Contact ion pairs and solvent-separated ion pairs from D-mannopyranosyl and D-glucopyranosyl triflates

ARTICLE *in* CARBOHYDRATE RESEARCH · JANUARY 2015

Impact Factor: 1.93 · DOI: 10.1016/j.carres.2014.10.013

3 AUTHORS:

Takashi Hosoya
University of Natural Resources and Life Sci…
35 PUBLICATIONS **601** CITATIONS
SEE PROFILE

Paul Kosma
University of Natural Resources and Life Sci…
283 PUBLICATIONS **4,334** CITATIONS
SEE PROFILE

Thomas Rosenau
University of Natural Resources and Life Sci…
343 PUBLICATIONS **3,258** CITATIONS
SEE PROFILE

Note: this is an authors' version without proof reading. **DOI:10.1016/j.carres.2014.10.013.**

Contact Ion Pairs and Solvent-separated Ion Pairs from D-Mannopyranosyl and D-Glucopyranosyl Triflates

Takashi Hosoya,*† Paul Kosma,† Thomas Rosenau†

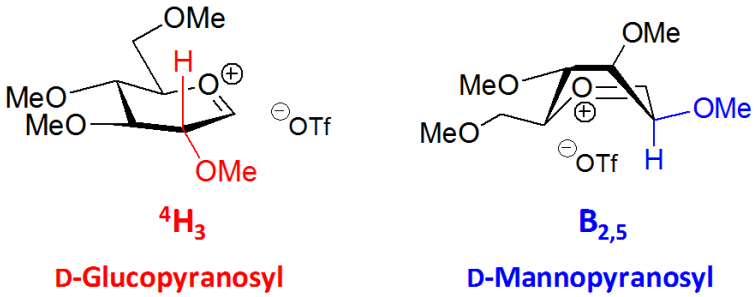
† Department of Chemistry, University of Natural Resources and Life Sciences, Department of Chemistry, Muthgasse 18, A - 1190 Vienna, Austria.

* Corresponding author: Email address: takashi.hosoya@boku.ac.at

Phone: +43-1-47654-6460

Abstract:

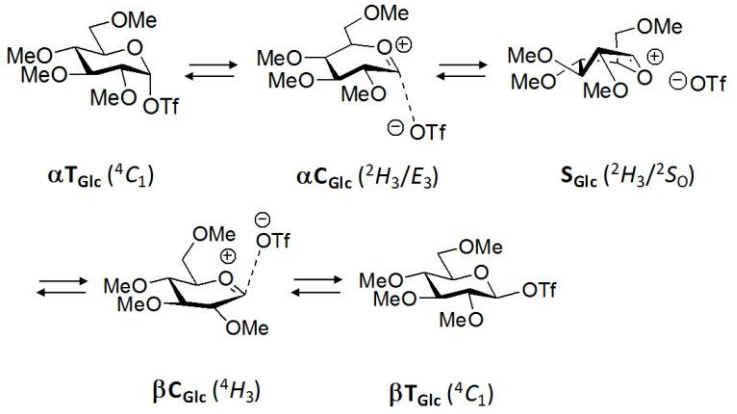
The chemical nature of contact ion pairs and solvent-separated ion pairs from 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl triflate was investigated at the DFT(M06-2X) level of theory. Comparison of the present results to those obtained for the D-glucopyranosyl counterpart in our previous study indicated that the ion pairs from the D-mannopyranosyl triflate adopt $B_{2,5}$-like conformations more preferably than those from the D-glucopyranosyl triflate. Similarly, 1,6-anhydro-D-mannopyranosyl dioxacarbenium ions bearing a $^1C_4$ conformation were shown to be more stable than the D-glucopyranosyl counterparts.



