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Structural and Computational Analysis of 2-Halogeno-Glycosyl Cations in Superacid: An Expansive Platform

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Abstract: An expansive NMR–based structural analysis of elusive glycosyl cations derived from natural and non-natural monosaccharides in superacids is disclosed. For the first time, it has been possible to explore the consequence of deoxygenation and halogen substitution at the C-2 position in a series of 2-halogenoglucosyl, galactosyl and mannosyl donors in the condensed phase. These cationic intermediates were characterized using low temperature *in situ* NMR experiments supported by DFT calculations. The 2-bromo derivatives display intramolecular stabilization of the glycosyl cations. Introducing a strongly electron withdrawing fluorine atom at C-2 exerts considerable influence on the oxocarbenium ion reactivity. In superacid, these oxocarbenium ions are quenched by weakly coordinating SbF_6^- anions, thereby demonstrating their highly electrophilic character and their propensity to interact with poor nucleophiles.

2-Deoxyhalogenated glycosyl donor derivatives are versatile building blocks for preparative glycochemistry. Inclusion of a functional handle at C-2 allows glycosylation to be influenced in a traceless fashion, rendering them ideal to access 2-deoxyglycosides.[1] This important class of carbohydrates appears frequently in bioactive natural products[2] but stereocontrolled glycosidic bond formation remains challenging.[3] Deoxyfluorinated glycosyl donors are a particularly prominent class of halo-sugars and have found widespread application in mechanistic enzymology.[4] These structures are also pivotal for the generation of glycoproteins containing the ^{19}F NMR active probe, promising candidates for carbohydrate vaccines[5] and in radiopharmaceutical chemistry.[6] The fluorine substituent has also been strategically employed to direct glycosylation selectivity, particularly when matched with protecting group electronics.[7] Chemical glycosylation is a mechanistic continuum that includes dissociative extreme featuring putative oxocarbenium ion intermediates.[8] Unlike simple oxocarbenium ions that are of comparable stability to benzylic ions,[9] the environment of the pyranose ring, containing multiple C-O bonds, reduces the stability and lifetime of these ionic species.[10,11] The synergistic electron withdrawing effect of an halogen atom at C-2 likely enhances this global effect by rendering the anomeric carbon atom even more electron deficient. Accordingly, while the direct observation of glycosyl cations in the gas phase by complementary spectroscopic methods[12,13] and indirect observation[14,15] has been reported, their direct characterization in the condensed phase has failed despite a number of very elegant attempts.[16] Strongly inspired by the work of Olah and Prakash, who unlocked large areas of carbocation chemistry exploiting non nucleophilic superacid conditions,[17] using HF/SbF_5 superacid as both a reagent and solvent, we recently generated and characterized glucosyl cations in a condensed phase.[18] However, this proof of concept study has been limited to glycosyl cations bearing only equatorial substituents. To address the urgent need for general strategies to enable the direct characterization of glycosyl cations, the impact of halogens at C-2 on the superacid-mediated transient and key glucosyl, galactosyl and mannosyl cation formation, structure and stability is presented (Fig. 1).

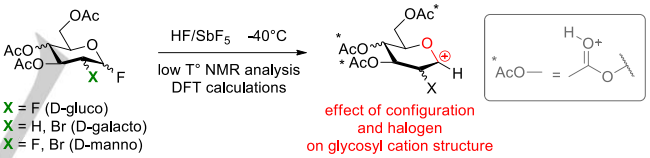

Figure 1. Superacid-mediated glycosyl cations generation and study.

The 2-deoxygalactopyranosyl donor **1** was first studied to evaluate the effect of an axial electron withdrawing substituent at C-4, as this subtle change has been shown to favor a through space stabilization of the transient glycosyl cation.[19], [20] Donor **1** was submitted to HF/SbF_5 conditions and cleanly furnished a polycationic species, which was analyzed by NMR, following our previously described protocol.[18a] Detailed NMR analysis of this species was in excellent agreement with the 2-deoxy-galactopyranosyl cation **2** (anomeric proton at 9.18 ppm and anomeric carbon at 228.5 ppm). The quality of the recorded NMR spectra allowed for the complete analysis of the homonuclear NMR coupling constants, which assisted by computational analysis, permitted to infer the major contribution of a ^4E envelope conformation to ion **2** (Fig. 2). Interestingly, this conformation was also assigned to the 2-deoxyglucosyl cation,[18a] in which the three sugar ring substituents adopted a pseudoequatorial orientation to minimize charge repulsion. Here, the acetate at C-4 remains axial. While neighboring group participation of the 2-OAc group was clearly operative, leading to the dioxalenium ion **4** when studying peracetylated D-galactosyl donor **3** (Fig. 2b), (see SI) potential participation of the 4-OAc of the 2-deoxy donor **1** was not observed in superacid.

