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SHORT COMMUNICATION

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Comparative Analysis of Fluorine-Directed Glycosylation Selectivity: Interrogating C2 [OH→F] Substitution in D-Glucose and D-Galactose

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The influence of C2 [OH→F] substitution on the stereochemical course of chemical glycosylation was interrogated in both D-glucose and its C4 epimer D-galactose. Molecular editing at C2 and configurational inversion at C4 were simultaneously investigated by variable-temperature glycosylation studies of both systems. Extrapolation of the differences in enthalpic ($\Delta\Delta H_{\beta\alpha}^{\ddagger}$) and entropic ($\Delta\Delta S_{\beta\alpha}^{\ddagger}$) contributions that discriminate these closely similar systems revealed that deoxofluorination at the C2 position induces an enthalpic bias that augments β-stereoselection. Intriguingly, the enhanced stereoselectivity of the C4 epimer D-galactose was found to be entropic in nature. Given the prominence of these scaffolds in chemical biology, delineating the factors that underpin selectivity will be critical in developing novel glycosylation methods and in rationalizing differences with the natural systems post facto.

Introduction

The prominence of 2-fluoroglucose in glycomimesis[1,2] and clinical medicine[3] is attributable to a shift in properties caused by the seemingly subtle OH→F substitution at C2 of the pyranose ring. The negligible steric penalty incurred by this subtle editing process is in stark contrast to the dramatic variation in molecular structure (Figure 1, left).[4] Owing to the unrivaled electronegativity of fluorine, the C–F bond is highly polarized (i.e., $C^{\delta+}$–$F^{\delta-}$), which leads to a lowering of the antibonding orbital. The stabilizing interactions involving this σ_{C-F}* orbital with electron-rich σ bonds and free electron pairs is responsible for the diversity of fluorine conformational effects that are routinely used in focused molecular design.[5] The strategic incorporation of fluorine can induce significant changes in molecular properties: an extreme case is that of Teflon® [cf. polytetrafluoroethylene (PTFE) and polyethylene (PE)].[6] In drug discovery, fluorination often confers a bioactive molecule with increased lipophilicity, which thus renders the process advantageous in improving pharmacokinetics.[7] Moreover, fluorination can be exploited to attenuate amine basicity (pK_a), alter hydrogen-bonding patterns, or simultaneously achieve multiple effects.[8] In carbohydrate chemistry, the strategic value of fluorine introduction is exemplified by 2-deoxy-2-(^{18}F)fluoro-D-glucose, commonly referred to as [^{18}F]FDG (Figure 1, top right). Recurrently employed as a radiotracer for positron emission tomography (PET), this essential radiopharmaceutical is consumed worldwide for routine noninvasive imaging, which renders it essential for diagnostic medicine.[9] The molecule's clinical success relies on both the introduction of the [^{18}F] radiolabel and the position of this radiolabel on the pyranose scaffold. The OH→F substitution at C2 ensures that the conventional glycolysis pathway[10] is blocked following

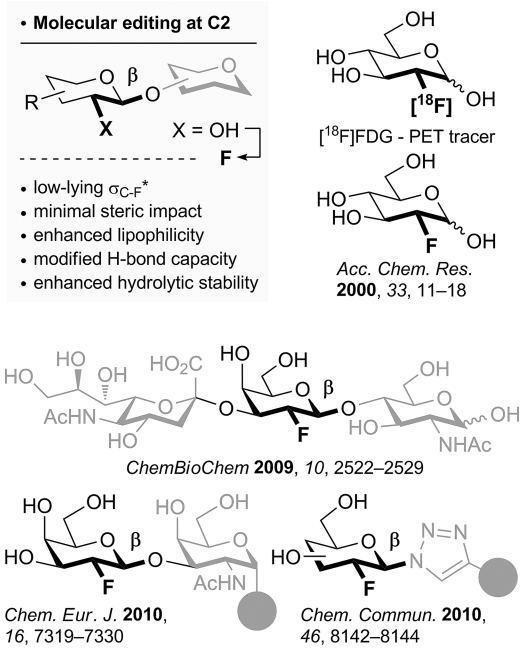

Figure 1. Molecular editing at C2 [OH→F] and the effects on structure. Right: Selected examples of biomolecules containing the 2-fluoro D-glucose and/or D-galactose moiety.

