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# Comprehensive structural analysis of halogenated sucrose derivatives: Revisiting the reactivity of sucrose primary alcohols

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**Abstract:** Regioselective halogenations of sucrose primary alcohols can simplify the synthesis of carbohydrate-based products. The Appel reaction, using carbon tetrahalide (CBr<sub>4</sub> or CCl<sub>4</sub>) and triphenylphosphine, offers efficient conversion of primary hydroxyl groups to halide. Previous halogenation of sucrose with limited amounts of Appel reagent gave obscure result—regarding the halogenation selectivity of sucrose primary alcohols at 6- and 6'-position. Within careful purification of its per-O-acetylated form, re-subjection of sucrose into Appel reaction resulted in two mono- and one dihalogenated products only at 6- and/or 6'-position. Extensive NMR analyses support the revision of previous literature's assignments. Comprehensive analysis of each monohalogenated sucrose at the primary position, including the first reported 1'-monohalogenated sucrose derivatives synthesis via regioselective enzymic deacetylation, provided halogenation of sucrose primary alcohols by the Appel reaction followed the order of 6>6'>>1'.

## Introduction

The halogenated sucrose derivatives at the primary positions are known as important synthesis intermediate,<sup>[1–3]</sup> reversible contraception in male rat<sup>[4]</sup> and, particularly for chlorinated products, commonly used as artificial sweetener.<sup>[5]</sup> In general, the reactivity of sucrose primary alcohols toward halogenation is comparatively followed the order of 6- and/or 6'-, then neopentyl-like 1'-position.<sup>[6]</sup> To date, various methods of selective halogenation, particularly for chlorination and bromination, only on sucrose primary hydroxyl groups have been reported previously. Indirect methods are include: the intermediate utilization;<sup>[2,7–9]</sup> selective cleavage of fully protected sucrose before further halogenation of the free primary alcohol counterpart;<sup>[10–12]</sup> or bulky functional groups protection and unprotection of one or two primary hydroxyl groups.<sup>[13–15]</sup> Procedures are also available that allow the direct replacement of primary hydroxyl groups with halogen, e.g. direct chlorination of sucrose by well-known sulphuryl chloride<sup>[16]</sup> that gave high selectivity for monochlorinated at 6'-position or the usage of other reagents.<sup>[3,17]</sup> Among these methods, Appel reaction,<sup>[18]</sup> by the use of carbon tetrahalide (bromide or chloride) and triphenylphosphine, has been shown to be an efficient<sup>[19]</sup> method for halogenation of sucrose primary alcohols. In 1978, excess amount of Appel reagents were introduced which resulted in the dihalogenated sucrose derivatives at 6- and 6'-position.<sup>[20]</sup> Further modification of this reaction was reported and observed that the mixture is not only consist of the diproducts but also 6- or 6'-

monohalo products. Moreover, even by further purification, these two isomers are difficult to separate.<sup>[21]</sup>

Many previous efforts<sup>[1,20,22–24]</sup> by Appel reaction utilized different proportion and condition for prior art of sucrose primary alcohols halogenations at 6- and 6'-position. By commonly maintaining the ratio 2:1 of triphenylphosphine and carbon tetrahalide, these reagents equivalency to sucrose can be neglected if 6,6'-dihalogenated sucrose is the desired product. Meanwhile, regioselectivity for 6- and 6'-monohalogenated sucrose attainable by limiting the proportions of Appel reagents (e.g. carbon tetrahalide < 1.5 equiv. from sucrose) is not completely identified. Previously, it has been shown that Appel reaction is regioselective for the 6-position over 6'.<sup>[25]</sup> In contrast, by limiting the proportions of Appel reagents (1.2 equiv. carbon tetrahalide, 2.4 equiv. triphenylphosphine), 6'-monohalogenated sucrose can be obtained in relatively high yield.<sup>[14]</sup> Despite this success, re-subjection by similar reaction condition is remaining the preponderant product of 6-halo as a mixture with 6'-halo<sup>[15]</sup> and no detailed considerations has been performed for this observation.

