Angewandte Chemie

Mapping the Reactivity of the C=C bond of Cyclic Enol Ether Derivatives of Sugars: Nucleophilicity Parameters of Glycals

--Manuscript Draft--

Manuscript Number:	202524329
Article Type:	Research Article
Corresponding Author:	Guillaume Berionni, PhD University of Namur: Universite de Namur Namur, BELGIUM
Corresponding Author E-Mail:	guillaume.berionni@unamur.be;guillaume.berionni@gmail.com
Order of Authors (with Contributor Roles):	Sophie Rodrigues
	Saloua Chelly
	Jenny Ha
	Lucie Pedussaut
	Sami Lakhdar
	Raphaël Robiette
	Stéphane P. Vincent
	Guillaume Berionni, PhD
Keywords:	Glycals; Nucleophilicity; Kinetic studies; Reactivity scales; Reactivity mapping
Manuscript Classifications:	Organic Chemistry; Physical and Theoretical Chemistry
Suggested Reviewers:	Daniel Werz daniel.werz@chemie.uni-freiburg.de Expert in bioorganic and carbohydrate chemistry
	Sébastien Thibaudeau sebastien.thibaudeau@univ-poitiers.fr Expert in carbocations and glycopyranosyl cations chemistry
	David Crich David.Crich@uga.edu Expert in mechanisms in carbohydrates
	Martin Breugst martin.breugst@chemie.tu-chemnitz.de Expert in reactivity parameters (experimental and computational)
	Boris Vauzeilles boris.vauzeilles@cnrs.fr Expert in carbohydrate chemistry and glycosylation reactions
	Robert Mayer robert.j.mayer@tum.de Expert in physical organic chemistry
Opposed Reviewers:	
Abstract:	Glycals are unsaturated sugar derivatives constituting a large family of polyhydroxylated synthons which are widely exploited as synthetic intermediates in the synthesis of natural products and as final molecules for biochemical applications. We report the first investigation in the understudied area of structure-reactivity relationship and quantitative mapping of reactivity in endo- and exo-glycals compounds. For quantifying the nucleophilicity of the C=C double bond of a series of endo- and exo-glycals, we performed kinetic investigations of their C-C bond formation with reference electrophiles of known electrophilicity parameters. Fast spectroscopic techniques experiments (stopped-flow and laser-flash photolysis) enabled us to determine the rate

	constant of hundreds of reactions, which allows the first comprehensive mapping and structure-reactivity analysis of the nucleophilic reactivity of this wide family of cyclic enol ethers. Quantum-chemical calculations corroborate with kinetic investigations and highlight the crucial role of ring strain variations to explain the relative nucleophilicity of endo- and exo-glycals. We examined also the influence of substitution and showed that alkoxy substituents decrease nucleophilicity through inductive effects and hyperconjugation.
Author Comments:	Dear Dr. Nathalie Weickgenannt, Dear Dr. Frank Maass, glycals belong to a large family of natural products sparking the interest of a multidisciplinary community of chemist working at the intersection of biochemistry, organic synthesis, supramolecular chemistry and drug design. To our great surprise and to the best of our knowledge, the nucleophilic reactivity of the C=C bond of endo and exo-glycals, which are widely used as building blocks and synthons in key transformations (C-, O- and N-glycosylation, fluorination reactions) has not yet been experimentally determined or computationally parametrized. With the rapid development of machine learning (ML) algorithms and computational chemistry predictions applied to chemistry, the quantitative elucidation of the kinetics and thermodynamic parameters involved in the C-C bond formation reactions of glycals is therefore a timely topic. We are thus now reporting the first experimental and computational calibration of the reactivity parameters of these key molecules using fast kinetics techniques (laser flash photolysis, stopped-flow investigations) and computational investigations (strain-deformation model, reactivity descriptors, etc). We believe that this first systematic reactivity mapping lays a very fundamental basis for the future development of new synthetic functionalisation methods of glycals. It will also allow to establish structure-reactivity relationships and predictive reactivity models in carbohydrate chemistry, for understanding the parameters governing the reactivity of glycosyl oxocarbenium ion intermediates. As our study combines advanced experimental kinetics, mechanistic and quantum-chemical calculations, we consider Angewandte Chemie as the best medium for publishing these results and we believe that this work will attract the interest of a broad readership. Yours sincerely, Prof. Guillaume BERIONNI
Section/Category:	
Additional Information:	
Question	**Response**
Do you agree to comply with the legal and ethical responsibilities outlined in the journal's Notice to Authors?	Yes
Has a previous version of this manuscript been submitted to this journal?	No
Is this manuscript, or part of it, currently under consideration elsewhere?	No
Is this manuscript, or part of it, published, posted, or in press? This includes content posted on preprint servers (preprint guidelines) or published as part of a thesis.	No
Please provide us with information about	First submission in a journal

the history of your manuscript, including previous submissions, transfers, or prior versions:	
Do you or any of your co-authors have a conflict of interest to declare?	No
Does the research described in this manuscript include animal experiments?	No
Does the research described in this manuscript include human research participants (including for experiments with sensors or wearable technologies) or tissue samples from human subjects (including blood or sweat)?	No
This journal supports data sharing and has adopted an Expects Data Sharing policy: - You are encouraged to make your data available, for instance in a public repository. - Your article must include a Data Availability Statement; please select a template from the options below or provide a custom Statement. - When data is openly available, please provide the name and URL/DOI of the repository and cite the data in the references section of your manuscript. **Is your data available?**	Data available in article supplementary material
Please confirm the selected template for your Data Availability Statement below, which will be published as part of your article if it is accepted for publication. as follow-up to "This journal supports data sharing and has adopted an Expects Data Sharing policy: - You are encouraged to make your data	The data that support the findings of this study are available in the supplementary material of this article.

available, for instance in a public repository. - Your article must include a Data Availability Statement; please select a template from the options below or provide a custom Statement. - When data is openly available, please provide the name and URL/DOI of the repository and cite the data in the references section of your manuscript. **Is your data available?"**	

WILEY-VCH

RESEARCH ARTICLE

Mapping the Reactivity of the C=C bond of Cyclic Enol Ether Derivatives of Sugars: Nucleophilicity Parameters of Glycals

Sophie Rodrigues,[a] Saloua Chelly,[b] Jenny Ha,[a] Lucie Pedussaut,[a] Sami Lakhdar*,[b] Raphaël Robiette*,[c] Stéphane P. Vincent*[a] and Guillaume Berionni*[a]

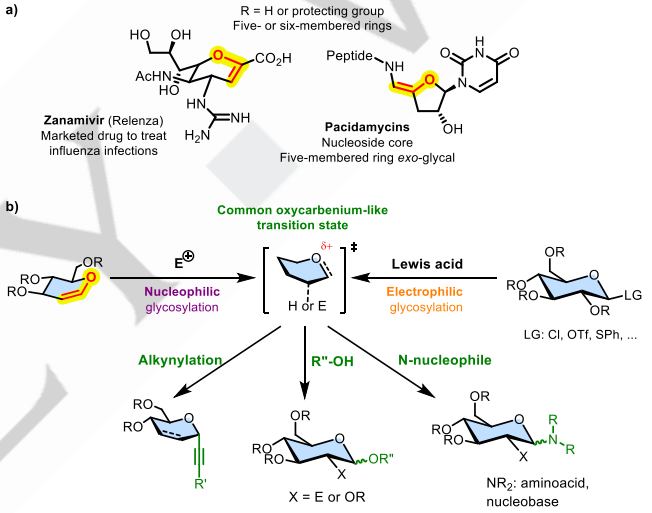
[a] Dr S. Rodrigues, J. Ha, Dr L. Pedussaut, Prof S. P. Vincent, Prof G. Berionni
Department of Chemistry and Namur Institute of Structured Matter (NISM). Université de Namur - 61 Rue de Bruxelles, 5000 Namur, Belgium
E-mail: guillaume.berionni@unamur.be
[b] Dr S. Chelly, Dr S. Lakhdar
CNRS, Université Paul Sabatier, Laboratoire Hétérochimie Fondamentale et Appliquée (LHFA, UMR5069)
118 Route de Narbonne, 31062 Cedex 09 Toulouse, France
[c] Prof R. Robiette
Institute of Condensed Matter and Nanosciences, Université Catholique de Louvain
Place Louis Pasteur 1 box L4.01.02, 1348 Louvain-La-Neuve, Belgium
Supporting information for this article is given via a link at the end of the document.