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cellular uptake; this assures that the tracer accumulates in target cells and subsequently decays by positron emission, which can be detected to generate a three-dimensional image.[11] In the field of mechanistic enzymology, the corresponding 2-deoxy-2-fluoro-D-glucose system bearing the natural isotope at C2 has an equally distinguished lineage (Figure 1, bottom right).

Seminal interrogations of glycosidase mechanism by Withers and co-workers established that the C2 [OH→F] substitution destabilizes the oxocarbenium ion like transition state by virtue of the inductive effects of fluorine.[12] Moreover, this modification removes a key H-bond between the active site and substrate whilst imposing a negligible steric impact on interactions with the enzyme.[13] The corresponding C4 epimer based on D-galactose has also found application in the design of probes of adhesion in *Toxoplasmosis*[14] and in the construction of fluoroglycopeptides and glycoproteins.[15,16] In recent years, the unraveling of mammalian and bacterial glycospace[17] has been an incentive to delineate the role of natural carbohydrates and to design structural analogues. The 2-fluoroglycosyl unit has emerged as a vital building block in this field, and this trend is set to continue. The growing interest in this motif necessitates that stereoselective methods be developed to facilitate the construction of fluorinated *glyco* structures.[18] This laboratory has reported an orthogonal set of highly selective 2-fluoroglycosyl donors based on the D-glucose, D-mannose, and D-galactose scaffolds (Figure 2).[19] Mechanistic analyses revealed that high diastereoselectivity (β/α ratio) was a consequence of a synergistic match between the configuration at C2 and the inductive nature of the peripheral protecting groups. The 1,2-*trans* relationship in the major glycoside product is consistent with a Felkin–Anh–Eisenstein induction model (Figure 2).[20] Invoking an oxocarbenium ion model to rationalize the stereochemical course of the reaction reflects the significant S_N1 character of 2-fluoroglycosylation: Independently submitting the α- and β-configured trichloroacetimidates to standard glycosylation conditions has been shown to furnish the β-glycoside predominatly (1,2-*trans*).[19]

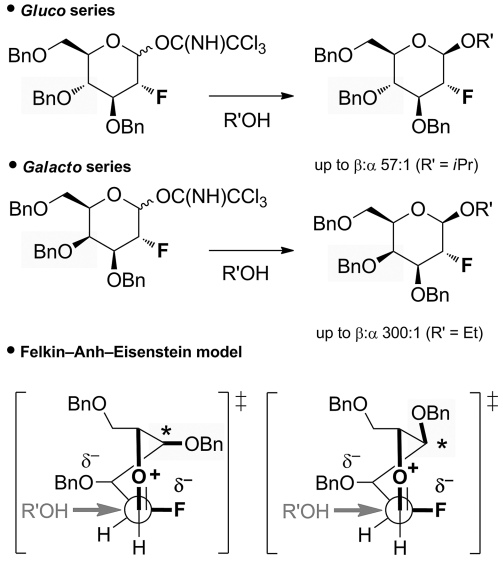


Figure 2. Fluorine-directed glycosylation: An overview of stereoselective 2-fluoroglycoslyation and 2-fluorogalactosylation, and the respective Felkin–Anh–Eisenstein induction models based on the assumption that the transformation has significant S_N1 character.

Intriguingly, the configuration of the C4 stereocenter was found to play a decisive role in determining the β/α selectivity ($r_{\beta\alpha}$) in subsequent glycosylation events (Figure 2). Upon individually treating the 2-deoxy-2-fluoro-D-glucose and 2-deoxy-2-fluoro-D-galactose trichloroacetimidate donors with *i*PrOH as the acceptor [–78 °C, trimethylsilyl trifluoromethanesulfonate (TMSOTf) in CH_2Cl_2], this ratio increased from 57:1 ($\Delta\Delta G_{\beta\alpha}^{\ddagger}$ = –6.6 kJ mol^{-1}) to 150:1 ($\Delta\Delta G_{\beta\alpha}^{\ddagger}$ = –8.1 kJ mol^{-1}).[19] Consequently, this study was extended to explore the effect of C2 substitution in both D-glucose and D-galactose (Figure 3). Given that the observed selectivity ($r_{\beta\alpha}$) reflects the relative rates of addition to the incipient oxocarbenium ion under the S_N1 paradigm, information concerning this selectivity-determining step can be extracted. Thus, by carrying out a series of glycosylation experiments at various temperatures the enthalpic ($\Delta\Delta H_{\beta\alpha}^{\ddagger}$) and entropic ($\Delta\Delta S_{\beta\alpha}^{\ddagger}$) contributions to the differences in free energy between the transition states (TS‡) leading to the β- and α-anomers ($\Delta\Delta G_{\beta\alpha}^{\ddagger} = \Delta\Delta H_{\beta\alpha}^{\ddagger} - T\times\Delta\Delta S_{\beta\alpha}^{\ddagger}$) can be derived by Eyring analysis.[21,22]