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Intuitively, inserting an electronegative substituent at C-2 is expected to increase the electrophilicity of the glycosyl oxocarbenium ion, thus favoring potential remote axial acetate participation to stabilize this species. Therefore, the behavior of the 2-bromo-2-deoxygalactosyl fluoride **5** in superacid was examined.

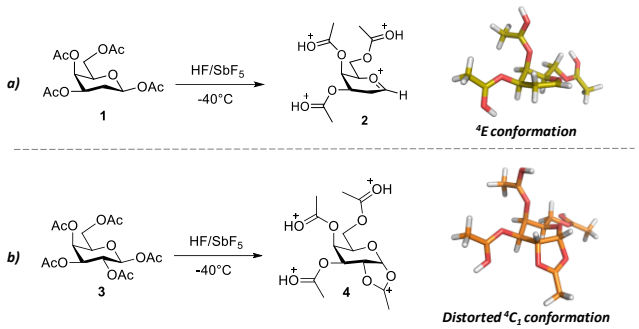

Figure 2. Generation of a) ion **2** after reaction of 2-deoxygalactopyranosyl donor **1** in HF/SbF_5 (conformation in solution); b) dioxalenium ion **4** after reaction of peracetylated D-galactosyl donor **3** in HF/SbF_5 (conformation in solution).

Under HF/SbF_5 conditions, the corresponding 2-deoxy-2-bromo-galactosyl cation **6** was produced according to the NMR data (Fig. 3). The signal for the anomeric carbon for ion **6** was not detected by ^{13}C NMR that can be attributed to the scalar relaxation effect of the quadrupolar bromine nucleus that causes severe line broadening effect on C-1. This effect, also operative in the 2-bromoglucose case (see SI), is a clear experimental demonstration of the existence of a stabilizing orbital overlap between Br and C-1. A $^4H_5$ conformation, placing the bromine in a *pseudo*-axial orientation, was attributed to the 2-bromo-2-deoxygalactosyl cation **6** by comparing the experimental and DFT-calculated coupling constants and ^{13}C chemical shifts for its optimized structure (see SI). This conformation allows the above-mentioned stabilization of the galactosyl cation by electron donation from the bromine lone pairs to the electron deficient antibonding orbital of O5-C1, as revealed by Natural Bond Order analysis.

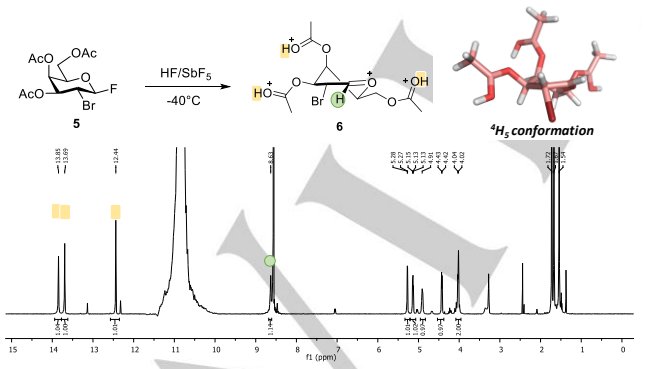

Figure 3. Generation and ^1H NMR spectrum of 2-bromogalactosyl oxocarbenium ion **6** in HF/SbF_5 at -40°C (conformation in solution).

Regarding remote anchimeric assistance, introduction of the bromine at C-2 failed to trigger 4-OAc participation, suggesting a instantaneous protonation of this ester in superacid that precludes its anchimeric assistance, unlike with the 2-OAc in the galactosyl donor **3**. The high electrophilic character of the postulated transient mannosyl cation,[21] illustrated by the trapping of silver perchlorate by peracetylated mannopyranosyl chloride,[22] and the challenge associated with its generation in solution led us to investigate this unique glycosyl donor. Peracetylated-*β*-D-mannopyranose **7** and its 2-bromo-2-deoxy fluoride counterpart **8**[23] were both treated with HF/SbF_5 superacid. Interestingly, while peracetylated gluco- and galactopyranose previously furnished the corresponding dioxalenium ions as single species, the mannosyl donor **7** furnished a mixture of the expected dioxalenium ion **9** observed as a distorted $^4C_1$ conformer (see SI) along with some unreacted mannosyl donor in its polyprotonated form **10**, emphasizing the singular reactivity of this unique stereoisomer. Gratifyingly, the 2-bromo 2-deoxymannosyl donor **8** furnished an ionic species whose NMR signals were in good agreement with a 2-bromomannosyl oxocarbenium ion **11** (anomeric proton at δ = 8.50 ppm and anomeric carbon at δ = 195.4 ppm). Flattening of the sugar ring adopting a $^4H_3$ conformation was evidenced by *J*-coupling constant analysis. Again, this conformation places the bromine atom in a *pseudo*-axial orientation allowing stabilization of the positive charge developed at the anomeric center by bromine (Fig. 4).