Abstract: Glycals are unsaturated sugar derivatives constituting a large family of polyhydroxylated synthons which are widely exploited as synthetic intermediates in the synthesis of natural products and as final molecules for biochemical applications. We report the first investigation in the understudied area of structure-reactivity relationship and quantitative mapping of reactivity in *endo*- and *exo*-glycals compounds. For quantifying the nucleophilicity of the C=C double bond of a series of *endo*- and *exo*-glycals, we performed kinetic investigations of their C-C bond formation with reference electrophiles of known electrophilicity parameters. Fast spectroscopic techniques experiments (stopped-flow and laser-flash photolysis) enabled us to determine the rate constant of hundreds of reactions, which allows the first comprehensive mapping and structure-reactivity analysis of the nucleophilic reactivity of this wide family of cyclic enol ethers. Quantum-chemical calculations corroborate with kinetic investigations and highlight the crucial role of ring strain variations to explain the relative nucleophilicity of *endo*- and *exo*-glycals. We examined also the influence of substitution and showed that alkoxy substituents decrease nucleophilicity through inductive effects and hyperconjugation.

Introduction

Glycals are unsaturated sugar derivatives constituting a large family of polyhydroxylated synthons which are widely exploited as synthetic intermediates in the synthesis of natural products[1-3] and as final molecules for biochemical applications (Scheme 1a).[4-6] The synthesis and functionalization of *endo*- and *exo*-glycals and their use as biochemical probes are the subject of increasing research interest in recent years.[7-14]

The reactivity of the C=C double bond of *endo*- and *exo*-glycals which engages the anomeric carbon is governed by many factors: 1) the size of their heterocyclic central core, mostly derived from 2,3-dihydrofuran and 2,3-dihydropyran (five- and six-membered rings, respectively), 2) the relative configuration of the remote stereogenic centers, 3) the hydroxyl protecting groups which influence the strain and global conformation of the ring, and by other stereoelectronic effects stabilizing the incipient oxonium ion intermediate (Scheme 1b).[15-17]



Scheme 1. a) Biologically relevant glycals; b) Putative common transition state of classical electrophilic glycosylation and nucleophilic reactivity of glycals to yield C-, O- and N-glycosides.

Glycals belong to the wide family of cyclic enol ethers, which have been extensively used as nucleophiles in organic synthesis and for which the nucleophilic reactivity was investigated in depth.[18-27] Surprisingly however, no quantitative investigation of the C=C bond reactivity of glycals has been reported so far, although recent investigations of photo-click reactions with glycals[28-29], and other works focusing on their C=C double bond functionalization[30-45] by us and others illustrate the importance of structure-reactivity analysis and reactivity predictions, crucial for the rational development of new synthetic methods to obtain highly functionalized drug-like scaffolds.

Results and discussions

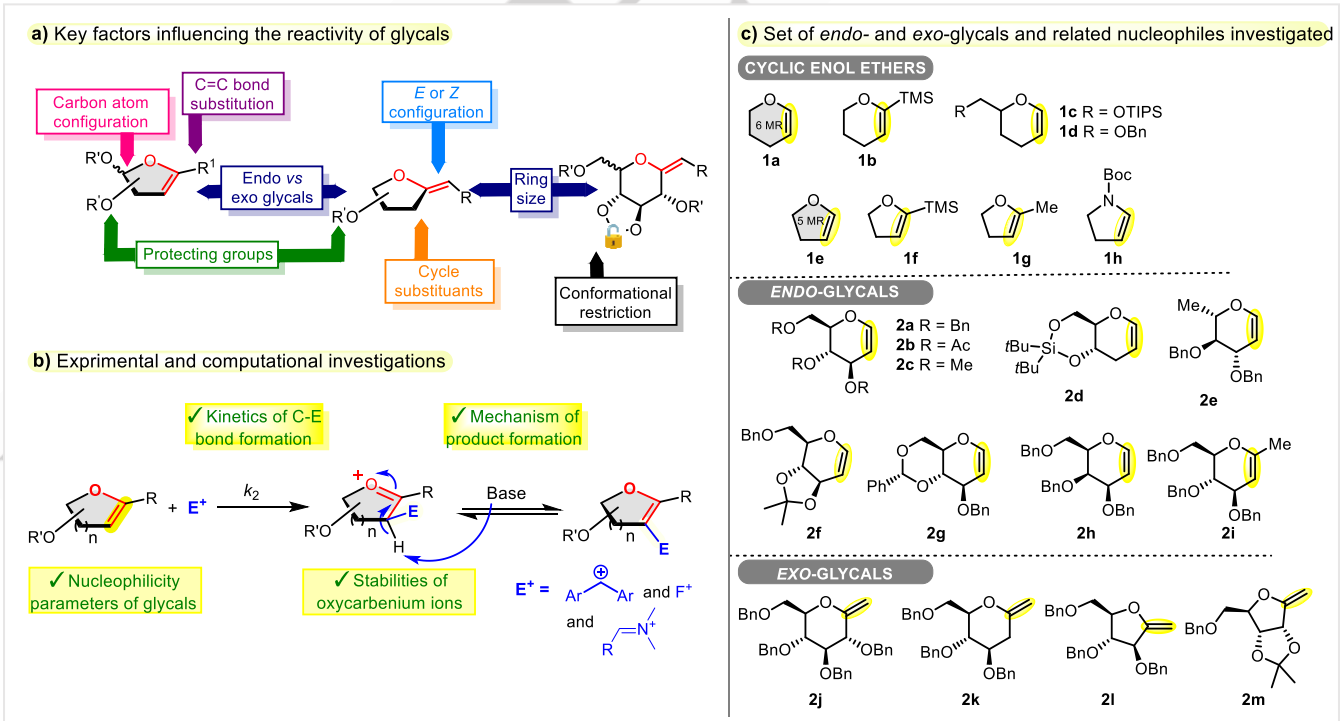
The electrophilicity of carbohydrates at the anomeric position has been extensively studied using competition experiments[46-48] which resulted in reactivity maps in which hexoses display reactivity differences of up to 4 orders of magnitude as a function of the protective group pattern, the presence of deoxy positions and ring constraints. Such a reactivity scale does not exist for glycals despite their use in glycosylation reactions.

Mechanistically, glycosylations using nucleophilic glycals or electrophilic carbohydrates share a common feature: the transition states of the two reactions display a substantial carbocationic character (Scheme 2b). Therefore, our objective was to assess whether the parameters that dramatically affect electrophilic glycosylations (that stabilize or destabilize carbocationic intermediates) also impact the reactivity of nucleophilic glycals.

Kinetic investigations

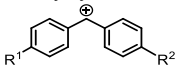
Due to the lack of reactivity model and structure-reactivity investigations on glycals, we started by a kinetic investigation of the C=C bond functionalization reactions of selected glycals with reference electrophiles covering a wide range of reactivity, using stopped-flow spectrophotometry and laser-flash photolysis spectroscopic techniques. The nucleophilicity parameter of a set of thirteen *endo*- and *exo*-glycals were determined according to the universal Mayr reactivity scales,[18,49,50] leading to the discovery that substituents and ring size add up to a factor of 10^3 on their C=C bond reactivity. Quantum-chemical calculations revealed that ring-strain energy release between the glycal and oxycarbenium ion intermediates dominate the reactivity of glycals together with substituent stereoelectronic effects and hyperconjugation stabilization in the oxycarbenium intermediate. The kinetic, thermodynamic and mechanistic investigations enabled us to elucidate the interplay between several key factors influencing reactivity (Scheme 2a).

