

Remarkable Oxidation Stability of Glycals: Excellent Substrates for Cerium(IV)-Mediated Radical Reactions

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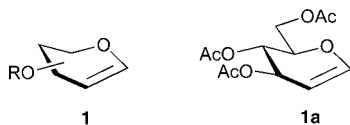
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Abstract: The remarkable stability of glycals under oxidative conditions becomes apparent by their redox data in solution, computed HOMO energies, and behavior on the addition of electrophilic radicals generated in the presence of cerium(IV) ammonium nitrate. Oxidation potentials up to 2.03 V vs ferrocene were obtained, which are exceptionally high for cyclic enol ethers but correlate nicely with the reaction times of the radical reactions. Protecting groups have a strong influence on the oxidation stability and HOMO energies of glycals as E_{ox} is shifted from *O*-silyl over *O*-benzyl to *O*-acetyl by more than 500 mV. Interestingly, this effect must be transmitted through σ -bonds, even up to the *para*-position of a benzoate group, as verified by a wide variation of remote substituents in the carbohydrate. Favorable interactions of the σ^* -orbital of the adjacent C–O bond with the HOMO of the double bond are proposed as a mechanistic rationale, which might be important for the redox behavior of other allylic systems. Finally, donors and acceptors in the 1-position exert the strongest influence on the oxidation stability, shifting the potentials by almost 1 V and resulting in different follow-up reactions of the cerium(IV)-mediated additions of malonates. It is the remarkable oxidation stability of glycals that makes them valuable building blocks in carbohydrate chemistry.

Introduction

Glycals (1,5- or 1,4-anhydrohex(pent)-1-enitols) **1** are 1,2-unsaturated carbohydrate derivatives that were described and denominated by Emil Fischer almost 100 years ago.¹ Their synthesis is easily accomplished by reductive elimination of *O*-protected glycosyl halides on a large scale,² and several of the most prominent and widely used glycals (e.g., tri-*O*-acetyl-D-glucal, **1a**) are nowadays commercially available.



Glycals have been applied as enantiomerically pure starting materials for various stereoselective transformations³ and the

total synthesis of natural products⁴ and as enzyme inhibitors.⁵ Importantly, epoxidation of glycals, discovered in the seminal work of Danishefsky, resulted in many examples from the synthesis of biologically interesting oligosaccharides and glycoconjugates.⁶ While dimethyldioxirane (DMDO) is a convenient reagent for this transformation, other oxidants such as methyltrioxorhenium (MTO) have received growing attention recently.⁷ These reactions work remarkably well with glycals **1**, whereas simple cyclic enol ethers such as 2,3-dihydropyran are easily cleaved under acidic conditions or in the presence of

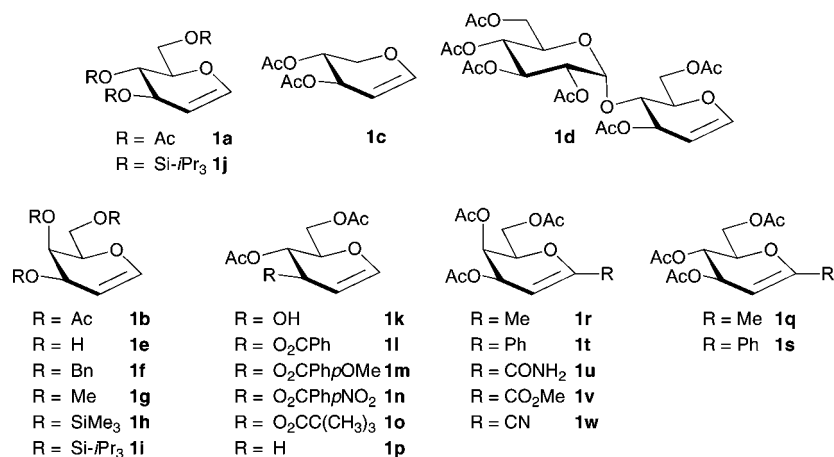
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Chart 1. Glycals **1a–w** with Various Configurations and Protecting Groups

46 manganese(III).⁸ Interestingly, the oxidation of glycals with
 47 hypervalent iodine reagents affects only the allylic position and
 48 leaves the double bond intact.⁹

49 During the course of our investigations on transition-metal-
 50 mediated radical reactions,¹⁰ we became interested in the
 51 addition of malonates to various glycals **1** in the presence of
 52 cerium(IV) ammonium nitrate (CAN).¹¹ This reaction is similar
 53 to Lemieux's azidonitration,¹² but provides easy access to C-2-
 54 branched carbohydrates, a valuable complement to the cyclo-
 55 propanation of glycals.¹³ More recently, we applied this
 56 methodology to other CH acidic radical precursors (e.g.,
 57 nitromethane or nitro esters)¹⁴ and to unsaturated carbohydrates
 58 with benzyl protecting groups.¹⁵ In all cases, the double bond
 59 of glycals **1** was not directly affected by CAN, although this
 60 reagent has an oxidation power ($E_{1/2}^{\text{ox}} = 1.52\text{--}1.60$ V vs
 61 NHE)¹⁶ sufficient to oxidize unsubstituted 2,3-dihydropyran (E_{pa}
 62 = 1.60 V vs NHE).¹⁷ Furthermore, the addition of radicals to
 63 2,3-dihydropyran was not successful.^{8d} Thus, glycals **1** exhibit

a reactivity remarkably different from that of simple cyclic enol
 ethers, which has been disregarded previously.