Detailed reaction mechanisms in chemical glycoside synthesis are among the hottest research subjects in carbohydrate chemistry.[1] Multiple previous studies on the mechanism have been carried out by means of experimental investigations.[2-8] and theoretical calculation, [2d,9-18] aiming mainly at improving the stereochemical outcome, i.e. α/β-anomer selectivity. The experimental studies focused especially on glycosyl triflate donors, which are well dissolved in organic solvents making experimental investigation easier.[2-5] Researchers have suggested that glycosylation with a triflate donor occurs through nucleophilic attacks of a glycosyl acceptor to covalent intermediates, contact ion pairs, and solvent-separated ion pairs, all of which are in equilibrium in solution. As the stereochemical outcome is determined by the stability and the reactivity of the covalent and the ion pair species, knowledge of their chemical properties, such as their energies and exact chemical structures, is of considerable importance. A better definition of

the ion pairs would be especially beneficial, as experimentally derived information on them is limited due to their extremely short lifetime in reaction solution.[1]

Our previous investigation of a covalent glucosyl triflate, 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl trilate (**αT$_{Glc}$**), at the DFT(M06-2X) level of theory revealed that the activation barrier of the ion pair formation from the covalent triflate in dichloromethane was so small (~13 kcal/mol) that the covalent triflate immediately formed an equilibrium mixture, composed of the α- and β-covalent triflates and the solvent-separated ion pair, as shown in Scheme 1.[18] The Gibbs energies of the α-contact, β-contact, and solvent-separated ion pairs were 9.5, 10.6, and 8.5 kcal/mol, respectively, larger than that of the most stable covalent α-triflate. Those ion pairs were most stable when they adopted $^4H_3$–like pyranosyl ring conformations (Scheme 1), while they became significantly less stable when bearing $B_{2,5}$–like conformations: for instance, a $B_{2,5}$ conformer of the β-contact ion pair was 7.2 kcal/mol less stable than the $^4H_3$ conformer. It was also seen that geometry optimization of those ion pairs was successful only when several solvent molecules were explicitly taken into account, indicating such explicit treatment of the solvent to be indispensable for accurate computational description of the ion pair formation. The successful geometry optimization of the ion pairs was also attributed to the M06-2X functional employed, since the functional well represented dispersion forces,[19] by which the solute-solvent interaction was correctly dealt with.



Scheme 1. Formation of the equilibrium mixture, composed of the covalent triflates and the ion pairs from the α-glucopyranosyl triflate **αT$_{Glc}$**.[18]

Based on these results for the D-glucopyranosyl triflate **αT$_{Glc}$**, this note addresses chemical nature of the ion pairs from the D-mannopyranosyl counterpart of the D-glucopyranosyl triflate, i.e 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl trilate (**αT$_{Man}$**), adopting computational methods similar to those employed for the former. We first focus on the α- and β-covalent triflates and then discuss the formation of the ion pairs from those triflates. We also compare the stability and the chemical structures of the covalent triflates and the ion pairs between the D-glucopyranosyl and the D-mannopyranosyl series.

The GAUSSIAN 09 software was employed in these calculations.[20] The DFT(M06-2X) level of theory[19] was employed throughout this study, as this DFT functional exhibited performance as accurate as MP4(SDQ) level calculations for our previous 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl triflate system.[18] We employed the 6-31(d) basis sets for geometry optimization, where a p-polarized function was put to all H atoms and a diffuse function was put to O, F, and Cl atoms. In the energy evaluation, cc-pVTZ basis sets were used for H, C, and S atoms and aug-cc-pVTZ ones were used for O, F, Cl atoms. In all calculations four solvent (dichloromethane) molecules were explicitly taken into account. The configuration of the dichloromethane molecules was taken as the same as in our previous study in all calculations[18]: three dichloromethane molecules were placed close to the three O atoms of the TfO moiety with the other dichloromethane molecule being placed on one side of the donor opposite to the location of the TfO group. Solvation effects were additionally taken into account in all calculations by means of the PCM method, where UFF parameters were employed for determining the cavity size. For the exocyclic rotation of the C-5–C-6 group, we focused our investigation on *gauche-gauche* (*gg*-) rotamers to reduce the computational cost for conformational search, as our previous study showed that *gg*-rotamers were the most stable in both covalent triflates and ion pairs.[18] We ascertained that each equilibrium geometry has no imaginary frequency and each transition state geometry has one imaginary frequency. Enthalpy and entropy at 195.15 K (-78°C) of the system were determined from frequency calculations at the DFT(M06-2X) level.

