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Dissecting the Influence of Oxazolidinones and Cyclic Carbonates in Sialic Acid Chemistry[**]

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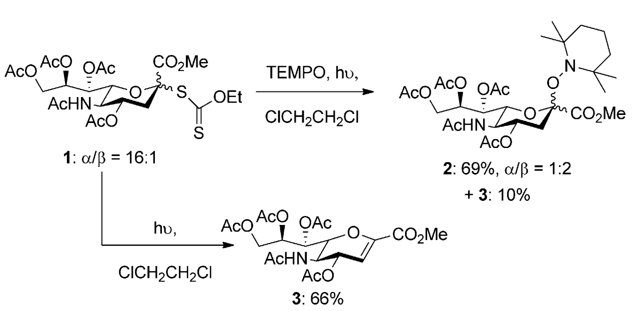
Dedicated to Professor William B. Motherwell

Protecting groups play major roles in carbohydrate chemistry and serve, in addition to blocking hydroxy groups, as modulators of reactivity and as stereodirecting groups in glycosylation.[1] Cyclic protecting groups are prominent in the latter respect and are of current interest.[2] For example, it has been demonstrated that a 2*N*,3*O*-oxazolidinone group strongly favors α- over β-glycosides in the glucosaminopyranosides, that is, it enhances the anomeric effect and facilitates anomerization.[3] In the sialic acids, a 4*O*,5*N*-oxazolidinone both with and without an additional *N*-acetyl group, favors the formation of α-*O*-,[4] *C*-,[5] and *S*-sialosides,[6] and presents the best solution currently available to the challenging problem of α-sialoside formation. The mechanism by which the oxazolidinone group directs stereoselective sialidation is therefore of considerable interest and prompted the efforts described herein.

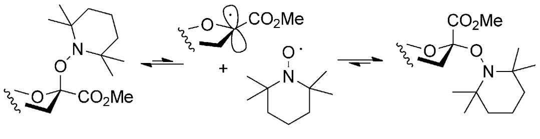
We first investigated the influence of the oxazolidinone ring on the anomeric effect. Studies on the mutarotation of sialosyl hemiacetals were thwarted by the discovery that the oxazolidinone-protected systems exist very significantly in the open-chain keto form, thus reflecting the strain imposed on the cyclic form by the presence of the *trans*-fused oxazolidinone moiety. The equilibration of actual glycosides under acidic conditions[7] was ruled out owing to the lability of the *N*-acetyloxazolidinone system. We turned to the persistent radical effect (PRE) for an alternative means of equilibration at the anomeric center, thus avoiding any ring-opened species.[8] Anomeric radical reactions are well known to give rise to axially quenched products under kinetic conditions,[9] with the notable exception of the sialic acids wherein poor selectivity is found.[10] Conversely, the equilibration of anomeric stereochemistry via radical intermediates is rare[11] and has not been applied explicitly to the study of the anomeric effect.

Attempted synthesis of sialosyl glycosides of 2,2,6,6-tetramethylpiperidine-1-ol (TEMPOL) were fruitless, so we focused on radical approaches to the desired glycosides. The known *S*-sialosyl xanthate **1**[12] was photolyzed in dichloroethane at room temperature in the presence of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO; 20 equiv), thus leading to a 69% yield of the desired TEMPO glycoside **2** as a separable 1:2 mixture of α- and β-anomers (Scheme 1). Resubjecting this mixture to the photolysis conditions did not result in a change in this ratio, thus indicating its kinetic origin. Attempted equilibration of the xanthate itself, by photolysis alone, gave only the glycal **3** in a process reminiscent of the photolytic elimination of thionobenzoate esters (Scheme 1).[13]



Scheme 1. Preparation of the TEMPO sialoside **2**.

A series of standard manipulations of **2** yielded the various protected TEMPO sialosides **4–6** (see Table 1 for structures) as described in the Supporting Information. Dilute solutions (0.05–0.1 M) of the TEMPO sialosides were heated under nitrogen at 90 °C in $ClCD_2CD_2Cl$ with periodic monitoring by NMR spectroscopy until equilibrium was attained (Scheme 2).[14] In this process equilibration takes place by homolytic scission of the anomeric TEMPO C–O bond to give the captodatively stabilized anomeric radical and the persistent radical TEMPO. Because of the PRE, radical combination takes place to give the hetero- rather than any homodimers, thus enabling scrambling at the anomeric center. Because of spin delocalization onto the ester group the anomeric radical is considered to be best represented as a planar sp^2-hybridized carbon center, rather than as the rapidly inverting sp^3-hybridized species found in simple anomeric radicals. In reality the exact nature of the inter-



Scheme 2. Equilibration by the persistent radical effect.