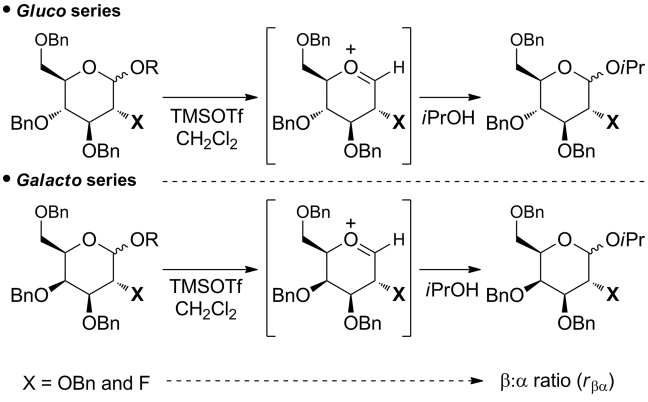


Figure 3. The aims and objectives of this study. Delineating the entropic ($\Delta\Delta S_{\beta\alpha}$) and enthalpic ($\Delta\Delta H_{\beta\alpha}$) factors that distinguish the selectivity differences between X = OBn vs. X = F for D-glucose (top) and D-galactose (bottom). R = $C(NH)CCl_3$.

Whereas the physical ramifications of the C2 [OH→F] substitution have found widespread application in molecular design, and synthetic routes to the target *glyco* structures have been developed, a comparative analysis based on experimentally derived reaction parameters would assist in delineating the enthalpic and entropic contributions that underpin the selectivity observed by this seemingly trivial structural adjustment. Herein, a variable-temperature glycosylation study of perbenzylated 2-deoxy-2-fluoro-D-glucose and 2-deoxy-2-fluoro-D-galactose is reported by using *i*PrOH as a model glycosyl acceptor. By determining $\Delta\Delta G_{\beta\alpha}^{\ddagger}$ and by extension the entropic ($\Delta\Delta S_{\beta\alpha}^{\ddagger}$) and enthalpic ($\Delta\Delta H_{\beta\alpha}^{\ddagger}$) data, the contributions to the β/α selectivity of these popular systems can be garnered and placed in context with the natural systems.

Results and Discussion

As a starting point for this study, trichloroacetimidate (TCA) donors **S1**–**S3** were prepared according to established literature precedent:[19] the α anomer was obtained almost exclusively (β/α < 1:20, Table 1 top). Subsequently, the donors were subjected to standard glycosylation conditions by using *i*PrOH (1.2 equiv.) and TMSOTf (0.1 equiv.) at temperatures ranging from 25 to –60 °C. To minimize solvent participation, CH_2Cl_2 was employed as the reaction medium (0.05 M). After 2 h at the specified temperature, the reactions were quenched by the addition of NEt_3 and then concentrated under reduced pressure, and the crude mixtures were directly analyzed by ^{19}F NMR (for **S1** and **S2**) or ^{1}H NMR (for **S3**) spectroscopy. Each reaction was repeated three times to ensure reproducibility, and this led to relative standard deviations ($\sigma_{\beta\alpha}/r_{\beta\alpha}$) ranging from 2.1 to 11.1%. These selectivity data were further complemented with values available in the literature for reactions performed at –50 and –78 °C.[19] Hence, a total of six and five data points were obtained for fluorinated compounds **S1**/**S2** and parent galactose system **S3**, respectively. These data are summarized in Table 1. Furthermore, predicted selectivity ratios ($r'_{\beta\alpha}$) based on experimentally derived $\Delta\Delta H_{\beta\alpha}^{\ddagger}$ and $\Delta\Delta S_{\beta\alpha}^{\ddagger}$ values (see above) are provided (Table 1, right).