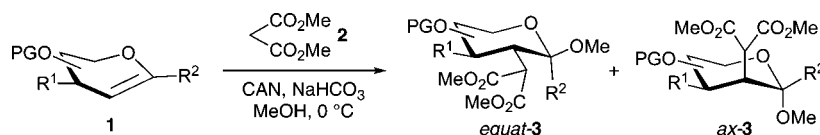
Herein, we describe a comprehensive study on the oxidation
 stability of variously substituted glycals **1** by a combination of
 cyclic voltammetry (CV), calculation of HOMO energies, and
 product distribution studies from radical additions. The present
 results establish a strong influence of protecting groups and of
 substitution patterns both in the allylic 3-position and in position
 1 of the double bond on the oxidation potentials. Furthermore,
 our studies provide a rationale for the unusual reactivity of
 glycals compared to simple enol ethers, demonstrating their
 value as stable starting materials for radical and other oxidative
 transformations.

Results

Synthesis of Glycals 1. To investigate the oxidation stability
 of a broad variety of glycals, we synthesized more than 20
 different 1,2-unsaturated carbohydrate derivatives. The simple
O-acetyl-protected glycals **1a–d** were easily available from the
 parent glycosyl bromides for pentoses, hexoses, and disaccha-
 rides on a large scale via known procedures.^{2,18} For further
 functionalized systems, we focused on derivatives of D-glucal
 and D-galactal, which furnished high yields and selectivities in
 radical additions in our previous studies.¹¹ Thus, the protecting
 groups were easily exchanged by literature procedures,¹⁹ and
 glycals **1e–j** were obtained in one- or two-step reactions from
 the corresponding tri-*O*-acetyl-D-glycals **1a** and **1b** (Chart 1,
 Supporting Information). To investigate the influence of various
 substituents adjacent to the double bond, we altered the
 structures in the 1- and 3-positions of the glycals requiring some
 more laborious transformations. The 3-*O*-acetyl group of glucal
1a was selectively removed by enzymatic saponification to give
1k,²⁰ and subsequent reaction with acid chlorides afforded esters

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Table 1. Oxidation Potentials (E_{ox}) of Various Glycals **1** Determined by CV and Addition of Dimethyl Malonate (**2**)^a

entry	D-glycal	PG	R ¹	R ²	t ^b (h)	eq-3 yield ^c (%)	ax-3 yield ^c (%)	E _{ox} ^g (V)	
1	1a	glucal	Ac	OAc	H	6	80	15	1.87 ^h
2	1b	galactal	Ac	OAc	H	6	87		1.89
3	1c	xylal	Ac	OAc	H	6	81	6	1.76
4	1d	maltal	Ac	OAc	H	6	83		1.87
5	1e	galactal	H	OH	H	0.5	<i>d</i>		1.35
6	1f	galactal	Bn	OBn	H	2	83		1.62
7	1g	galactal	Me	OMe	H	1	76		1.48
8	1h	galactal	SiMe ₃	OSiMe ₃	H	0.5	<i>d</i>		1.37
9	1i	galactal	Si(<i>i</i> -Pr) ₃	OSi(<i>i</i> -Pr) ₃	H		<i>e</i>		<i>i</i>
10	1j	glucal	Si(<i>i</i> -Pr) ₃	OSi(<i>i</i> -Pr) ₃	H		<i>e</i>		<i>i</i>
11	1k	glucal	Ac	OH	H	2	45	3	1.67
12	1l	glucal	Ac	O ₂ CPh	H	12	78	16	2.03
13	1m	glucal	Ac	O ₂ CPhpOMe	H	6	74	20	1.86
14	1n	glucal	Ac	O ₂ CPhpNO ₂	H	12	73	17	2.00
15	1o	glucal	Ac	O ₂ CC(CH ₃) ₃	H	6	75	16	1.94
16	1p	glucal	Ac	H	H	2	47	40	1.62
17	1q	glucal	Ac	OAc	Me	1	71		1.57
18	1r	galactal	Ac	OAc	Me	1	73		1.55
19	1s	glucal	Ac	OAc	Ph	1	89		1.41
20	1t	galactal	Ac	OAc	Ph	1	82		1.35
21	1u	galactal	Ac	OAc	CONH ₂	8	70		1.96
22	1v	galactal	Ac	OAc	CO ₂ Me	12	38 ^f		>2.2 ^f
23	1w	galactal	Ac	OAc	CN	12	53 ^f		>2.2 ^f
24	2,3-dihydropyran								1.21 ^k