For decades, many studies have successfully synthesized mono- and dihalogenated sucrose at the primary positions,<sup>[2,7–17,20–24,26–29]</sup> but the properties of all former mono and dihalogenated sucrose derivatives at 6- and/or 6'-position were limited, prominently within no detail <sup>1</sup>H and <sup>13</sup>C NMR assignment. NMR analyses are important to describe the substitution site, but many reports are mainly focused the halogenation selectivity by consideration on identical comparison of optical rotation with the previous literature data which made the regioselectivity for sucrose is obscure due to unclear structural identifications of each monohalogenated sucrose (especially its halomethylene portions, summarized in Table SI 1–17 on Supporting Information). Therefore, the needs to comprehensively analysis of all monohalogenated sucrose are essential. In the present study, we focused on re-subjection of sucrose into Appel reaction, by following previous condition,<sup>[14]</sup> to afford the mono- and disubstituted products at 6- and/or 6'-position. The 1'-monohalogenated sucrose was exclusively synthesized via chemoenzymatic reaction. Thus, allowing the comprehensive study of structure elucidation by extensive NMR analyses of halogenated sucrose at the primary positions to reveal the Appel reaction regioselectivity on sucrose primary alcohols.

## Results and Discussion

Direct substitution of sucrose (**1**) with 1.2 equiv. carbon tetrahalide (bromide or chloride) and 2.4 equiv. triphenylphosphine at 60 °C for 1.5 h,<sup>[14]</sup> afforded complex mixture of several unprotected halogenated sucrose derivatives. The separation of the mixture was complicated and identification for each isomer by <sup>1</sup>H NMR analysis is difficult due to observation of overlap signals, especially the modified primary centers. Even though number of substituted carbon was readily distinguished by the upfield location of their signals by <sup>13</sup>C NMR, but it is not easy to interpret the substitution site in this form. Most of the previous studies on Appel reaction directly quenched these modified unprotected sucrose derivatives. In fact, the dihalogenated sucrose product was easily to be obtained, but our attempts to isolate the monohalogenated sucrose products always remained as a mixture between a few isomers, which more pronounced for the

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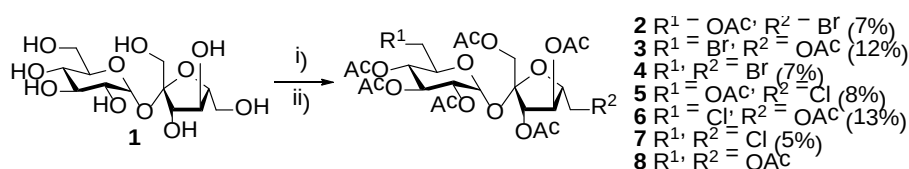
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Supporting information for this article is given via a link at the end of the document.

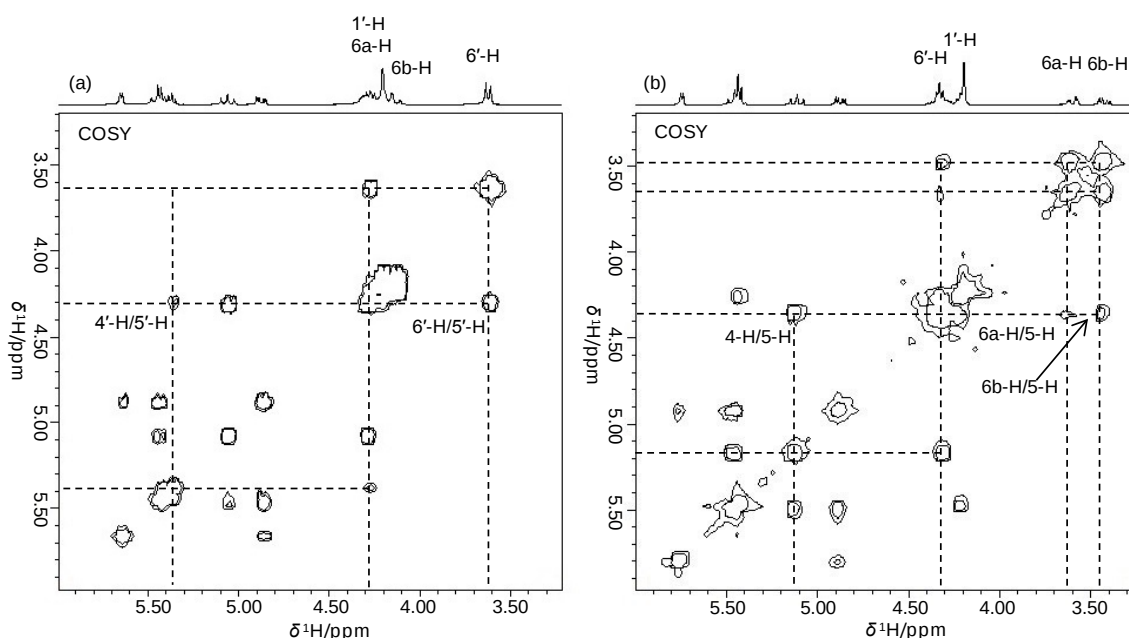
chlorinated sucrose,<sup>[15]</sup> or contaminated with the by-product,<sup>[21]</sup> and no detail study were reported for this conditions previously. Our effort to isolate and identify all brominated products was conducted by conventional acetylation (Scheme 1) and found that the mixture consist of not only one<sup>[14]</sup> major product in the TLC. When ethyl acetate or dichloromethane system was utilized, it is not completely resolve the purification. Diethyl ether as the mobile phase was superior for the isolation, not only to obtain the dihalogenated product, but also two monohalogenated products. Thus, pure compounds can be obtained for clear NMR establishment. Separation between the two per-*O*-acetylated monohalogenated regioisomers on silica column is a formidable endeavor. This terms cause the NMR assignment is misinterpreted in previous study<sup>[14]</sup> and indeed the overlap signals that associated from protons of several monoproducts<sup>[15]</sup> can hamper the substitution site identification. In presents, four compounds are isolated from brominated mixture after column chromatography: two compounds that indicated as per-*O*-acetylated monohalogenated counterparts (2 or 3), one compound of per-*O*-acetylated dihalogenated counterparts (4) and the last is unreacted portion of sucrose pentaacetate 8. Each counterpart were subject to 1D NMR (<sup>1</sup>H and <sup>13</sup>C) by the aid of 2D NMR (COSY, HETCOR, HMQC, HMBC, and NOESY), optical rotation and the composition were confirmed by HRMS analysis. The low isolated yield for each counterpart is due to: (i) set up

