ORGANIC LETTERS

2008
Vol. 10, No. 17
3769−3772

Origin of Stereoselectivity in the Reduction of a Planar Oxacarbenium

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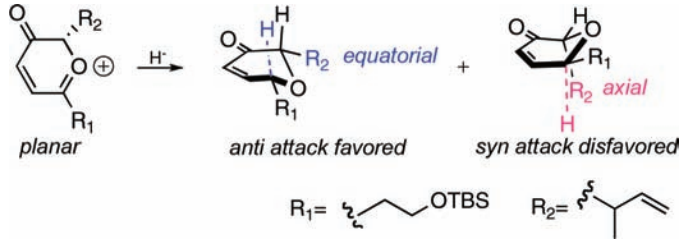
Received June 23, 2008

ABSTRACT

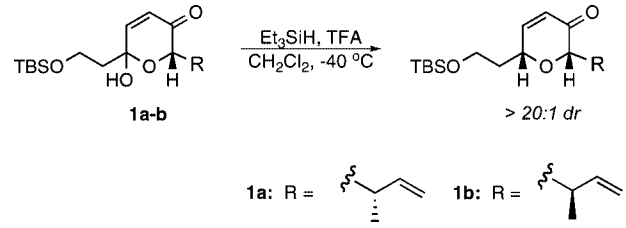


The Kishi reduction of a planar oxacarbenium was investigated theoretically. The high diastereoselectivity for hydride transfer to the oxacarbenium intermediate is attributed to the conformation of the transition state that places the allyl side chain in an equatorial position in the major transition state and axial position in the minor. The minor transition state is destabilized by a 1,3-diaxial strain between the attacking hydride and the *syn* allyl side chain.

One of our groups recently reported an efficient synthesis of two pyranopyran subunits of norhalichondrin B.[1] A highlight of the assembly is the remarkably diastereoselective Kishi reduction[2] of hemiacetals **1a** and **1b** (Scheme 1).

Diastereoselective nucleophilic addition to saturated glycosides has been explained on the basis of anchimeric assistance[3] (**2**, Scheme 2) as well as selective *anti* addition to the favored ground-state conformation of **3** (Scheme 2).[4] However the greater than 20:1 diastereoselectivity obtained in the reduction of pyrananone **1**, which does not bear such directing groups, cannot be explained by these models. We now report a computational investigation that provides an explanation for the high reduction selectivity observed. All structures were computed in the gas phase using density functional theory B3LYP[5] with the 6-31G(d)[6] basis set as implemented in the Gaussian 03[7] suite of programs. All stationary points were verified as minima or first-order saddle points by vibrational

Scheme 1



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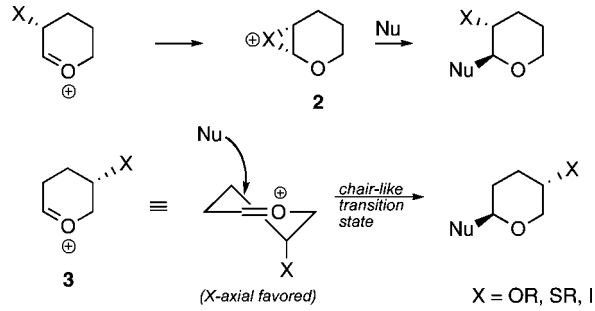
10.1021/ol801421n CCC: $40.75
Published on Web 07/23/2008

Scheme 2



frequency analysis.

Evidence strongly suggests that the reductions of hemiacetals **1a** and **1b** proceed through discrete oxacarbenium ions. The hemiacetals are formed as a mixture of diastereomers ranging from 3:1 to 9:1 dr, while subsequent reduction yields material with greater than 20:1 diastereoselectivity. If the reaction were to proceed via an S_N2 mechanism or ion pairs in which one face is shielded by the leaving group, one of the hemiacetal diastereomers must be selectively destroyed, which is unlikely (although not impossible). Crich and co-workers have performed work which also provides evidence that the transition states for glycosylation reactions have high oxacarbenium character.[8]

Oxacarbenium **4** (Figure 1) was used to model the oxacarbenium intermediates obtained from **1a** and **1b**. The