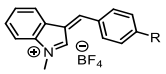
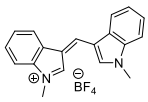
We started by monitoring the kinetics of the reactions between the cyclic enol ethers **1a**-**h**, the *endo*-glycals **2a**-**i** and the *exo*-glycals **2j**-**m** (Scheme 2c) with the reference benzhydrylium **3** and indolyl-methylium **4** ions of calibrated electrophilicity parameters (Table 1).[51] Kinetics of these reactions have been monitored by time-resolved UV-Vis spectroscopy at the maximum wavelength of absorption λ_{max} of the electrophiles (Table 1). In the presence of at least two equivalents of a nucleophile **1**-**2**, mono-exponential decays at the λ_{max} of the carbenium ions **3**-**4** were observed, indicating a pseudo first-order kinetic against the electrophiles. In most cases, the benzhydrylium ions **3a-i** or indolyl-methylium ions **4a-d** were completely consumed, and plots of k_{obs} (s^{-1}) against nucleophile concentrations [**1-2**] (M) were linear with negligible intercepts (Figure 1b).



Scheme 2. a) Key parameters influencing the nucleophilicity of the C=C double bond of *endo*- and *exo*-glycals; b) Kinetic, thermodynamic and computational investigations performed in this work for rationalizing the reactivity of glycals; c) Cyclic enol ethers **1a**-**1h,** *endo*-glycals **2a**-**2i** and *exo*-glycals **2j**-**2m** synthesized and investigated in this work.

Table 1. Structures, λ_{max} and electrophilicity parameter *E* for the benzhydrylium ions **3a-i** and indolyl-methylium ions **4a-d** used as reference electrophiles.[51]

Benzhydrylium ions **3** 	R^1	R^2	λ_{max} / nm in CH_3CN	*E*
3a	H	H	443	+5.47
3b	F	F	447	+5.01
3c	H	Me	456	+4.43
3d	Me	Me	473	+3.63
3e	OMe	OMe	500	0.00
3f	$NMe(CH_2CF_3)$	$NMe(CH_2CF_3)$	586	−3.85
3g	NPh_2	NPh_2	645	−4.72
3h	$N(CH_2CH_2)_2O$	$N(CH_2CH_2)_2O$	618	−5.53
3i	NMe_2	NMe_2	607	−7.02

Indolyl-methylium ions **4**		λ_{max} / nm in CH_3CN	*E*
4a	R = H	425	−1.80
4b	R = Me	431	−2.19
4c	R = OMe	492	−3.02
4d		540	−5.99

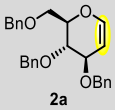
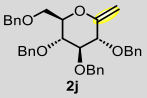
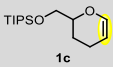
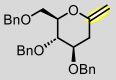
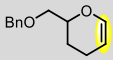
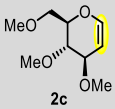
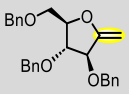
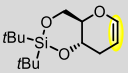
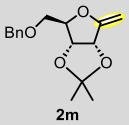
Reactivity parameters of glycals

The slope of these correlations gave the second-order rate constants k_2 (Table 2 and SI) which are used for the determination of the nucleophilicity parameters of the cyclic enol ethers **1a-h** and glycals **2a-m** according to Mayr and Patz equation (Eq. 1).[18-27] This equation characterizes electrophiles by the electrophilicity parameter *E*, and nucleophiles by the nucleophilicity parameter *N* and the nucleophile-specific sensitivity parameter s_N, while k_2 is the second-order rate constant (in $M^{-1}.s^{-1}$) of the reaction between an electrophile and a nucleophile.

$$\log(k_{2\ (20\ °C)}) = s_N(E+N) \qquad \text{(Eq. 1)}$$

Plots of $\log(k_2)$ *vs.* *E* are linear (Figure 1c), indicating the applicability of Eq. 1 and providing the nucleophilicity parameters *N* and s_N of the cyclic enol ethers **1a-h** and glycals **2a-m**. The slopes of the correlations are in the range of $0.57 < s_N < 1.37$, comparable to structurally related π-nucleophiles (alkenes, enamines, acyclic enols ethers, silyl enols ethers).[18-22,25-27,51] The reference electrophiles **3** and **4** have been used to determine the nucleophilicity parameters of hundreds of alkenes, enamines, enol ethers, silyl enol ethers in the Mayr nucleophilicity scale,[18-27] and we can thus directly compare their reactivity with those of our set of cyclic enols ethers, *endo*- and *exo*-glycals (Figure 2).

Table 2. Second-order rate constants k_2 for the reaction of cyclic enol ethers **1a-h**, *endo*-glycals **2a-i** and *exo*-glycals **2j-m** with the benzhydrylium **3a-i** or indolyl-methylium **4a-d** ions in CH_3CN or CH_2Cl_2 at 20 °C, and the resulting nucleophilicity *N* and nucleophile-specific sensitivity parameter s_N of **1-2**.

Cyclic enol ethers **1a-h**	E^+	k_2 / $M^{-1}\,s^{-1}$	*Endo*-glycals **2a-i**	E^+	k_2 / $M^{-1}\,s^{-1}$	*Exo*-glycals **2j-m**	E^+	k_2 / $M^{-1}\,s^{-1}$
 **1a** **N = 3.01** s_N = 1.43	**3e**	4.12×10^{7}	 **2a** **N = 1.71** s_N = 1.16	**3a**	1.13×10^{9}	 **2j** **N = 4.01** s_N = 0.91	**4a**	1.18×10^{2}
	4a	6.91		**3c**	1.09×10^{8}		**4b**	4.47×10^{1}
	4c	9.73×10^{-1}		**3d**	3.95×10^{7}		**4c**	7.12
	3f	2.33×10^{-1}		**4a**	6.34×10^{-1}		**3f**	1.03
							3g	2.88×10^{-1}
 **1c** **N = 2.87** s_N = 0.66	**4a**	5.18	 **2b** **N = 1.80** s_N = 1.14	**3a**	6.48×10^{8}	 **2k** **N = 6.19** s_N = 0.79	**4b**	1.37×10^{3}
	4b	2.94		**3c**	1.51×10^{8}		**4c**	3.60×10^{2}
	4c	7.20×10^{-1}		**3d**	6.02×10^{7}		**3f**	5.85×10^{1}
	3f	2.38×10^{-1}		**4a**	6.90×10^{-1}		**3g**	1.51×10^{1}
 **1d** **N = 2.81** s_N = 0.57	**4a**	4.36	 **2c** **N = 1.50** s_N = 1.37	**3b**	3.72×10^{8}	 **2l** **N = 5.50** s_N = 0.76	**4b**	3.15×10^{2}
	4b	2.21		**3c**	1.79×10^{8}		**4c**	8.72×10^{1}
	4c	5.54×10^{-1}		**3d**	2.10×10^{7}		**3f**	1.66×10^{1}
	3f	3.10×10^{-1}		**4a**	3.35×10^{-1}		**3g**	3.99
 **1e** **N = 5.02** s_N = 0.63	**4a**	1.29×10^{2}	 **2d** **N = 1.98** s_N = 1.09	**3a**	3.00×10^{8}	 **2m** **N = 5.35** s_N = 0.88	**4c**	1.06×10^{2}
	4c	1.77×10^{1}		**3c**	1.65×10^{8}		**3f**	2.05×10^{1}
	3f	3.91		**3d**	4.05×10^{7}		**3g**	4.74
	4d	2.92×10^{-1}		**4a**	1.05		**3h**	5.87×10^{-1}

