Tetrahedron Letters 51 (2010) 1550–1553

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regioselective glycosylation reactions based on computational predictions

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ARTICLE INFO

Article history:
Received 10 December 2009
Revised 8 January 2010
Accepted 12 January 2010
Available online 18 January 2010

Keywords:
Regioselectivity
Glycosylation
Fukui function
Computational chemistry

ABSTRACT

Regioselectivity is a major issue in glycosylation reactions. Better understanding of regioselectivity of acceptors can greatly facilitate and simplify the syntheses of oligosaccharides. The reactivity of diol acceptors is often affected by stereochemistry and protecting groups, which make prediction the regioselectivity of diol acceptors extremely difficult. Quantum mechanic methods were used to study the relationship between protecting groups and reactivity of diol acceptor and a correlation between Fukui function and regioselectivity is established through series of glycosylation reactions.

Oligosaccharides, the third major class of biopolymers after peptides and oligonucleotides, play very important roles in various biological processes, such as cell adhesion, cell recognition, immunization and so on.[1–4] The synthesis of oligosaccharides, however, is far more difficult than other biopolymers, such as peptides and oligonucleotides due to the high regio- and stereoselectivity required in the formation of glycosidic linkages. What makes the chemical synthesis of oligosaccharides even more difficult is the low predictability of glycosylation reactions, where little changes in the structure of glycosyl monomers (such as protecting groups or stereochemistry) can often cause dramatic change in reaction results.[5–7] Prediction of glycosylation reaction and rational design of oligosaccharide synthesis are therefore of particular interest.[8,9] Here we report a successful prediction of the reactivity of a series of 2,3-diol mannosyl acceptors using computational chemistry methods.

Regioselectivity is a major issue in carbohydrate synthesis. Better understanding and control of regioselectivity can not only facilitate regioselective protection of acceptors, but may also realize regioselective glycosylations without or with only minimum protections. Currently, reactivity of acceptor hydroxyls can only be predicted based on a few empirical rules, such as: primary hydroxyl groups are more reactive than secondary hydroxyl groups and equatorial hydroxyl groups are more reactive than axial hydroxyl groups.[10] However, these empirical rules have limitations. First, it is difficult to predict reactivity when both hydroxyl groups are equatorial or axial. Second, it cannot be used to estimate the difference between acceptors with only subtle difference in structures, such as change of protecting groups. Better understanding of the relative reactivity of hydroxyl groups in diol or triol acceptors, especially the relationship between protecting groups and reactivity, is therefore very important for prediction of glycosylation reactions and rational design of oligosaccharide synthesis.

Changing protection groups can introduce both steric and electronic effects to the acceptors, whereas electronic effects are what we cannot predict based on our current knowledge. Since computational chemistry is good at explaining and predicting properties related to electron distribution in organic molecules, we feel application of computational chemistry in carbohydrate chemistry could be a good way to help us understand the influence of protecting groups on acceptor reactivity. Fukui function, first introduced by Parr and Yang, is defined as the differential change in electron density due to an infinitesimal change in the number of electrons.[11–13] It can be expressed in a condensed form as:

$$f_k^- = q_k(N) - q_k(N-1) \quad (1)$$

$$f_k^+ = q_k(N+1) - q_k(N) \quad (2)$$

where $q_k(N)$ is Mulliken's charge on the k-atom of the molecule with N electrons and $q_k(N+1)$, $q_k(N-1)$ are the charges on the k-atom of the molecule with $(N+1)$ and $(N-1)$ electrons in a frozen orbital approximation, respectively.

