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Glycosylation intermediates studied using low temperature 1H- and 19F-DOSY NMR: new insight into the activation of trichloroacetimidates†

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Low temperature 1H- and 19F-DOSY have been used for analyzing reactive intermediates in glycosylation reactions, where a glycosyl trichloroacetimidate donor has been activated using different catalysts. The DOSY protocols have been optimized for low temperature experiments and provided new insight into acid catalyzed glycosylation chemistry. From the study a new glycosylation intermediate was characterized.

The mechanism of the glycosylation reaction is central to carbohydrate chemistry.1 As the reactions often are complex mixtures containing excess amounts of promoters and additives, such as acid scavengers, drying agents and acceptors, intermediates are notoriously difficult to analyze and impossible to isolate.2 Half a century ago NMR spectroscopy became available and was immediately applied to study carbohydrates and soon also reactive intermediates at low temperature.3 The study of glycosylation reactions with low temperature NMR has recently experienced a renaissance, where especially the Crich group has used it extensively to study reactive intermediates, such as glycosyl triflates, and on this basis suggested mechanisms e.g. for β-mannosylation.4 The work by Crich and others5 in combination with better hardware and software has made this technology accessible and doable for most research groups. The culmination of this development has recently led to the first observation of a carbohydrate oxocarbenium ion by NMR.5 Despite the advances in NMR resolution one major obstacle remains, i.e. the highly complex spectra contain several carbohydrate derived compounds and it is therefore tedious if not impossible to analyze the data fully. To get more information about the intermediates formed and to separate them in order to analyze and to get information about both the relative amount and the number of intermediates we have studied the use of 1H- and 19F diffusion ordered NMR spectroscopy (DOSY) at low temperature.

Measurements of molecular diffusion by NMR have been carried out since the eighties, but only in recent years has it been part of the routine experiments provided by NMR-manufacturers. The diffusion is dependent on the molecular size, shape and whether the molecule is non-covalently interacting with other species.6 The relationship between molecular size and diffusion coefficient has been used by several groups to estimate the molecular weights of intermediates7 and complexes8 by the use of internal reference compounds. This approach has been applied mainly to 1H-DOSY, but also 19F-DOSY studying Brønsted acid-base complexes.9 We envisaged that a combination of 1H- and 19F-DOSY could provide information about the intermediates formed under the catalytic activation of trichloroacetimidate (TCA) donors. The most used catalysts, i.e. trimethylsilyl trifluorosulfonate (TMSOTf) or BF3·OEt2, contain fluorine, whereas the TCA donors do normally not. By using this double determination, i.e. 1H- and 19F-DOSY, it should be possible to distinguish between intermediates having the catalyst bound or not.

Trichloroacetimidates (TCAs) are one of the most commonly used glycosyl donor types due to its simplicity and catalytic activation.10 It has therefore been studied using VT-NMR to elaborate the influence of additive,11 intermolecular participation12 and it has been used as a source of glycosyl triflates (as B in Fig. 1)13 by using TMSOTf or similar reagents in equivalent amounts. Despite its excessive use, the mechanism of the activation of TCA has only been sparsely investigated and only little is known about the reaction mechanism. It has commonly been illustrated that the Lewis (or Bronsted) acid reacts with the nitrogen atom in the trichloroacetimidate (like A in Fig. 1). This activates the TCA group and results in the formation of an oxocarbenium ion intermediate (C in Fig. 1) followed by the attack by the nucleophile (acceptor); commonly a hydroxyl group, i.e. an S,N1 type of reaction. (Fig. 1, C).14 Recent studies by Peng and Schmidt have

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shown that such deduction might not always be the scenario, and that the catalyst in some cases could be activated by forming a nucleophile–catalyst complex (similar to A in Fig. 1).15

As a model donor for our NMR study, 2-O-benzyl-3,4,6-tri-O-acetyl α-D-glucopyranosyl trichloroacetimidate 116 was chosen. It has a commonly used protective group pattern consisting of benzyl and acetyl groups. The 2-O-benzyl group was required in order to avoid neighboring group participation, which would give a dioxolonium ion, which is well known and has been thoroughly studied for 2-O-acetyl groups.17 The remaining hydroxyl groups are acetylated, which reduces the donor reactivity and could thereby increase the lifetime of the glycosylation intermediate (not an oxacarbenium ion).18 Glycosylation reactions with trichloroacetimidates are most often catalyzed by TMSOTf or BF3·OEt2 and these catalysts were therefore the starting point for the study.19

As a standardized donor, the donor was dissolved in CD2Cl2 (conc.: 0.04 M20) together with Tris-(trifluoromethyl)-benzene as the internal 19F-reference compound. In the initial studies the decomposition temperature, i.e. when the reactive intermediates disappeared to give a stable product, was determined using the different catalysts. On this basis it was decided to initiate the reactions at −55 °C using different amounts of the catalyst first in sub-stoichiometric amounts, then in equivalent and finally in excess. The different conditions were analyzed using low temperature NMR. The catalysts were additionally analyzed under the same conditions but independently, i.e. without donor presence, to give reference spectra and to check whether they aggregated at low temperature.