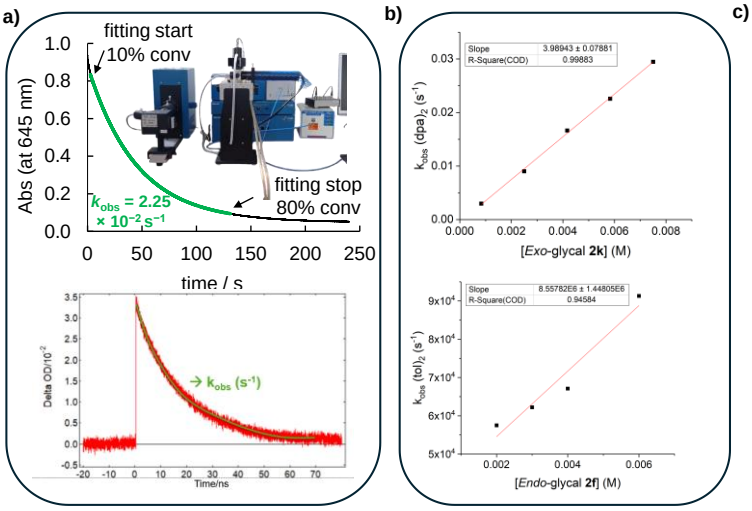


Figure 1. a) Top: Exponential decay of the absorption of the cation **3g** ([**3g**] = 10^{-4} mol L^{-1}) at λ_{max} = 645 nm while reacting with an excess of *exo*-glycal **2l** ([**2l**] = 5.83×10^{-3} mol L^{-1}) in CH_2Cl_2 at 20 °C and determination of k_{obs} (k_{obs} = 2.25 × 10^{-2} s^{-1}) by exponential fitting. Bottom: Exponential decay of the absorption of the cation **3d** ([**3d**] = 10^{-4} mol L^{-1}) at λ_{max} = 473 nm during the reaction with the *endo*-glycal **2f** ([**2f**] = 2.00×10^{-3} mol L^{-1}) in CH_2Cl_2 at 20 °C and determination of k_{obs} (k_{obs} = 5.75×10^{4} s^{-1}); b) Top: Determination of the second-order rate constant k_2 of the reaction between cation **3g** and glycal **2l** from the dependence of k_{obs} on the concentration of nucleophile **2l**. Bottom: determination of k_2 of the reaction between **3d** and **2f** from the dependence of k_{obs} on the concentration of **2f**; c) Plots of the logarithms of the second-order rate constants log(k_2) for the reactions of enol ethers **1f-g** and glycals **2d-f**, **2h**, **2j**, **2l** with benzhydrylium ions **3a-i** or indolyl iminium ions **4a-d** *versus* their electrophilicity parameters *E* [see Eq. 1, and Tables 1 and 2] used for determining *N* parameters.

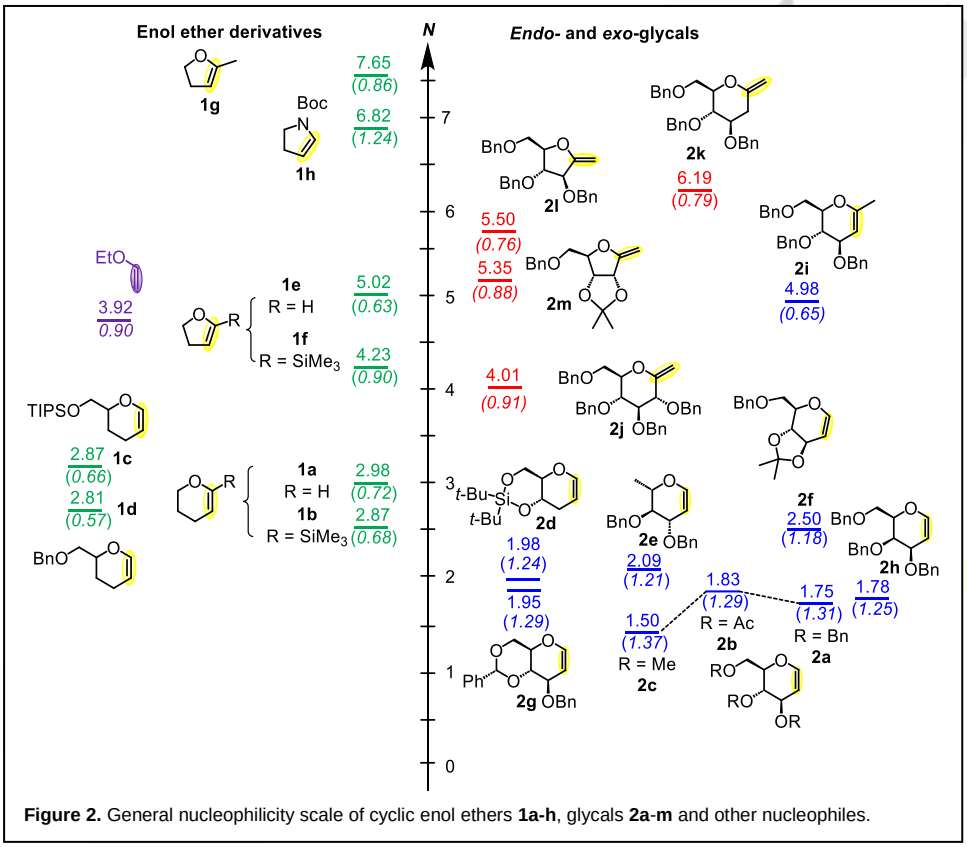


Figure 2. General nucleophilicity scale of cyclic enol ethers **1a-h**, glycals **2a-m** and other nucleophiles.

We thus compared the nucleophilicity of glycals with that of other π-systems such as alkenes, enamines, and enol ethers by incorporating them. This revealed that the C=C double bond of *endo*-glycals is much less nucleophilic than classical cyclic enol ethers by one or two orders of magnitude. This can be illustrated by observing that the *endo*-glycal **2a** is *ca.* ten times less reactive towards carbocations than the cyclic enol ether **1a**.

One can observe however that the nucleophilicity of glycals is not very sensitive to the nature of the alkoxy protecting groups as shown by comparing **2a-d**, for instance. This result highly contrasts with the reactivity rules applied in carbohydrate chemistry: while electron-withdrawing (disarming) groups such as esters are strongly deactivating because they destabilize the cationic transition state, electron-donating (arming) groups (Bn or Me ethers) activate the sugar ring and accelerate the reactions.[46-48] Surprisingly, the comparison of molecules **2a**, **2b** and **2c** shows that such a rule (arming and disarming effects)[52-49] does not apply for glycals. To confirm the *N* values obtained for the *endo*-glycals, competition reactions were realized between representative pairs of glycals and the Eschenmoser iminium ion (*N*,*N*-dimethyl methaniminium iodide). The reaction between **2a** and **2e** showed that *endo*-glycal **2e** reacts indeed faster towards this electrophile (see SI, p S58). The same conclusion can be drawn from the competition reactions between glycals **2b** and **2e**, glycals **2e** and **2f**, and glycals **2b** and **2f**. These experiments corroborate the *N* values obtained for *endo*-glycals and shows their applicability to other types of electrophiles of interest in synthesis.

Quantum chemical calculations

As quantified experimentally, in contrast to common belief, the reactivity of the C=C bond of glycals is not strongly affected by the substitution pattern and quantum chemical calculations show that ring strain energy overcompensates electronic effects.

In classical glycosylations, deoxy sugars are much more reactive than their alkoxy counterparts (typically 25 times faster).[46] Such a trend was also observed with deoxy glycals **2d** and **2e** being more reactive than *e.g.* **2a** or **2h** (Figure 2) but at a much lower magnitude, showcasing that the classical electronic effects that are at play in electrophilic glycosylation reactions are much less contributing to the overall nucleophilic reactivity of glycals.