The α- and β-D-mannopyranosyl triflates, $\alpha\mathbf{T}_{\mathbf{Man}}$ and $\beta\mathbf{T}_{\mathbf{Man}}$, were first compared with regard to the stability of the α- and β-covalent triflates. As shown in Figure 1, $\alpha\mathbf{T}_{\mathbf{Man}}$ was 2.2 kcal/mol more stable than $\beta\mathbf{T}_{\mathbf{Man}}$ on the basis of Gibbs energy. This result is in agreement with the

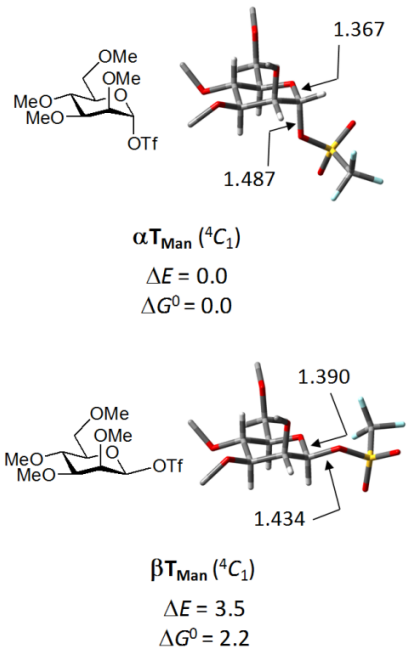


Figure 1. Geometries of the α- and β-covalent triflates, optimized at the DFT(M06-2X) level, along with their potential (after zero-point correction) and Gibbs energies (in kcal/mol).

