5.7 α:*β*) in CD_2Cl_2 was treated with $(PhSO_2)_2O$ (0.18 equiv), *n*-Bu_2SO (0.25 equiv), $PhSO_3H$ (2.10 equiv), TBP (2.53 equiv), and 2-propanol (2.03 equiv). After 100 min, ^{1}H NMR showed no change in the anomeric ratio of **9**, indicating that the glycoside product did not equilibrate under the reaction conditions and that the observed 1: 1 α:*β* mixture of glycosidic products in the glycosylation of 2-propanol to mannose hemiacetal **3** was under kinetic control.

(33) The intermediacy of an oxocarbenium species is consistent with previous observations. See: (a) Stubbs, J. M.; Marx, D. *J. Am. Chem. Soc.* **2003**, *125*, 10960−10962. (b) Abdel-Rahman, A. A.-H.; Jonke, S.; El Ashry, E. S. H.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2972−2974. (c) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386-5389.

However, the data present in Scheme 14 are by themselves insufficient to distinguish between the distinct glycosylation pathways. Future detailed studies on the glycosylation event of this reaction will examine the hybridization of the anomeric carbon in the rate determining transition state for the formation of both α- and β-mannoside (**15**) products through the measurement of kinetic isotope effects.[33c,34]

Conclusion

The concept of sulfoxide-covalent catalysis has been established in the context of a versatile hemiacetal hydroxyl activation/substitution reaction for the formation of anomeric linkages. Mechanistic studies focused on the hemiacetal activation process show that this transformation proceeds through the intermediacy of a glycosyl sulfonate species (**10**), which serves as a resting state prior to the addition of an external nucleophile and subsequent glycosidic bond formation. Successful determination of the proportion of ^{18}O-incorporation in **10** as a function of its formation, via the technique of dynamic monitoring of ^{13}C−$^{16/18}$O isotopic chemical shift perturbations, provides strong evidence that hemiacetal activation proceeds through initial nucleophilic addition of the hemiacetal hydroxyl to the *S*(*IV*)-center of putative sulfonium sulfonate **6**. Further confirmation was obtained through the independent synthesis, structure verification, and ^{1}H NMR detection of glycosyl oxosulfonium **11** during the sulfoxide-catalyzed conversion of hemiacetal **3** to glycosyl sulfonate **10**. Future studies will focus on the mechanism of anomeric bond formation following the addition of an external nucleophile to glycosyl sulfonate **10**. The results of these studies should allow for the expansion of the scope of sulfoxide-covalent catalysis to more general hydroxyl functionalization reactions.

Experimental Section

General Procedures. All reactions were performed in flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of argon unless otherwise noted. NMR tubes were dried over calcium sulfate at high vacuum. Dichloromethane, acetonitrile, and toluene were purified by passage through two packed columns of neutral alumina under an argon atmosphere. d_2-Dichloromethane was dried by vacuum transfer from calcium hydride. 2-Propanol was distilled from calcium hydride at 760 Torr onto magnesium from which it was freshly distilled at 760 Torr as needed. Benzenesulfonic anhydride was recrystallized[35] from 10:1 diethyl ether:benzene, dried by azeotropic removal of water with acetonitrile followed by dichloromethane in vacuo, and subsequently handled and stored under a nitrogen atmosphere. *n*-Butyl sulfoxide was dried over 4 Å molecular sieves at 50 °C, stored under argon, and melted under argon prior to use. ^{18}*O*-Labeled *n*-butyl sulfoxide was dried by azeotropic removal of water with toluene in vacuo, and then melted under argon prior to use. 2,4,6-Tri-*tert*-butylpyridine was dried by azeotropic removal of water with toluene in vacuo and subsequently handled and stored under a nitrogen atmosphere. Trimethylsilyl trifluoromethanesulfonate was distilled at reduced pressure prior to use. Infrared (IR) spectra were obtrained using a Perkin-Elmer Spectrum BX spectrophotometer referenced to a polystyrene standard. Data are presented as the frequency of absorption (cm^{-1}) and intensity of absorption (s = strong, m = medium, w = weak). Proton and carbon-13 nuclear magnetic resonance (^{1}H NMR or ^{13}C NMR) spectra were recorded on a Varian 500 or a Varian Inova 500 NMR spectrometer; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual protium in the NMR solvent ($CHCl_3$: δ 7.26 for ^{1}H NMR, δ 77.00 for ^{13}C NMR).

Benzenesulfonyl 2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranose (10). To a solution of 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl fluoride (**12**)[19] (15.7 mg, 0.066 mmol, 1.0 equiv) in CD_2Cl_2 (660 μL) at 0 °C was added trimethylsilyl benzenesulfonate[20] (41 μL, 0.20 mmol, 3.0 equiv). After stirring for 5 h at −2 °C, the reaction was warmed to 22 °C and transferred via cannula to a dry 5 mm NMR tube at 22 °C fitted with a rubber septum whereupon it was placed in the NMR probe at 20 °C. The mannosyl sulfonate **10** (85% conversion) was then characterized by ^{1}H and ^{13}C NMR (Scheme 9).

