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"Armed and Disarmed" Theory in the Addition of Azide Radical to Glucals

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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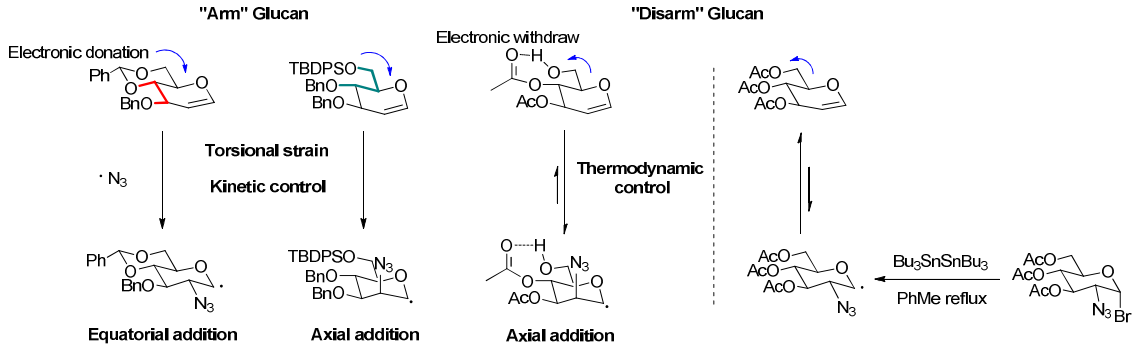

In this report, "armed and disarmed" theory was used to explain the selectivity of azide radical addition to the glucals. We discovered that "arm" glucals were prone to undergo kinetic process. The torsional strains govern the selectivity. Meanwhile, "disarmed" glucals preferred thermodynamic radical addition. We also applied our method to synthesize a sialic acid containing trisaccharide.

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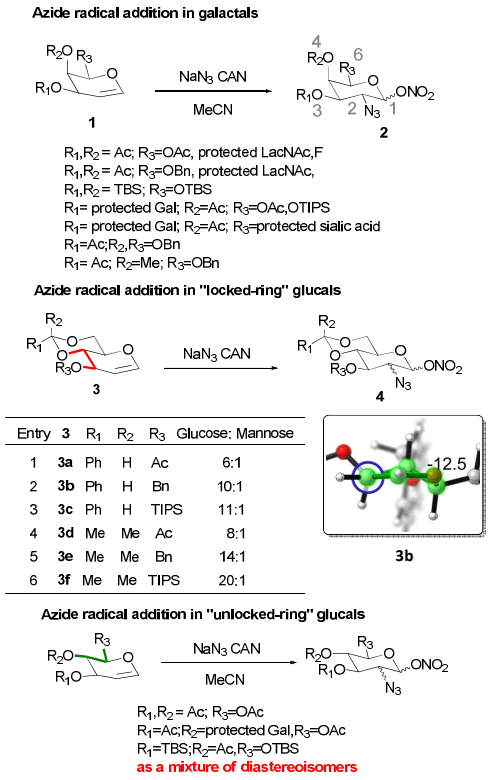
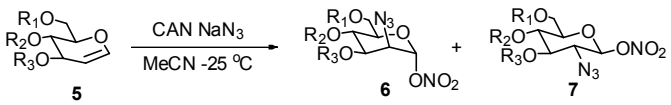


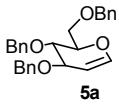
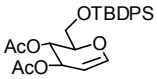
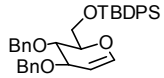
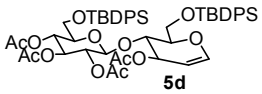
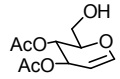
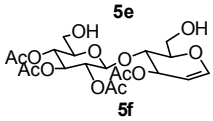
Scheme 1. The synthesis of hexosamines from glycals