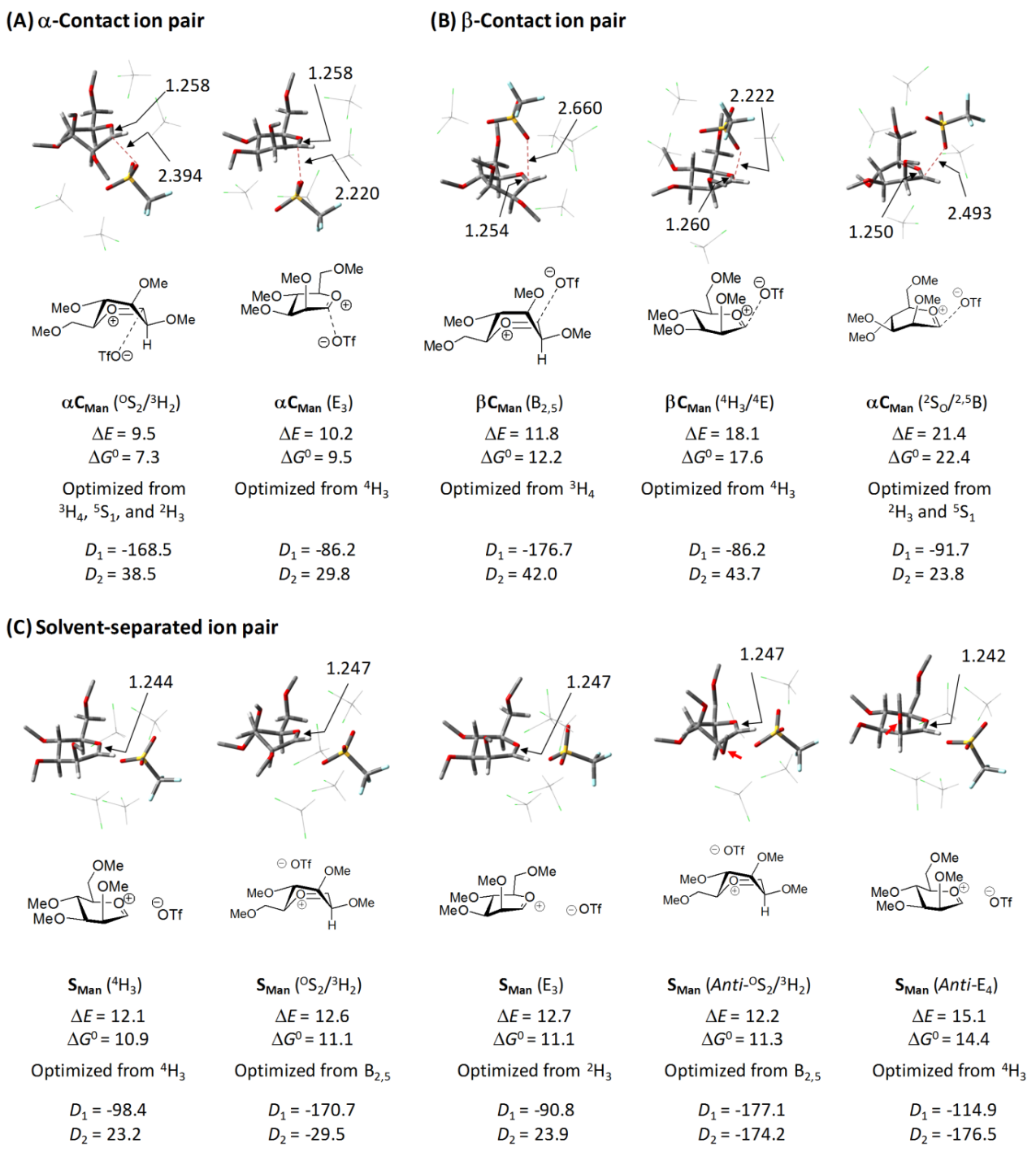


Figure 2. Geometries of the α-contact ion pair (A), the β-contact ion pair (B), and the solvent-separated ion pair (C) optimized at the DFT(M06-2X) level, along with their potential (after zero-point correction) and Gibbs energies (in kcal/mol) relative to $\alpha\mathbf{T}_{\mathbf{Man}}(^4C_1)$. The pyranosyl ring conformation of the starting geometries is shown below the energies. D_1 and D_2 represent the O-5–C-1–C-2–O-2 and H–C-2–O-2–C(H_3) dihedral angles in degree, respectively. The configurations of the solvent molecules and TfO^- of the solvent-separated ion pair were taken as the same as those of the most stable solvent-separated ion pair from the D-glucopyranosyl triflate reported elsewhere.[18] *Anti*-conformers of the C-2–O-2 bond are also shown for the solvent separated ion pair; see $\mathbf{S}_{\mathbf{Man}}(anti\text{-}^{O}S_2/^{3}H_2)$ and $\mathbf{S}_{\mathbf{Man}}(aniti\text{-}^{4}H_3)$ and the red arrows in their geometries. Optimization of the solvent-separated ion pair starting from $^3H_4$ and $^5S_1$ conformations resulted in the dioxacarbenium ion with the $^1C_4$ conformation; see Figure 3.

experimental fact that usually only α-triflates are observable in low-temperature NMR experiments.[2c,5] The dominance of the α-triflate **αT$_{Man}$** over the β-triflate **βT$_{Man}$** is greater than that calculated for the glucopyranosyl series: **αT$_{Glc}$** is only 1.2 kcal/mol more stable than **βT$_{Glc}$**.[18] This can be explained by the anomeric effect being generally stronger in D-mannosides than in D-glucosides and the destabilizing Δ2-effect derived from the axial OMe group of the D-mannopyranosyl moiety.[5b,21]

