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COMMUNICATION

In pursuit of larger lipophilicity enhancement: an investigation of sugar deoxychlorination

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The excessive hydrophilicity of carbohydrates hampers their application in drug discovery. Deoxyfluorination is one of the strategies to increase sugar lipophilicity. However, lipophilicities of dideoxy-difluorinated monosaccharides are still well below the desired range for oral drug candidates. Here we investigate the power of deoxychlorination to increase sugar lipophilicities. A series of dideoxygenated chloro-fluorosugars was synthesized and for these substrates it was shown that deoxychlorination increased the log*P* with an average of 1.37 log*P* units, compared to 0.83 log*P* units for analogous deoxyfluorination. This shows the potential of deoxychlorination of carbohydrates to increase lipophilicity while limiting the number of potentially important hydrogen bond donating groups to be sacrificed, and will be of interest for glycomimetic development.

Given the pivotal role of carbohydrates in human health,[1] there is much interest in investigating and manipulating protein-carbohydrate interactions or activities of carbohydrate-processing enzymes.[2] The sugar scaffold itself is a very challenging starting point for drug development, with its very high hydrophilicity/very low lipophilicity (log*P*) as one of the main reasons.[3] One of the strategies in glycomimetic design thus rests on reducing the hydrophilic character, for example by the functionalization of sugar alcohols with apolar groups, alcohol deoxygenation or deoxyfluorination.[4-7] Our group reported a straightforward method for lipophilicity determination of the non UV-active fluorinated carbohydrates, and it was established that each successive deoxyfluorination increased the log*P* by an order of magnitude, with variations depending on fluorination position and stereochemistry.[8] The latter aspect has been further investigated in detail by the Giguère group.[9, 10]

While there are reports that chlorinated glycans bind to proteins, including examples with higher and lower affinity,[11] it is remarkable that compared to sugar fluorination,[12] sugar chlorination is much less investigated in glycomimetic design. This is surprising given that sucralose (Figure 1), a trichlorinated sucrose derivative which is used as an artificial sweetener,[13, 14] is arguably the most synthesized halogenated sugar. It is resistant against enzymatic hydrolysis – hence its non-calorific properties – and generally posesses good chemical stability due to the strengthening of the C–Cl bonds by the combined effect of the many electronegative substituents.

Chlorine introduction is also very well established in drug development, albeit mostly on aromatic rings, as a monovalent hydrophobic substituent. There is the possibility for beneficial halogen bonding effects, which in some cases contributes to marked affinity increases, and chlorination is typically associated with a lipophilicity increase on a par with methyl group introduction.[15, 16] Lipophilicity information for chlorinated sugars is scarce. The log*P* of sucralose (-0.51 log*P* units)[17] is three orders of magnitude higher than that of sucrose (-3.3 units).[18] Recently the Giguère group reported the higher lipophilicity of the chlorodifluoroallose analogue **2** compared to its trifluorinated analogue **1**.[19]
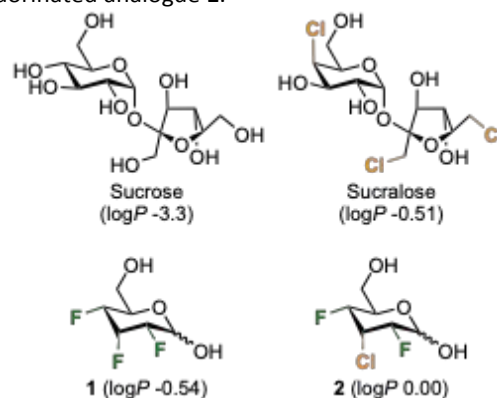

Figure 1. Examples of increase in lipophilicity upon deoxychlorination or fluorine-chlorine replacement of sugars. [17-19]

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The alcohol groups in sugars are often essential hydrogen bond donors and/or acceptors in a binding event, imposing limitations on the number of alcohol groups that can be sacrificed for increasing lipophilicity. Hence, methods to maximise the increase in lipophilicity without significant addition to the sugar conformation and steric footprint are of interest. In this context, we became interested in investigating sugar deoxychlorination and to quantify the effect of deoxychlorination on sugar lipophilicity. In this communication, we report on the effect of mono-deoxychlorination of sugars.

