Deuterium-isotope study on the reductive ring opening of benzylidene acetals†

I-Chi Lee, a Medel Manuel L. Zulueta, a,b Chi-Rung Shie, a Susan D. Arco b and Shang-Cheng Hung**a,c

Received 30th June 2011, Accepted 18th August 2011
DOI: 10.1039/c1ob06056b

Specific deuterated reference compounds were prepared to probe the stereoselectivity of the reductive ring opening of carbohydrate-based benzylidene-type acetals. AID3 revealed a retentive stereoselectivity probably through the rare SNi (internal nucleophilic substitution) mechanism. An SN1-like mechanism occurs in the acid-promoted regioselective BD, THF- or Et3SiD-reductive ring opening.

Regioselective protections of multiple hydroxyls are obligatory steps in the chemical synthesis of complex carbohydrates and natural products.1 Here, the readily installed and easily manipulated benzylidene-type acetals gained immense importance and widespread use. These base-resistant yet acid-labile functionalities are typically used to block 4- and 6-hydroxyls of hexopyranoses as well as vicinal cis-diols to give fused 1,3-dioxane and 1,3-dioxolane backbones, respectively. Aside from protecting two hydroxyl groups simultaneously, they also exhibit significant influence on the stereochemical outcome of chemical glycosylations.2 Another highly useful advantage is their capability to be reductively opened in a regioselective manner exposing a free hydroxyl and a benzyl-type ether enabling the opportunity for further transformations.

The LiAlH4 and AlCl3 combination is the first reagent set used in the reductive ring opening of cyclic acetals.3 They generate, depending on mixing proportions, the alane species (i.e. AlHCl2, AlH2Cl and AlH3) that participate in the actual hydride transfer.4 In the case of 4,6-O-benzylidene-type acetals, the ring opening mediated by alanes occurs at the less hindered and more basic 6-O forming the 4-O-benzyl-type derivative (Scheme 1).5 Not surprisingly, this regioselectivity is also shared by i-Bu3AlH.6 The NaN3BH5/HCl tandem, later introduced by Garegg, notably favoured the opposite regioselectivity—the ring opening at the 4-O position.7 In the case of the fused 1,3-dioxolanes, both the alanes and NaCNBH3/HCl gave identical regioselectivity in the benzylidene acetal cleavage that is dependent on the stereochemical orientation of the aromatic group.8 The so-called 3X (eXo gives a Xial hydroxyXyls) rule of thumb9 was realized as a general tendency during the openings of these 5-membered rings. Cleavage of the 1,3-dioxolanes was also found possible in the presence of the 6-membered counterpart.9 Over the years, a number of boron-,10 silicon-,10h,11 and tin-based12 hydride reagents in combination with a similarly diverse set of Lewis and Brønsted acids were introduced and applied to reductively open benzylidene-type acetals. Variations in hydride source, ligand, temperature, solvent and the accompanying acid displayed profound effects on the regioselectivity of the ring opening.

The mechanistic aspects of the acid-mediated nucleophilic addition to cyclic acetals resulting in ring opening have been widely investigated. Regioselectivity rests on the stability of the initial complex between the acid and the acetal oxygens and the relative acid strengths of the Lewis acid and ligand on the relative acid strengths of the Lewis acid and ligand.13 Due to insufficient evidence,13 due to insufficient evidence at the time. Recent reports highlighted the influence of solvent and ligand on the relative acid strengths of the Lewis acid and the reducing agent, which subsequently determines the regio- and stereoselectivity of the ring opening.13

Scheme 1 Representative examples of the reductive ring opening of benzylidene acetals.
In our preliminary isotope study, the benzylidene acetal in compound 1 was regioselectively opened using either BD₃·THF or Et₃SiD both catalysed by Cu(OTf)₂. Based on the NMR analysis of the products, BD₃·THF generated a deuterated 4-O-benzyl derivative with a 5:1 diastereomeric ratio whereas Et₃SiD formed the deuterated 6-O-benzyl counterpart with apparent stereorandomization (i.e. 1:1 ratio of diastereomers). The NMR data gathered, however, was inadequate to fully distinguish the configuration of the isomers. Overall, the stereoselective inclinations of the reducing ring opening of benzylidene-type acetals remain highly speculative without the full confirmation of the structure of the deuterated products.

Analysis of the NMR spectra alone cannot be used to ascertain the absolute structure designation of deuterated products in the reductive ring opening of carbohydrate-based benzylidene acetals. We, therefore, decided to synthesize deuterium-labelled reference compounds to probe the stereoselectivity of the nucleophilic attack on the acetal carbon (Scheme 2). The preparations made use of the deuterated tosylate 6 as benzylating reagent via Williamson etherification. An approximately 30% ee compound has been reported which is not appropriate for our study. Alternatively, (S)-(+)-benzyl-α-δ alcohol, generated by the enantioselective reduction of PhCDO with (R)-alpine borane (reportedly attainable in 96% ee), was tosylated to provide the desired 6. Considering the possible ring openings of a 4,6-O-benzylidene acetal and the ring cleavage of a 2,3-O-benzylidene with an exo-oriented phenyl group, the alcohols 7,8 and 9 were treated with 6, and NaH to generate the deuterated benzyl ethers 10 (64%), 11 (78%), and 12 (86%), respectively. Desilylation of 10 with tetra-n-butyrammonium fluoride (TBAF) furnished the target 6-O-ring opening reference compound 13R in 95% yield. Subsequent cleavage of the 2-naphthylmethyl (2-NAP) and p-methoxybenzyl (PMB) groups of compounds 11 and 12 gave the individual reference alcohols 14R (95%) and 15R (93%), respectively. All the reference compounds are expected to carry the deuterated carbon in the R-configuration.