Geometry optimization of the ion pairs from the covalent triflates was then performed, taking into account four explicit solvent (dichloromethane) molecules. The geometry optimization was started from $^{4}H_{3}$, $^{3}H_{4}$, $^{5}S_{1}$, and E_{3} pyranosyl ring conformations, as oxacarbenium ions were previously reported to adopt these conformations.[4,15,16a] As shown in Figure 2, many of the optimization calculations resulted in significant deviations in the conformation from the starting geometries: $^{O}S_{2}/^{3}H_{2}$ and E_{3} conformations for the α-contact ion pair, $B_{2,5}$, $^{4}H_{3}/^{4}E$, and $^{2}S_{O}/^{2,5}B$ for the β-contact ion pair, and $^{4}H_{3}$, $^{2}S_{O}/^{3}H_{2}$, and E_{3} for the solvent-separated ion pair. One of the reasons for this conformational variation is that the TfO^{-} anion has been explicitly involved in this study whereas it was not included in the previous studies. This outcome suggests that the conformation of oxacarbenium ions is strongly dependent on the location of the counter anion. We also optimized two transition states **αTS$_{Man}$** and **βTS$_{Man}$** connecting **αT$_{Man}$** to **αC$_{Man}$** and **βT$_{Man}$** to **βC$_{Man}$**, respectively; see Figure S1 in supplemental data for the detailed structures of these transition states. Calculated activation barriers for these transitions were small: 12.3 kcal/mol for **αTS$_{Man}$** and 17.7 kcal/mol for **βTS$_{Man}$** relative to the most stable **αT$_{M}$**. Hence, it is likely that **αT$_{Man}$** readily forms an equilibrium mixture composed of these ion pairs at low temperature, such as -78 ^{o}C, as the D-glucopyranosyl triflate **αT$_{Glc}$** did.[18]

The contact ion pairs, **αC$_{Man}$** and **βC$_{Man}$**, were most stable in $^{O}S_{2}/^{3}H_{2}$ and $B_{2,5}$ conformations, respectively, these two conformations being quite similar to each other (Figure 2). In case of the solvent-separated ion pair, a $^{4}H_{3}$ conformer was the most stable one (ΔE=12.1 kcal/mol and ΔG^{0}=10.9 kcal/mol), but also the $^{O}S_{2}/^{3}H_{2}$ conformer exhibited potential and Gibbs energies (ΔE=12.6 kcal/mol and ΔG^{0}=11.1 kcal/mol) very close to those of the $^{4}H_{3}$ one. These results are interesting when being compared to those obtained for the D-glucopyranosyl series[18]: the ion pair from **αT$_{Glc}$** are the most stable when they take $^{4}H_{3}$–like conformations with $B_{2,5}$–like conformers being significantly less stable (see above). It is thus concluded that $B_{2,5}$–like conformations become much more stable by the stereochemical inversion at the C-2 position. Whitfield and his research group have reported that O-2 in oxacarbenium ions has a strong preference for being in the plane of the O-5–C-1.[17] This effect explains the inversion of conformational preference observed in this study: the O-5–C-1–C-2–O-2 dihedral angel (D_1 in Figure 2) is very close to planner in case of the $B_{2,5}$-like conformers. Crich and his group have suggested that D-mannopyranosyl oxacarbenium ions with a 4,6-diacetal structure, e.g. 4,6-*O*-benzylidene, tend to bear $B_{2,5}$–like conformations in contrast to their D-glucopyranosyl counterparts, whose oxacarbenium ions prefer $^{4}H_{3}$–like conformations.[1a,2f] Our current results lend theoretical support to their suggestion.