compounds and (ii) completely isolate each of the components to measure with reliable NMR analyses.

In the middle of our approach to identify the monobrominated products, two main regions of the spectrum are characterized in the <sup>1</sup>H NMR. The protons resonance of aliphatic sugar groups were observed in the downfield, thus it can be differentiated from the halogenated methylene groups that located in the upfield. As for NMR solvent, all the spin system are more visible to be conducted in CDCl<sub>3</sub>,<sup>[23]</sup> rather than those in DMSO-*d*<sub>6</sub>.<sup>[15]</sup> For compound 2 (Fig. 1(a)), a clear doublet at  $\delta = 3.62$  ppm ( $J = 6.6$  Hz) corresponding for two protons of brominated methylene is showed in <sup>1</sup>H NMR spectrum. These spin system are correlated with 5'-H on COSY assignment, thus ascertained the bromination position at C-6'. Multiplet assignment for 5'-H can be differentiated by the COSY cross-peak between 5'-H to 4'-H and outer-space NOESY correlation of 5'-H to 3'-H. The halogenated terminal of C-6' at  $\delta = 31.3$  ppm is most proved by HMBC technique with the observation of cross-peak of this carbon to 4'-H. HETCOR and HMQC coupling between the protons and carbon at 6'-position support our assignment for the substitution site recognition. The differentiation between the glucose and fructose rings signals of protons and carbons with other position, especially at the C-3, C-5, C-3', C-4', and C-5', were confirmed by HETCOR, HMQC and NOESY spectra (Supporting Information). These assignments allowed the structure (gross) of 2 was per-*O*-acetylated 6'-bromo-



**Scheme 1.** Regioselective halogenation of sucrose at the 6- and/or 6'-positions by Appel reaction (bromination products of 2–4 and chlorination products of 5–7); i) 1.2 equiv. CX<sub>4</sub> (X= Br or Cl), 2.4 equiv. PPh<sub>3</sub>, pyridine, 1.5 h, 60 °C; ii) acetic anhydride, rt, overnight.<sup>[14]</sup>



**Figure 1.** Selected COSY spectrum at 500 MHz (CDCl<sub>3</sub>) of 6'-bromo-6'-deoxysucrose heptaacetate (2) (a); Selected COSY spectrum at 500 MHz (CDCl<sub>3</sub>) of 6-bromo-6-deoxysucrose heptaacetate (3) (b).

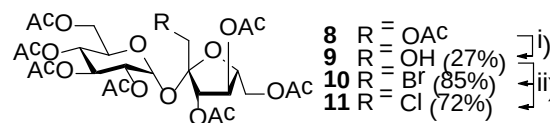
optimized condition for highest yields of each monohalogenated 6'-deoxysucrose heptaacetate.

