Nucleophilic Substitution

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Participation of Alkoxy Groups in Reactions of Acetals: Violation of the Reactivity/Selectivity Principle in a Curtin–Hammett Kinetic Scenario**

*Angie Garcia, Jillian R. Sanzone, and K. A. Woerpel**

Abstract: *Nucleophilic substitution reactions of acetals having benzyloxy groups four carbon atoms away can be highly diastereoselective. The selectivity in several cases increased as the reactivity of the nucleophile increased, in violation of the reactivity/selectivity principle. The increase in selectivity with reactivity suggests that multiple conformational isomers of reactive intermediates can give rise to the products.*

Neighboring-group participation[1] is a powerful strategy for controlling the stereochemical outcomes of acetal substitution reactions. This approach is used extensively in carbohydrate chemistry, where a substituent at the 2-position, usually an acyloxy group, controls the stereochemical configuration of substitution.[2–4] An acyloxy group can form a fused ring system resembling **1** (Figure 1), and opening of the five-membered ring by a nucleophile installs the nucleophile *trans* to the participating group.[2,5] Acyloxy groups at remote positions can also exert influences on stereoselectivity.[6–10] By contrast, participation by an alkoxy group via an oxonium ion is not generally considered to occur.[10–15]

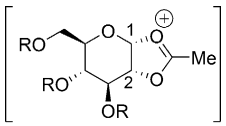

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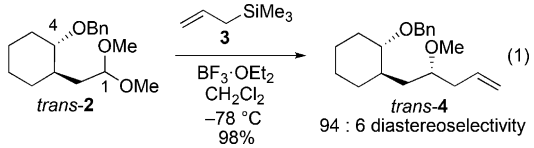
Figure 1. Participation of an acyloxy group at C2 of a carbohydrate.

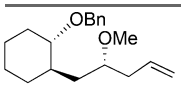
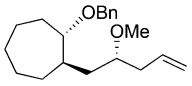
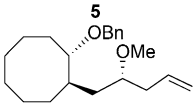
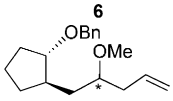
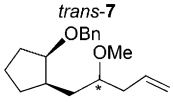
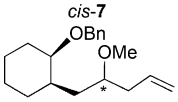
Herein, we demonstrate that an alkoxy group, positioned to form a five-membered ring as in the oxonium ion **1**, can control the stereochemical course of nucleophilic substitution reactions of an acetal.[16–18] These reactions exhibit an atypical trend for acetal substitution reactions:[19,20] as the reactivity of the nucleophile increased, selectivity increased, in direct opposition to the reactivity/selectivity principle, a frequently misapplied concept.[21] We provide evidence that selectivity can increase as reactivity increases if the product can be formed by reactions of multiple reactive intermediates.

Consistent with their ability to accelerate ionization of acetals,[22,23] alkoxy groups exert considerable control on the stereoselectivity of nucleophilic substitution reactions of acetals. Treatment of the alkoxy-substituted acetal *trans*-**2** with allyltrimethylsilane (**3**) and a Lewis acid gave the product *trans*-**4** with high selectivity [Eq. (1)]. The yield was highest using $BF_3{\cdot}OEt_2$ as the Lewis acid in CH_2Cl_2, although the use of other Lewis acids ($TiCl_4$, $SnCl_4$, Me_3SiOTf) and solvents (toluene, MeCN) gave similar results.



The allylations of related acetals proceeded with a range of selectivities. The data in Table 1 represent those stereoselectivities and the relative rates of hydrolysis of the acetals, which indicate the extent of interaction of the benzyloxy group with the acetal during ionization. The stereochemical

Table 1: Diastereoselectivities for acetal substitution reactions similar to that in Equation (1).