We also summarize the H–C-2–O-2–C(H_3) dihedral angle of the ion pairs; see D_2 in Figure 2. The dihedral angles of the ion pairs other than $\mathbf{S_{Man}}$(*anti*-$^{O}S_2/^{3}H_2$) and $\mathbf{S_{Man}}$(*aniti*-$^{4}H_3$) were in the range of -30 to 45 degrees, indicating that these ion pairs took *syn*-conformations regarding to the C-2–O-2 bond. On the other hand, the solvent-separated ion pairs $\mathbf{S_{Man}}$(*anti*-$^{O}S_2/^{3}H_2$) and $\mathbf{S_{Man}}$(*aniti*-$^{4}H_3$) took the dihedral angles of -174.2 and -176.5 degrees, respectively, and hence these ion pairs adopted *anti*-conformations regarding to the C-2–O-2 bond. Comparing the geometries and energies of $\mathbf{S_{Man}}$($^{O}S_2/^{3}H_2$) and $\mathbf{S_{Man}}$($^{4}H_3$) to those of $\mathbf{S_{Man}}$(*anti*-$^{O}S_2/^{3}H_2$) and $\mathbf{S_{Man}}$(*anti*-$^{4}H_3$), it becomes clear that the *syn*-conformers are more stable than the *anti*-conformers on the basis of Gibbs energy. Although we did not investigate *syn*-conformers of the contact ion pairs, this *syn*-preference will be the case also for the contact ion pairs, expected from geometrical and energetical similarity between the contact ion pairs and the solvent separated ion pairs; see Figure 2. Whitfield and his research group reported a similar *syn*-preference of oxacarbenium ions without taking counter anions into account.[14,17] This study supports their suggestion and indicates further that the syn-preference also exist when the counter anion is explicitly dealt with.

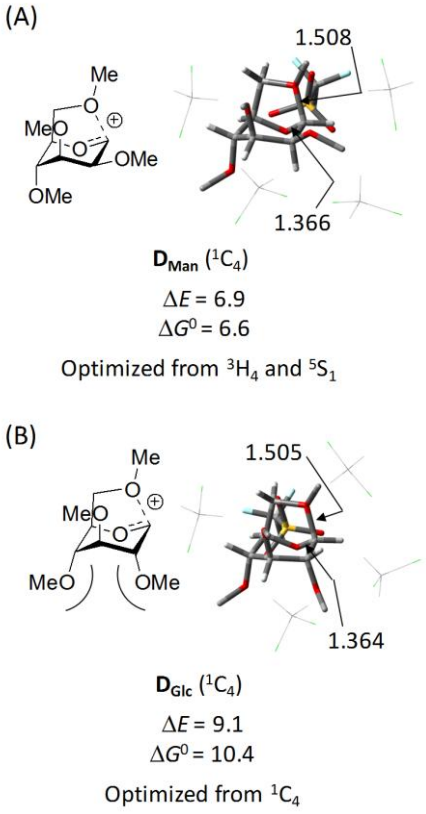


Figure 3. Geometries of the ion pairs consisting of the dioxacarbenium ion from the D-mannopyranosyl triflate (A) and the D-glucopyranosyl triflate (B) optimized at the DFT(M06-2X) level, along with their potential (after zero-point correction) and Gibbs energies (in kcal/mol) relative to the corresponding a-covalent triflate. We newly optimized the geometry of $\mathbf{D_{Glc}}$ in this study as our previous report did not mention the dioxacarbenium ion.

In addition to the ion pairs just discussed, we also found another type of the ion pairs $\mathbf{D_{Man}}$ and $\mathbf{D_{Glc}}$ that involved a dioxacarbenium ion, in which the glycosyl moiety harbored a 1,6-anhydro structure with a $^{1}C_4$ pyranosyl ring conformation, as shown in Figure 3. Whitfield and his research group also computed similar dioxacarbenium ions, referring to the possibility that such