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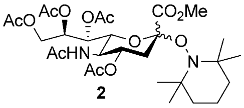
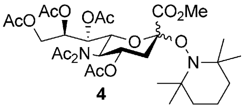
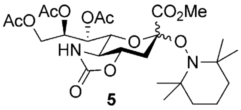
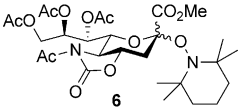
mediate anomeric radical is of no consequence in this thermodynamically controlled process.

From the equilibrium ratios obtained (Table 1) it is apparent that the protecting group array at O4 and N5 influences the magnitude of the anomeric effect.

Table 1: Anomeric equilibrium ratios for TEMPO sialosides.[a]

Entry	Compound	α/β ratio
1	 **2**	3.1:1
2	 **4**	3.9:1
3	 **5**	7.0:1
4	 **6**	6.2:1

[a] Equilibrium ratios were the same within experimental error (± 0.2) irrespective of the anomer used as the substrate.

In all cases studied, the α-glycoside, in which the bulky TEMPO adopts the equatorial position, is preferred (Table 1). This is presumably for steric reasons because in the simple methyl glycoside of the *N*-acetylneuraminic acid methyl ester the β-isomer, with the axial glycosidic bond, is reportedly very highly favored[7] and avoids 1,3-diaxial interactions between the bulky carboxylate and H4 and H6. While steric reasons obviously underlie the overall preference for the α-isomers in the TEMPO sialosides, they do not explain the differences in the anomeric ratios observed across this series of compounds (Table 1). We suggest that they correlate best with the electron-withdrawing ability of the 4*O*,5*N*-protecting group as manifested in its dipole moment with respect to acyclic equivalents (Figure 1).[15]

Among the protecting-groups employed the greatest stabilization of the α-anomer is obtained with the simple 4*O*,5*N*-oxazolidinone, which has the largest dipole moment (Table 1, entry 3; Figure 1). The second highest selectivity in favor of the α-anomer is obtained with the *N*-acetyloxazoldinone protecting group, and is consistent with this protecting group also having a large dipole moment (Table 1, entry 4; Figure 1). In both the oxazolidinone **5** and *N*-acetyloxazolidinone **6** systems the overall dipole moment of the heterocyclic system is aligned parallel to the pyranose C4−O4 and C5−N5 bonds, thereby enhancing their inherent electron-withdrawing ability (Figure 2). This arrangement contrasts with the situation in the simple amide **2**,[7] wherein the carbonyl dipole is aligned approximately orthogonal to the C5−N5 bond (the result of the *trans*-amide conformation and the approximately 180° H5-C5-N5-NH torsion angle with $^{3}J_{\mathrm{NH,H5}} = 10$ Hz). In the *N*-acetyl system **6** the dipole moment of the heterocyclic system is moderated by the presence of the *N*-acetyl group, which preferentially adopts an antiperiplanar conformation with respect to the oxazolidinone carbonyl bond. This conformation is known for imides in general and is seen in X-ray crystallographic analyses of derivatives of **6**,[4c] and moderates the influence of the oxazolidinone.

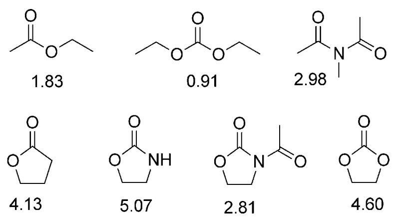


Figure 1. Dipole moments (Debye units) of open chain and cyclic carbonyl functionalities in nonpolar solvents.

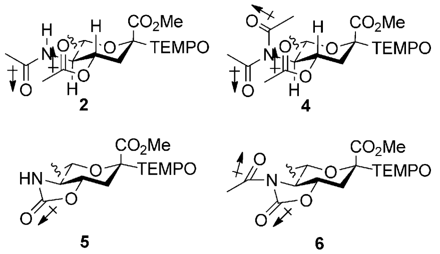
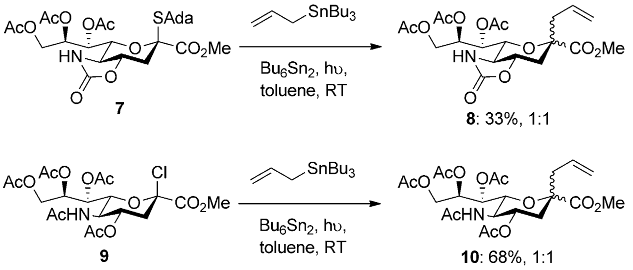


Figure 2. Orientations of the key O4 and N5 protecting-group carbonyl dipole moments in the TEMPO sialosides (side chains omitted for clarity).