The first activation of the TCA-donor using TMSOTf was carried out, and α-triflate 2 was found to be the main product formed as expected from the examples in the literature (Scheme 1).13 The stereochemistry was confirmed by the small 3J1-2 (3 Hz) coupling constant, which is unambiguous for α-D-glucoses in the 4C1 conformation. When using 0.3 equiv. TMSOTf it was found that the donor reacted in a 1:1 ratio and hence did not undergo a catalytic transformation in the absence of an acceptor (see the ESI†). Due to the equal size of the donor and the product, these could not be clearly separated by DOSY, but from the comparison of 1H- and 19F-DOSY it was clear that the triflate group indeed was attached to the sugar moiety (19F-DOSY), whereas the TMS group was not (1H-DOSY). This confirms the formation of glucosyl triflate 2. Upon addition of equivalent amounts or excess of the catalyst full transformation to the α-triflate was observed. In time an additional product was formed under the reaction conditions at −55 °C. This product was assigned to be the corresponding trihaloacetamide 3. The ratio between triflate 2 and amide 3 remained stable until −5 °C. Between −5 °C and 5 °C the signals corresponding to the α-triflate disappeared completely. When a sub-stoichiometric amount (∼50%) of BF3·OEt2 was added to model donor 1 in CD2Cl2, the TCA was only consumed according to the amount of catalyst added (approx. 40%) and hence there was no catalytic transformation. Two new products appeared with anomeric signals between 5 and 6 ppm. From the unusual coupling pattern it could be confirmed that the α- and β-glycosyl fluorides 4αβ had been formed.21 19F-NMR gave rise to three new major peaks, where 19F-DOSY confirmed that two of them had similar diffusion coefficients and were connected to the sugar moiety (similar diffusion coefficients based on 1H-DOSY and hence similar size). The 1H-DOSY confirms the existence of two new sugar species with very similar diffusion coefficients and that the signals of diethyl ether (from BF3·OEt2) are not associated with the sugar. Adding additionally 0.7 equiv. of BF3·OEt2 resulted in approx. 65% conversion of the TCA, which remained a stable ratio – the donor is not fully consumed even after adding more than 1 equiv. catalyst. The resulting mixture of glucosyl fluorides 4αβ and donor 1 remained stable for >7 h at −55 °C. Increasing the temperature stepwise (10 °C steps) resulted in a slow disappearance of the β-fluoride and at −15 °C mainly the α-anomer could be observed. Re-cooling did not change the composition of the sample.

From the results using TMSOTf or BF3·OEt2, it was clear that the activation mode of the trichloroacetimidate depends on the catalyst and in particular its counter ion. When this is a triflate ion a clean conversion to the α-glycosyl triflate 2 was observed; but what if the counter ion is less nucleophilic? Would it then be possible to avoid substitution of the activated trichloroacetimidate and instead observe an activated complex? To study this hypothesis TMSNTf2 22,23 as a catalyst was investigated, since it has been found to be more Lewis acidic than TMSOTf,24 but with a less nucleophilic counter ion.25 To our surprise the NMR, of the catalyst alone at −55 °C revealed 2 peaks in 1H- and 19F-NMR and therefore the existence of 2 compounds (Scheme 2). Upon increasing the temperature to 20 °C one broad signal was observed and hence the compounds are in a slow equilibrium; presumable as the mono- and dimer. This was further supported
by increasing the concentration of the catalyst by a factor 5, which increases the amount of the proposed dimer in the sample (Scheme 2). Adding a sub-stoichiometric amount of MeOH (model acceptor) to the catalyst at −55 °C immediately resulted in the disappearance of the peak from the dimer (in 1H- and 19F-NMR) and the formation of a new peak assigned to [MeOH–TMS]† appeared. The addition of more MeOH resulted in full conversion (Scheme 2). MeOH seems to catalyze the monomerization.

When TMSNTf₂ was added (0.3 equiv.) to model donor 1 at −55 °C no dimer was detected and the signal from trichloroacetimide 1 disappeared rapidly (Scheme 3), which is in contrast to the same conditions using TMSOTf as the catalyst, where a one to one reaction took place. 1H-NMR showed a mixture of at least two compounds and 19F-NMR showed three peaks. 1H-DOSY of the mixture confirmed the presence of two sugar based compounds with a small difference in diffusion coefficient and hence size. From 1H-DOSY it is, however, clear that the TMS group from the catalyst is covalently attached to the sugar in contrast to when using TMSOTf. 19F-DOSY does not indicate that the sugar and the TMS signals were observed – one attached to the sugar (DOSY) and the other (internal reference) caught our interest. The compounds in our study are larger and the solvent is CD₂Cl₂ a new calibration curve was prepared. A number of reference compounds with a similar three-dimensional structure were chosen and their diffusion coefficients determined in the presence of one internal reference 1,3,5-tris(trifluoromethyl)benzene, which can be used as a reference in both 1H- and 19F-DOSY. For the 1H-DOSY calibration curve, carbohydrate based structures were preferred, and masses in the range from 74 to 1226 were included (6 compounds, see the ESI† for details). For 19F-DOSY the available carbohydrate based compounds were limited and only one, i.e. 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride, was part of the calibration curve (see the ESI† for details). With the calibration curves in hand the DOSY experiments were repeated to estimate the Mₛ of the formed intermediates. Excess of the catalysts were used in order to ensure the formation of mainly one compound and the temperature was kept at −55 °C.

From the initial NMR studies and DOSY experiments good evidence for the structures of the intermediates formed had been obtained and hence their molecular weights (Mₛ) could be predicted and compared with calculated values based on the calibration curve and the internal reference compound (Table 1). Estimation of Mₛ from the calibration curves gave a good estimation for the intermediates formed when using BF₃·OEt₂ and TFSNTMS as the catalysts. The deviation is within 10% and the predicted Mₛ is in-between the results from the two
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Notes and references


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