To understand the origin of the observed nucleophilicity variations according to structural changes, we performed a computational study. We first investigated why dihydrofurans are more reactive than dihydropyran derivatives, using **ani$_2$CH** as the model electrophile, and **1a, 1e** and **5a** as model nucleophiles. The calculated free energy barriers for addition (Table 3) align well with the experimentally observed higher reactivity of **1e** compared to **1a** (Figure 2). However, most computed electronic parameters failed to predict the correct relative reactivity – only the HOMO energy showed some correlation, though weak (see SI). This suggests that electronic effects are not the primary factor behind this reactivity difference. Additionally, similar computed trends for proton affinity (PA), methyl cation affinity[60-62] (MCA) and free energy of addition onto **ani$_2$CH** (see SI) suggest that sterics are not significant in these reactions. We therefore focused on ring strain. Our results show that the increased nucleophilicity of 5-membered *endo*-glycals arises mainly from a decrease in ring strain during the reaction, whereas 6-membered ring derivatives exhibit an increase in ring strain (see Table 3, and SI for full data). Next, we explored how allylic substituents (*e.g.* C^3 substituent) affect the nucleophilicity of *endo*-glycals, by considering OMe and OAc as model substituents. Computed free energy barriers reveal a consistent drop in reactivity with substitution by an oxygenated group (Table 3), in good agreement with determined nucleophilicity parameters (see Figure 2). The reduced nucleophilicity of substituted *endo*-glycals is explained by negative hyperconjugation between the $p_{C=C}$ and the s^*_{C3-O} orbitals, as shown by NBO analysis (Figure 3).

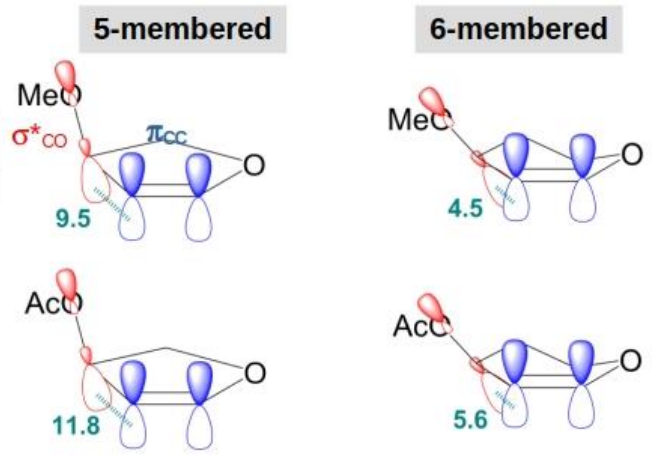
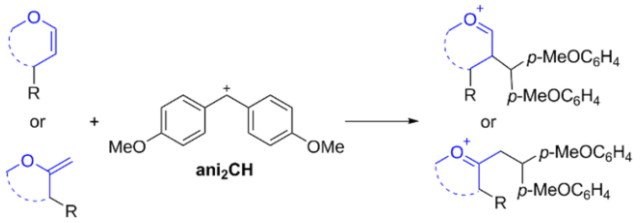


Figure 3. Influence of allylic substituents on the C=C double bond reactivity on 5 and 6-membered ring model endo-glycals throug negative hyperconjugation.

Table 3. Computed activation free energy of addition of selected enol ether and glycals onto the reference benzhydrylium ion ani$_2$CH **3e** ($\Delta G^‡$ in kcal.mol^{-1}), and evolution of the ring strain along the reaction (D_{BDE} in kcal.mol^{-1}). Experimental values (in brackets) were estimated using Eq. 1 with the determined *N* and s_N parameters and the *E* parameters for **3e**.



Non-cyclic enol ethers	*Endo*-glycal models	*Exo*-glycal models	*Endo*-glycal compound
6a $\Delta G^‡$ = 9.1	**1e** $\Delta G^‡$ = 12.1 (12.9) D_{BDE} = -0.9	**1m** $\Delta G^‡$ = 10.3 D_{BDE} = -5.2	**2c** $\Delta G^‡$ = 18.4 D_{BDE} = 9.5 p -> $s_{CO^•}$ = 6.1
6b $\Delta G^‡$ = 9.3	**1a** $\Delta G^‡$ = 15.5 (14.3) D_{BDE} = 2.6	**1n** $\Delta G^‡$ = 10.8 D_{BDE} = -4.6	
6c $\Delta G^‡$ = 16.4	**1i** $\Delta G^‡$ = 14.8	**1o** $\Delta G^‡$ = 13.4	
6d $\Delta G^‡$ = 17.9	**1j** $\Delta G^‡$ = 16.5	**1p** $\Delta G^‡$ = 14.0	
6e $\Delta G^‡$ = 11.6	**1k** $\Delta G^‡$ = 17.8		
	1l $\Delta G^‡$ = 18.0		

This interaction also explains why deactivation is more pronounced for the pseudo-axial approach, despite lower steric hindrance. Indeed, the orbital overlaps between the s^*_{C3-O} and the $p_{C=C}$ is more efficient when the substituent is in pseudo-axial position. This interaction also explains why the de-activation is less pronounced for the 6-membered derivatives as the orbital overlaps between the s^*_{C3-O} and the $p_{C=C}$ is less efficient in this latter case.

The experimentally determined nucleophilicity parameters show *exo*-glycals to be more nucleophilic than their *endo* counterpart (Table 2 and Figure 2). The similar computed free energy of activation for non-cyclic enol ethers **6a** and **6b** (Table 3, left)

suggests that the origin is not related to sterics nor to the secondary *vs* tertiary nature of the carbenium which is formed.

As various computed electronic parameters of gycals are not predicting the correct relative experimental reactivity (see SI), we surmised that the enhanced reactivity of *exo*-glycals likely stems from the cyclic nature of glycals. We therefore examined, here also, the variation of ring strain along the reaction.

Our results show that ring strain decreases significantly during the reaction for both 5- and 6-membered *exo*-glycals (evolution of the ring strain along the reaction ~5 kcal kcal.mol^{-1}) whereas the decrease is less marked for 5-membered *endo*-glycals and the ring strain even increases along the reaction of 6-membered *endo*-glycals (see Table 3). The greater nucleophilicity of *exo*-glycals over *endo*-glycals can therefore be accounted for by ring strain energies variations along the reaction with the electrophiles.

Conclusions

This first quantitative reactivity mapping of the nucleophilicity of *endo*- and *exo*-glycals provides a systematic overview of the impact of several key parameters on their C=C bond reactivity. With a pronounced transmission of substituents hyperconjugative effects and important role of ring strain, we found that glycal covers a wide range of almost five orders of magnitude (N = 1.50 for **2c** to 6.19 for **2k**). Interestingly the parameters affecting electrophilic glycosylations and nucleophilicity of glycals are different, despite the common cationic character at the transition state for the two reactions. We found that ring strain contributes more to the reactivity of glycals yielding some counter-intuitive trends especially for “disarmed” or deoxy-sugars.

Supporting Information

The authors have cited additional references within the Supporting Information.[63-86]

Acknowledgements

We acknowledge the F.W.B. for the ARC grant (EXO-sugar-MAP), the University of Namur and the Fond National de la Recherche Scientifique (F.R.S.-FNRS) for financial support (Grant Numbers: T.0012.21 (G.B)). Computational resources have been provided by the supercomputing facilities of the Université Catholique de Louvain (CISM/UCL) and the Consortium des Équipements de Calcul Intensif en Fédération Wallonie Bruxelles (CÉCI) funded by the Fonds de la Recherche Scientifique-FNRS (F.R.S.-FNRS) under convention 2.5020.11 and by the Walloon Region. We thank the PC^2 (UNamur) technological platforms for access to all characterization instruments. RR is a Maître de Recherche of the F.R.S.-FNRS. The authors are grateful to the generous support from the CNRS, the Agence Nationale de la Recherche (ANR, PhotoFlat N° 220424, DePhi), and the Université of Toulouse.

Keywords: Glycals • Nucleophilicity • Kinetic studies • Reactivity scales • Reactivity mapping

References

[1] Y. Yadav, R. Sagar, “Glycals as Chiral Synthons in Organic Synthesis of Privileged Molecular Scaffolds” *Chem. Asian J.* **2025**, *20*, e202401773.

[2] G. Goti, “Catalytic Radical Reactions of Unsaturated Sugars” *ChemCatChem*, **2022**, *14*, e202200290.