Fukui function is the DFT analogue of the frontier orbital regioselectivity for nucleophilic (f^+) and electrophilic (f^-) attack.[14–16] Fukui function has been successfully used in explaining and predicting regioselectivity in organic reactions, especially reactions involving nucleophiles and electrophiles, such as dipole addition reactions and Michael reaction.[16–18] Since glycosylation of glycosyl acceptors can be considered as an electrophilic attack of the OH

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doi:10.1016/j.tetlet.2010.01.044

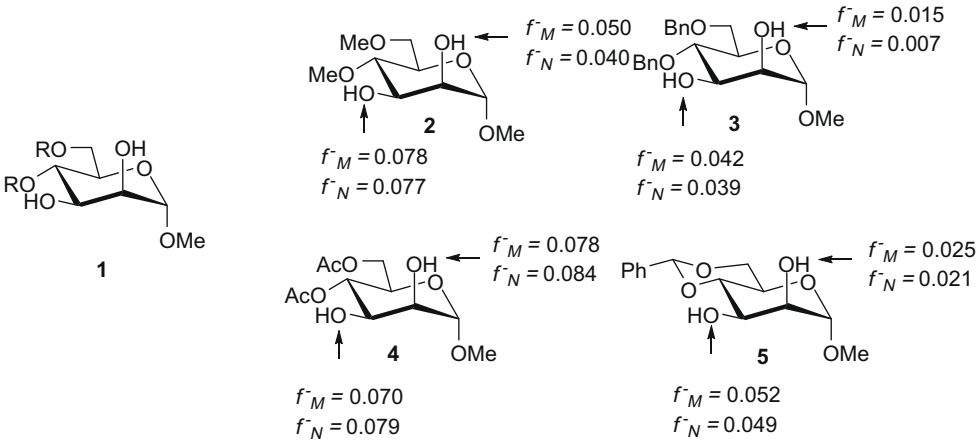

Figure 1. Mannose 2,3-diol acceptors.

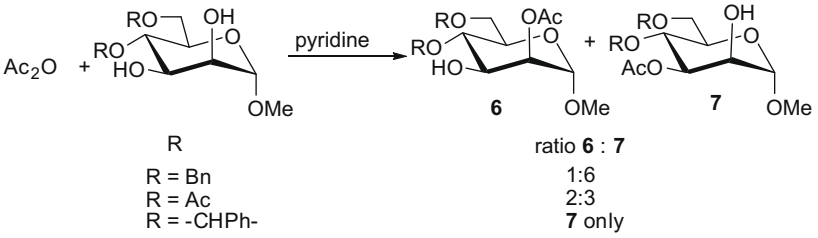

Figure 2. Acetylation of diol acceptors.

group by an oxocarbenium ion intermediate, f^- could be a good indicator for the regioselectivity of hydroxyl groups in diol glycosyl acceptors.

As part of our effort to develop a regioselective synthesis of high mannose type N-glycan oligosaccharides, we needed a regioselective diol acceptor like compound **1** (Fig. 1). To search for such a diol acceptor, a set of 2,3-diol mannose acceptors (Fig. 1 and **2**–**5**) were selected as candidates for a preliminary study. Fukui function was calculated using Q-CHEM 3.2, at B3LYP/6-31+G* level for all four diol acceptors.[19] Both Mulliken charges and NBO[20] charges were used for the calculation. Two different charges gave different but comparable Fukui function values. All f^- values (f^-_M (Mulliken charge) and f^-_N (NBO charge)) for oxygen atom of each hydroxyl group are shown in Figure 1. Since f^- is used as the indicator for electrophilic attack, we expect oxygen atoms with higher Fukui function value to be the preferred reaction sites. In compound **2**, Fukui function at 3-OH is about 1.5 times of 2-OH. In compound **3**, Fukui function at 3-OH is about 2.8 times of 2-OH. In compound **4**, 2-OH and 3-OH have about the same Fukui function values. In compound **5**, the Fukui function at 3-OH is about 2.1 times of 2-OH. These results suggest that 3-OHs of compound **2**, **3,** and **5** are the more reactive sites when react with electrophiles, whereas 2-OH and 3-OH in compound **4** are of similar reactivity.