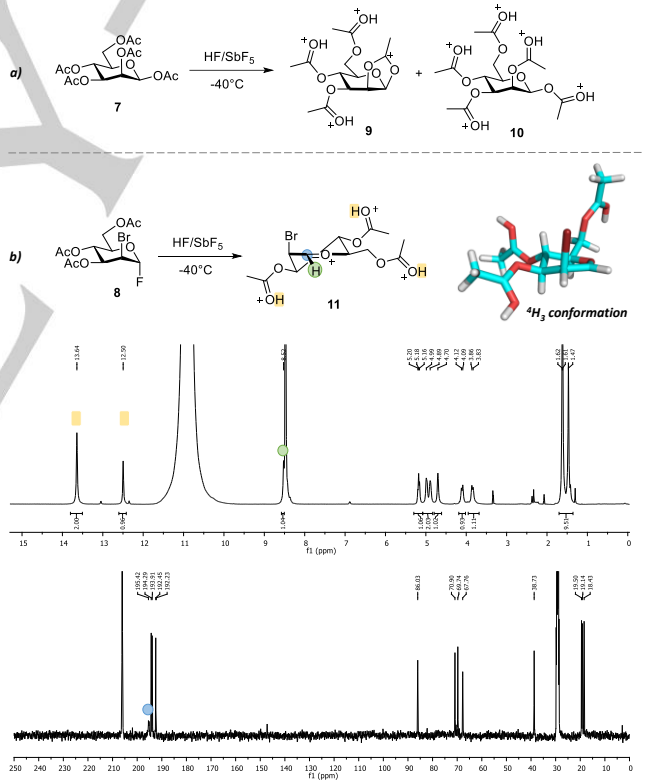

Figure 4. a) Generation of mannosyl ions **9** and **10** after reaction of peracetylated-β-mannopyranose **7** in HF/SbF_5 at -40 °C; b) Generation and NMR spectra of 2-bromomannosyl oxocarbenium ion **11** in HF/SbF_5 at -40 °C (conformation in solution).

Having demonstrated the through space stabilization of the glycosyl cation exerted by the bromine at C-2 whatever the glycosyl donor stereochemistry, in superacid, we switched to 2-fluoro derivatives that was expected to behave differently. Due to its unique properties,[24] the “magic fluorine” atom has attracted considerable attention in recent years and has been implicated in

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the discovery of new chemical entities possessing unique physicochemical properties.[25] Glycoscience is no exception and the incorporation of fluorine atoms into carbohydrates is well documented.[26] The 1-acetyl-2-fluoro tetrahydropyran **12** was selected as a 2-fluoro glycosyl donor model and yielded the corresponding cyclic oxocarbenium ion **13** upon treatment with HF/SbF_5 (δH1 = 8.79 ppm; δC1 = 227.3 ppm, $^2J_{C\text{-}F}$ = 35 Hz; see SI). This result confirmed that unstable and highly intriguing α-fluorinated cyclic carboxonium ions,[27-29] can be observed by low-temperature NMR spectroscopy in superacid solutions (Fig. 5a).