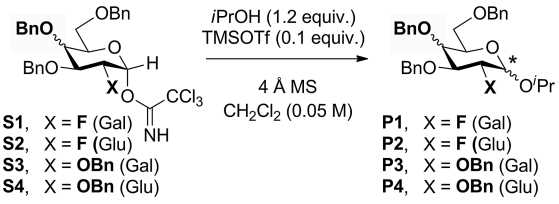
Consistent with previous studies,[19] these data support the initial report that the C4 configuration is decisive in orchestrating diastereocontrol, and the 2-deoxy-2-fluorogalactose scaffold significantly outperforms the glucose congener, even at ambient temperature.

The ratio $r_{\beta\alpha}$(**P1**)/$r_{\beta\alpha}$(**P2**) remains constant and/or slightly increases at lower temperatures, the implications of which will be discussed later. For the parent 2-benzyloxy systems, a more favorable β/α ratio is also observed for the *galacto*-configured donor, although the difference is less pronounced than in the fluorinated case. In addition, the ratio $r_{\beta\alpha}$(**P3**)/$r_{\beta\alpha}$(**P4**) constantly decreases as the temperature is lowered with values of 1.6 and 1.1 at 25 and –78 °C, respectively. To extract the thermodynamic parameters of interest from the selectivity data measured, linearization by means of an Eyring plot [Equation (1) and Figure 4] was performed.

By linear regression analyses on the acquired data sets [$\ln(r_{\beta\alpha}) \sim T^{-1}$] the enthalpic ($\Delta\Delta H_{\beta\alpha}^{\ddagger}$) and entropic ($\Delta\Delta S_{\beta\alpha}^{\ddagger}$) contributions to the difference in free energy between the β and α transition states ($\Delta\Delta G_{\beta\alpha}^{\ddagger} = \Delta G_{\beta}^{\ddagger} - \Delta G_{\alpha}^{\ddagger}$) were calculated, as summarized in Table 2. All fits afforded high correlation coefficients ($R^2 > 0.99$). The quality of the data was further supported by considering the ratio of predicted selectivities ($r'_{\beta\alpha}$) and experimental values ($r_{\beta\alpha}$), $r'_{\beta\alpha}/r_{\beta\alpha}$. This descriptor ranged from 0.82 to 1.18: the optimal value is $r'_{\beta\alpha}/r_{\beta\alpha} = 1$ for perfect congruence.

Perhaps most prominent from inspection of the $r_{\beta\alpha}$-(**P1**)/$r_{\beta\alpha}$(**P2**) ratio is that the 2-fluoro-2-deoxy sugars studied feature identical enthalpic stabilizations of the β-TS over the α-TS, within the precision of the measurements, with respective values of –16.2 ± 0.6 (for **S1**) and –15.8 ± 0.7 kJ mol^{-1} (for **S2**). That is, the set of lines represented in the Eyring plot that correspond to these measurements are parallel (Figure 4, black top set of lines). This

Table 1. Summary of selectivity data for donors **S1**–**S4** at various temperatures.



S1, X = **F** (Gal) **P1**, X = **F** (Gal)
S2, X = **F** (Glu) **P2**, X = **F** (Glu)
S3, X = **OBn** (Gal) **P3**, X = **OBn** (Gal)
S4, X = **OBn** (Glu) **P4**, X = **OBn** (Glu)