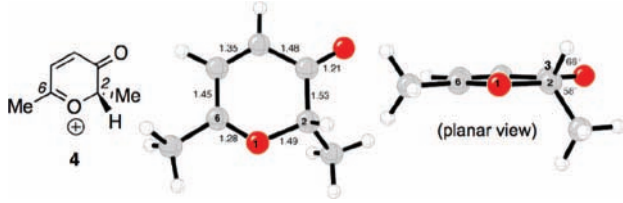


Figure 1. Modeled oxacarbenium **4**.

optimized structure of **4** is found to have a nearly perfectly planar six-membered ring. Starting from a variety of nonplanar geometries, calculations always converged to the planar conformation shown in Figure 1. The torsion angles around every ring bond are less than 1°, and a Newman projection along C2−C3 shows nearly perfect staggering around this bond.

Attempts to locate transition structures for reaction of **1a**,**b** with SiH_4 resulted in proton abstraction from the oxacarbenium ion. To model the attack of hydride on **4**, the energy was scanned as a function of the forming C−H distance (Table 1).[9] Because the free energy difference

Table 1. Energy vs C−H Distance

	anti (major)			*syn* (minor)		
C−H		G_{rel}	H_{rel}		G_{rel}	H_{rel}
1.11	(**5**)	0.0	0.0	(**6**)	1.5	1.5
1.21	(**7a**)	2.2	1.9	(**8a**)	3.9	3.6
1.31	(**7b**)	7.5	7.2	(**8b**)	9.4	9.0
1.41	(**7c**)	14.2	13.9	(**8c**)	16.2	15.9
1.51	(**7d**)	21.3	20.8	(**8d**)	23.5	23.0
1.61	(**7e**)	29.0	28.5	(**8e**)	31.2	30.7
1.71	(**7f**)	36.0	35.6	(**8f**)	38.3	37.8
1.81	(**7g**)	42.4	42.0	(**8g**)	44.7	44.2
1.91	(**7h**)	48.1	47.7	(**8h**)	50.4	49.9
2.01	(**7i**)	53.1	52.8	(**8i**)	55.3	54.9
2.11	(**7j**)	57.5	57.2	(**8j**)	59.6	59.3
2.21	(**7k**)	61.4	61.2	(**8k**)	63.4	63.1
2.31	(**TS1**)	64.9	64.8	(**TS2**)	66.7	66.5

between attack from the favored and disfavored faces remains constant throughout the bond scan (approximately 2 kcal/mol), it is reasonable to conclude that the same factors which cause this energy difference also account for the selectivity observed in the transition state. One imaginary frequency for hydride transfer to **4** first appeared at a distance of 1.51 Å for both the major (**7d**) and minor (**8d**) faces of attack and continued through distances of 2.31 Å. Structures optimized at distances greater than 2.31 Å resulted again in proton abstraction from the oxacarbenium. Conformational changes were similar throughout the scan (compare **7d** and **TS1**, and **8d** and **TS2**, Figure 2). The geometries obtained at 2.31 Å were selected as representative transition structures for the *anti* and *syn* attacks. These structures are represented as **TS1** and **TS2**, respectively (Figure 2).

The C2 substitutent that is *syn* to the attacking hydride—H in **TS1** and methyl in **TS2**—adopt axial positions. To investigate the origin of this conformational change, the transition structure for hydride transfer to unsubstituted oxacarbenium **9** was modeled (**TS3**, Figure 3). Like oxacarbenium **4**, model **9** optimizes to a planar geometry. And like **TS1** and **TS2**, the C2 substituent that is *syn* to the attacking hydride (hydrogen) becomes axial in **TS3**.

The transition-state conformation results from the well-known fact that nucleophiles favor *anti* addition to p-bonds. This has been found for alkenes and alkynes (Scheme 3),[10] and the preference arises to maintain maximum (*anti*) overlap of the orbitals corresponding to the π orbitals of the reactant.