[3] H. H. Kinfe, “Versatility of glycals in synthetic organic chemistry: coupling reactions, diversity-oriented synthesis and natural product synthesis” *Org. Biomol. Chem*. **2019**, *17*, 4153.

[4] D. Goyard, B. Kónya, A. S. Chajistamatiou, E. D. Chrysina, J. Leroy, S. Balzarin, M. Tournier, D. Tousch, P. Petit, C. Duret, P. Maurel, L. Somsák, T. Docsa, P. Gergely, J.-P. Praly, J. Azay-Molhau, S. Vidal, “Glucose-derived spiro-isoxazolines are anti-hyperglycemic agents against type 2 diabetes through glycogen phosphorylase inhibition” *European Journal of Medicinal Chemistry* **2016**, *108*, 444.

[5] C. Frédéric, A. Tikad, J. Fu, W. Pan, R. B. Zheng, A. Koizumi, X. Xue, T. L. Lowary, S. P. Vincent, “*Synthesis of unprecedented sulfonylated phosphono-exo-glycals designed as inhibitors of the three mycobacterial galactofuranose processing enzymes*” *Chem. Eur. J*. **2016**, *22*, 15913.

[6] Z. Yu, D. Inoue, N. Sawada, H. Takinami, T. Ghosh, N. Sasaki, M. Abe, T. Taniguchi, T. Koike, T. Nokami, “Photochemical transformations of glycosyl bromides in the presence of amines” *Carbohydrate Research* **2025**, *552*, 109436.

[7] J. Bautista-Nava, L. F. Porras-Santos, L. Quintero, J. A. Pérez-Bautista, P. López-Mendoza, F. Sartillo-Piscil, “Oxa-Ferrier Rearrangement Reaction Mediated by TEMPO Cation and $NaClO_2$: Application to the Total Synthesis of Passifetilactones B and C” *J. Org. Chem*. **2025**, *90*, 6251.

[8] J. Li, Z. Fu, Z. Qiao, D. Xie, L. Zhang, Y.-Z. Liu, J. Yang, J.-X. Yan, X. Ma, “Controllable 1,3-Bis-Functionalization of 2-Nitroglycals with High Regioselectivity and Stereoselectivity Enabled by a H-Bond Catalyst” *JACS Au* **2024**, *4*, 974.

[9] F. Trauner, B. Boutet, F. Pilz, V. Weber, D. Didier, “Zweifel olefination for C-glycosylation” *Commun. Chem*. **2024**, *7*, 306.

[10] J. Regier, S. Ghanty, Y. Bolshan, “Stereoselective Palladium-Catalyzed Arylation of Exo-Glycals with Aryl Iodides” *J. Org. Chem.* **2022**, *87*, 524.

[11] Y. Yang, B. Yu, “Recent Advances in the Chemical Synthesis of C-Glycosides” *Chem. Rev.* **2017**, *117*, 12281.

[12] C. J.-M. Frédéric, S. P. Vincent, “Synthesis of exo-glycals and their biochemical applications” *Tetrahedron* **2018**, *74*, 6512.

[13] D. C. Koester, E. Kriemen, D. B. Werz, “Flexible Synthesis of 2-Deoxy-C-Glycosides and (1→2)-, (1→3)-, and (1→4)-Linked C-Glycosides” *Angew. Chem. Int. Ed.* **2013**, *52*, 2985.

[14] E. Bokor, S. Kun, D. Goyard, M. Tóth, J.-P. Praly, S. Vidal, L. Somsák, “C-Glycopyranosyl Arenes and Hetarenes: Synthetic Methods and Bioactivity Focused on Antidiabetic Potential” *Chem. Rev.* **2017**, *117*, 1687.

[15] A. Franconetti, A. Ardá, J.-L. Asensio, Y. Blériot, S. Thibaudeau, J. Jiménez-Barbero, “Glycosyl Oxocarbenium Ions: Structure, Conformation, Reactivity, and Interactions” *Acc. Chem. Res*. **2021**, *54*, 2552.

[16] M. Armand, A. Nin-Hill, A. Ardá, E. Berrino, J. Désiré, A. Martin-Mingot, B. Michelet, J. Jiménez-Barbero, Y. Blériot, C. Rovira, S. Thibaudeau, “Glycosylium Ions in Superacid Mimic the Transition State of Enzyme Reactions” *J. Am. Chem. Soc.* **2024,** *146*, 32618.

[17] P. Pal, A. K. Shaw, “The evolution of comprehensive strategies for furanoid glycal synthesis and their applications” *RSC Adv.* **2017**, *7*, 25897.

[18] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, "Reference Scales for the Characterization of Cationic Electrophiles and Neutral Nucleophiles" *J. Am. Chem. Soc.* **2001**, *123*, 9500.

[19] H. Mayr, B. Kempf, A. R. Ofial, "π-Nucleophilicity in Carbon−Carbon Bond-Forming Reactions" *Acc. Chem. Res.* **2003**, *36*, 66.

[20] T. Tokuyasu, H. Mayr, "Nucleophilic Reactivities of Ketene Acetals" *Eur. J. Org. Chem.* **2004**, *2004*, 2791.

[21] A. D. Dilman, H. Mayr, "Nucleophilic Reactivities of Silyl Ketene Acetals and Silyl Enol Ethers Containing $(C_6F_5)_3SiO$ and $(C_6H_5)_3SiO$ Groups" *Eur. J. Org. Chem.* **2005**, *2005*, 1760.

[22] H. A. Laub, H. Yamamoto, H. Mayr, "Effect of the "Supersilyl" Group on the Reactivities of Allylsilanes and Silyl Enol Ethers" *Org. Lett.* **2010**, *12*, 5206.

[23] H. Asahara, H. Mayr, "Electrophilicities of Bissulfonyl Ethylenes" *Chem. Asian J.* **2012**, *7*, 1401.

[24] H. A. Laub, D. Gladow, H.-U. Reissig, H. Mayr, "The Influence of Perfluorinated Substituents on the Nucleophilic Reactivities of Silyl Enol Ethers" *Org. Lett.* **2012**, *14*, 3990.

[25] J. Ammer, C. Nolte, H. Mayr, "Free Energy Relationships for Reactions of Substituted Benzhydrylium Ions: From Enthalpy over Entropy to Diffusion Control" *J. Am. Chem. Soc.* **2012**, *134*, 13902.

[26] R. Appel, S. Chelli, T. Tokuyasu, K. Troshin, H. Mayr, "Electrophilicities of Benzaldehyde-Derived Iminium Ions: Quantification of the Electrophilic Activation of Aldehydes by Iminium Formation" *J. Am. Chem. Soc.* **2013**, *135*, 6579.

[27] A. I. Leonov, D. S. Timofeeva, A. R. Ofial, H. Mayr, "Metal Enolates – Enamines – Enol Ethers: How Do Enolate Equivalents Differ in Nucleophilic Reactivity?" *Synthesis* **2019**, *51*, 1157.

[28] B. D. Fairbanks, L. J. Macdougall, S. Mavila, J. Sinha, B. E. Kirkpatrick, K. S. Anseth, C. N. Bowman, "Photoclick Chemistry: A Bright Idea" *Chem. Rev.* **2021**, *121*, 6915.

[29] Y. Fu, H. Helbert, N. A. Simeth, S. Crespi, G. B. Spoelstra, J. M. van Dijl, M. van Oosten, L. R. Nazario, D. van der Born, G. Luurtsema, W. Szymanski, P. H. Elsinga, B. L. Feringa, "Ultrafast Photoclick Reaction for Selective ^{18}F-Positron Emission Tomography Tracer Synthesis in Flow" *J. Am. Chem. Soc.* **2021**, *143*, 10041.

[30] N. Hussain, A. Hussain, "Advances in Pd-catalyzed C–C bond formation in carbohydrates and their applications in the synthesis of natural products and medicinally relevant molecules" *RSC Adv.* **2021**, *11*, 34369.