Donor	T [K][a]	$r_{\beta\alpha}$	$\sigma_{\beta\alpha}$[b]	$r'_{\beta\alpha}$	$r'_{\beta\alpha}/r_{\beta\alpha}$
S1					
(X = F, Gal)	298.15 (25)	4.29	0.47 (11.1)	4.25	0.99
S1	273.15 (0)	7.97	0.24 (3.1)	7.73	0.97
S1	232.15 (–41)	26.62	3.08 (11.6)	27.32	1.03
S1	223.15 (–50)	40[c]	–	38.35	0.96
S1	212.15 (–61)	51.18	4.91 (9.6)	60.36	1.18
S1	195.15 (–78)	150[c]	–	134.54	0.90
S2					
(X = F, Glu)	298.15 (25)	1.98	0.14 (7.2)	2.25	1.13
S2	273.15 (0)	4.26	0.10 (2.3)	4.02	0.94
S2	228.15 (–45)	17.68	0.56 (3.2)	15.85	0.90
S2	223.15 (–50)	21[c]	–	19.09	0.91
S2	212.15 (–61)	29.41	1.02 (3.5)	29.68	1.01
S2	195.15 (–78)	57[c]	–	64.73	1.14
S3					
(X = OBn, Gal)	298.15 (25)	1.94	0.04 (2.1)	1.84	0.95
S3	273.15 (0)	2.29	0.06 (2.7)	2.34	1.02
S3	232.15 (–41)	3.50	0.09 (2.5)	3.86	1.10
S3	212.15 (–61)	5.44	0.14 (2.7)	5.28	0.97
S3	195.15 (–78)	7.5[c]	–	7.26	0.97
S4					
(X = OBn, Glu)[d]	298.15 (25)	1.22	0.06 (4.7)	1.24	1.01
S4	273.15 (0)	1.44	0.10 (6.7)	1.69	1.18
S4	243.15 (–30)	3.27	0.19 (5.7)	2.68	0.82
S4	213.15 (–60)	5.52	0.22 (4.1)	4.84	0.88
S4	193.15 (–80)	6.82	0.33 (4.9)	7.94	1.16

[a] Values in parentheses are the temperatures in °C. [b] Relative standard deviations $\sigma_{\beta\alpha}/r_{\beta\alpha}$ are given in parentheses. [c] Values taken from ref.[19] [d] Values taken from ref.[22] $r'_{\beta\alpha}$ = calculated selectivity. $r_{\beta\alpha}$ = measured selectivity.

$$\ln(r_{\beta\alpha}) = -\Delta\Delta H_{\beta\alpha}^{\ddagger} \times (RT)^{-1} + \Delta\Delta S_{\beta\alpha}^{\ddagger} \times R^{-1} \quad (1)$$

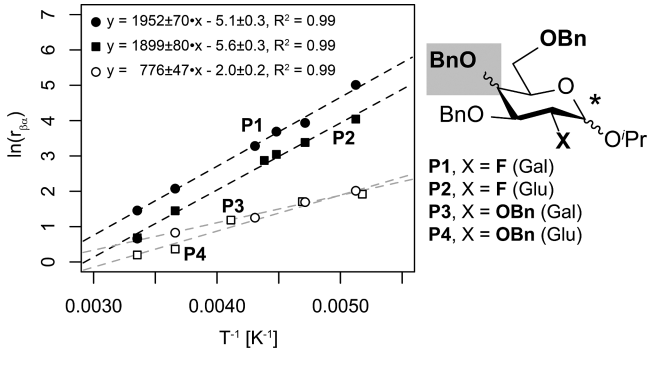


Figure 4. Eyring plot of the selectivity data summarized in Table 1. Error bars are presented as $2 \times \sigma'_{\beta\alpha}$ with $\sigma'_{\beta\alpha} = \sigma_{\beta\alpha}/r_{\beta\alpha}$; data for **P4** included from ref.[22]

Table 2. Compilation of experimentally determined thermodynamic data for donors **S1**–**S4**.

	$\Delta\Delta H_{\beta\alpha}^{\ddagger}$ [kJ mol^{-1}]	$\Delta\Delta S_{\beta\alpha}^{\ddagger}$ [J mol^{-1} K^{-1}]
S1 (X = F, Gal)	–16.2 ± 0.6	–42.4 ± 2.5
S2 (X = F, Glu)	–15.8 ± 0.7	–46.4 ± 2.9
S3 (X = OBn, Gal)	–6.4 ± 0.4	–16.6 ± 1.7
S4 (X = OBn, Glu)[a]	–8.6 ± 1.1	–26.8 ± 4.5

[a] Values taken from ref.[22]