^a Reaction of glycal **1** (1.0 mmol) with malonate **2** (10 mmol) in the presence of anhydrous CAN (3–6 mmol) and NaHCO₃ (4.0 mmol) in MeOH (10 mL) at 0 °C. ^b Reaction time until TLC showed complete conversion of glycal **1**. ^c Yield of isolated product after column chromatography. ^d Decomposition of glycal **1**. ^e Glycals **1i** and **1j** were not soluble in methanol. ^f Formation of ortho esters **4** and other minor side products. ^g Oxidation potentials E_{ox} (V) obtained from cyclic voltammograms from the anodic peak potential. Determined at 100 mV/s in acetonitrile (10⁻³ M) in the presence of Bu₄NPF₆ (0.1 M) vs ferrocene. ^h Literature value 1.80 V.²⁷ ⁱ Glycals **1i** and **1j** were not soluble in acetonitrile. ^j No oxidation peak was observed, due to dominating oxidation of the bare electrolyte solution at $E_{ox} > 2.2$ V. ^k Literature value 1.20 V.¹⁷

1l–o in high yields (Supporting Information). Finally, 3-deoxyglucal **1p** was obtained by Ferrier rearrangement and reduction with lithium aluminum hydride.²¹

To alter the electronic nature of the double bond, which should have an influence on the oxidation stability, we introduced donor and acceptor groups into the 1-position. Due to the acidity of the vinylic position, deprotonation of silyl-protected glycals is possible with strong bases.^{2c,22} After alkylation or arylation and exchange of the protecting groups, the 1-C-methyl- and 1-C-phenylglycals **1q–t** were isolated in moderate to good overall yields in analytically pure form (Chart 1, Supporting Information). Acceptor-substituted galactals **1u**^{23a} and **1w**^{23b} were prepared by methods published earlier. Ester **1v**^{23c} was obtained from C-(3,4,6-tri-*O*-acetyl-2-deoxy-D-*lyxo*-hex-1-enopyranosyl)carbaldehyde by oxidation with MnO₂ and subsequent in situ esterification (Chart 1, Supporting Information). In summary, we have synthesized more than 20 different glycals **1**, some of which were hitherto unknown. Due to the broad variation of the substitution pattern, these unsaturated

carbohydrates should provide sufficient information for the subsequent studies.

Cyclic Voltammetry of Glycals 1. Although anodic and PET oxidations of enol ethers are of significant synthetic interest, their oxidation potentials are not well established.^{17,24} Besides oxidative DNA damage via nucleotide radical cations, whose kinetics has been thoroughly studied,²⁵ the oxidation potential of only one glycal, i.e., tri-*O*-acetyl-D-glucal (**1a**), has been described until now.²⁶ Therefore, we investigated the redox behavior of various glycals **1** by CV (Table 1).²⁷ All measurements were conducted in dry acetonitrile with tetra-*n*-butylammonium hexafluorophosphate (Bu₄NPF₆) as the supporting electrolyte applying a scan rate of 100 mV/s (Supporting Information). Most glycals were readily soluble, except the silyl-

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protected derivatives **1i** and **1j**. The cyclic voltammograms of glycols **1** displayed irreversible oxidation peaks in the broad range from 1.35 to 2.03 V vs ferrocene, which are remarkably higher than that of 2,3-dihydropyran (1.21 V, entry 24). Furthermore, the oxidation potential (E_{ox}) of the acceptor-substituted carbohydrates **1v** and **1w** must be very high ($E_{ox} > 2.2$ V, entries 22 and 23), since only the anodic current of the bare electrolyte solution was observed. As is typical for chemical follow-up reactions after the electron transfer step, i.e., for EC or ECE mechanisms, the anodic peak of all glycols shifted to higher potentials with increasing scan rate, with the peak current dropping in the second sweep.²⁸ In summary, for the first time we obtained a whole data set of oxidation potentials of a broad variety of glycols **1**. The high values of 1.35–2.03 V vs ferrocene demonstrate their remarkable oxidation stability and the strong influence of the substitution pattern on their reactivity.