For another product of monohalogenated sucrose **3**, a typical pair of double doublet at  $\delta = 3.42$  and  $3.60$  ppm ( $J = 4.6, 11.5$  Hz and  $J = 3.0, 11.5$  Hz) are shown in  $^1\text{H}$  NMR. The observation of the large geminal coupling for these spin systems can be distinguished in COSY analyses by their correlation across the 5-H (Fig. 1(b)). Moreover, HMBC correlation among these spins systems with C-4 support the identification of bromination of sucrose hydroxyl groups at 6-position. HETCOR and HMQC correlation of protons at 6-position with C-6 at  $\delta = 31.1$  ppm also support this assignment, which confirmed by NOESY, to elucidate compound **3** was the complete structure of 6-bromo-6-deoxysucrose heptaacetate. Accordingly, spin system on  $^1\text{H}$  NMR of 6- and 6'-monobrominated sucrose can be differentiated (Supporting Information). Based on alteration of these comprehensive assignments between 6- and 6'-monobrominated sucrose, the previous reported study<sup>[14]</sup> was misinterpreted NMR analysis of 6'-bromo-6'-deoxysucrose heptaacetate. In their report, 6'-bromo-6'-deoxysucrose heptaacetate was afforded pair of double doublet with the observation of geminal coupling in  $^1\text{H}$  NMR. Hence, in this study, the assignment was revised from their previous compound of 6'-bromo-6'-deoxysucrose heptaacetate to 6-bromo-6-deoxysucrose heptaacetate and also refined new full description between these two monobrominated products (**2** and **3**) to support our comprehensive structure recognition. As for 6,6'-dibrominated **4**, splitting pattern in the upfield region of  $^1\text{H}$  NMR is consist of combination to those of the 6- and 6'-monobrominated regioisomers. By the same tendency, per-*O*-acetylated mono- and dichloro products (**5-7**) also showed a typical  $^1\text{H}$  NMR profile from those in the per-*O*-acetylated mono- and dibrominated sucrose derivatives. Furthermore, our achievement for isolation of per-*O*-acetylated monohalogenated sucrose (**2**, **3**, **5** and **6**), by using silica column with diethyl ether system, completely resolved the  $^1\text{H}$  NMR assignment. The multiplicity of overlap protons of halomethylene moiety at 6- or 6'-position on previous report<sup>[15]</sup> can be identified by the observation of distinguishable signals with specific splitting pattern in the upfield region of  $^1\text{H}$  NMR.

Except the per-*O*-acetylated derivatives, several protected form<sup>[2,8–10,12,17,20]</sup> of halogenated sucrose at 6- and/or 6'-position also have been previously synthesized. To meet our purpose, the protection by conventional acetylation seems suitable. It is also common opinion in many literatures that acetylation of the sugar derivatives facilitates and simplifies the NMR analysis.<sup>[6]</sup> But, up to date, detail structure characterization of per-*O*-acetylated halodeoxysucrose derivatives at 6- or 6'-position (**2-7**) is still not completely identified. Indeed, the  $^1\text{H}$  NMR assignment of proton at 6 and 6'-position has been reported as multiplet<sup>[15]</sup> and hampered the substitution site recognition. Comparison with the literature data for all compounds also described for support our comprehensive structural elucidation (See Table SI 1–17 in Supporting Information for detail previous literature data comparison).

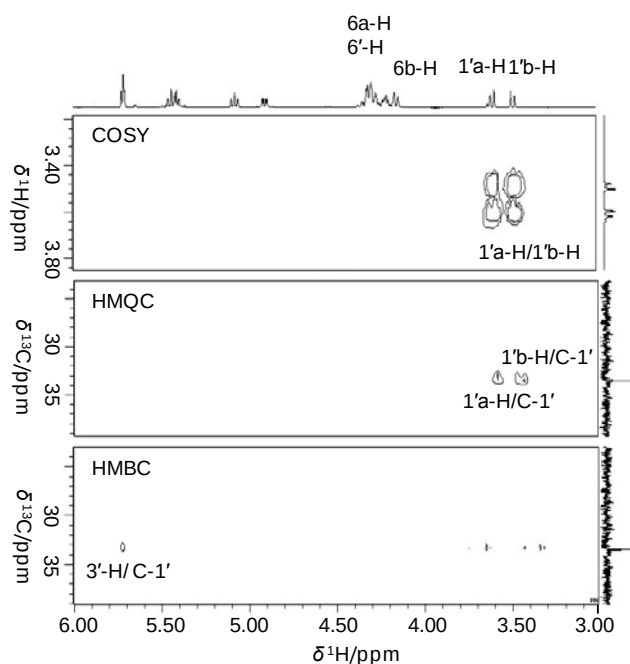
Our comprehensive NMR analysis revealed that the use of limited proportion of Appel reagents resulted in unsubstituted hydroxyl groups either at secondary position or the most hindered 1'-position. Based on NMR analysis (Fig. 1), monohalogenated sucrose derivatives at 6 or 6'-position can be distinguished. Multiplicity for protons at 6'-position of 6'-monohalo **2** and **5** is observed with no geminal coupling at  $^1\text{H}$  NMR. Theoretically, this term is belonging to protons at 1'-position of 1'-monohalogenated sucrose counterpart (**10** or **11**). To ensure these results, the structure analysis was continued to exclusive synthesis of 1'-monohalogenated sucrose. The attempt to halogenate 1'-position was studied via chemoenzymatic reaction (Scheme 2). From the previous reported selective enzymatic hydrolysis of **8**, several enzymes are available to regioselectively deacetylate at the 1'-acetyl group. Alcalase seems suitable for the purpose due to its