suggests that the enhanced selectivity observed for the C4 *galacto* configuration likely arises from a less entropically disfavored β-TS than in the C4 *gluco* system, that is, $\Delta\Delta S_{\beta\alpha}^{\ddagger}$(**S1**) > $\Delta\Delta S_{\beta\alpha}^{\ddagger}$(**S2**). The situation for the parent 2-benzyloxy systems is more complex, as is reflected by convergence of the two lines as the temperature decreases (Figure 4, gray bottom set of lines). Taking into consideration only the enthalpic term $\Delta\Delta H_{\beta\alpha}^{\ddagger}$, it is reasonable to expect that glucose-derived donor **S4** (–8.6 ± 1.1 kJ mol^{-1}) might furnish higher levels of diastereoselectivity ($r_{\beta\alpha}$) than **S3** (–6.4 ± 0.4 kJ mol^{-1}) on account of a larger stabilization of the β-TS. Conversely, the difference in entropy of activation associated with **S3** is more favorable ($\Delta\Delta S_{\beta\alpha}^{\ddagger}$ = –16.6 ± 1.7 J mol^{-1} K^{-1}) than in **S4** ($\Delta\Delta S_{\beta\alpha}^{\ddagger}$ = –26.8 ± 4.5 J mol^{-1} K^{-1}) for achieving β-selectivity. Ultimately, this should lead to a situation in which *gluco* system **S4** outperforms galactose-derived donor **S3**; this is indicated by the intersection on the Eyring plot.

Conclusions

The influence of C2 [OH → F] substitution on the stereochemical course of chemical glycosylation was interrogated in both D-glucose and its C4 epimer D-galactose. These scaffolds remain at the forefront of carbohydrate mimesis and medicine. C2 fluorine installation confers significant improvements in glycosylation selectivity in the D-glucose system; this is even more pronounced in D-galactose. Variable-temperature glycosylation studies of both systems allowed the effect of molecular editing at C2 and configurational inversion at C4 to be simultaneously investigated. Assuming a mechanism with significant S_N1 character, the observed selectivity ($r_{\beta\alpha}$) reflects the relative rates of addition to one of two faces of the planar oxocarbenium ion. Through a series of temperature-dependent glycosylation experiments it was possible to extrapolate the differences in enthalpic ($\Delta\Delta H_{\beta\alpha}^{\ddagger}$) and entropic ($\Delta\Delta S_{\beta\alpha}^{\ddagger}$) contributions that discriminate these closely similar systems. These data indicate that deoxofluorination at C2 results in significant stabilization of the β transition state in terms of enthalpy with differences between C2–F and C2–OBn of 9.8 and 7.2 kJ mol^{-1} for the *galacto* and *gluco* configurations, respectively. This data is in line with the original supposition that orbital control by a Felkin–Anh–Eisenstein model (Figure 5) is of central importance in the creation of the 1,2-*trans* (i.e., β) glycosidic linkage. Whereas orbital mixing in the developing transition state is expected for both the BnO and F systems in the $^3H_4$ half-chair conformation, the effect should be more pronounced for the lower-lying accepting antibonding orbital (σ_{C-F}* vs. σ_{C-O}*). This more favorable enthalpy of activation reflects a more bonded, or presumably later, transition state. Importantly, the orthogonal orientation of the $\pi_{C=O}$ system and σ* orbital is absent in the $^4H_3$ configured transition state, which ultimately leads to the minor α anomer. In all cases, the negative differences in entropic contributions are consistent with reduced translational and rotational freedom in the β transition state, which in turn is fully consistent with augmented fluorine stereoelectronic (σ→σ*) and electrostatic (dipole) effects in the incipient oxocarbenium ion. In conclusion, this study demonstrated that the seemingly innocent installation of fluorine at the C2 position of a perbenzylated pyranose scaffold induces an enthalpic bias that augments β-stereoselection in a model glycosylation reaction. Furthermore, this analysis indicated that the origin of the enhanced stereoselectivity of the C4 epimer D-galactose is entropic in nature. The increasing prominence of fluorinated *glyco* structures in chemical biology will create a demand for more versatile and selective glycosylation methodologies. Delineating the factors that underpin selectivity will be pivotal both in the development of novel technologies and in the post facto rationalization of anomalous differences between fluorinated structures and their natural counterparts.

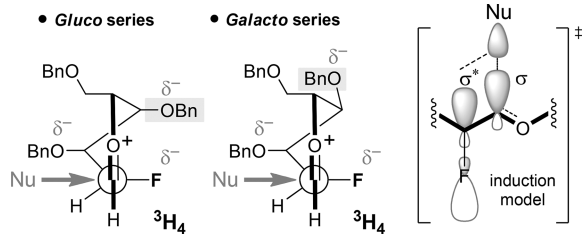


Figure 5. Tentative transition states implicating orbital control (σ_{C-F}*) to account for β selectivity in chemical glycosylation.

Supporting Information (see footnote on the first page of this article): Full experimental details.

Acknowledgments

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