Radical Additions to Glycols 1. Radical reactions in the presence of tri-*n*-butyltin hydride have become an important methodology for the selective formation of carbon–carbon bonds.²⁹ Electrophilic radicals, typically characterized by adjacent acceptor groups, are conveniently generated by transition-metal-mediated oxidation of CH acidic precursors.³⁰ In previously reported addition reactions of such radicals to glycols **1a–c**, the enol ether structure was not directly affected by CAN and the *C*-2-branched analogues **3** were isolated in high yields.¹¹ To examine the scope and limitations of the addition of dimethyl malonate (**2**) and to find an explanation for the remarkable oxidation stability of glycols **1**, we compared more than 20 substrates (Table 1, Supporting Information). Reaction times, which are indicative of the reactivity of the glycols **1** toward the electrophilic malonyl radicals, were measured by monitoring full conversion by thin layer chromatography (TLC). The rate of addition was expected to reflect the electronic nature of the double bond and should correlate with the determined redox potentials (see the Discussion).

Additions to the per-*O*-acetylated glycols **1a–d** proceeded smoothly within 6 h, affording products **3** in high overall yields (entries 1–4). The exclusive formation of one regioisomer and the higher selectivity observed with galactals have already been explained in our previous studies.¹¹ No influence of the configuration on the reaction time was observed. On the other hand, the protecting groups altered the reactivity of the glycols **1e–h** remarkably (entries 5–8). The benzyl- and methyl-substituted substrates **1f** and **1g** gave already faster conversions and still high yields of the addition products **3f** and **3g** (entries 6 and 7), whereas the completely unprotected (**1e**) and tri-

Table 2. Comparison of Oxidation Potentials, Calculated HOMO Energies, and Reactivities in CAN-Mediated Radical Reactions of Various Configured and Protected Glycols **1**

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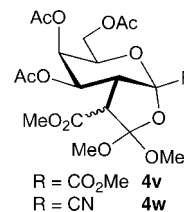
entry	D-glycol	PG	E_{ox}^a (V)	t^b (h)	HOMO energy ^c (eV)	
1	1a	glucal	Ac	1.87	6	−9.66
2	1b	galactal	Ac	1.89	6	−9.72
3	1c	xylal	Ac	1.76	6	−9.63
4	1d	maltal	Ac	1.87	6	−9.62
5	1f	galactal	Bn	1.62	2	−9.36
6	1g	galactal	Me	1.48	1	−9.16
7	1h	galactal	SiMe ₃	1.37	0.5 ^e	−8.55
8	1i	galactal	Si(<i>i</i> -Pr) ₃	<i>d</i>	<i>d</i>	−8.59
9	1e	galactal	H	1.35	0.5 ^e	−8.87
10	2,3-dihydropyran	1.21	0.5 ^e		−9.22	

^a Oxidation potentials E_{ox} (V) vs ferrocene obtained from cyclic voltammograms. ^b Reaction time until TLC showed complete conversion of glycol **1**. ^c HOMO energies computed by the semiempirical PM3 method implemented in MOPAC from Sybyl 8.0. All structures were minimized by the Tripos force field using the Gasteiger–Hückel method. ^d Glycol **1i** was not soluble in acetonitrile or methanol. ^e Decomposition of glycol **1**.

methylsilyl-protected (**1h**) glycols afforded only oxidative decomposition after short reaction times. An acid-catalyzed cleavage of the silyl groups is unlikely, due to the presence of sodium bicarbonate as the base. The triisopropylsilyl-protected glycols **1i** and **1j** were not soluble in methanol, and no reaction times were obtained (entries 9 and 10).

To further elucidate the influence of functional groups on the oxidation stability of glycols, we altered the substitution pattern at the 3-position (entries 11–16). Indeed, even a remote effect of *para*-substituents of the benzoate groups on the reaction time was established (entries 12–14), and again, the unprotected 3-position afforded some oxidative byproduct (entry 11).

Finally, variation of the 1-position of glycols **1q–w** resulted in the strongest change in both reactivity and product distribution (entries 17–23). We performed the CAN-mediated addition of dimethyl malonate (**2**) to donor-substituted unsaturated carbohydrates for the first time, and the products **3q–t** were isolated in good yields in analytically pure form after only 1 h (entries 17–20, Supporting Information). On the other hand, acceptor groups reduced the rate of additions remarkably, and the unexpected ortho esters **4v** and **4w** were obtained in moderate yields as diastereomeric mixtures.