To probe the influence of the oxazolidinone ring on the kinetic selectivity of the 2-sialyl radical, the thioglycoside **7**[4d] was photolyzed at room temperature in toluene in the presence of hexabutyldistannane and allyl tributylstannane,[16] leading to a 33 % yield of a 1:1 mixture of the known[5] *C*-glycosides **8** (Scheme 3). This lack of selectivity mirrors that observed upon reaction of the sialyl chloride **9** with allyl tributylstannane under similar reaction conditions (Scheme 3).[10] Clearly, the oxazolidinone ring has no significant influence on the face selectivity of the 2-sialyl radical under kinetic conditions, that is, the presence of the oxazolidinone does not bias the pyranose ring toward reaction on either one of its two faces.

As there is no reason to consider that the putative 2-sialyl oxocarbenium ion **11** adopts a conformation other than that



Scheme 3. Lack of influence of the oxazolidinone on the kinetic selectivity of the 2-sialyl radical.

of the 2-sialyl radical **12** in the presence of the conformationally locking oxazolidinone ring (Figure 3), and as the reactions of glycosyl oxocarbenium ions are exothermic with early transition states,[17] we deduce that reactions of the oxocarbenium ion **11** would show a lack of face selectivity similar to that of the radical **12**.

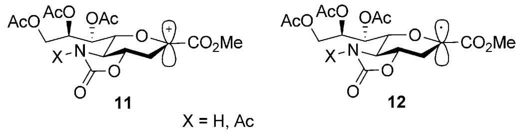
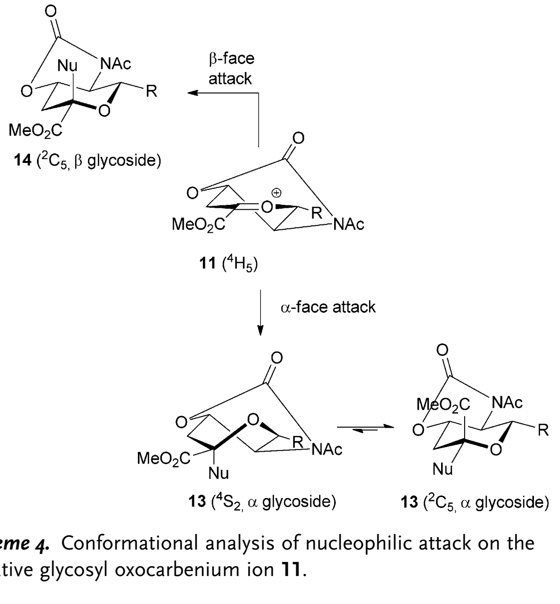


Figure 3. Conformationally related 2-sialyl oxocarbenium ion **11** and radical **12**.

Indeed, it is apparent from consideration of the only reasonable conformations available to the oxonium ion **11**, which approximates the $^4H_5$ half-chair conformer, that significant selectivity in its reactions with nucleophiles is unlikely. Thus, neither face of **11** appears to be significantly more shielded than the other. Moreover, attack of a nucleophile on the α-face of **11** provides the α-product **13** in the $^4S_2$ twist-boat conformation, whereas attack on the β-face affords the β-product **14** directly in the $^2C_5$ chair conformation (Scheme 4).

To probe the influence of the protecting groups on the energetics of sialyl oxocarbenium ions we turned to mass spectrometry and an investigation of the threshold energy required for the fragmentation of a suitable anomeric derivative as a function of the protecting group. The use of threshold fragmentation energies has been previously identified by Denekamp and Sandlers as a useful means of assessing the influence of protecting groups on the stability of glycosyl oxocarbenium ions, albeit not in the sialic acid series.[18]

With the thioglycosides the loss of an acetoxy group was the primary fragmentation pathway. Therefore, we turned to the glycosyl phosphates introduced by Wong and co-workers,[4f] and synthesized **15**–**17** (Figure 4; see the Supporting Information) using the reported methodology. We also synthesized the 2-keto-3-deoxy-D-glycero-D-galactonulosonic acid (KDN) phosphates **18** and **19** (see the Supporting Information) as we have previously demonstrated[4j] that the 4,5-*O*-cyclic carbonate in the KDN series serves the same stereodirecting purpose as the oxazolidinone in neuraminic acid. All sialyl phosphates were isolated as single β-anomers, with the exception of **18** which was obtained as a mixture highly enriched in the β-isomer, and their anomeric stereochemistry was confirmed by the $^3J_{\mathrm{H3ax-CO2}}$ coupling constants.[19]



Scheme 4. Conformational analysis of nucleophilic attack on the putative glycosyl oxocarbenium ion **11**.

