Evidence for an Oxocarbenium Ion Intermediate in Lewis Acid Mediated Reactions of Acyclic Acetals

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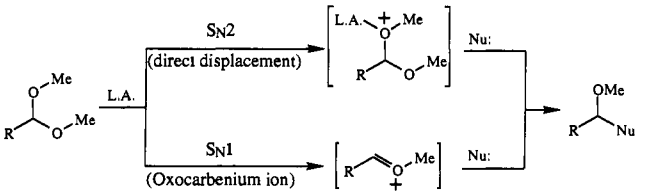
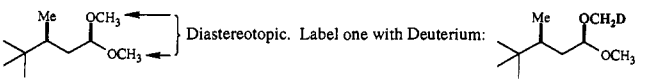
The Lewis acid mediated addition of carbon nucleophiles to acetals is a common reaction in organic synthesis that is widely used for the formation of carbon–carbon bonds.[1] This reaction was first reported in 1974 by Mukaiyama[2] and has since been studied in depth by a number of workers. Variations of this reaction have been reported which use chiral acetals[3] and which provide nonracemic products. As part of a broader program in asymmetric synthesis, we are interested in understanding the mechanism of this and related reactions.[4] There are two extreme mechanisms which can be envisioned for the addition of nucleophiles to acetals (Scheme 1), ranging from direct nucleophilic displacement of a Lewis acid–ether complex (S_N2) to prior formation of a cationic intermediate that subsequently undergoes attack by a nucleophile (S_N1). The recent disclosure by Denmark and Willson of an interesting experiment that provides evidence that certain cyclization reactions may proceed by an S_N2 mechanism has also prompted our interest in the mechanism of this reaction.[5] We recently described a strategy for distinguishing between S_N1 and S_N2 mechanisms in addition reactions to chiral, cyclic acetals that utilizes a stereospecifically incorporated deuterium label.[6] This label allows us to differentiate the two oxygens of the acetal and determine which is cleaved along the reaction coordinate and thereby rule out one of the two limiting mechanisms. We have extended this strategy to acyclic acetals, and we report our findings on the mechanism of intermolecular additions to these species in this communication.

A general method for distinguishing between S_N1 and S_N2 mechanisms is to examine the stereospecificity of a particular reaction with a chiral substrate. A stereospecific reaction is consistent with an S_N2 mechanism, whereas a stereorandom reaction is consistent with an S_N1 mechanism. The specifically deuterated acetal[7] shown in Scheme 2 can serve as a probe for the stereospecificity of the reaction and is therefore capable of distinguishing between these mechanisms. In this substrate one of the two diastereotopic alkoxy groups has been labeled with deuterium. Lewis acid mediated addition of nucleophiles to this acetal provides two diastereomeric products which can differ in their deuterium content depending on the mechanism of the reaction. If the reaction proceeds by an S_N2 mechanism, then each of the diastereomeric products is derived from complexation to and displacement with inversion of one of the two diastereotopic alkoxy groups. Isomer **A** will therefore be derived from displacement of the deuterated alkoxy group whereas isomer **B** will be derived from displacement of the nondeuterated alkoxy group. Thus, stereospecific incorporation of deuterium should be observed in the product with one isomer containing all of the deuterium (Scheme 3). On the other hand, if the reaction proceeds by an S_N1 mechanism, then the diastereomeric products are derived from nucleophilic addition to an oxocarbenium ion intermediate. This intermediate is in turn derived from Lewis acid complexation and ionization of each C–O bond of the acetal. Two oxocarbenium ion intermediates will therefore be produced from ionization of either of the alkoxy groups, one bearing a deuterium label, the other not. The deuterated oxocarbenium ion intermediate produced in this way will provide both diastereomeric products bearing deuterium (isomers **A** and **B** deuterio), while the nondeuterated oxocarbenium ion intermediate will provide both diastereomeric products bearing no deuterium (isomers **A** and **B** protio, Scheme 4). Furthermore, the ratio of deuterium incorporation in the products will depend only on the ratio of deuterated vs nondeuterated oxocarbenium ions produced. Thus, the ratios of **A** protio/**A** deuterio and **B** protio/**B** deuterio should be identical. Since different results must be observed by the different mechanisms, this experiment allows us to rule out one of the two and provide strong evidence for the other.

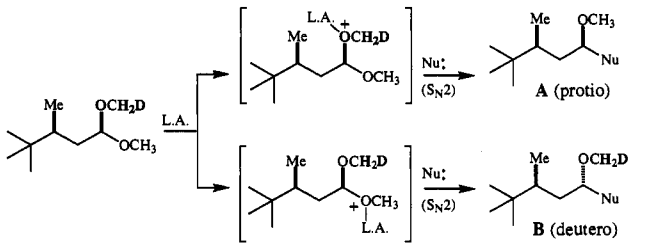
Scheme 1



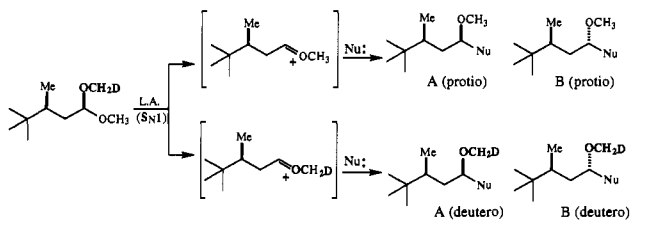
Scheme 2



Scheme 3



Scheme 4



Results of reactions with the deuterated acetal and various nucleophiles using $TiCl_4$ or TMSOTf as the Lewis acid are shown in Table 1. We chose these Lewis acids because Denmark observed a difference in mechanism depending on the identity of the Lewis acid. He concluded that, with dimethyl acetals, milder Lewis acids, such as TMSOTf, favor S_N2 reactivity, while stronger Lewis acids, such as $TiCl_4$, favor S_N1 reactivity.[8] However, we have found that, in all cases examined using these Lewis acids, a nearly