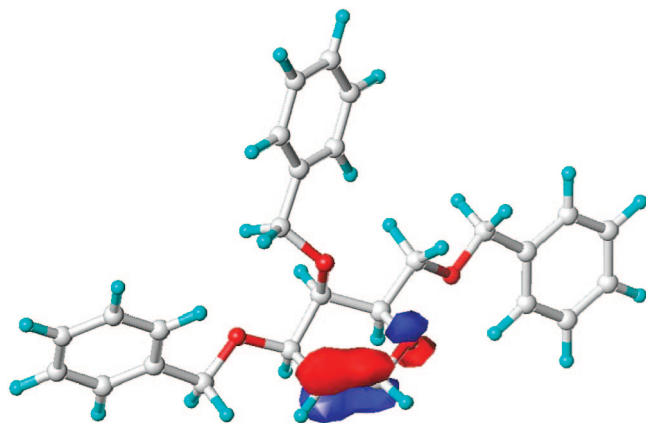
Discussion

Influence of the Configuration and the Protecting Groups on the Oxidation Stability of Glycols 1. With a large data set of oxidation potentials (E_{ox}) for variously substituted glycols **1** at hand, their electronic properties on one side and reactivities toward malonates on the other side can now be compared (Table 2). It is well-known that the addition of radicals to alkenes proceeds by orbital control, suggesting a strong interaction of the SOMO of the electrophilic malonyl radical with the HOMO

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Chart 2. Electron Density of the HOMO of Tri-*O*-benzyl-D-galactal (**1f**)

of the double bond component.²⁹ This interaction is very sensitive to the substitution pattern and correlates directly with the rate of radical addition. Thus, if the HOMO energy is increased, the reaction with malonates is much faster, which is indicated qualitatively by the reaction times (Table 2). For the addition of malonyl radicals to *para*-substituted styrenes, detailed kinetics were measured and even Hammett correlations were obtained, irrespective of the generation of the radicals by CAN or tri-*n*-butyltin hydride.³¹ Likewise in our systems, the addition of the radicals to the double bond seems to be involved in the rate-determining step, apparently preceded by the formation of a cerium(IV)–malonyl radical complex in a preequilibrium. Indeed, if no glycal **1** was added to the reaction mixture, no conversion and decoloration of CAN was observed. To further investigate the importance of orbital interactions, HOMO energies were calculated by the semiempirical PM3 method. Indeed, the HOMO of tri-*O*-benzyl-D-galactal (**1f**) (Chart 2) has its highest electron density at the double bond, and thus, an oxidation of protecting groups is unlikely. Overall three parameters (oxidation potentials, reaction times, HOMO energies) are available to discuss the remarkable oxidation stability of glycals.

Although the reaction times may reflect the kinetics only qualitatively, they nicely correlate with the oxidation potentials. For example, the *O*-acetyl-protected derivatives **1a–d** with the highest E_{ox} (up to 1.89 V vs ferrocene; see entries 1–4) reacted with the malonyl radicals only slowly. No influence of the configuration of the glycals **1** on the oxidation potential was observed; only di-*O*-acetyl-D-xylal (**1c**) has a slightly lower oxidation potential, due to one missing *O*-acetyl group. Thus, the functional groups seem to be responsible for the remarkable oxidation stability of glycals. In contrast, the completely unsubstituted 2,3-dihydropyran is oxidized already at 1.21 V, furnishing only decomposition products with CAN after 30 min (entry 10).

To further understand the influence of protecting groups, a look at galactals **1e–i** (Table 2, entries 5–9) is highly instructive. A simple change from an *O*-acetyl to an *O*-benzyl group shifts the oxidation potential cathodically by a notable 270 mV. The same clear trend is reflected in the reaction times and especially the calculated HOMO energies (entries 2 and 5). For additional insight, we compared tri-*O*-acetyl-D-galactal

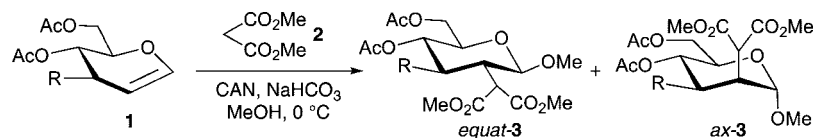
(**1b**) and tri-*O*-benzyl-D-galactal (**1f**) in a competition experiment. Dimethyl malonate (**2**) was added to a 1:1 mixture of both substrates in the presence of CAN, and the reaction was monitored by NMR spectroscopy at different times (Supporting Information). After 60 min, 82% of the electron-rich *O*-benzyl-protected galactal **1f** was consumed, whereas 70% of **1b** remained unreacted. This difference in reactivity can be rationalized by the higher propensity of an ester group to withdraw electrons compared to a benzyl ether. However, since the functional groups are not directly linked to the double bond, this remarkable influence must be transmitted through space or σ -bonds. Such strong transmission was hitherto unknown for radical additions to glycals and will be discussed in the next section. Interestingly, this phenomenon can be considered as a new manifestation of the known arming–disarming effect of protecting groups observed and utilized in glycosylations.³² Although not directly comparable to radical additions, for such cationic reactions at the anomeric center, the influence of various functional groups over many bonds was semiquantified by Ley³³ and Wong.³⁴

To exclude a direct oxidation of the benzyl ethers,³⁵ we investigated the corresponding tri-*O*-methyl-D-galactal (**1g**) equipped with oxidation-stable protecting groups. Its oxidation potential ($E_{\text{ox}} = 1.48$ V vs ferrocene, entry 6) is even lower than that of the benzyl-protected galactal **1f** (entry 5), in good accordance with the calculated HOMO energies. The addition of dimethyl malonate (**2**) in the presence of CAN proceeded with both substrates smoothly, without affecting the protecting groups (Table 1). Thus, the redox potentials indeed reflect the MO energies of the double bonds and not those of the protecting groups.