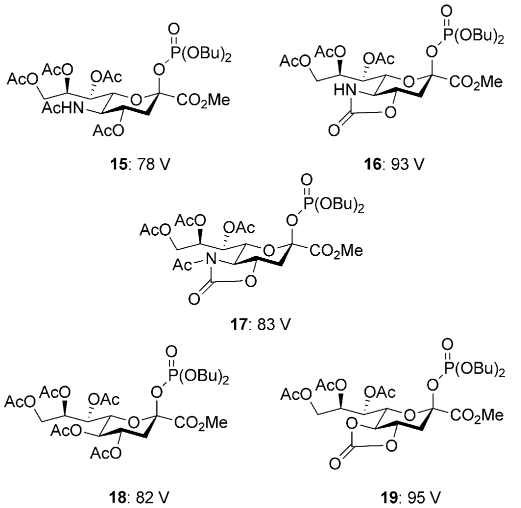
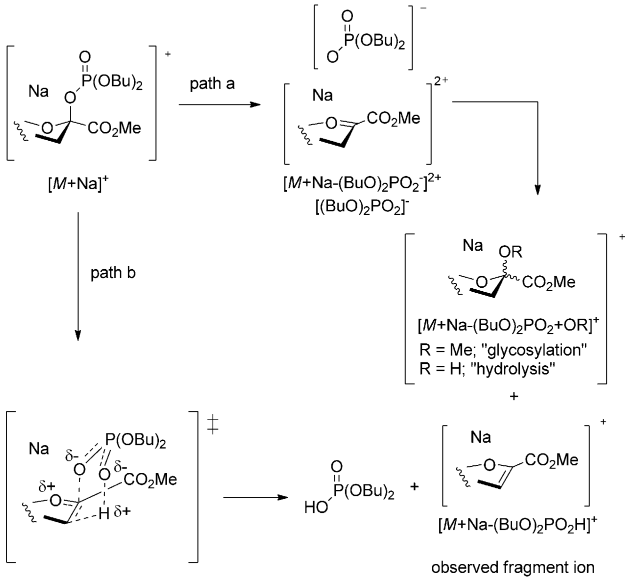


Figure 4. Onset cone voltages for fragmentation of sialyl phosphates.

Methanolic solutions of the phosphates **15**–**19** were examined by ESI mass spectrometry. At the standard cone voltage of 40 volts, each substance exhibited a clean sodiated molecular ion and the absence of any fragment ions from loss of the phosphate group. The cone voltage was then increased incrementaly until the onset of fragmentation leading to the values reported in Figure 4. In each case the fragment ion observed resulted from the overall loss of dibutyl phosphoric acid from the molecular ion, and was typically accompanied by peaks arising from the overall replacement of dibutyl phosphate by methanol or water, namely glycosylation or hydrolysis by the infusion solvent.

We interpret the observed fragmentations in terms of expulsion of the dibutyl phosphate anion to give the corresponding sialyl oxocarbenium ion with subsequent deprotonation to afford the observed fragment ion (path a, Scheme 5). Alternatively, a one-step pericyclic *syn* elimination (McLafferty rearrangement) leads directly to the fragment ion (path b, Scheme 5). As such a concerted mechanism is likely to be asynchronous, and to involve a transition state with significant positive charge on the anomeric carbon atom, the main difference between paths a and b in Scheme 5, for the purposes of this experiment, is simply one of the differing extents of the positive charge build-up on the anomeric carbon atom. As the appearance of the fragment ion is



Scheme 5. Mass spectral fragmentation and adduct formation.

coincident with that of the glycosylation and hydrolysis products, which necessarily arise from the oxocarbenium ion, we consider path a to be the more likely of the two alternatives.