Allylation product	Relative rate of acetal hydrolysis[a]	Diastereoselectivity[b]
 *trans*-**4**	1.0	94:6
 **5**	2.0	87:13
 **6**	2.5	82:18
 *trans*-**7**	0.04	72:28[c]
 *cis*-**7**	0.23	64:36
 *cis*-**4**	0.38	55:45

[a] Rates of acetal hydrolysis[22,23] relative to that of the acetal *trans*-**2**. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by ^{13}C NMR spectroscopy.[28]

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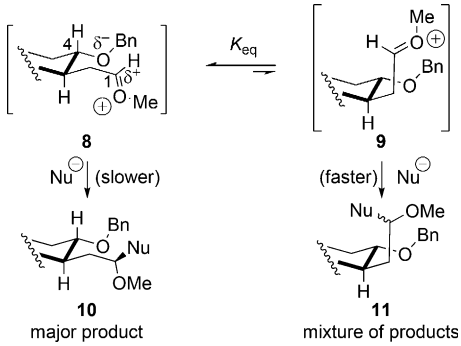
configuration of alkenes *trans*-**4** and **6** were established by X-ray crystallographic analysis of derivatives,[24] but all efforts to obtain crystalline products from the alkene **5** were unsuccessful. The assignment of stereochemistry for **5** was made by analogy to the alkenes *trans*-**4** and **6**, so it is tentative. The stereochemical configurations of the other products were not assigned.

The results presented in Table 1 can be understood by considering the structures of the relevant oxocarbenium ion intermediates (**8**; Scheme 1). The alkoxy group at C4, which bears partial negative charge, would approach the partially



Scheme 1. Origin of stereoselectivity with weaker nucleophiles.

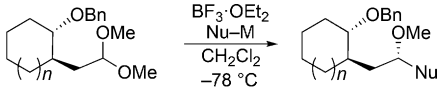
positively charged carbon atom (C1) in this cation.[25] The substrates that showed close interactions between the benzyloxy group and the acetal carbon atom, based upon their rates of ionization,[22,23] would position those two groups relatively close to each other. Nucleophilic attack on **8** from the more accessible front face would lead to the major product **10**.[26]

Selectivity of substitution would depend upon how much the benzyloxy group stabilized the oxocarbenium ion. If there were little interaction between the benzyloxy group and the acetal carbon atom, the oxocarbenium ion would be far from the benzyloxy group, so little facial discrimination would be expected.[27] The low selectivities for the formation of the alkenes *cis*-**4**, *trans*-**7**, and *cis*-**7** (Table 1) result from that relatively small interaction.[22,23]

The observation of lower selectivity when the interaction between the two groups was large, as observed for the acetals leading to the products **6** and **7**, can be explained by considering that the product is formed from more than one reactive intermediate. The stabilized form of the oxocarbenium ion **8** (Scheme 1) would react more slowly with nucleophiles than a less stabilized form,[29] so reaction could occur through higher-energy conformational isomers of the oxocarbenium ion,[30] in accord with the Curtin–Hammett principle.[31] Those conformational isomers in which electrostatic stabilization is weaker, such as in **9**, would react more rapidly, and because the benzyloxy groups and oxocarbenium ion are further apart in these conformers, the faces of the cation are not as well differentiated.

Table 2 indicates that substitution reactions can be highly diastereoselective for alkoxy-substituted acetals.[32] The major stereoisomers in all cases possess the same stereochemical configurations as the products shown in Table 1.[24] The

Table 2: Diastereoselectivities for acetal substitution reactions.[a]



n = 1, *trans*-**2**
n = 2, **12**
n = 3, **13**

M = $SiMe_3$, $SnBu_3$

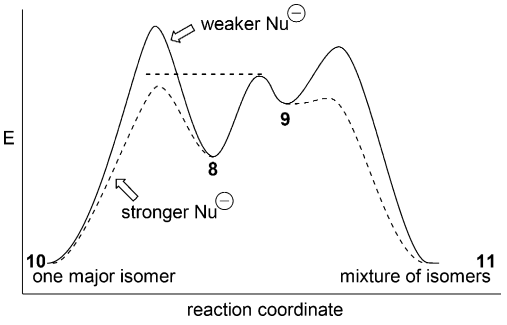
n = 1, **14**
n = 2, **15**
n = 3, **16**

Nu-M	*N*[b]	**14**	**15**	**16**
$SiMe_3$ **3**	1.8	94:6	87:13	82:18
$OSiMe_3$ *t*Bu **17**	3.8	–	96:4	96:4
$SiMe_3$ Me **18**	4.4	≥97:3	≥97:3	≥97:3
$SnBu_3$ **19**	5.5	≥97:3	≥97:3	94:6
$OSiMe_3$ Ph **20**	6.2	≥97:3	≥97:3	≥97:3