dioxacarbenium ions might play some roles in chemical and enzymatic glycosylation.[15] According to Figure 3, it becomes clear that the 1,6-anhydro-type dioxacarbenium ion is not very stable in case of the D-glucosyl series, but substantially stable in the D-mannosyl series. This is likely due to the fact that electrostatic repulsion between O-3 and O-5 does not exist in case of the D-mannosyl dioxacarbenium ion. These results might suggest that mannosylation reactions prone to involve the dioxacarbenium ions. To clarify the detailed role of these dioxacarbenium ions in glycosylation, however, it is necessary to evaluate their reactivity toward glycosyl acceptors.[22] It is also noted that the formation of the dioxacarbenium ions during geometry optimization strongly depends on the C-5-C-6 rotation of the staring geometry, according to Whitfield and his research group.[9,10] As this study limits the C-5-C-6 rotation to the *gauche-gauche* type (see above), it is possible that $^{3}H_{4}$ and $^{5}S_{1}$ ring conformers, which led to the dioxacarbenium ions as shown in Figure 3, exist as stable minimums when they take the other *gauche-trans* and/or *trans-gauche* C-5–C-6 conformations.

In conclusion, we unveiled two major differences between the D-mannopyranosyl and D-glucopyranosyl ion pairs: 1) the ion pairs from the D-mannopyranosyl triflate adopt $B_{2,5}$-like conformations more preferably than those from the D-glucopyranosyl triflate. 2) The dioxacarbenium ion with the 1,6-anhydo structure is more stable in the D-mannopyranosyl series, and hence more likely to play roles in glycosylation reactions. These remarkable differences are expected to cause considerable mechanistic differences between D-glucosylation and D-mannosylation. The chemical nature of the ion pairs clarified in this study, however, are only some of the factors determining the overall stereochemical outcome of glycoside synthesis. As reported in many mechanistic studies, chemical properties of the acceptor, *i.e.* steric property, nucleophilicity, acceptor type (*O*- or *C*-glycosylation), etc, also play profound roles in glycoside formation. Hence, it is indispensable to simulate the overall process of glycoside synthesis including the nucleophilic attack of acceptors, to get deeper insight on the detailed mechanisms. It is also noted that the chemical nature of the ion pairs can be significantly altered when different protecting groups are employed.[1c] Our upcoming study will report how the stability and the structures of the ion pairs are affected by a 4,6-diacetal protecting group, which has drawn attention as a powerful protecting group upon highly stereoselective glycosylation, especially β-mannosylation.

Acknowledgements

We performed quantum chemical calculations at the workstation in the Sakaki group, Fukui institute for fundamental chemistry at Kyoto University, Japan, and would like to thank for the access. The financial support of the Austrian Christian Doppler Research Society (CDG) through the CD-lab "Advanced cellulose chemistry and analytics" is gratefully acknowledged.

References

1. Recent reviews for the mechanism of chemical glycosylation: (a) Crich, D. *Acc. Chem. Res.*, **2010**, *43*, 1144-1153. (b) Crich, D. *J. Org. Chem.*, **2011**, *76*, 9193-9209. (c) Walvoort, M. T. C.;

Dinkelaar, J.; van den Bos, L. J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Carbohydr. Res.*, **2010**, *345*, 1252-1263. (d) Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.*, **2010**, 497-510.