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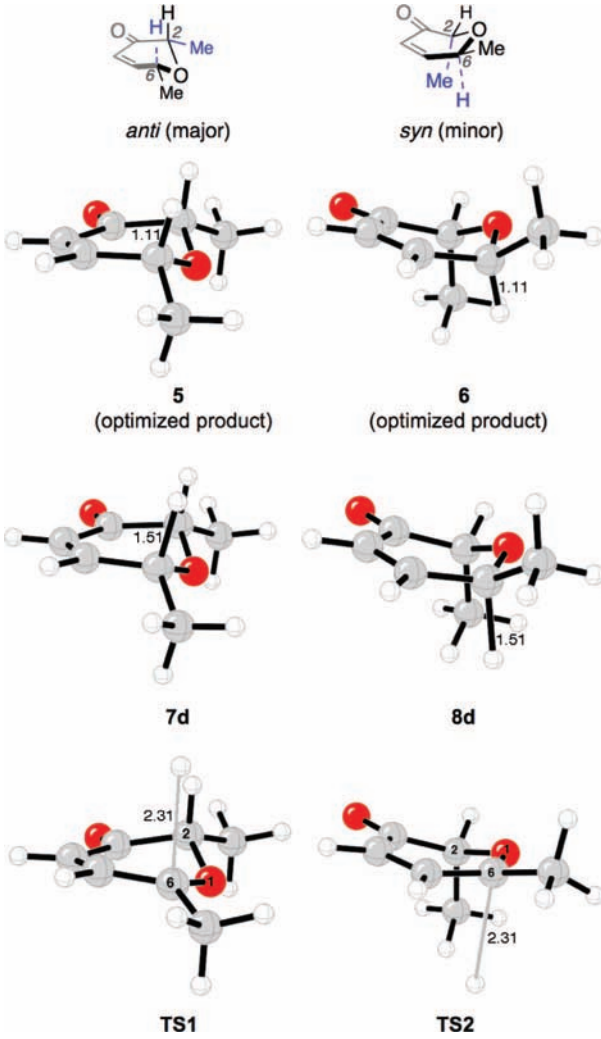


Figure 2. Reduced pyranones **5** and **6** and select structures for hydride attack on **4**.

In the case of **TS3**, hydride attack on C6 of **TS3** occurs *anti* to a developing lone pair of the ring oxygen (Figure 4). There is staggering of bonds to C2 with respect to lone pairs on the ring oxygen, causing a 1,3-diaxial relationship between

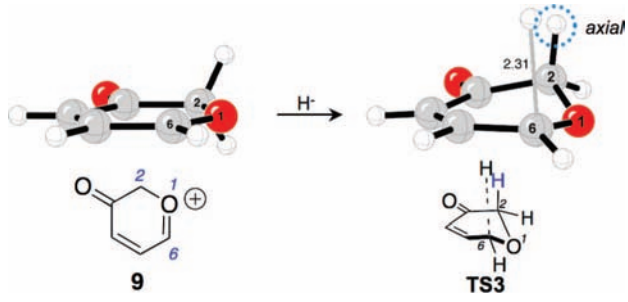
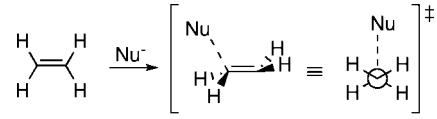


Figure 3. Unsubstituted oxacarbenium and transition-state model for hydride attack.

Scheme 3



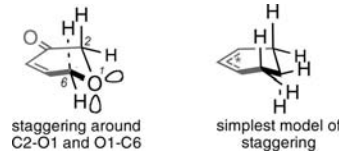


Figure 4. Staggering models.

the hydride and the *syn* C2 substitutent. In other words, hydride attack occurs with optimal staggering around the C2−O1 and O1−C6 bonds.