The selection of the substrates was in the first instance guided both by synthetic and log*P* determination considerations. As starting points we used 6- and 4-deoxyfluorogalactose (**3a** and **4a**), as well as 3-fluoroglucose **5**, with the fluorine atom serving as handle for ¹⁹F NMR based log*P* determination.[8] The corresponding methyl galactosides **3b** and **4b** were also investigated (Figure 2).
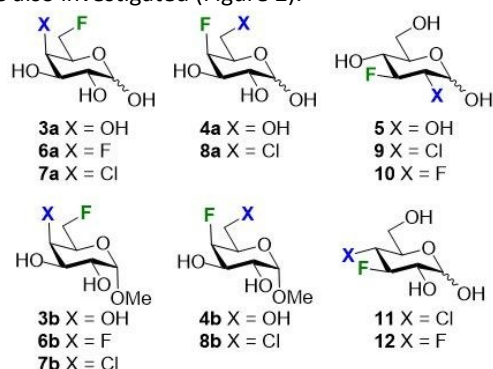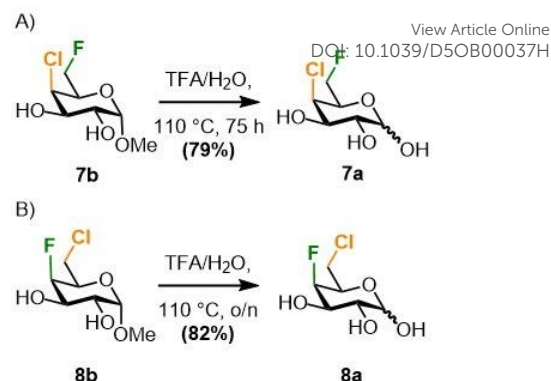
Figure 2. Substrates involved in this study.

The monofluorinated galactoses at C6 (**3a-b**) and C4 (**4a-b**) were obtained as described in the literature,[20-22] and the difluorinated analogues **6a-b** were synthesized starting from methyl α-D-glucopyranoside as reported by our group (not shown).[23] The novel galactose derivatives **7a** and **8a** (Scheme 1) were synthesised from known **7b** and **8b**, both also obtained from commercially available methyl α-D-glucopyranoside,[23] by anomeric hydrolysis in good yields.

The synthesis of **9** and **11** (Scheme 2) was achieved from levoglucosan, using a synthetic route that mirrored the known[8, 10] syntheses of the corresponding difluorinated sugars. The two
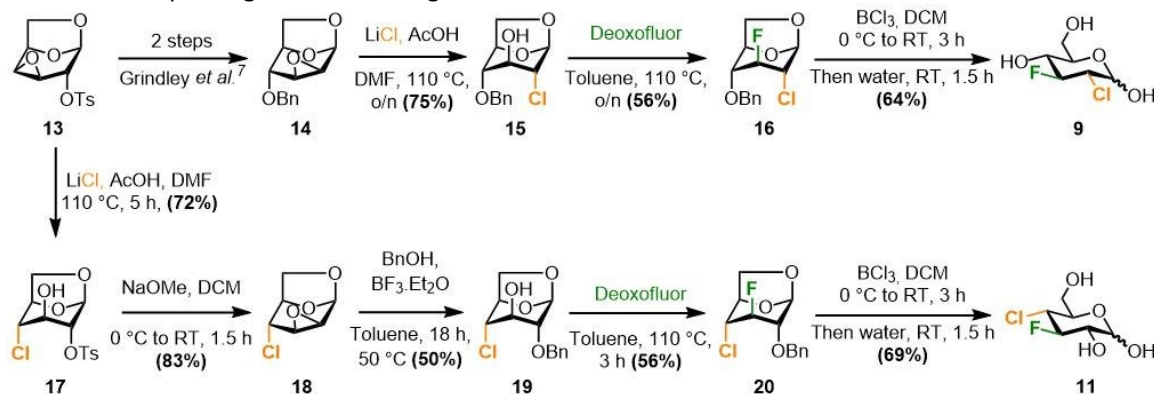
Scheme 1. Anomeric hydrolysis of the methyl chloro-fluorogalctosides **7b**[23] and **8b**[23] towards the reducing sugars **7a** and **8a**.