shorter reaction time and higher yield of sucrose heptaacetate (**9**) as the major product.<sup>[30(a)]</sup>



**Scheme 2.** Chemoenzymatic synthesis of 1'-monohalogenated sucrose derivatives (**10** and **11**); i) Alcalase 2.4 L, 0.1 M sodium phosphate (pH 7.0)—DMF (3:1), 24 h, 37 °C;<sup>[30]</sup> ii)  $\text{TiF}_4$ , pyridine,  $\text{CH}_2\text{Cl}_2$ , 0 °C; 4.0 equiv. LiX (X= Br or Cl), DMF.

By the partly acetylated sucrose of 2,3,4,6,3',4'-hexa-*O*-acetyl-sucrose,<sup>[11]</sup> the free hydroxyl group at 1'-position was observed to be not reactive with Appel reagents. Accordingly, compound **9** was then trifluoromethanesulfonylated and halogenated by using lithium halide (bromide and chloride) to give 1'-bromo-1'-deoxysucrose heptaacetate (**10**) for bromination and 1'-chloro-1'-deoxysucrose heptaacetate<sup>[13,28]</sup> (**11**) for chlorination. However, brominated chemoenzymatic product of **10** and its deacetylated counterpart (**20**) is firstly reported in this study.

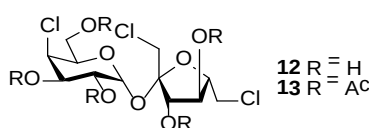


**Figure 2.** Selected COSY, HMQC and HMBC spectrum at 500 MHz ( $\text{CDCl}_3$ ) of 1'-bromo-1'-deoxysucrose heptaacetate (**10**).

The assignment of the regioisomeric halogenated sucrose per-*O*-acetylate of 1'-monobromo **10** can be verified by a distinct pair of doublet with large geminal coupling constants ( $J = 12.0$  Hz) at  $\delta = 3.61$  and  $3.49$  ppm assigned for protons at 1'-position (Fig. 2). NOESY correlation of these spins system with proton at 1-position showed that bromination conducted near the anomeric carbon. By the long range coupling assignments of protons at 1'-position to C-2' on HMBC, along with the HMQC correlation to ensure these protons associated on the same carbon, this particular spin-system of monobrominated at 1'-position can be differentiated from 6 and 6'-halo (Fig.1 and Supporting Information). Next, the

assignment of 1'-monochloro per-*O*-acetylate **11** is similar to those in 1'-monobromo per-*O*-acetylate **10**.

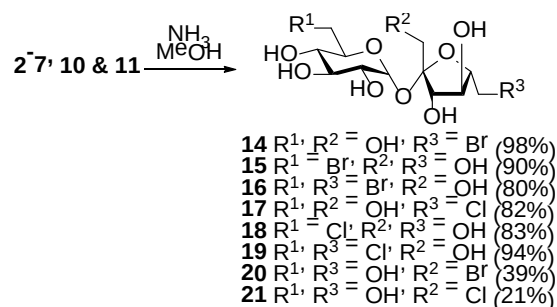
Sucralose<sup>[31]</sup> (**12**, Fig. 3)—commercial available artificial sweetener produced from sucrose—important synthesis intermediate is known as sucralose pentaacetate<sup>[10,32]</sup> (**13**, Fig. 3), was additionally assigned to NMR analysis (Supporting Information). Compound **13** that promoted chlorination at its 4-, 1'-, and 6'-positions were easily to identify by <sup>1</sup>H NMR, especially its halogenated center at 1'-, and 6'-positions. The complete assignment of sucralose pentaacetate **13** in this study, supported by 2D NMR results, allowed brief structural analysis thus compared with the chlorinated sucrose derivatives, e.g. protons at 6'-positions of per-*O*-acetylated 6'-monochloro **6** that showed as doublet ( $J = 12.2$  Hz) and proton at 1'-position of per-*O*-acetylated 1'-monochloro **11** that showed as pair of doublet ( $J = 12.0$  Hz).