(1) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043.
(2) Mukaiyama, T.; Hayashi, M. *Chem. Lett.* **1974**, 15.
(3) For a recent review of the chemistry of chiral acetals, see: Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.
(4) For other mechanistic work on acetal addition reactions, see: (a) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259. (b) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. (c) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089. (d) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458. (e) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485. (f) Sammakia, T. S.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997.
(5) Denmark, S. E.; Willson T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475. Denmark, S. E.; Willson T. M. In *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D,, Ed.; Kluwer Academic Publishers: Boston, 1989; p 247.
(6) Sammakia, T. S.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998.
(7) This compound was prepared in seven steps from pinacolone. We do not know the relative stereochemistry of the product; however, we have prepared both isomers, and they are consistent in their behavior. See supplementary material for details.

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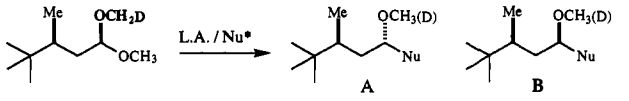
Table 1[a]

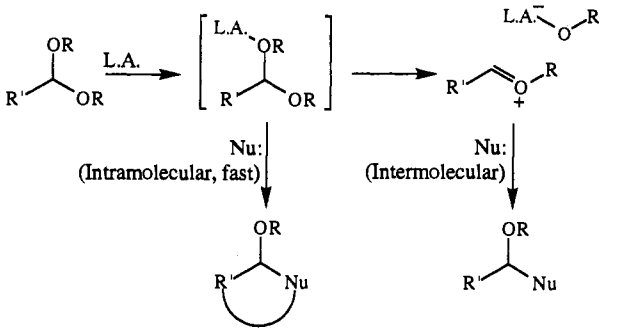


Lewis Acid (Solvent)	Nucleophile	Conversion (%)	Product Ratio (A : B)#	%D-Enrichment‡ (A / B)
TMSOTf (CH_2Cl_2)	$SnBu_3$	84	1.2 : 1.0	38.7 / 39.0 (1)
$TiCl_4$		60	1.0 : 1.2	59.1 / 59.4 (1)
TMSOTf (CH_2Cl_2)	TMSCN	39	1.3 : 1.0	39.6 / 39.6 (2)
TMSOTf (CH_2Cl_2)	OTMS, t-Bu	21	1.3 : 1.0	37.5 / 37.9 (3)
$TiCl_4$		56	1.5 : 1.0	47.9 / 47.9 (3)
$TiCl_4$ (toluene)	OTMS, t-Bu	63	1.3 : 1.0	40.6 / 41.1 (3)

[a] (*) Conditions, TMSOTf: 0.6 equiv of TMSOTf, 5 mol % di-*tert*-butylpyridine, CH_2Cl_2, −78 °C, rapid addition. $TiCl_4$: 0.4 equiv of $TiCl_4$, CH_2Cl_2, −78 °C, rapid addition. (#) The product ratio could be **B**:**A** rather than **A**:**B** since the stereochemistry of the products has not been determined. (‡) Deuterium enrichment values are corrected for the percent deuterium in the starting acetal. (1) Starting acetal contained 82.3% D incorporation; (2) starting acetal contained 89.4% D incorporation; (3) starting acetal contained 93.0% D incorporation.

identical amount of deuterium incorporation is observed in the two diastereomeric products.[9] Consequently, we do not observe a change in mechanism upon changing the Lewis acid. Furthermore, this result is not consistent with S_N2 reactivity and implies that the reaction is proceeding via an oxocarbenium ion intermediate. We therefore conclude that, under the ordinary conditions of intermolecular additions to acetals, the reaction occurs by an S_N1 mechanism via an oxocarbenium ion intermediate.

Scheme 5



The different outcomes of our study and the Denmark study can be understood in terms of a difference in the fate of the Lewis acid–ether complex for the two substrates (Scheme 5). The overall mechanism of the reaction is determined by the difference in the rate of nucleophilic displacement of this complex versus the rate of dissociation to the oxocarbenium ion. It is likely that the rate of dissociation is similar for the two studies; however, the rate of addition is almost certainly faster in Denmark's study due to the intramolecular nature of his reaction. It therefore appears that rapid cyclization reactions can proceed by an S_N2 pathway while slower, intermolecular reactions proceed by an S_N1 pathway. Further studies that test this hypothesis are in progress.

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Supplementary Material Available: Experimental data for the preparation and reactions of **1** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) Mori et al. have also obtained indirect evidence for an S_N2 mechanism in intermolecular additions to acetals using $TiCl_4$ as the Lewis acid and silyl enol ethers as the nucleophiles in toluene (see ref 4b). We have reproduced their conditions in our study with our deuterated substrate and found that the reaction is not consistent with S_N2 reactivity and is consistent with S_N1 reactivity.

(9) In all cases shown, we have recovered the unreacted starting material from the reaction mixture and observed less than 10% isomerization. In some cases, the starting material isomerized more rapidly than the reaction. This occurred with TMSOTf and boron trifluoride etherate catalyzed addition of allyltrimethylsilane. Results with these systems are therefore invalid and are not included.