required epoxide intermediates, **13** and **14**, are easily available from levoglucosan on multigram scale,[24, 25, 26-28] and were chosen as handles for chlorine introduction. Procter *et al.* had reported that reaction of **14** with *in-situ* generated allyl magnesium chloride in THF as solvent delivered the 2-deoxy-2-chloro derivative **15** in 76% yield instead of the aniticipated allylation product.[24] However, in our hands, reaction of a commercially available 2 M solution of allyl magnesium chloride in THF with **14** led to the allylation product. A procedure by Paulsen *et al.*, in which reaction of **13** with an ammonium fluoride and chloride mixture was reported to give **17**,[25] gave no conversion. In contrast, a method using lithium chloride, reported by Sofian and Lee on disaccharides,[29] successfully afforded compound **15** from **14** in good yield. This reaction could easily be upscaled to a 3 g scale. The same method was then used to synthesize the 4-deoxy-4-chloro derivative **17** from **13**. Treatment of the latter with base afforded the 2,3-anhydro group in **18**,[25] which allowed benzyloxy introduction at the 2-position. With **15** and **19** in hand, the stage was set for fluorine introduction at C3, which is typically effected by DAST or Deoxyfluor with retention of configuration.[30, 31] In both cases, this reaction was successful, delivering the 2,3-dideoxy-2-chloro-3-fluoro and 3,4-dideoxy-4-chloro-3-fluoro derivatives **16** and **20,** both in 56% yield. A chlorine atom is a more powerful partner in neighboring group participation, potentially leading to a weaker bond between the chlorine and C2/C4, yet the
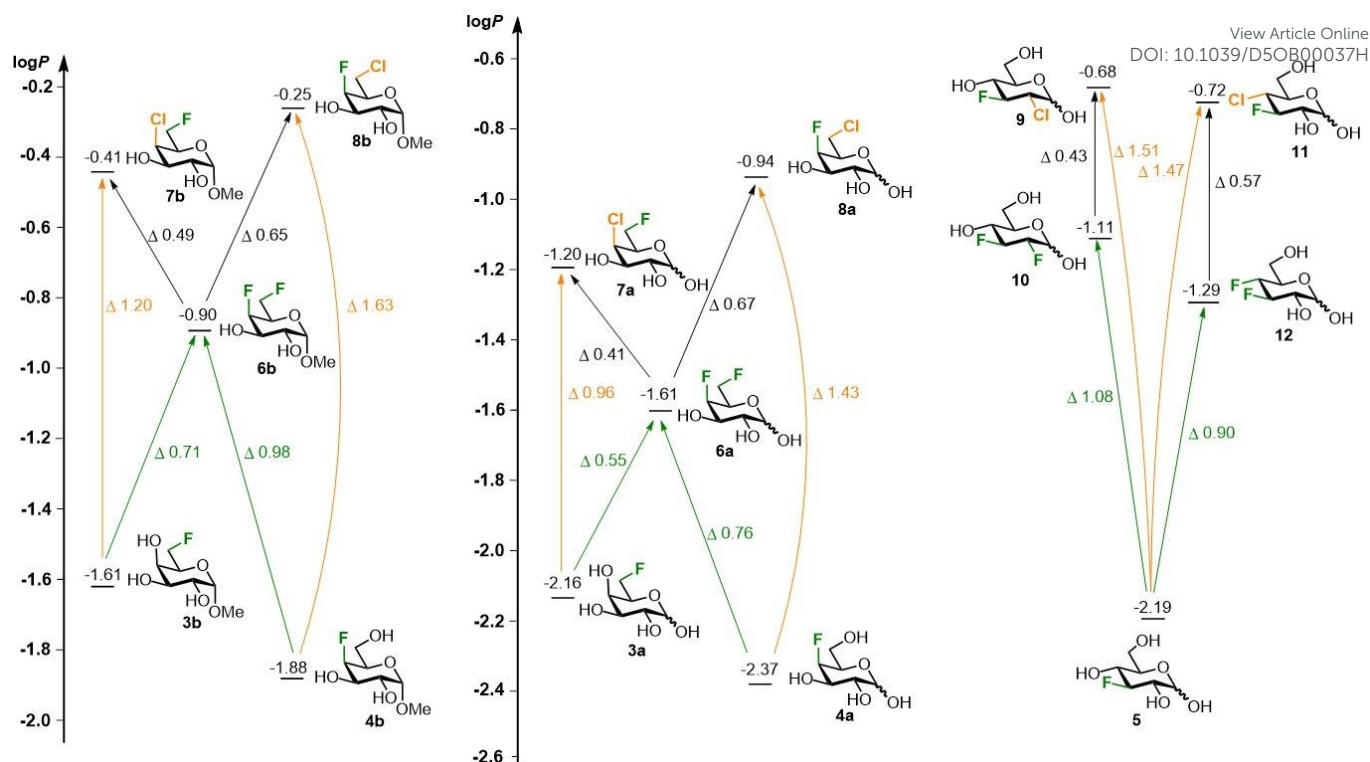
Scheme 2. Synthesis of the two chloro-fluoro glycopyranoses **9** and **11**.