**Figure 3.** Structure of sucralose (**12**) and sucralose pentaacetate (**13**).

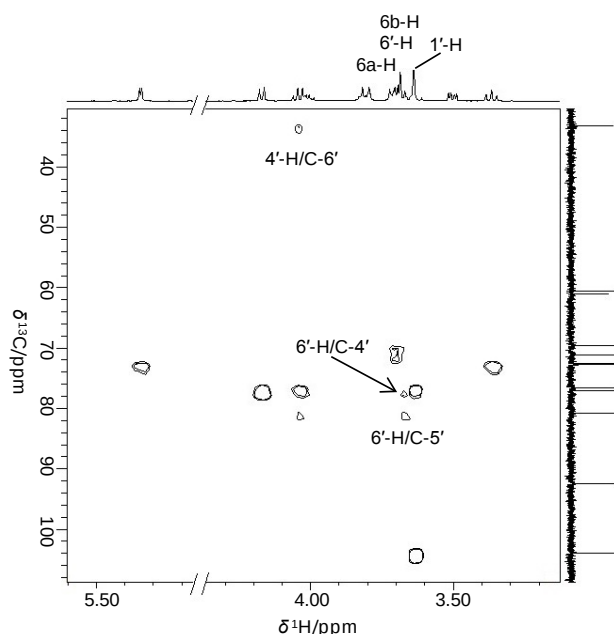
In Appel reaction, monohalosubstituted sucrose at the 6-position (**3** and **6**) emerged as the major products with yields of 12% and 13%, respectively. Based on these results, the regioselectivity for monohalogenation (bromination and chlorination) of unprotected sucrose by using limited proportions of Appel reaction followed the order  $6 > 6' > 1'$ . The mechanism of Appel reaction involved formation of alkoxytriphenylphosphorane intermediates.<sup>[18]</sup> The regioselectivity was observed in this reaction presumably because of nucleophilic displacement of triphenylphosphine oxide by halide anion, which preferred 6- rather than 6'-position. By the basis of the solution conformations of sucrose in aprotic solvents such as pyridine,<sup>[33]</sup> the 1'-position is the type of neopentyl like, more hindered position, and considerably less reactive with a bulky nucleophile under mild conditions of Appel reaction.<sup>[6,34]</sup> In the case of chlorination, selective displacement required a large excess of  $\text{CCl}_4$  due to its volatility.<sup>[15]</sup> Moreover, the second substitution might occur in slow manner, therefore moderate yields of the diproducts **2** and **5** could still be observed.

Complete structural elucidation of regioselective per-*O*-acetylated monohalogenated (**2**, **3**, **5**, **6**, **10** and **11**) and dihalogenated sucrose derivatives (**4** and **7**) were conducted by deprotection (Scheme 3) and also assigned for the detail analyses (Supporting Information). Due to complex mixtures were afforded by sodium methoxide, deacetylation was conducted using saturated ammonium in methanol. Structure elucidation of all regioisomeric halogenated sucrose derivatives, in particular for identification of among protons of the three possible substitution site at 6-, 1'- and 6'-position, was complicated because of several overlapping <sup>1</sup>H NMR signals. It is not easy to distinguish the sample that contained small amounts of by products on <sup>1</sup>H NMR for this deacetylated form. However, the per-*O*-acetylated form is advance for clear structure construction since its specific region and splitting pattern of in <sup>1</sup>H NMR spectrum simply identifies halogenated position rather than directly assigned the unprotected form.