Applying this model to the reduction of **4**, favored transition structure **TS1** shows perfect staggering, with the C2 methyl in an equatorial position (Figure 5). By contrast,

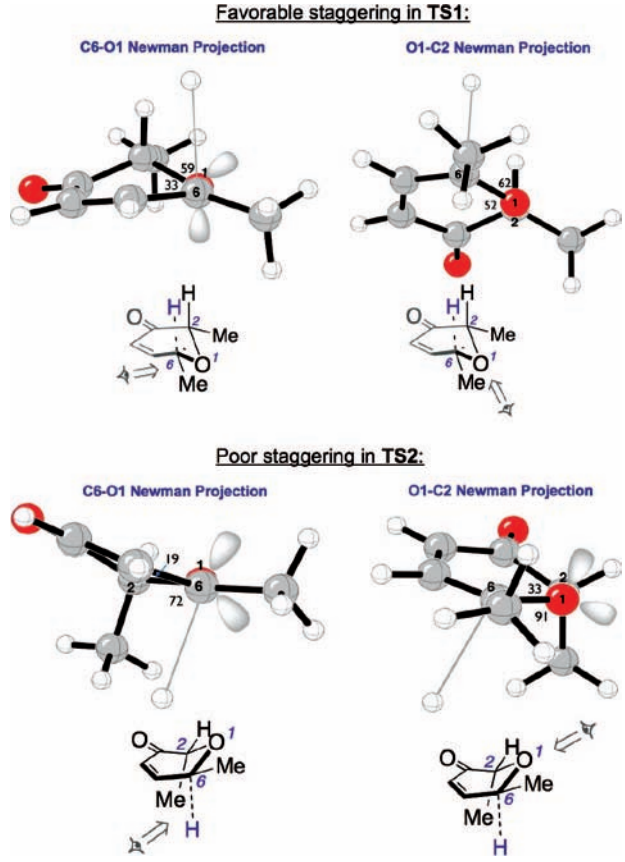


Figure 5. Staggering along C6−O1 and O1−C2 in **TS1** and **TS2**.

TS2 is distorted away from the ideal geometry because it must overcome very large 1,3-diaxial interaction between

the axial methyl group and the forming C−H bond (Figure 6). A related structure is 2-methyltetrahydropyran in which

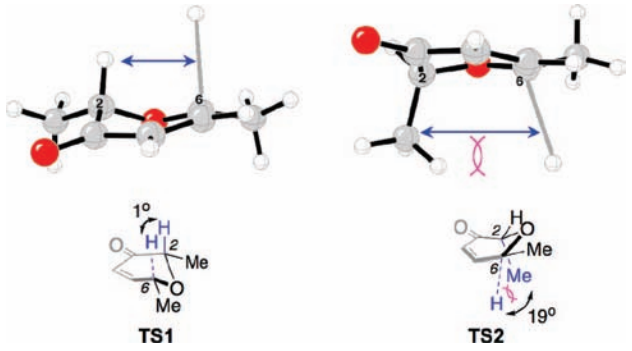


Figure 6. Repulsion between hydride and C2 methyl group in disfavored **TS2**.

the axial-methyl conformer is 2.9 kcal/mol less stable than the equatorial.[11] Boons and co-workers have shown that the glycosylation of arabinofuranosyl oxacarbenium ions also favors a staggered mode of nucleophilic attack.[12] It is remarkable that our oxacarbenium ions, which do not bear the ground-state steric or torsional effects noted by Boons, react with such high diastereoselectivity.

To determine the effect of the pyranosyl ring conformation changes on the energies of **TS1** and **TS2**, single-point energy calculations were performed on the frozen transition structures with the hydride removed. In the absence of hydride, the oxacarbenium ion geometry in **TS1** is disfavored by 3.7 kcal•mol^{-1}, presumably due to favorable C2-Me and C6-cationic interactions in the **TS2** geometry.

In conclusion, the oxacarbenium intermediate of the Kishi reduction is planar but becomes staggered around the C2−O1 and O1−C6 bonds in the transition state. This places the allyl side chain in an axial position for *syn* attack. This is less stable than the *anti* attack, where the allyl side chain is equatorial.

The preference for staggering in this case further extends the role of torsional steering in the control of stereoselectivity.[13]

Acknowledgment. We are grateful to the National Institute of General Medical Sciences, National Institutes of Health (G36700, K.N.H.), and the National Cancer Institute (CA110246, A.J.P.) for support of our work.

Supporting Information Available: Cartesian coordinates and energies of all reported structures and full authorship of ref.[7] This material is available free of charge via the Internet at http://pubs.acs.org.

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