[31] M. de Robichon, D. Branquet, J. Uziel, N. Lubin-Germain, A. Ferry, "Directed Nickel-Catalyzed *pseudo*-Anomeric C−H Alkynylation of Glycals as an Approach towards *C*-Glycoconjugate Synthesis" *Adv. Synth. Catal.* **2021**, *363*, 5138.

[32] X.-P. Gong, Y. Li, H.-C. Liu, Z. Zhang, Z.-J. Niu, Y.-N. Ding, Y. An, X. Chen, Y.-C. Huang, R.-Q. Jiao, X.-Y. Liu, Y.-M. Liang, "Palladium-Catalyzed One-Step Synthesis of Stereodefined Difunctionalized Glycals" *CCS Chem.* **2023**, *5*, 741.

[33] A. Dubey, N. Singh Chauhan, Z. Azeem, P. Kumar Mandal, "Directed Palladium-Catalyzed *pseudo*-Anomeric C−H Functionalization of Glycal-Type Substrates: Access to Unsymmetrical *gem*-Diarylmethyl *C*-Glycosides" *Adv. Synth. Catal.* **2023**, *365*, 820.

[34] Y.-N. Ding, M.-Z. Xu, Y.-C. Huang, L. Ackermann, X. Kong, X.-Y. Liu, Y.-M. Liang, "Stereoselective assembly of C-oligosaccharides via modular difunctionalization of glycals" *Nat. Commun.* **2024**, *15*, 2794.

[35] A. Chen, Y. Han, R. Wu, B. Yang, L. Zhu, F. Zhu, "Palladium-catalyzed Suzuki-Miyaura cross-couplings of stable glycal boronates for robust synthesis of C-1 glycals" *Nat. Commun.* **2024**, *15*, 5228.

[36] C. J.-M. Frédéric, J. Cornil, M. Vandamme, L. Dumitrescu, A. Tikad, R. Robiette, S. P. Vincent, "Highly (*Z*)-Diastereoselective Synthesis of Trifluoromethylated *exo*-Glycals via Photoredox and Copper Catalysis" *Org. Lett.* **2018,** *20*, 6769.

[37] J. Cao, S. P. Vincent, "Synthesis of Spirocyclic Cyclopropyl Glycosyl-1-phosphate Analogues" *Org. Lett.* **2022**, *24*, 4165.

[38] M. Liu, K.-M. Liu, D.-C. Xiong, H. Zhang, T. Li, B. Li, X. Qin, J. Bai, X.-S. Ye, "Stereoselective Electro-2-deoxyglycosylation from Glycals" *Angew. Chem. Int. Ed.* **2020**, *59*, 15204.

[39] D. C. Koester, D. B. Werz, "Sonogashira–Hagihara reactions of halogenated glycals" *Beilstein J. Org. Chem.* **2012**, *8*, 675.

[40] N. Hussain, A. Ahmed, D. Mukherjee, "2- Halo Glycals as "Synthon" for 2- C- Branched Sugar: Recent Advances and Applications in Organic Synthesis" *Asian J. Org. Chem.* **2020**, *9*, 882.

[41] M. Maheshwari, N. Hussain, "Difunctionalization of Glycals and their Derivatives: Strategies and Applications in the Synthesis of Bioactive Compounds" *Adv. Synth. Catal.* **2025**, *367*, e202401517.

[42] P. Saha, D. K. Sharma, "Visible Light-Induced, Persulfate-Promoted Synthesis of 2 Haloglycals from Glycals" *J. Org. Chem.* **2025**, *90*, 13082.

[43] M. Maheshwari, N. Hussain, "Synthesis of Branched Sugars and Chiral Aromatic Building Blocks Derived from Glycals" *Synlett* **2025**, *36*, 2180.

[44] Y. Xiong, X. Tan, W. Yang, S.-F. Ni, Y. Dai, "Metal-free synthesis of diverse 2-deoxy-β-*N*-glycosides through regio- and stereospecific aminoselenenylation of glycals" *Green Chem.* **2025**, *27*, 10784.

[45] K. A. Othman, Y. Xiang, Y. Wang, N. Huang, N. Wang, L. Li, H. Yao, "Stereoselective synthesis of *C*-glycosides from glycals and organotrifluoroborate salts" *Chem. Commun.* **2025**, *61*, 7867.

[46] Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, "Programmable One-Pot Oligosaccharide Synthesis" *J. Am. Chem. Soc.* **1999**, *121*, 734.

[47] N. L. Douglas, S. V. Ley, U. Lucking, S. L. Warriner, "Tuning glycoside reactivity: New tool for efficient oligosaccharide synthesis" *J. Chem. Soc., Perkin Trans. 1* **1998**, 51.

[48] P. O. Adero, T. Furukawa, M. Huang, D. Mukherjee, P. Retailleau, L. Bohé, D. Crich, "Cation Clock Reactions for the Determination of Relative Reaction Kinetics in Glycosylation Reactions: Applications to Gluco- and Mannopyranosyl Sulfoxide and Trichloroacetimidate Type Donors" *J. Am. Chem. Soc.* **2015**, *137*, 10336.

[49] H. Mayr, A. R. Ofial, "Philicities, Fugalities, and Equilibrium Constants" *Acc. Chem. Res.* **2016**, *49*, 952.

[50] H. Mayr, A. R. Ofial, "Philicity, fugality, and equilibrium constants: when do rate-equilibrium relationships break down?" *Pure Appl. Chem.* **2017**, *89*, 729.

[51] R. J. Mayer, N. Hampel, P. Mayer, A. R. Ofial, H. Mayr, "Synthesis, Structure, and Properties of Amino-Substituted Benzhydrylium Ions – A Link between Ordinary Carbocations and Neutral Electrophiles" *Eur. J. Org. Chem.* **2019**, *2019*, 412.

[52] M. Bols, C. M. Pedersen, "Silyl-protective groups influencing the reactivity and selectivity in glycosylations" *Beilstein J. Org. Chem.* **2017**, *13*, 93.

[53] C. M. Pedersen, L. U. Nordstrøm, M. Bols, ""Super Armed" Glycosyl Donors: Conformational Arming of Thioglycosides by Silylation" *J. Am. Chem. Soc.* **2007**, *129*, 9222.

[54] C. M. Pedersen, L. G. Marinescu, M. Bols in *Glycosyl donors in "unusual" conformations – influence on reactivity and selectivity*, Comptes Rendus. Chimie, Chimie et Biochimie des hydrates de carbone – première partie, Volume 14, **2011**, pp. 17-43.

[55] P. O. Adero, H. Amarasekara, P. Wen, L. Bohé, D. Crich, "The Experimental Evidence in Support of Glycosylation Mechanisms at the S_N1–S_N2 Interface" *Chem. Rev.* **2018**, *118*, 8242.

[56] J. Guo, X.-S. Ye, "Protecting Groups in Carbohydrate Chemistry: Influence on Stereoselectivity of Glycosylations" *Molecules* **2010**, *15*, 7235.

[57] D. Crich, M. Li, "Revisiting the Armed−Disarmed Concept: The Importance of Anomeric Configuration in the Activation of S-Benzoxazolyl Glycosides" *Org. Lett.* **2007**, *9*, 4115.

[58] D. Crich, "Mechanism of a Chemical Glycosylation Reaction" *Acc. Chem. Res.* **2010**, *43*, 1144.

[59] D. R. Mootoo, P. Konradsson, U. Udodong, B. Fraser-Reid, "Armed and disarmed n-pentenyl glycosides in saccharide couplings leading to oligosaccharides" *J. Am. Chem. Soc.* **1988**, *110*, 5583.

[60] Y. Wei, T. Singer, H. Mayr, G. N. Sastry, H. Zipse, "Assessment of theoretical methods for the calculation of methyl cation affinities" *J. Comput. Chem.* **2008**, *29*, 291.

[61] Y. Wei, G. N. Sastry, H. Zipse, "Methyl Cation Affinities of Commonly Used Organocatalysts" *J. Am. Chem. Soc.* **2008**, *130*, 3473.