**Scheme 3.** Deacetylation of per-*O*-acetylated halodeoxysucrose derivatives (**2**–**7**, **10** and **11**).

Commonly, differentiation within <sup>1</sup>H NMR specific region for modified unprotected sucrose is performed by comparison against sucrose. It also have been studied<sup>[35]</sup> that by the comparison with sucrose and galacto-sucrose based on epimerisation at C-4 chemical shift, can tentatively predicted the <sup>13</sup>C NMR assignment of the halogenated primary carbons (C-6', C-1', and C-6). However, even though the halogenated counterparts are readily distinguished by the upfield location of their signals in <sup>1</sup>H and <sup>13</sup>C NMR, but differentiation for the substitution site is still unsolved. In agreement, many previous study elucidate the modified counterpart of halogenated unprotected sucrose by subsection into HMBC analysis.<sup>[36]</sup> For our case, the integration of several 2D NMR analyses is needed for brief overlap signal utilization to distinguish the substitution site and also fully construct the gross structure of each unprotected halogenated sucrose derivatives (**14**–**21**) (Supporting Information).



**Figure 4.** Selected HMBC spectrum at 500 MHz ( $\text{D}_2\text{O}$ ) of the first purified 6'-bromo-6'-deoxysucrose (**14**).

Examples of selected HMBC correlation of 6'-bromo-6'-deoxysucrose (**14**) are shown in Figure 4. Up to date, structural elucidation of compound **14** was hampered due to difficulties on its isolation—always remained as a mixture with the 6-halo.<sup>[15,21]</sup> Herein, the first purified 6'-bromo-6'-deoxysucrose (**14**) detailed analyses was stated and even assigned another monobrominated

derivatives (include the monochlorinated products, see Supporting Information) to clearly distinguished its structure. Protons at 6'-position can be differentiated from other spin system or primary center's protons at 6- and 1'-position, majorly by the aid of COSY, NOESY and HMQC. The three-bond coupling of the halogenated methylene and 4'-H was observed in HMBC, confirming the place of the substituent at C-6'. By compilation with HETCOR analyses, the gross structure of **14** was constructed (Supporting Information). However, all the unprotected halogenated sucrose derivatives (**14–21**) structures and substitution site were consistent with those in per-*O*-acetylated form (**2–7**, **10** and **11**).

## Conclusions

In many previous studies, halogenated sucrose derivatives at the primary position are not completely established brief NMR assignments (Supporting Information). This term made the difficulties to distinguish each of the substitution sites, if structural elucidation was only based on  $^1\text{H}$  NMR—due to observation of overlap proton's signal between halogenated methylene and sugar moiety spin system. These tendencies also promoted ambiguous result for Appel reaction reactivity. In this study, comprehensive NMR analyses for each monohalogenated sucrose moieties at the primary position is described and also constructed the reactivity of the Appel reaction based on its isolated per-*O*-acetylated compounds. The NMR characterization was then revisited for 6'-bromo-6'-deoxysucrose heptaacetate (**3**) to show that previous report structural assignment of this molecule was misinterpreted and revised their assignment as the 6-bromo-6-deoxysucrose heptaacetate (**4**). Hence, the pure de-*O*-acetylated 6'-bromo-6'-deoxysucrose (**14**) can be clearly assigned in this study. The regioselective Appel reaction of sucrose followed the halogenation order of  $6>6'>1'$ . The regioselective enzymic deacetylation synthesis of monohalogenated sucrose derivatives at the 1'-position led to the first reported synthesis of compounds 1'-bromo-1'-deoxysucrose heptaacetate (**10**) and 1'-bromo-1'-deoxysucrose (**20**). The establishment of three isomers of monohalogenated sucrose modified at the primary position will be useful to expend the novelty and diversity of carbohydrate-based products and comprehensive analysis of these compounds was led to the reactivity for sucrose primary alcohols order by  $6\text{-OH}\approx 6'\text{-OH}>1'\text{-OH}$ .

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**Keywords:** Appel reaction • NMR • Primary alcohol • Regioselective halogenations • Sucrose