Figure 3. Experimentally determined log*P* values of dihalogenated glucoses and galactoses.

epoxide opening remained fully regioselective, as dictated by the Fürst-Plattner effect[32] (chairlike transition state). The regio- and stereoselective introduction of the C–F bond was easily established by ^{1}H and [19]F *J*-value analysis. Finally, preparation of the desired final compounds **9** and **11** could be established by hydrolytic cleavage of the 1,6-anhydro bridge with concomittent benzyl group removal in good yields.

The lipophilicity data of the chloro-fluorosugars is shown in Figure 3. The chlorinated sugar derivatives invariably have a higher lipophilicity compared to the corresponding fluorinated derivatives. The log*P* values of the regioisomeric 4,6-dihalogenated galactoses **7b** (log*P* -0.41) and **8b** (log*P* -0.25), have an appreciable difference and are higher than the difluorinated analogue **6b** (log*P* -0.90, average increase of 0.57 log*P* units). Compared to the corresponding monofluorinated saccharides **3b/4b** (log*P* -1.61/-1.88) there is a significant increase of 1.20/1.63 log*P* units upon deoxychlorination at C4/C6. In contrast, analogues deoxyfluorination 'only' delivers a 0.71/0.98 log*P* increase. A similar picture is seen for the more polar reducing halogenated galactose equivalents **3a–8a**, with similar differences between the difluorinated galactose **6a** (log*P* -1.61)[33] and the chlorofluorogalactoses **7a/8a** (log*P* -1.20/-0.94), but with slightly reduced differences compared to the monofluorinated galactoses **3a** and **4a** (log*P* -2.16/-2.37). This is due to the lower increase in lipophilicity upon methyl glycosidation of the monofluorinated galactoses compared to the dihalogenated ones (the difference between **3a/4a** with **3b/4b** is ~0.53 log*P* units, compared to ~0.73 for the other derivatives). The reducing glucoses show larger lipophilicity differences. The log*P*-values of **9** (log*P* -0.68) and **11** (log*P* -0.72) are very similar, with a 1.5 log*P* increase compared to 3-

fluoroglucose **5** (log*P* -2.19).[10] The corresponding difluorinated glucoses **10** (log*P* -1.11)[8] and **12** (log*P* 1.29)[10] have a larger difference in lipophilicity but on average, the lipophilicity increase compared to **5** is 'only' 1.0 log*P* units.

In summary, the synthesis of a series of dideoxygenated chloro-fluoro galactoses and glucoses has been achieved and their lipophilicities were determined. These values were compared to those measured for analogous difluorinated and the monofluorinated monosaccharides. It was established that deoxychlorination leads to an increase of the log*P* with an average of 1.37 log*P* units, compared to 0.83 log*P* units for analogous deoxyfluorination. Substitution of fluorine for chlorine in carbohydrates thus results in a significant average increase in lipophilicity of 0.54 log*P* units. With these results, we show that deoxychlorination is a powerful tool to increase lipophilicity while limiting the number of potentially important hydrogen bond donating groups to be sacrificed, which will be of interest in glycomimetic design.

Conflicts of interest

There are no conflicts to declare.

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Data availability statement

The data supporting this article have been included as part of the Supplementary
Information.