The limit for synthetic applications of cerium(IV)-mediated additions of radicals to glycals **1** was reached with silyl-substituted systems **1h** and **1i** or the unprotected D-galactal **1e**, since the unsaturated carbohydrates were not soluble or decomposed within minutes (entries 7–9). For glycal **1h**, deprotection under the reaction conditions cannot be excluded, but the low oxidation potential of 1.37 V vs ferrocene is in the same range as that of 2,3-dihydropyran (1.21 V, entry 10), supporting an oxidation of the double bond. In summary, we established (i) the remarkable oxidation stability of glycals and (ii) a strong influence of protecting groups, thus providing a rationale for this unusual behavior. However, the way the protecting groups influence the oxidation potential of the enol ether structure through space or σ -bonds is not yet explained properly and will be discussed in the next section.

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Table 3. Comparison of Oxidation Potentials, Calculated HOMO Energies, and Reactivities in CAN-Mediated Radical Reactions of Various 3-Substituted Glycals **1**

entry	glucal	R	E_{ox}^a (V)	t^b (h)	HOMO energy ^c (eV)	eq-3 yield ^d (%)	ax-3 yield ^d (%)
1	1a	OAc	1.87	6	-9.66	80	15
2	1l	O ₂ CPh	2.03	12	-9.80	78	16
3	1m	O ₂ CPh- <i>p</i> -OMe	1.86	6	-9.54	74	20
4	1n	O ₂ CPh- <i>p</i> -NO ₂	2.00	12	-9.99	73	17
5	1o	O ₂ CC(CH ₃) ₃	1.94	6	-9.70	75	16
6	1k	OH	1.67	2	-9.52	45	3
7	1p	H	1.62	2	-9.47	47	40

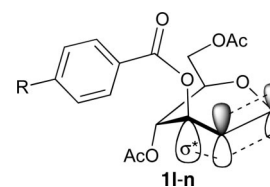
^a Oxidation potentials E_{ox} (V) vs ferrocene obtained from cyclic voltammograms. ^b Reaction time until TLC showed complete conversion of glycal **1**. ^c HOMO energies computed by the semiempirical PM3 method implemented in MOPAC from Sybyl 8.0. All structures were minimized by the Tripos force field using the Gasteiger–Hückel method. ^d Yield of isolated product after column chromatography.

Influence of the Substituents at the 3-Position on the Oxidation Stability of Glycals 1. To find a mechanistic rationale for the remarkable influence of protecting groups on the oxidation stability of glycals, we varied the substitution pattern at the 3-position that is located adjacent to the double bond. To exclude poor overlap with the electrode by steric interactions, possibly leading to slow heterogeneous electron-transfer, we selected 3-*O*-pivaloylglucal **1o** as a test substrate (entry 5). Even for this bulky substituent, the oxidation potential was in the expected range, suggesting that exclusively electronic effects are operative. The successful comparison of oxidation potentials, calculated HOMO energies, and reactivities was thus applied again (Table 3).

The change of the *O*-acetyl into an *O*-benzoyl group resulted in an anodic shift of the oxidation potential by 160 mV and a longer reaction time (entry 2). Such findings can be explained by the slightly stronger acceptor propensity of the benzoyl group and are in accordance with a decrease in the HOMO energy by 140 mV. Even the remote *para*-substituent of the *O*-benzoyl group exerted an influence on the redox potential and reaction time, promoting a faster addition of malonyl radicals to the donor (OMe) than to the acceptor (NO₂) substituted system (entries 3 and 4). Why the benzoyl and *p*-nitrobenzoyl showed almost the same oxidation potential could not be explained until now, as the nitro compound **1n** displayed the lowest calculated HOMO energy (-9.99 eV) in the whole series of 3-substituted glycals, about 190 mV more negative than that of **1l** (Ph). For the (*p*-methoxybenzoyl)glucal **1m**, on the other hand, the oxidation potential and the computed HOMO energies are in due agreement (entry 3).

These influences of substituents are very interesting, since such remote effects over many bonds, including σ -bonds, were hitherto unknown in radical reactions. However, the results can again be compared with the stereoelectronic effects in glycosylation reactions, transmitted through space or σ -bonds as well.^{32–34} In contrast to the ester-substituted systems, the unprotected and 3-deoxy substrates exhibited considerably lower oxidation potentials and faster reaction times (Table 3, entries 6 and 7), which can be explained by the lack of an acceptor group.