Azide radical is a powerful tool in organic chemistry to introduce C-N bond. The addition of azide radical to 1, 5-anhydro-2-deoxy-hex-1-enitols called "glycal" conveniently converting them into hexosamines, has widespread applications in carbohydrate chemistry. Previous reports were summarized in Scheme 1. Galactal derivatives **1** were diastereoselectively converted to the corresponding 2-deoxy-2-azide galactoses **2**.[1]Similarly, 2-deoxy-2-azide glucose derivatives **4** can be obtained from "locked-ring" glucals **3** with satisfactory selectivity.[2] Based on the high reactivity of radical and antiparallel addition products, empirical analysis suggested that allylic 1, 2-strain may lead to the kinetic addition. However, other "unlocked-ring" glucals only provided equatorial addition products with poor selectivity.[3] These results are contrary to the previous hypothesis. Until now, due to the poor selectivity, axial addition products (ManNAc derivatives) haven't been got by this method. In this report, we intend to explain the selectivity of azide radical addition in these cases with "armed and disarmed" theory.

The addition of azide rediacl to glucals **3** showed that bulky substituents on C3 of "lock-ring" glucal enhance the equatorial addition. The result of molecular modelling of glucal **3b** shows that the substitution group on C3 adopts a parallel position with the olefin plane. Furthermore, it has been reported that interactions between substituents on oxygen atoms could dramatically impact the low energy conformations of glucals.[4] Hence, it is reasonable to surmise that torsional strain may play a decisive role on the selectivity instead of allylic 1, 2-strain. Specifically, the above results sustained that the torsional strain contributed by dihedral angel assigned in red (Scheme 1) facilitated the equatorial addition. This observation propelled us to envisage that substrates bearing bulky substituents on the C4 and C6 (highlighted with green) would be prone to undergo the axial addition. Unsurprisingly, as showned in Table 1, the desired axial addition products were obtained in the initial attempts (Entries 1 and 2) with moderate selectivity. A significant raise in selectivity was realized in entry 3. As can be seen, the glucal **5c** with a TBDPS group on C6 and a benzyl group on C4 provided the axial face addition product 6c in 15:1 dr. In entry 4, glucal **5d**, which had more bulk on C4 than glucal **5c** provided the axial face addition product **6d** exclusively. The high selectivity of above results sustained the dramatic effect of torsional strain on the selectivity. The axial selective addition was also obtained in entry 5. In this case, a hydrogen bond between the hydroxyl group and acetyl group on C4 of the glucal **5e** was supported to result in the highly selective axial addition product **6e**. The poor selectivity of Entry 6 further supports this assumption.

Table 1. The synthesis of ManNAc derivatives with glucals[a]



Entry	Substrates 5	Products(dr)[b] (6, 7)	Time(h)	Yield[b]
1	 5a	**6a**, **7a** (2:1)	1.5	75%
2	 5b	**6b**, **7b** (4:1)	4	82%
3	 5c	**6c**, **7c** (15:1)	1.5	72%
4	 5d	**6d**	2	75%
5	 5e	**6e**	6	80%
6	 5f	**6f**, **7f** (1:2)	6	40%

[a] The reaction was typically performed by addition of 3 equiv of CAN portion-wise to a solution of 1.5 equiv of NaN_3 and 1 equiv of glycal at -25°C
[b] The ratio of two diastereoisomers is determined by ^1H NMR.

To further illustrate the mechanism, the relative energy of substrates, transition states, intermediates were studied by Gaussian 09.[5] Exhausted conformational search was performed to locate the most stable geometries of compounds **5c**, **5e**, **3b** and relative species (see supporting information for details). Then, gas-phase geometry optimization was computed using the B3LYP/6-31G(d) method, and further solvation free energy correction in acetonitrile (SMD single point calculation) was computed using the X3LYP/6-311+G(d,p) method.[6] These methods are verified to be reliable to work on radical species.

As shown in the figure 1, the axial addition of glucal **5c** need lower activation energy than the equatorial addition (10.9 kcal/mol vs 9.8 kcal/mol), and the intermediate of equatorial addition is slightly more stable than the axial one. Therefore, the axial addition should be preferred kinetically. We also stimulated the energy profile of glucal **3b**. The predominant equatorial addition product **4b** was proved to be preferred in kinetic process (10.3 kcal/mol vs 7.0 kcal/mol). Furthermore, our theoretical ratio was consistent with the experimental result (see supporting information for details). These data thus verified our previous postulate.