[62] D. Kadish, A. D. Mood, M. Tavakoli, E. S. Gutman, P. Baldi, D. L. Van Vranken, "Methyl Cation Affinities of Canonical Organic Functional Groups" *J. Org. Chem.* **2021**, *86*, 3721.

[63] E. Follet, G. Berionni, P. Mayer, H. Mayr, "Structure and Reactivity of Indolylmethylium Ions: Scope and Limitations in Synthetic Applications" *J. Org. Chem.* **2015**, *80*, 8643.

[64] V. Rautenstrauch, "Sigmatropic Reactions in Carbanions. I. The 5, 6-dihydro-2H-pyran-2-ide cyclopropyl-enolate rearrangement" *Helv. Chim. Acta* **1972**, *55*, 594.

[65] Y.-M. Tsai, H.-C. Nieh, C.-D. Cherng, "Cyclizations of Functionalized Acylsilanes To Form 2-Silyldihydropyrans and 2-Silyldihydrofurans" *J. Org. Chem.* **1992**, *57*, 7010.

[66] D. Lainé, M. Fujita, S. V. Ley, "Dispiroketals in synthesis. Part 24. [1]Preparation and use of chiral 2,2 - bis(triisopropylsilyloxymethyl)bi(dihydropyran)s as new protecting and resolving agents for 1,2-diols" *J. Chem. Soc., Perkin Trans. 1.*, **1999**, 1639.

[67] O. El-Sepelgy, A. Brzozowska, L. M. Azofra, Y. K. Jang, L. Cavallo, M. Rueping, "Experimental and Computational Study of an Unexpected Iron-Catalyzed Carboetherification by Cooperative Metal and Ligand Substrate Interaction and Proton Shuttling" *Angew. Chem. Int. Ed.* **2017**, *56*, 14863.

[68] F. T. Oakes, J. F. Sebastian, "Direct observation of acyl anion equivalents by carbon-13 Fourier transform nuclear magnetic resonance" *J. Org. Chem.* **1980**, *45*, 4959.

[69] J. S. Clark, F. Romiti, B. Sieng, L. C. Paterson, A. Stewart, S. Chaudhury, L. H. Thomas, "Synthesis of the A–D ring system of the gambieric acids" *Org. Lett.* **2015**, *17*, 4694.

[70] M.-C. Belhomme, T. Poisson, X. Pannecoucke, "Copper Catalyzed β-Difluoroacetylation of Dihydropyrans and Glycals by Means of Direct C–H Functionalization" *Org. Lett.* **2013**, *15*, 3428.

[71] J. Wang, C. Deng, Q. Zhang, Y. Chai, "Tuning the Chemoselectivity of Silyl Protected Rhamnals by Temperature and Brønsted Acidity: Kinetically Controlled 1,2-Addition vs Thermodynamically Controlled Ferrier Rearrangement" *Org. Lett.* **2019**, *21*, 1103.

[72] A. Fernandez-Mayoralas, A. Marra, M. Trumtel, A. Veyrières, P. Sinaÿ, "Convenient syntheses of substituted pyranoid glycals from thiophenyl glycosides and glycosyl phenylsulfones" *Tetrahedron Lett.* **1989**, *30*, 2537.

[73] A. Fernandez-Mayoralas, A. Marra, M. Trumtel, A. Veyrières, P. Sinaÿ, "Preparation of pyranoid glycal derivatives from phenyl thioglycosides and glycosyl phenyl sulphones" *Carbohydrate Research* **1989**, *188*, 81.

[74] J. Du Bois, C. S. Tomooka, J. Hong, E. M. Carreira, "Novel, Stereoselective Synthesis of 2-Amino Saccharides" *J. Am. Chem. Soc.* **1997**, *119*, 3179.

[75] A. Lipták, L. Lázár, A. Borbás, S. Antus, "Reactions of phenyl and ethyl 2-O-sulfonyl-1-thio-α-D-manno- and β-D-glucopyranosides with thionucleophiles" *Carbohydrate Research* **2009**, *344*, 2461.

[76] E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, "α-Selective organocatalytic synthesis of 2-deoxygalactosides" *Angew. Chem. Int. Ed.* **2012**, *51*, 9152.

[77] D. Calimente, M. H. D. Postema. "Preparation of *C*-1 Glycals via Olefin Metathesis. A Convergent and Flexible Approach to *C*-Glycoside Synthesis" *J. Org. Chem.* **1999**, *64*, 1770.

[78] Y. Deng, A. Frezel, F. Mehner, P. Friedel, J. Gaitzsch, "Amine-bearing cyclic ketene acetals for pH-responsive and degradable polyesters through radical ring-opening polymerisation" *Polym. Chem.* **2023**, *14*, 4275.

[79] R. Csuk, B. I. Glänzer, "Methylenation of aldonolactones" *Tetrahedron* **1991**, *47*, 1655.

[80] D. Waschke, J. Thimm, J. Thiem, "Highly Efficient Synthesis of Ketoheptoses" *Org. Lett.* **2011**, *13*, 3628.

[81] P. Camps, J. Cardellach, J. Font, R. M. Ortuño, O. Ponsati, "Studies on structurally simple α,β-butenolides—II: (−)-(*S*)-γ-hydroxymethyl-α,β-butenolide and derivatives from d-ribonolactone efficient synthesis of (−)-ranunculin" *Tetrahedron* **1982**, *38*, 2395.

[82] K. H. Dötz, E. G. da Silva, "Organometallic NucleosideAnalogues: An Adenine-Analogue Fischer Carbene- Complex" *Synthesis* **2003**, *2003*, 1787.

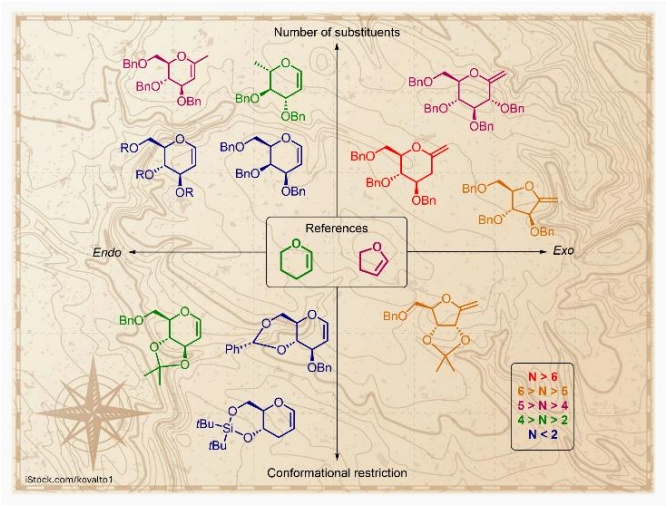
[83] S. Dharuman, Y. D. Vankar, "N-halosuccinimide/$AgNO_3$-efficient reagent systems for one-step synthesis of 2-haloglycals from glycals: application in the synthesis of 2C-branched sugars via Heck coupling reactions" *Org. Lett.* **2014**, *16*, 1172.

[84] Jaguar 8.5, Schrodinger, Inc., New York, NY, **2014**.

[85] NBO 6.0. E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, C. R. Landis, and F. Weinhold (Theoretical Chemistry Institute, University of Wisconsin, Madison, WI, **2013**).

[86] T. Dudev, C. Lim, *J. Am. Chem. Soc.* **1998**, *120*, 4450.

Entry for the Table of Contents



Background illustration: iStock.com/kovalto1

Endo or *Exo*? The first quantitative kinetic mapping of the nucleophilic reactivity of *endo*- and *exo*-glycal compounds highlighted that *endo*-glycals are typically 10^2 times less reactive than their corresponding parent cyclic enol ethers while *exo*-glycals are 10^3 more nucleophilic. This experimental and computational structure-reactivity study highlights the crucial role of multiple parameters on the nucleophilicity parameter of the C=C bond of glycals, which are covering a wide range of nearly six orders of magnitude in reactivity.

Institute and/or researcher usernames: @Dr_Berionni