The 6-O-ring opening of compound 1 was carried out using AlD₃ or BD₃·THF as deuteride source. Inversion of configuration at the acetal carbon would result in the 6-alcohol 13R whereas retention would lead to 13S (Fig. 1). Comparison with the 1H NMR spectrum of the undeuterated 6-alcohol 2 identified the 4-O-benzyl proton of our reference compound (13R) at around 4.61 ppm. The product of AlD₃ treatment only showed a very minor signal for 13R with a significant peak, ascribed to the 4-O-benzyl proton of 13S, appearing at 4.86 ppm. The reaction is highly stereoselective (13R/13S = 6/94) providing compelling evidence for a retentive deuteride addition. In previous papers, we reported the benzylidene 6-O-ring opening in compound 1 with BH₃·THF catalysed by various metal triflates in excellent yields. Examination of the stereoselectivity of the BD₃·THF-mediated transformation in tandem with some selected metal triflates as well as TMSOTf revealed notable similarities in the 13R/13S ratios (approx. 1/5). Stereochemo retention is favoured but inversion is more pronounced in contrast to that of AlD₃. The proportion of the diastereomers also appears to be independent of the quantity of added Lewis acid as shown for TMSOTf (0.5 equiv versus 1.1 equiv).

The 4-O-ring opening of the benzylidene acetal in compound 1 was then carried out using Et₃SiD in the presence of Cu(OTf)₂, BF₃·Et₂O, or CF₃COOH. In this transformation, the reference compound 14R corresponds to retentive substitution whereas 14S represents inversion. The identified signal relating to the 4-O-benzylic proton of our reference compound (14R) in comparison to that of the 4-alcohol 3 appears at 4.50 ppm. As illustrated in Fig. 2, the diastereomers 14R and 14S are generated in nearly equal amounts in all cases (14S is measured from the resonance...
The data clearly demonstrates stereorandomization that is independent of the nature of the acid used.

The stereoselectivity of the ring opening of the 1,3-dioxolane in compound 16 was next probed (Fig. 3). With the exo orientation of the phenyl ring, the reductive ring opening is predicted to favor the formation of the 2-alcohol \([17]^{1b}\) instead of the 3-alcohol counterpart. Thus, the diastereomers \(15R\) (retentive reduction) and \(15S\) (inversive reduction) are the possible products upon reduction with \(\text{AlD}_3\). The resonance at 4.71 ppm, indicated by the reference compound (\(15R\)), fully coincides with the major peak of the ring-opening product. Comparison with the minor signal at around 4.86 ppm attributed to \(15S\) (in reference to the \(^1\)H NMR spectrum of compound 17) gave a 91/9 ratio (\(15R/15S\)) clearly favoring the retentive introduction of the deuteride.

With the reference compounds and their corresponding \(^1\)H NMR data, the stereoselectivity of the reductive ring opening of benzylidene acetals is now evident. The \(\text{AlD}_3\)-mediated ring opening possesses retentive stereoselectivity for acetals with both 1,3-dioxane and 1,3-dioxolane backbones. By applying our NMR data, the previously reported\(^{1c}\) inversive ring opening of a deuterated derivative of compound 1 with the LiAlH\(_4\)/AlCl\(_3\) tandem was found to agree with our result; the original interpretation was based on a wrong stereochemical assignment. The highly retentive deuteride addition by \(\text{AlD}_3\) led us to suggest the mechanism following the rarely observed internal nucleophile substitution (\(S_{\text{NI}}\)). As depicted in Scheme 3, \(\text{AlD}_3\) weakly coordinates with the less hindered and more nucleophile 6-O and subsequently transfers a deuteride to the acetal carbon on the same side of the departing 6-O. The same mechanism is also expected for the reductive ring opening by \(i\)-BuAlH. The BD\(_3\)-THF cleavage of the benzylidene acetal also displayed a preference for a retentive deuteride addition with relatively minor inversion. Together with the requirement for a Lewis acid, the NMR data precludes the \(S_r,2\)-like substitution suggested for intimate ion pairs\(^{1c,15c}\) or a mechanism similar to that of \(\text{AlD}_3\). We propose that the acid complexation with 6-O generated a separated ion pair with an oxocarbenium ion involving O-4. The stereochemical bias is probably caused by asymmetric induction of the nearby chiral center (4-C of the sugar) leading to more retention rather than inversion. The reduction carried out by \(\text{Et}_3\text{SiD}\) together with an acid appears to include an oxocarbenium ion intermediate. Full stereorandomization suggests deuteride addition in an \(S_{\text{NI}}\)-like fashion. The acid may in principle interact with either acetal oxygen granting more preference for 6-O; but, in this case, the resultant 4-O-benzyl cation cannot be reduced as \(\text{Et}_3\text{SiD}\) is bulky and not very reactive. On the other hand, the silane can readily approach either side of the 6-O-benzyl cation formed by the initial acid complexation with 4-O.

In conclusion, the deuterated reference compounds we prepared were successfully utilized to clarify the stereoselectivity of the reductive benzylidene ring opening. The data we presented can supplement further selectivity and mechanistic analysis of this type of reaction.

**Acknowledgements**

This work was supported by the National Science Council (NSC 97-2113-M-001-033-MY3, NSC 98-2119-M-001-008-MY2, NSC 98-3112-B-007-005, NSC 98-2627-B-007-008) and Academia Sinica.
Notes and references


20 Subsequent NMR analysis of the corresponding benzylic proton of compound 14R gave a diastereomeric ratio of 97/3. This would translate to an enantiomeric excess of 94% for compound 6 ignoring any possible racemization during the predicted inversive etherification step.