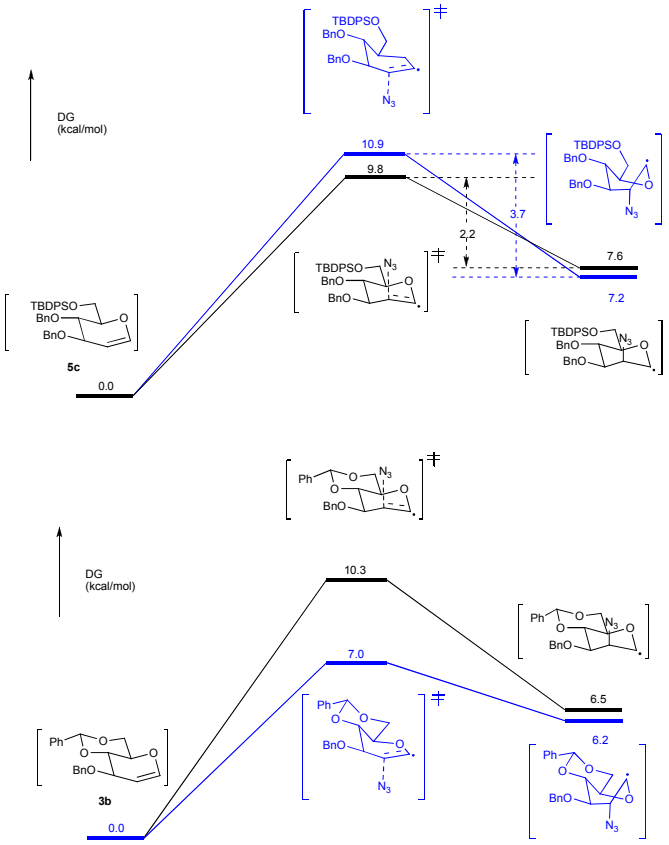


Figure 1. Free energy profile of glucal **5c**, **3b** and relative species

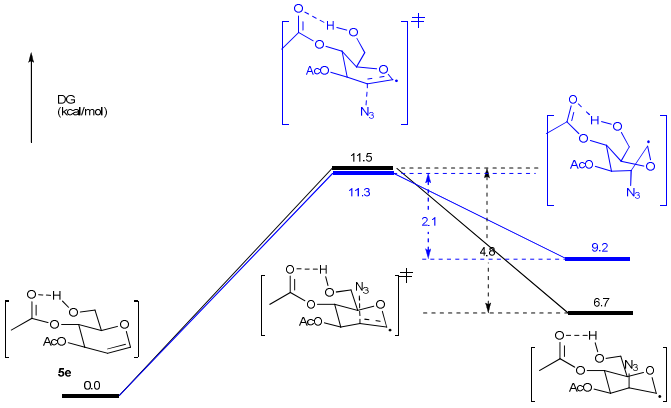


Figure 2. Free energy profile of glucal **5e** and relative species

For glucal 5e and relative species, the conformation with the hydrogen bond (shown in figure 2) was found to be more stable than

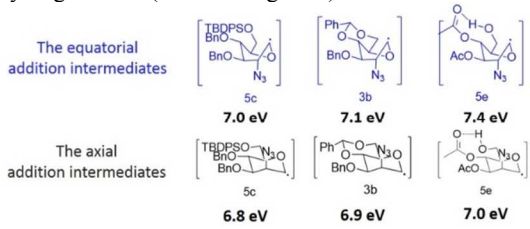
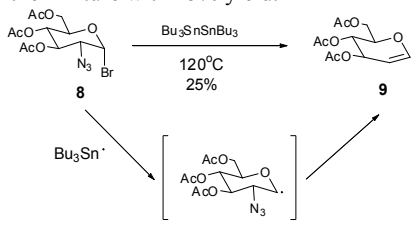