2. (a) Crich, D.; Vinogradova, O. *J. Org. Chem.*, **2006**, *71*, 8473-8480. (b) Crich, D.; de la Mora, M.; Vinod, A. U. *J. Org. Chem.*, **2003**, *68*, 8142-8148. (c) Crich, D.; Sun, S. *J. Am. Chem. Soc.*, **1997**, *119*, 11217-11223. (d) Huang, M.; Garrett, G. E.; Birlirakis, N.; Bohé, L.; Pratt, D. A.; Crich, D. *Nat. Chem.*, **2013**, *4*, 663-667. (e) Huang, M.; Retailleau, P.; Bohé, L.; Crich D. *J. Am. Chem. Soc.*, **2012**, *134*, 14746-14749. (f) Crich, D.; Li, L. *J. Org. Chem.*, **2007**, *72*, 1681–1690.
3. Ngoje, G.; Li, Z. *Org. Biomol. Chem.*, **2013**, *11*, 1879-1886.
4. (a) Dinkelaar, J.; de Jong, A. R.; van Meer, R.; Somers, M.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.*, **2009**, *74*, 4982-4991. (b) Frihed, T. G.; Walvoort, M. T. C.; Codée, J. D. C.; van der Marel, G. A.; Bols, M.; Pedersen, C. M. *J. Org. Chem.*, **2003**, *78*, 2191-2205.
5. (a) Callam, C. S.; Gadikota, R. R.; Krein, D. M.; Lowary, T. L. *J. Am. Chem. Soc.*, **2003**, *125*, 13112-13119. (b) Hou, D.; Taha, H. A.; Lowary, T. L. *J. Am. Chem. Soc.*, **2009**, *131*, 12937-12948.
6. (a) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *J. Org. Chem.*, **2009**, *74*, 8039-8050. (b) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *Org. Lett.*, **2008**, *10*, 4907-4910. (c) Beaver, M. G.; Woerpel, K. A. *J. Org. Chem*., **2010**, *75*, 1107-1118.
7. Jensen, H. H.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.*, **2004**, *126*, 9205-9213.
8. Baek, J. Y.; Lee, B.; Jo, M. G.; Kim, K. S. *J. Am. Chem. Soc.*, **2009**, 131, 17705–17713.
9. A review on computations: Whitfield, D. M. *Adv. Carbohydr. Chem. Biochem.*, **2009**, 62, 83–159.
10. (a) Whitfield, D. M. *Carbohydr. Res.*, **2012**, *356*, 180–190. (b) Whitfield, D. M. *Carbohydr. Res.*, **2007**, *342*, 1726–1740. (c) Whitfield, D. M. *Carbohydr. Res*., **2012**, *356*, 191–195.
11. Kumar R.; Whitfield, D. M. *J. Org. Chem.*, **2012**, *77*, 3724−3739.
12. Li, Z. *Carbohydr. Res.*, **2010**, *345*, 1952–1957.
13. Satoh, H.; Hansen, H. S.; Manabe, S.; van Gunsteren W. F.; Hünenberger, P. H. *J. Chem. Theory Comput.*, **2010**, *6*, 1783–1797.
14. Ionescu, A. R.; Whitfield, D. M.; Zgierski, M. Z. *Carbohydr. Res.*, **2007**, *342*, 2793–2800.
15. Ionescu, A. R.; Whitfield, D. M.; Zgierski, M. Z.; Nukada, T. *Carbohydr. Res.*, **2006**, *341*, 2912–2920.
16. (a) Nukada, T.; Bérces, A.; Wang, L.; Zgierski, M. Z.; Whitfield, D. M. *Carbohydr. Res.*, **2005**, *340*, 841–852. (b) Nukada, T.; Bérces, A.; Whitfield, D. M. *Carbohydr. Res.*, **2002**, *337*, 765–774.
17. Ionescu, A. R.; Wang, L.; Zgierski, M. Z.; Nukada, T.; Whitfield, D. M. Two Unexpected Effects Found with 2,3,4,6-Tetra-O-methyl-D-Gluco- and Mannopyranosyl Oxacarbenium ions: An O-2 Pseudo-equatorial Preference and a large H-2-C-2--O-2-CH3 syn Preference. In NMR Spectroscopy and Modeling of Carbohydrates; Vliegenhart, H., Woods, R. J. Eds; *Am. Chem. Soc. Symp. Ser.*, 2006; vol. 930, pp. 302-319.

18. Hosoya, T.; Takano, T.; Kosma, P.; Rosenau, T. *J. Org. Chem.*, **2014**, *79*, 7889-7894.
19. Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.*, **2008**, *120*, 215-241.
20. Gaussian 09, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.
21. Reeves, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1499−1506.
22. The formation of the 1,6-anhydro structure becomes significant under pyrolytic conditions; see for example, Matsuoka, S.; Kawamoto. H.; Saka, S. *J. Anal. Appl. Pyrol.* **2013**, *103*, 300-306.