To test how the prediction based on Fukui function correlates to real reactivity of the hydroxyl groups towards electrophiles, compounds **3**, **4,** and **5** were tested in acetylation reactions (Fig. 2).[21,22] Compound **2** was not tested in reactions because methyl group is not a commonly used protecting group in glycosylation reactions. In the acetylation reactions, acceptor **3** and **5** showed great regioselectivity with mostly 3-*O*-acetyl products isolated in the reactions. Compound **4** didn't show significant regioselectivity, with similar amount of 2-O- and 3-O-acetylation products isolated. These results are clearly consistent with the predictions based on Fukui function, which suggest that 3-OH is more reactive in compound **3** and **5**, but not in compound **4**. From the steric point of view, 3-OH (equatorial) should be more reactive than 2-OH (axial), but this is not the case in compound **4**. This result is probably due to the fact that the electrophile used in the experiment is relatively small and less sterically demanding. Under this circumstance, the Fukui function f^- is an effective indicator to predict the correlation between the protecting groups and the relative reactivity.

Encouraged by the acetylation reaction results, we further tested the regioselectivity of these diol acceptors in glycosylation reactions. We first tested mannose donors in glycosylation, because the disaccharides obtained from these reactions are useful intermediates for the syntheses of the core structure of N-glycan and some other types of oligosaccharides.[23] Three tetraacetylmannosyl donors (**8a**, **8b**, **8c**) were tested in glycosylation reactions (Fig. 3). Similar to acetylation reactions, acceptor **3** and **5** showed great regioselectivity. Only 1,3-disaccharides **10** were isolated in reactions between all three donors and compound **3** and **5**, no 1,2-disaccharides **9** were observed (Table 1). The difference between compound **3** and **5** is that compound **3** gave a small amount of trisaccharide products in reactions with bromide donor and trichloroacetimmidate donor. In case of acceptor **4**, both 1,2- and 1,3-disaccharides were isolated in the reactions, together with a small amount of trisaccharide.

The main difference between glycosylation and acetylation of the diol acceptors is the regioselectivity of compound **4**, which showed no selectivity in acetylation, whereas a substantial selectivity (1:3) in glycosylation. This difference can be explained by steric effect. The equatorial hydroxyl group is generally considered less sterically hindered and is thus more reactive than the axial hydroxyl group. However, when the electrophile is small, like acetyl group, the steric effect is not strong enough to control the reaction outcome. The electronic effect becomes the key factor under this circumstance and the Fukui function is a better indicator for the regioselectivity. When the electrophile is bigger, like glycosyl donor, the steric effect is more substantial and contributes more to the control of the regioselectiv-

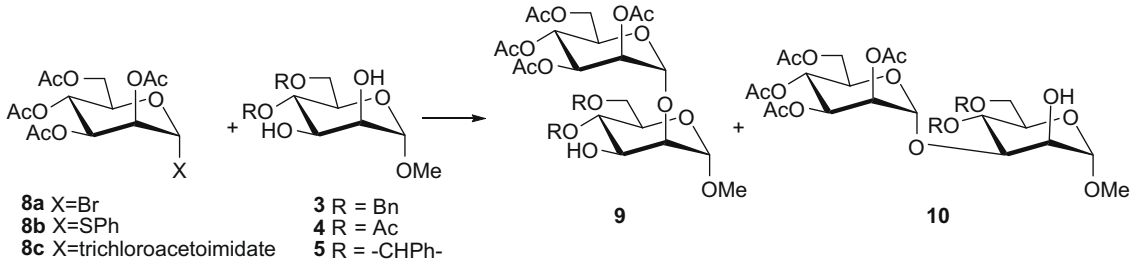

Figure 3. Glycosylation of diol acceptors.

Table 1
Glycosylation results

	Compound **3**	Compound **4**	Compound **5**
Donor	**9**:**10**	**9**:**10**	**9**:**10**
8 X = Br	**10** only	1:3[c]	**10** only
9 X = SPh	**10** only[a]	1:3[c]	**10** only
10 X = trichloroacetoimidate	**10** only[b]	1:3[c]	**10** only

[a] With about 10% of trisaccharide.
[b] With about 15% of trisaccharide.
[c] Trisaccharides are present at similar amount to 1,2-disaccharides.[24]

ity. Under this circumstance, both steric effect and electronic effect must be considered to explain the regioselectivity. Diol acceptor **3** and **5**, where both steric and electronic effects favor 3-OH are therefore more regioselective than diol acceptor **4**, which is only favorable when considering the steric effect.