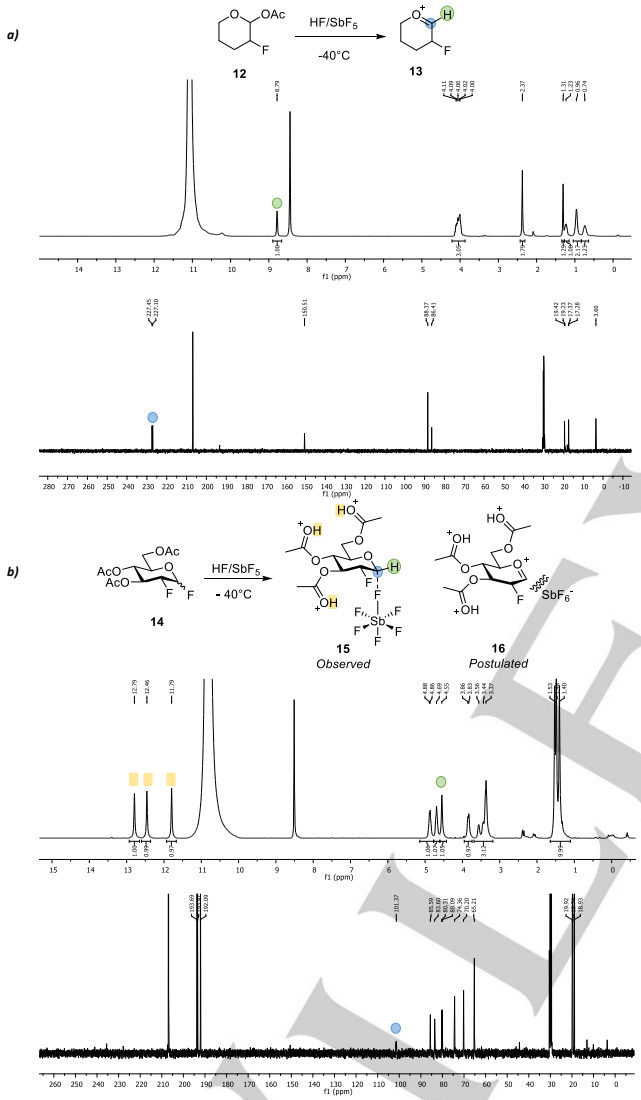

Figure 5. a) Generation and NMR spectra of 2-fluorotetrahydropyranyl ion **13** in HF/SbF_5 at -40 °C; b) Generation and NMR spectra of ion **15** resulting from reaction of 1,2-difluorinated glucosyl donor **14** with HF/SbF_5 at -40 °C and calculated 2-fluoroglucosyl oxocarbenium ion **16**.

The absence of large $^3J_{H\text{-}F}$ NMR coupling constants suggests a flattened conformation in solution, with the H-C-C-F dihedral angle close to 90°C,[30] in line with the idea that an electronegative substituent located in the vicinity of the cyclic oxocarbenium ion must strongly influence its ground state conformation.[7,31] The reactivity of the 1,2-difluorinated glucosyl donor **14** was next examined. Its activation under optimized superacid conditions led to a cationic species whose anomeric NMR shifts (δH1 = 4.55 ppm; δC1 = 101.3 ppm) (Fig. 5b) did not match those of the calculated 2-fluoroglucosyl cation **16** (see SI). Indeed, the NMR data strongly support a α-configured species **15** adopting a $^4C_1$ conformation resulting from cation stabilization by SbF_6^- counterion. This species perfectly illustrates the dramatic difference in reactivity between a simple tetrahydropyranyl oxocarbenium ion and a glycosyl cation bearing several electron-withdrawing C-O substituents. We were particularly puzzled by the unusual broad signal in the ^{13}C NMR spectrum recorded at -40 °C exhibited by the anomeric carbon of **15** (Fig. 6b) and by the absence of NMR coupling constants of H-1 and C-1 with the F of the SbF_6^-. In order to corroborate the structure of **15**, its ^{13}C NMR spectrum was recorded at higher temperatures (up to 10°C). Fittingly, a sharper doublet peak with a large coupling (24Hz) was obtained for C-1, in agreement with an unconventional coordination phenomenon triggered by the "non-coordinating" SbF_6^- anion (Fig. 6b).[32]

