and synergistic control of a multitude of processes in concert[7]. This systems chemistry[8] approach is destined to push the boundaries of what synthetic molecular machines can and will accomplish. ❐

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Published online: 21 December 2015

CARBOHYDRATE REACTIVITY

Glycosyl cations out on parole

The reactivity of glycosyl donors is often explained by invoking putative glycosyl cation intermediates but, until now, they have not been observed in the condensed phase.

Luis Bohé and David Crich

Just as chemistry is the central science, carbohydrate chemistry is central to glycoscience. Within carbohydrate chemistry there is arguably no reaction more important than the formation of glycosidic bonds — those between a sugar and a hydroxyl or other functional group of another molecule — known as glycosylation or glycosidation.

In glycosylation a glycosyl donor reacts with a glycosyl acceptor, typically in the presence of a promoter, to form the glycosidic bond (Fig. 1a). The efficiency and stereoselectivity of this process is affected by a multitude of factors, not least the configuration and substitution pattern of the glycosyl donor. Such factors are commonly considered to exert their influence at the level of a putative intermediate glycosyl oxocarbenium ion — or glycosyl cation — in terms of both reactivity and face selectivity. Indeed this cation-centric model dominates to the extent that the enormous majority of papers in the area omit any consideration of counterions, whether in the form of covalent intermediates, or contact (CIP) or solvent separated (SSIP) ion pairs, and consider the oxocarbenium ion essentially in a vacuum[1].

In recent years, however, this view has been increasingly challenged as NMR spectroscopic studies have failed to provide evidence for glycosyl oxocarbenium ions in the condensed phase, despite the relative ease with which simple alkyl oxocarbenium ions are detected[1,2]. Moreover, it has been demonstrated that even relatively weakly nucleophilic counterions such as trifluoromethanesulfonate prefer to form covalently bound intermediates rather than to exist in ion pairs with the putative glycosyl oxocarbenium ions[3]. The field of glycosyl oxocarbenium ions is therefore at a similar level of development as that of carbenium ions in general in the 1960s following Winstein's seminal concept of the role of ion pairs in nucleophilic substitution[4], but prior to the fundamental studies of Olah and co-workers that enabled their observation by NMR spectroscopic methods in superacidic media. Now, following closely on the heels of a poster by Akien and Subramanian[5], Blériot and co-workers disclose in *Nature Chemistry* the generation, NMR spectroscopic characterization, and preliminary reactions of free 2-deoxy and 2-bromo-2-deoxy glucopyranosyl oxocarbenium ions liberated from close proximity with any counterion by the hydrofluoric acid–antimony pentafluoride (HF/SbF_5) superacidic medium[6].

Blériot and co-workers report that on dissolution in an approximately 4:1 mixture of HF and SbF_5 at −40 °C, 2-deoxy-β-D-glucopyranose tetraacetate (lacking a strongly electron-withdrawing substituent at the two position) gave ^1H and ^{13}C NMR spectra consistent with conversion to the fully protonated form of the tri-*O*-acetyl-2-deoxyglucopyranosyl oxocarbenium ion as characterized by the anomeric proton and carbon resonances with chemical shifts (δ) of 8.89 and 229.1, respectively (Fig. 1b). DFT calculations and coupling constant analysis point to the preferential adoption of a ^4E envelope conformation in which the three protonated substituents take up pseudoequatorial positions. Variable-temperature NMR spectroscopy demonstrated the cation to be stable to at least 20 °C in the HF/SbF_5 mixture.

On dissolution in the same HF/SbF_5 mixture, peracetyl-2-bromo-2-deoxy-β-D-glucopyranose lost the anomeric acetate and afforded a triprotonated cation assigned to a $^4H_5$ half-chair conformation containing a loose unsymmetrical cyclic bromonium ion, whose presence was revealed by the anomeric proton and carbon resonances of δ 8.36 and 198.1, respectively (Fig. 1c).

Extension of the method to peracetyl-α-D-glucopyranose and peracetyl-2-acetamido-2-deoxy-α-D-glucopyranose gave spectra consistent with participation by the neighbouring acetoxy or acetamido groups and the formation of fused dioxalenium and protonated oxazolines such as have been previously characterized[7]. Attempted application to peracetyl-2-azido-2-deoxy-β-D-glucopyranose only afforded a spectrum consistent with protonation of the substrate on each of the four acetate groups and the azide moiety, without expulsion of the anomeric acetate. This latter experiment reveals the limits of the method, and more importantly highlights the influence of electron-withdrawing substituents on the formation and stability of carbenium and oxocarbenium ions. Indeed, it is the multiplicity of electron-withdrawing substituents that explains the instability of glycosyl oxocarbenium ions in contrast with simple oxocarbenium ions, which are well-known to be more stable than analogous carbenium ions.