A greater cone voltage is required to fragment a molecular ion carrying a cyclic protecting group spanning positions 4 and 5, than one lacking the cyclic protection (Figure 4). Furthermore, the simple oxazolidinone-protected system requires a higher cone voltage for fragmentation than the corresponding *N*-acetyl oxazolidinone. We interpret these observations in terms of the oxazolidinone and carbonate groups exerting a powerful electron-withdrawing effect that retards the build-up of positive charge at the anomeric center, thus necessitating the higher cone voltages for the onset of fragmentation. Consistent with the explanation advanced for the influence of the oxazolidinone on the anomeric effect, the powerful electron-withdrawing effect of the oxazolidinone and of the cyclic carbonate is seen as a function of their large dipole moment (Figure 1), which is aligned with the carbonyl group in the mean plane of the pyranose ring and reinforces the inherent electron-withdrawing effect of the C4–O4 and C5–N5/O5 bonds (Figure 5). In contrast, the carbonyl dipole on the O4 ester group and the O5 ester/N5 amide of the systems lacking cyclic protection are roughly orthogonal to the dipoles of the C4–O4 and C5–O5/N5 bonds and do not reinforce their electron-withdrawing effect to the same extent. Again consistent with the explanation advanced for influence on the anomeric effect, the antiperiplanar orientation of the *N*-acetyl and oxazoldinone dipoles in **17** moderates its electron-withdrawing influence relative to the simple oxazolidinone, thereby lowering the minimum cone voltage required for fragmentation.

We conclude that the oxazolidinone and carbonate groups are powerful electron-withdrawing protecting groups when *trans*-fused to pyranose ring systems by virtue of their strong dipole moments in the mean plane of the ring system. This effect has two consequences. First, equatorial glycosides are stabilized with respect to monocyclic systems by the diminished propensity of the pyranosyl ring oxygen atom to donate electron density into the σ* orbital of an axial glycosidic bond.[20] Second, the oxazolidinone and carbonate groups exert their highly effective stereodirecting influence by destabilizing the glycosyl oxocarbenium ions and, thus, by suppressing unselective dissociative reaction pathways. In doing so they favor pathways closer to the associative end of the S_N1–S_N2 mechanistic continuum[21] for glycosylation, that is, mechanisms involving S_N2-like pathways, possibly via so-called exploded transition states with their relatively long partial bonds, or pathways taking place through functionally equivalent contact or tight ion pairs. Possible intermediates in such mechanisms include β-glycosyl nitrilium ions,[22] β-glycosyl triflates, glycosyl sulfoxonium ions,[23] and spirocyclic intermediates arising from participation of the anomeric ester group related to the spirocyclic α-lactones sometimes discussed[24] in relation to the mechanism of sialidase enzymes and the spirocyclic imidate proposed by Kajihara and coworkers.[25] The exact nature of these intermediates will depend on the reaction conditions and the promotion system employed. Although S_N2 reactions at tertiary centers are usually considered to be strongly disfavored,[26] there is considerable stereochemical[27] and kinetic[28] precedent for such mechanisms at tertiary centers adjacent to carboxylate esters.

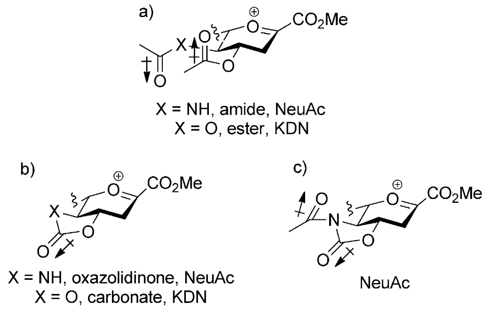


Figure 5. Protecting group dipoles in relation to the oxocarbenium ion: a) acyclic, b) oxazolidinone or carbonate, and c) N-acetyl oxazolidinone protection. Side chains are omitted for clarity.

Experimental Section

Equilibration: A solution of the TEMPO sialoside (0.05–0.1 M) in deuterated dichloroethane in an NMR tube was degassed, blanketed with nitrogen, and heated at 90 °C. With periodic monitoring by ^{1}H NMR spectroscopy, heating was continued until equilibrium was achieved.

Mass spectral fragmentation: A methanol solution of the phosphate (ca. 10 nM) was infused into the ESIMS source at room temperature and the cone voltage gradually increased from 40 V through the fragmentation threshold.

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[20] Alternatively, it may be considered that this thermodynamic effect arises from minimization of repulsion between the anomeric C-O dipole and the strong dipole of the oxazolidinone or carbonate ring.

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