Another factor that can affect the regioselectivity of diol acceptor is the intramolecular hydrogen bonding.[25] Even though both 2-OH and 3-OH are trans to the neighboring groups, which is considered unfavorable for the formation of intramolecular hydrogen bond, 3-OH can still form hydrogen bond with neighboring group (at 4-position), because it is equatorial. At the same time 2-OH cannot form hydrogen bond with neighboring group (at 1-position) due to its axial orientation. This can explain why 3-OH is more reactive than 2-OH, because it has been suggested that hydroxyl group involved in stronger hydrogen bond is more reactive.[26] However, this effect cannot explain the difference between acetyl- and benzyl-protected acceptors. Acetyl is expected to form a stronger hydrogen bonding and should show a higher regioselectivity, which is opposite to the experimental observation. There must be other factors that make 3-OH of compound **2** and **3** more reactive, which could be the more favorable Fukui function value at the 3-position. A comprehensive consideration of Fukui functions and other factors (like steric factors and hydrogen bondings) could therefore give more accurate prediction of the regioselectivity of diol acceptors.

In summary, Fukui functions were calculated for a series of mannose diol acceptors and successfully applied in predicting the regioselectivity of these acceptors in reactions with electrophiles. Computational chemistry and Fukui function could be a good indicator for predicting the reactivity of glycosyl acceptors, especially the electronic effect and the influence of protecting groups. More studies will be conducted to further understand and extend the application to more glycosyl acceptors.

Acknowledgments

We thank Professor Paul W. Ayers of McMaster University for interesting discussion on using Fukui function for reaction prediction. We also thank James Switzer and Professor Jim Dix of the Department of Chemistry for help in setting up our computational program. The financial support is provided by Binghamton University Research Foundation.

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24. *General procedure for acetylation reactions:* The diol (0.27 mmol) and pyridine (0.27 mmol) were dissolved in anhydrous CH_2Cl_2 (2 mL) and cooled to 0 °C. Acetic anhydride (0.27 mmol, in 1 mL of CH_2Cl_2) was added dropwise within 30 min. The reaction was allowed to warm up to room temperature and stirred overnight. The reaction mixture was then concentrated and purified by flash chromatography to give the products. *General glycosylation procedure for glycosyl bromide donors:* The diol (0.27 mmol) and glycosyl donor (0.27 mmol), in anhydrous CH_2Cl_2 (5 mL) were stirred at room temperature in flame-dried molecular sieves 3 Å under nitrogen atmosphere for 30 min. The mixture was cooled to −30 °C, silver triflate (0.27 mmol) was added and the reaction was allowed to warm up to room temperature. After 30 min, it was quenched with triethylamine, concentrated, and purified by flash chromatography to give the products. *General glycosylation procedure for thioglycoside donors:* The diol (0.27 mmol) and glycosyl donor (0.27 mmol) in anhydrous CH_2Cl_2 (5 mL) were stirred at room temperature in flame-dried molecular sieves 3 Å under nitrogen atmosphere for 30 min. The mixture was cooled to −30 °C, NIS (0.41 mmol) was added, after stirring for 5 min, $BF_3{\cdot}Et_2O$ (0.27 mmol) was added and the reaction was allowed to warm up to room temperature. After 30 min, it was quenched with saturated aqueous sodium bicarbonate and 10% aqueous sodium thiosulphate, extracted with dichloromethane, and washed with brine. It was dried over sodium sulfate, concentrated, and purified by flash chromatography to give the products. *General glycosylation procedure for trichloroacetimidate donors:* The diol (0.27 mmol) and glycosyl donor

(0.27 mmol) in anhydrous CH_2Cl_2 (5 mL) were stirred at room temperature in flame-dried molecular sieves 3 Å under nitrogen atmosphere for 30 min. The mixture was cooled to −78 °C, $BF_3{\cdot}Et_2O$ (0.14 mmol) was added, after 20 min the reaction was quenched with triethylamine concentrated and purified by flash chromatography to give the products.

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