Figure 3. the average local ionization of intermediates

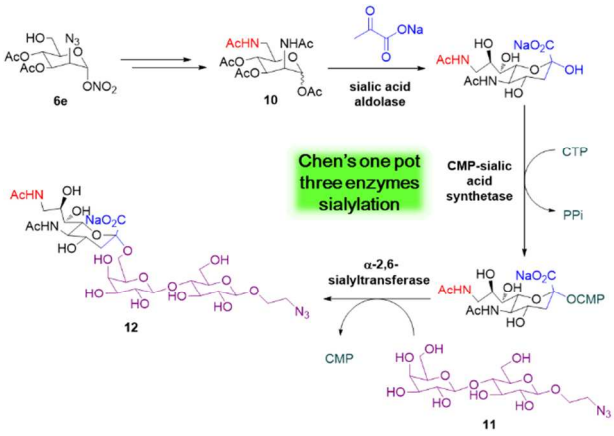
any other conformations (9.2 kcal/mol vs 6.7 kcal/mol). Free energy pathways based on this conformation are shown in Figure 1. Surprisingly, compared with the equatorial addition, the axial addition required nearly the same activation energy but offer the more thermodynamically stable intermediate. Hence, alcohol 6e is the thermodynamic favored product. To confirm the reversibility of azide radical addition intemediates, an intermediate was obtained with bromide glycoside and hexa-n-butylditin by thermolysis (scheme 2). The proposed glucal produced by reverse reaction was isolated from the mixture with 25% yield.



Scheme 2. The reversibility of azide radical addition

In order to reveal the relationship between electronic property with reactivity, average local ionization energy was calculated to estimate the oxidizability of radical atom C1 in radical intermediates of 5c, 5e and 3b. As shown in the figure 3, the average local ionization energy of intermediates of 5e is larger than intermediates of 5c and 3b, meaning that the intermediates of 5e is more stable than its counterparts. "Armed and Disarmed" theory, which was first established by Fraser-Reid and coworkers in 1988,[7] usually used to interpret the reactivity of glycosyl donors. In glycosylation reactions, "armed" donors bearing electron-donating groups on C4 and C6 was more reactive than "disarmed" ones. In this report, the evidence suggests this theory was also instructive to the reactivity of radical on the C1. The acetyl group and hydrogen bond of glucal 5e decreased the electron density on the C1 and make the radical relatively inert to further oxidize. And also, the glucals are more stable than their intermediates. These properties made the reverse reaction possible.

Herein, we also provide a convergent route to C9 modified neuraminic acids based on our discovery (scheme 3). The strategy was initiated by the synthesis of ManNAc derivative 10 with alcohol 6e via substitution, catalytic hydrogenation, acetylation and deprotection. The trisaccharide 12 was synthesized using E. coli K-12 sialic acid aldolase, N. meningitides CMP-sialic acid synthetase (NmCSS) and Photobacterium damsela α-2,6-sialyltransferase (Pd2,6ST) from sodium pyruvate, CTP, disaccharide **11** and compound **10** in 80% yield, according to Chen's one pot three enzymes procedure.[8] This kind of neuraminic acids have proved to be ligands of CD22 (Siglec-2) and have potential therapeutic utilities in B cells correlated diseases.[9]



Scheme 3. The synthesis of C9 modification neuraminic acid derivative **12** from **6e**

Conclusions

In conclusion, to the best of our knowledge, this is the first report about stereoselectively synthesis of ManNAc derivatives with glucals. And we showed a potential application of our method in the chemo-enzymatic synthesis of neuraminic acid derivatives. Experimental results and systematic high accuracy computational studies revealed that "armed" glucals, as "armed" donors in glycosylation, are more reactivity in the radical addition and prone to offer kinetic-controlled products. In the kinetic process, torsional strain plays a decisive role in the selectivity by influencing the relative energies of diastereomeric transition state. And "disarmed" glucals are relatively inertia in the reaction. Due to this property thermodynamic stable diastereoisomer could be accessed as predominant product. We hope our discovery has positive impacts in the understanding the property of radical on the ring system.

Acknowledgements

We thank the Natural Science Foundation of China (No.21332006, 21372130) for financial support and Natural Science Foundation of Tianjin (No. 12JCYBJC18600).

Notes and references

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