Bis(*n*-butyl)sulfonium 2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranoside (11). To a solution of 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl fluoride (**12**)[19] (15.2 mg, 0.058 mmol, 1.0 equiv) in CD_2Cl_2 (585 μL) at −78 °C was added trimethylsilyl trifluoromethanesulfonate (63 μL, 0.35 mmol, 6.0 equiv). After 2 min, the solution was warmed to −45 °C for 23 min, and then cooled again to −78 °C at which point *n*-butyl sulfoxide (80 μL, 0.41 mmol, 7.0 equiv) was added via syringe. The reaction was warmed to 21 °C and transferred via cannula to a dry 5 mm NMR tube at 21 °C fitted with a rubber septum whereupon it was placed in the NMR probe at 20 °C. The mannosyl oxosulfonium **11** (66% conversion) was then characterized by ^{1}H NMR (Scheme 12).

Bis(*n*-butyl)sulfonium 2,3,4,6-Tetra-*O*-methyl-α-D-[1-^{13}C, $^{16/18}$O]-mannopyranoside (11$_{[13C1-18O]}$). To a solution of 2,3,4,6-tetra-*O*-methyl-α-D-[1-^{13}C]-mannopyranosyl fluoride (**12**$_{[13C1]}$)[19] (16.3 mg, 0.068 mmol, 1.0 equiv) in CD_2Cl_2 (680 μL) at −78 °C was added trimethylsilyl trifluoromethanesulfonate (75 μL, 0.41 mmol, 6.0 equiv). After 3 min, the solution was warmed to −45 °C for 30 min, and then cooled again to −78 °C at which point *n*-butyl sulfoxide (49% ^{18}O-incorp) (94 μL, 0.48 mmol, 7.0 equiv) was added via syringe. The reaction was warmed to 21 °C, and transferred via cannula to a dry 5 mm NMR tube at 22 °C fitted with a rubber septum whereupon it was placed in the NMR probe at 20 °C. The mannosyl oxosulfonium **11**$_{[13C1-18O]}$ (53% conversion) was then characterized by ^{13}C NMR (Scheme 12).

Activation of 2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranose (3) To Form Benzenesulfonyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranose (10). 2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranoside (**3**) (7.5 mg, 0.032 mmol, 1.0 equiv) in a 5 mm NMR tube was dried by azeotropic removal of water with CH_3CN (250 μL, ×2) and then CH_2Cl_2 (250 μL) in vacuo. To the dried mannose hemiacetal was added 2,4,6-tri-*tert*-butylpyridine (19.6 mg, 0.079 mmol, 2.5 equiv) and benzenesulfonic anhydride (11.5 mg, 0.038 mmol, 1.2 equiv) whereupon the NMR tube was fitted with a rubber septum. The resulting solid mixture was dissolved in CD_2Cl_2 (615 μL) and inserted into the NMR probe equilibrated at 20 °C. After acquisition of an ^{1}H NMR spectrum, the reaction was removed from the NMR probe and a solution of *n*-butyl sulfoxide (1.5 μL, 0.0077 mmol, 0.24 equiv) in CD_2Cl_2 (20 μL) was added via syringe. The reaction was briefly agitated (∼5 s using a vortex apparatus, holding the NMR tube at a 45° angle) and then replaced in the NMR probe. ^{1}H NMR spectra were acquired at a rate of once every 10 s. Consumption of **3** was complete

(34) For kinetic isotope effects associated with glycosidic bond formation/hydrolysis, see: Schramm, V. L. In *Enzyme Mechanism from Isotope Effects*; Cook, P. F., Ed.; CRC Press: Ann Arbor, MI, 1991; pp 367−388. (b) Bennet, A. J.; Sinnot, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 7287−7294. (c) Lee, J. K.; Bain, A. D.; Berti, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 3769−3776.

(35) Field, L. *J. Am. Chem. Soc.* **1952**, *74*, 394−398.

within 30 min to give benzenesulfonyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranoside (**10**) (>95% conversion) (Scheme 13).

Glycosylation with Benzenesulfonyl 2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranose (10) To Form Isopropyl 2,3,4,6-Tetra-*O*-methyl-D-mannopyranoside (9). 2-Propanol (9.8 μL, 0.13 mmol, 4.0 equiv) was added to a solution of benzenesulfonyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranoside (**10**) (0.032 mmol, 1.0 equiv) in CD_2Cl_2 (635 μL) at 20 °C in a 5 mm NMR tube (vide supra). The reaction was briefly agitated (~5 s using a vortex apparatus, holding the NMR tube at a 45° angle) and then placed in the NMR probe. ^{1}H NMR spectra were acquired at a rate of once every 20 s. Consumption of **10** was complete within 100 min to give isopropyl 2,3,4,6-tetra-*O*-methyl-D-mannopyranoside (**9**) as a 1:1 mixture of anomers (Scheme 14).

Acknowledgment. This research was supported by the NIH (GM58833) and the Camille and Henry Dreyfus Foundation. A Pharmacia Graduate Fellowship awarded to T.A.B. is gratefully acknowledged. NMR spectra were obtained in the Varian Oxford Instrument Center for Excellence in NMR Laboratory, funded in part by the W. M. Keck Foundation, the National Institutes of Health (Grant PHS 1 S10 RR10444), and the National Science Foundation (Grant NSF CHE 96-10502). The assistance of Drs. Vera Mainz, Feng Lin, and Paul Molitor of the VOICE NMR Spectroscopy Lab at the University of Illinois is recognized.

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