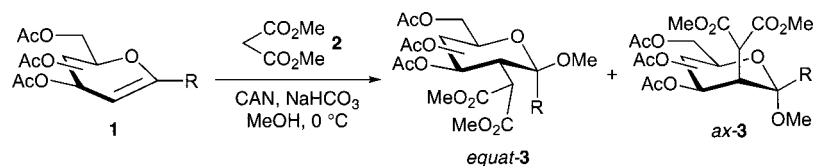
Our explanation for the remarkable influence of the substituents in the 3-position on the oxidation potentials and reactivities through σ -bonds is based on orbital interactions (Chart 3). Thus, electron acceptors such as esters are expected to lower the energy of the σ^* -orbital of the C–O bond, resulting in a stronger

Chart 3. Orbital Interactions in Glycals **1l–n**

interaction with the adjacent HOMO of the double bond. As a result, the HOMO energy drops (as demonstrated by computations) and a higher oxidation potential is measured by cyclic voltammetry. Even the *para*-substituents R on the aromatic ring slightly influence the oxidation potentials (entries 2–4), which is also reflected in the calculations of the HOMO energies. For a perfect overlap, the σ^* - and π -orbitals should adopt an almost parallel alignment, which is readily possible in the quite flexible ring system of glycals. The important influence of orbital interactions on the conformation of carbohydrates is nicely reflected in the structure of glycosyl radicals.³⁶ In summary, we could provide a mechanistic rationale for the unusual oxidation stability of glycals by variation of the functional groups in the 3-position. The effect is transmitted through σ -bonds even up to the *para*-substituents of the benzoate rings, which might be important for the discussion of the redox behavior of other allylic systems.

Influence of the Substituents in the 1-Position on the Oxidation Stability of Glycals 1. With substituents in the 3-position already exhibiting a sizable influence on the HOMO energies of glycals, this effect is expected to be much stronger in the 1-position. Now the functional group is directly connected with the double bond and interacts by conjugation and not through σ -bonds. Indeed, glycals **1u–z** showed the broadest alteration of oxidation potentials, calculated HOMO energies, and reactivities (Table 4). Compared to tri-*O*-acetyl-D-glucal (**1a**), already the presence of a methyl group reduced the anodic peak potential in **1q** by 300 mV (entry 2), demonstrating the strong donor propensity of this substituent. Even lower oxidation potentials were obtained for the better electron-donating phenyl groups (entries 4 and 5), confirmed by the HOMO energies shifting from -9.66 to -9.52 and -9.23 eV. The carbohydrate C-2 analogues **3q–t** were isolated in high yields (entries 2–5),

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Table 4. Comparison of Oxidation Potentials, Calculated HOMO Energies, and Reactivities in CAN-Mediated Radical Reactions of Various 1-Substituted Glycals **1**

entry	glycal	group in 4-position	R	E_{ox}^a (V)	t^b (h)	HOMO energy ^c (eV)	eq-3 yield ^d (%)	ax-3 yield ^d (%)
1	1a	eq	H	1.87	6	-9.66	80	15
2	1q	eq	Me	1.57	1	-9.52	71	
3	1r	ax	Me	1.55	1	-9.43	73	
4	1s	eq	Ph	1.41	1	-9.23	89	
5	1t	ax	Ph	1.35	1	-9.17	82	
6	1u	ax	CONH ₂	1.96	8	-9.80	70	
7	1v	ax	CO ₂ Me	>2.2 ^e	12	-10.03	38 ^f	
8	1w	ax	CN	>2.2 ^e	12	-10.41	53 ^f	

^a Oxidation potentials E_{ox} (V) vs ferrocene obtained from cyclic voltammograms. ^b Reaction time until TLC showed complete conversion of glycal **1**. ^c HOMO energies computed by the semiempirical PM3 method implemented in MOPAC from Sybyl 8.0. All structures were minimized by the Tripos force field using the Gasteiger–Hückel method. ^d Yield of isolated product after column chromatography. ^e No oxidation peak was observed, due to dominating oxidation of the bare electrolyte solution at $E_{ox} > 2.2$ V. ^f Formation of ortho esters **4** and other minor side products.

372 and for the first time we prepared methyl glycosides with
373 quaternary anomeric centers by this radical methodology.