With the existence and structures of the triprotonated triacetyl-2-deoxyglucosyl oxocarbenium ion and its 2-bromo congener established in HF/SbF_5, attention was focused on their stereoselectivity when quenched with either deuteride or

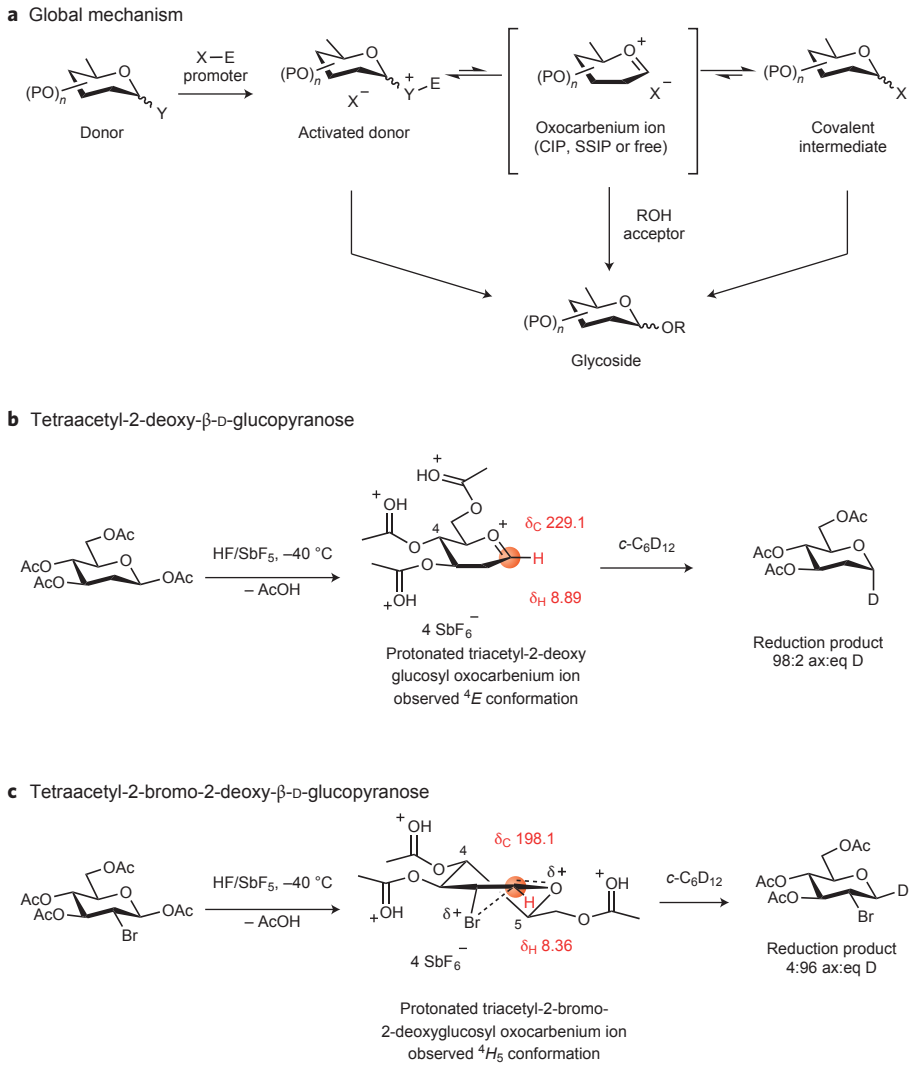

Figure 1 | Oxocarbenium ions and their role in glycosylation. **a**, Global mechanism showing the location of oxocarbenium ions. **b**, Formation, structure and irreversible quenching of the fully protonated triacetyl-2-deoxy-D-glucopyranosyl oxocarbenium ion. **c**, Formation, structure and irreversible quenching of the fully protonated triacetyl-2-bromo-2-deoxy-D-glucopyranosyl oxocarbenium ion.

methanol. Thus, treatment of the 2-deoxy oxocarbenium ion with cyclohexane-d_{12} afforded the corresponding reduced product with very high selectivity for incorporation of deuterium in the axial position of the resulting 1-deoxy sugars as predicted on stereoelectronic grounds for oxocarbenium ions adopting the ^4E envelope or neighbouring half-chair conformations[8,9]. Conversely, the 2-bromo-2-deoxy oxocarbenium ion was attacked with high selectivity from the pseudoequatorial direction by cyclohexane-d_{12}, reflecting the importance of the loosely bridging bromonium ion. When methanol was employed as a nucleophile, a large excess was required and selectivities were lower. This probably reflects the reversible nature of the addition under the superacidic reaction conditions and necessarily raises questions about the potential applicability of the method for stereoselective glycosidic bond formation.

According to most current hypotheses[8–10], glycosyl oxocarbenium ions are predicted to adopt conformations in organic solution which maximize the number of pseudoaxial C–O bonds so as to take advantage of through-space electrostatic stabilization of the positive charge at the anomeric center. The fully protonated nature of the triacetyl-2-deoxyglucosyl oxocarbenium ion precludes any such stabilization and results in the observed conformation that favours the pseudoequatorial placement of the substituents. This fundamental difference in conformation between the spectroscopically observed protonated oxocarbenium ion in superacid media and putative oxocarbenium ions in neutral organic media urges caution in the use of the former as a predictor of the conformation and stereoselectivity of the latter, unless Curtin–Hammett kinetic schemes are invoked.

Finally, we return to the question of the counterion and of covalent intermediates and ion pairs reacting through S_N2-like transition states. By their very design, experiments conducted in superacid media exclude participation by external counterions. Caution must therefore be exercised in extrapolating the observation and characterization of glycosyl oxocarbenium ions in superacids by NMR spectroscopy[5,6], to explain the reactivity and selectivity of glycosyl donors in organic solution. Any such predictions should take into account reaction kinetics and computational work conducted with properly solvated counterions, both of which are increasingly available[3,11].

All told, the Article by Blériot and co-workers[6] is ground-breaking and brings the field of glycosyl oxocarbenium ions into line with that of other carbenium ions, of which they are a microcosm. As with carbenium ions in general, however, the jury must remain out when it comes to their intermediacy in substitution reactions to the exclusion of ion pairs and covalent intermediates. Glycosyl oxocarbenium ions are effectively out on parole, but whether they will remain free to roam at will must depend on further experimentation. ❐

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