[a] Determined by ^{1}H NMR spectroscopy. Yields of isolated products are within the 60–90% range. [b] Higher nucleophilicity parameters (*N*) correspond to more reactive nucleophiles.[29]

general increase in selectivity as the reactivity of the nucleophile increases is opposite to what has been observed in systematic studies of other acetal substitution reactions,[19,20] although some substitutions exhibit similar patterns.[27,33–35]

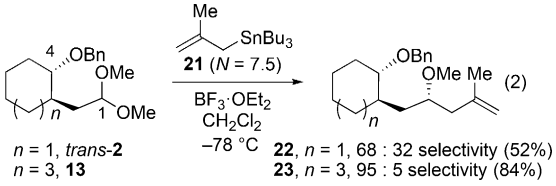
The trend of higher selectivity with increased reactivity of the nucleophile is consistent with a kinetic scenario where two forms of a reactive intermediate can lead to product (Scheme 2).[31] With weak nucleophiles, reaction with the more reactive conformer (**9**) would be faster than reactions



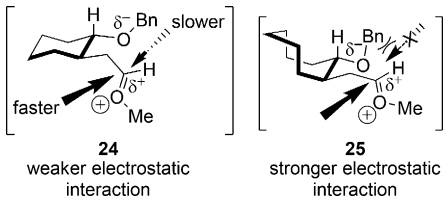
Scheme 2. Reaction coordinate diagram illustrating how selectivity could increase with reactivity. Structures for the compounds can be found in Scheme 1.

with the more stabilized conformer **8** (solid line in Scheme 2). When strong nucleophiles are used (dashed line), however, the more stabilized intermediate **8** could react with the nucleophiles directly. The major conformer **8**, as noted above, exhibits better discrimination between the two diastereotopic faces of the electrophile than the higher-energy conformer **9**, so selectivity would increase with increased reactivity.

Additional studies using a highly reactive nucleophile also suggest that the products would be formed from multiple reactive intermediates. Substitution reactions with methallyltributylstannane (**21**)[29] resulted in diverging stereoselectivities. Whereas the stereoselectivity with the cyclohexane-derived acetal *trans*-**2** decreased, the selectivity for the eight-membered ring acetal **13** remained high [Eq. (2)].



The difference in selectivity shown in Equation (2) can be understood by considering how the stability of an oxocarbenium ion influences its reactivity. With a highly reactive nucleophile, the products would be formed exclusively from the lower-energy oxocarbenium ion (Scheme 2). The cyclohexane-derived oxocarbenium ion **24** involves weaker interactions between the benzyloxy group and the cationic carbon atom when compared to that of the cyclooctane-derived ion **25** (Scheme 3). Computational studies on these oxocarbenium ions reveal that the distance between the oxygen atom of the



Scheme 3. Stabilization of the oxocarbenium ion and consequences for stereoselectivity.

benzyloxy group and the cationic carbon atom are longer for **24** (1.99 Å) than for **25** (1.61 Å).[23] As a result, the back face of **24** is accessible, although attack from this face should be slower because it is more sterically hindered. As the rates of nucleophilic attack on **24** increase with strong nucleophiles,[19] selectivity should decrease because the rate of addition from both faces would increase asymptotically to the diffusion rate limit.[21] By contrast, the back face of **25** is much more sterically hindered because of the close interaction between the benzyloxy group and the oxocarbenium ion carbon atom, so attack from this face would be prohibitively slow. The increased stabilization of **25** relative to **24** also suggests that the rate of addition would remain below the diffusion rate limit, so reactions would continue to be selective even with highly reactive nucleophiles.

In conclusion, an alkoxy group can control the stereochemical course of substitution reactions of acetals, in many cases with greater than 97 % diastereoselectivity. Electrostatic stabilization is strong enough to form a structure which can be trapped by nucleophiles to give products with high diastereoselectivity. The observation of increased selectivity with increased reactivity suggests that the products were formed from multiple conformational isomers of the reactive intermediates, thus leading to inverse correlations of reactivity and selectivity.

Keywords: allylic compounds · carbocations · nucleophilic substitution · synthetic methods · through-space interactions

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