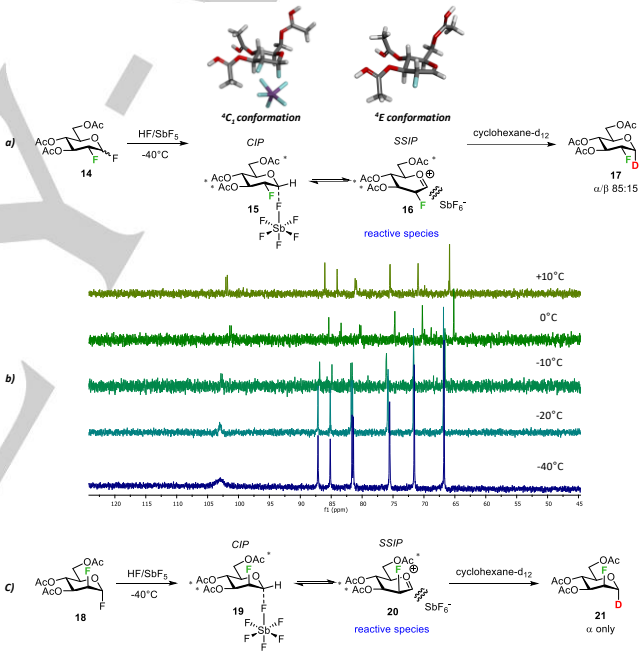

Figure 6. a) Formation and observed privileged conformation of ion **15** in superacid HF/SbF_5 solution; deuteration and calculated privileged conformation of the postulated SSIP fluorinated glucosyl cation analogue **16**; b) Sharpening of the anomeric carbon signal of ion **15** with increasing temperature; c) Formation of mannose-derived ionic species **19**, observed by low-temperature NMR in superacid HF/SbF_5 solution and deuteration of its postulated SSIP fluorinated mannosyl cation analogue **20**.

Collectively, these data suggest that, unlike in the 2-Br case, the media counter anions interact with the "superelectrophilic"[33] 2-fluoro glucosyl cation leading to a fast equilibrium between an observed contact ion pair **15** and a transient solvent separated ion pair **16** found to adopt a ^4E conformation by calculations (see SI) that could not be observed on the NMR time scale. This hypothesis was indeed supported by the observation of at least two major coordinated species when the reaction was performed in magic acid (HSO_3F/SbF_5), a solution known to contain mixtures of fluoro-fluorosulfato ($SbF_{6-n}^-(SO_3F)_n^-$) and fluoro ($Sb_nF_{5n+1}^-$)

antimonates (see SI).[34,35] Thus, in the absence of nucleophile in the reaction medium, this superelectrophilic glucosyl cation can be trapped by "non-coordinating" $Sb_nF_{5n+1}^-$ species.[36] The transient formation of the 2-deoxy-2-fluoro-glucosyl cation **16** in HF/SbF_5 was confirmed by performing a kinetic ionic deuteration that furnished the axially deuterated pyranose **17** as the major product (Fig. 6a). To further confirm this trend, the peracetylated 2-fluoromannosyl fluoride **18** was examined. Similarly, a mannosyl coordinated species **19** adopting a $^4C_1$ conformation and displaying a broad NMR signal for the anomeric carbon was observed (see SI). Treatment of the reaction mixture with cyclohexane-d_{12} led to the isolation of an axially deuterated monosaccharide **21** in agreement with the formation of a transient 2-fluoromannosyl cation **20** in the superacid medium (Fig 6c). The preferred deuteration of both glycosyl cations **16** and **20** from the α face must arise from their specific conformation and counter ion distribution in their coordinating sphere.[37]

In conclusion, this study demonstrates that the union of superacids and NMR analysis provides an expansive platform to explore glycosyl cations in the condensed phase. The initial generation of D-gluco-configured glycosyl cations in superacid,[18a] has been significantly extended to include other natural and non-natural sugars that are biologically relevant. For the first time, galactose and mannose-derived systems could be interrogated. Working in superacid also allowed for the analysis of 2-deoxy systems, as well as unnatural analogues bearing halogens at C-2. A combined experimental and computational approach has demonstrated the profound effect that halogens can have on conformation: a seemingly subtle switch from C2-F to C2-Br causes very different conformational behavior. Whilst analysis of the 2-bromo derivatives indicate a through space intramolecular stabilisation of the glycosyl cation whatever the stereochemistry, investigation of the 2-fluoro glycosyl donors suggests that intermolecular stabilization of the transient glycosyl cation by poorly nucleophilic fluoroantimonate species is operational. It is evident that for these fluorinated species, even in a "non-nucleophilic" environment, counter ion matters. This result may pave the way for glycosylation reactions with unprecedented weak nucleophiles.

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Keywords: glycosylation • oxocarbenium • fluorine • superelectrophile • reaction mechanisms

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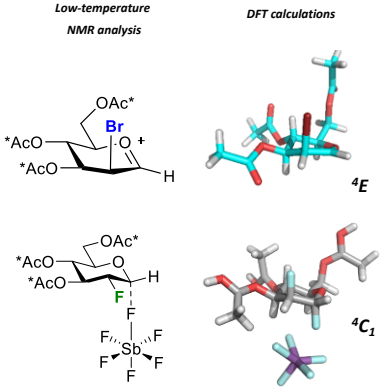
Halogen substitution effect on superacid-generated glucosyl, galactosyl and mannosyl cations conformation was explored by low temperature *in situ* NMR experiments and supported by DFT calculations.



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