374 On the other hand, 1-acceptor-substituted glycals **1u–w**
375 reacted only sluggishly with dimethyl malonate (**3a**), most likely
376 due to the remarkably lowered HOMO energies and conse-
377 quential unfavorable orbital interactions. This is in accordance
378 with other transition-metal-mediated radical reactions, which
379 do not proceed efficiently with electron-poor alkenes.³⁰ The
380 cyclic voltammograms support this mechanistic rationale, since
381 only the anodic current of the bare electrolyte solution ($E_{ox} \approx$
382 2.1 V) was observed for glycals **1v** and **1w** (entries 7 and 8).
383 Therefore, the oxidation potentials of such acceptor-substituted
384 unsaturated carbohydrates must be >2.2 V, a value never before
385 observed for enol ethers. The difficult electrochemical oxidation
386 of glycals **1v** and **1w** was confirmed by computations, as they
387 showed the HOMO energies to be below -10 eV. Thus, the
388 orbital interaction of the electrophilic malonyl radicals with the
389 double bond is drastically diminished, resulting in slower
390 additions and lower yields. Additionally, the glycals **1v** and **1w**
391 afforded ortho esters **4** and no methyl glycosides **3** as addition
392 products in moderate yields (Table 3, entries 7 and 8). The
393 formation of such bicyclic compounds is interesting from the
394 mechanistic point of view and was explained previously.^{11c}

395 Conclusions

396 We established a remarkable oxidation stability of glycals
397 and provide an explanation for their unusual reactivity and their
398 application as valuable starting materials for other synthetic
399 transformations. More than 20 variously substituted unsaturated
400 carbohydrates were synthesized and investigated under oxidative
401 reaction conditions. The method of choice was a combination
402 of CV, calculation of HOMO energies, and examination of the
403 product distribution from cerium(IV)-mediated additions of
404 radicals. Depending on the substitution pattern, the oxidation
405 potentials of glycals were in the range of 1.35–2.03 V vs
406 ferrocene. Compared with 2,3-dihydropyran ($E_{ox} = 1.21$ V),
407 such high values are unusual for enol ethers and demonstrate a
408 remarkable oxidation stability of 1,2-unsaturated carbohydrates,
409 which was hitherto disregarded. Moreover, the different reaction
410 times for the addition of dimethyl malonate in the presence of
411 CAN correlate nicely with the oxidation potentials and the
412 HOMO energies. This was rationalized by the interaction of

the SOMO of the electrophilic malonyl radical with the HOMO 413
of the double bond. 414

415 The configuration of the glycals had no influence on their
416 oxidation stability. On the other hand, a strong dependence of
417 the oxidation potentials over 500 mV on the protecting groups
418 was found. Thus, *O*-silylated and unprotected glycals were
419 readily oxidized to undesired side products, proving themselves
420 as unsuitable substrates for radical additions under oxidative
421 conditions. On the contrary, per-*O*-acetylated glycals exhibited
422 the highest oxidation stability (E_{ox} up to ~ 2 V), but benzyl ethers
423 were tolerated as well. These results are important for the general
424 applicability of oxidation reactions in carbohydrate chemistry,
425 with a high tolerance of various functional groups.

426 Interestingly, the protecting groups influence the oxidation
427 stability of the enol ether structure through σ -bonds. This effect
428 was verified by variation of the substitution pattern in the 3-position,
429 with a remarkable spread of oxidation potentials over 400 mV.
430 As a mechanistic model, we propose a favorable interaction of the
431 σ^* -orbital of the adjacent C–O bond with the HOMO of the double
432 bond. Thus, electron acceptors in the allylic position lower the
433 HOMO energy, which was nicely supported by calculations. This
434 effect is transmitted even into the *para*-substituents of the benzoate
435 rings, which may be important for the discussion of the redox
436 behavior of other allylic esters.

437 Finally, donors and acceptors in the 1-position had the strongest
438 influence on the oxidation stability, obviously due to the direct
439 conjugation to the double bond. The potentials varied over a range
440 of almost 1 V, and the radical additions in the presence of CAN
441 proceeded via different follow-up reactions. With strong acceptor
442 groups, the intermediate radicals at the captodatively substituted
443 anomeric center were not further oxidized, and ortho esters were
444 isolated as carbohydrate C-2 analogues.

445 Besides these new mechanistic aspects, the results are
446 important for synthetic applications of transition-metal-mediated
447 radical reactions in carbohydrate chemistry and the scope and
448 limitations of the addition of CH acidic compounds to glycals.
449 Due to oxidative decomposition by CAN, substrates with too
450 low oxidation potentials are not suitable, whereas radical
451 addition to glycals with a too high oxidation potential proceeds
452 inefficiently. Thus, a window of 1.5–2.0 V for the oxidation
453 potential seems to be ideal, provided by per-*O*-acetylated and
454 -benzylated glycals. By following these guidelines, we expect

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455 many applications for the synthesis of C-2-branched carbohy-
456 drates or other oxidative transformations of glycals to arise in
457 the near future.

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461 (Norvartis) for a generous gift of the crude glycal **1k**.

Supporting Information Available: Experimental part in-
cluding spectroscopic data and complete characterization of
all new compounds and voltammograms of glycals **1**. This
material is available free of charge via the Internet at <http://pubs.acs.org>.

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