- [1] A.-de. Raadt, A. E. Stutz, *Tetrahedron Lett.* **1992**, 33, 189–192.
- [2] L. Hough, K. S. Mufti, *Carbohydr. Res.* **1972**, 25, 497–503.
- [3] R. Khan, C. Lal Bhardwaj, K. S. Mufti, M. R. Jenner, *Carbohydr. Res.* **1980**, 78, 185–189.
- [4] W. C. L. Ford, G. M. H. Waite, *J. Reprod. Fert.* **1978**, 52, 153–157.
- [5] L. Hough, R. Khan, *Trends Biochem. Sci.* **1978**, 3, 61–63.
- [6] S. Jarosz, M. Mach, *Eur. J. Org. Chem.* **2002**, 769–780.
- [7] R. Khan, *Carbohydr. Res.* **1972**, 25, 504–510.
- [8] C. H. Bolton, L. Hough, R. Khan, *Carbohydr. Res.* **1972**, 21, 133–143.
- [9] L. Hough, K. S. Mufti, *Carbohydr. Res.* **1973**, 27, 47–54.
- [10] R. Khan, M. R. Jenner, K. S. Mufti, *Carbohydr. Res.* **1975**, 39, 253–262.
- [11] H. Kakinuma, H. Yuasa, H. Hashimoto, *Carbohydr. Res.* **1996**, 284, 61–72.
- [12] N. D. Sachinvala, W. P. Niemczura, M. H. Litt, *Carbohydr. Res.* **1991**, 218, 237–245.
- [13] R. D. Guthrie, I. D. Jenkins, J. J. Watters, *Aust. J. Chem.* **1980**, 33, 2487–2497.
- [14] M. M. Andrade, M. T. Barros, P. Rodrigues, *Eur. J. Org. Chem.* **2007**, 3655–3668.
- [15] M. T. Barros, K. T. Petrova, P. Correia-da-Silva, T. M. Potewar, *Green Chem.* **2011**, 13, 1897–1906.
- [16] J. M. Ballard, L. Hough, A. C. Richardson, P. H. Fairclough, *J. Chem. Soc., Perkin Trans. 1.* **1973**, 1524–1528.
- [17] B. Castro, Y. Chapleur, B. Gross, *Carbohydr. Res.* **1974**, 36, 412–419.
- [18] R. Appel, *Angew. Chem., Int. Ed. Engl.* **1975**, 14, 801–811.
- [19] R. Khan *Pure Appl. Chem.* **1984**, 56, 833–844.
- [20] A. K. M. Anisuzzaman, R. L. Whistler, *Carbohydr. Res.* **1978**, 61, 511–518.
- [21] M. K. Bhattacharjee, R. M. Mayer, *Carbohydr. Res.* **1985**, 142, 277–284.
- [22] C.-C. Chen, R. L. Whistler, *Carbohydr. Res.* **1983**, 117, 318–321.
- [23] W. J. Lees, G. M. Whitesides, *J. Am. Chem. Soc.* **1993**, 115, 1860–1869.
- [24] L. Hough, L. V. Sinchareonkul, A. C. Richardson, F. Akhtar, M. G. Drew, B. *Carbohydr. Res.* **1988**, 174, 145–160.
- [25] J. L. J. Blanco, J. M. G. Fernandez, A. Gadelle, J. Defaye, *Carbohydr. Res.* **1997**, 303, 367–372.
- [26] H. Kakinuma, F. H. Yuasa, H. Hashimoto, *Carbohydr. Res.* **1998**, 312, 103–115.
- [27] L. Hough, S. P. Phadnis, E. Tarelli, *Carbohydr. Res.* **1975**, 44, 37–44.
- [28] R. Khan, M. R. Jenner, H. Lindseth, *Carbohydr. Res.* **1980**, 78, 173–183.
- [29] J. C. Christofides, D. B. Davies, J. A. Martin, E. B. Rathbone, *J. Am. Chem. Soc.* **1986**, 108, 5738–5743.
- [30] a) K.-Y. Chang, S.-H. Wu, K.-T. Wang, *Carbohydr. Res.* **1991**, 222, 121–129; b) S. Bornemann, J. M. Cassells, J. S. Dordick, A. J. Hacking, *Biocatalysis* **1992**, 7, 1–12; c) Y. Tsunekawa, K. Masuda, M. Muto, Y. Muto, Y. Murai, Y. Hashidoko, Y. Orikasa, Y. Oda, Y. Hatanaka, M. Hashimoto, *Heterocycles* **2012**, 84, 283–290.
- [31] F.-W. Liu, H.-M. Liu, Y. Ke, J. Zhang, *Carbohydr. Res.* **2004**, 339, 2651–2656.
- [32] P. H. Fairclough, L. Hough, A. C. Richardson, *Carbohydr. Res.* **1975**, 40, 285–298.
- [33] F. W. Lichtenthaler, S. Mondel, *Pure Appl. Chem.* **1997**, 69, 1853–1866.
- [34] F. W. Lichtenthaler, S. Peters, *C. R. Chim.* **2004**, 7, 65–90.
- [35] L. Hough, S. P. Phadnis, E. Tarelli, *Carbohydr. Res.* **1976**, 47, 151–154.
- [36] M. T. Barros, K. T. Petrova, P. Correia-da-Silva, Sucrose chemistry: Fast and Efficient Microwave-assisted Protocols for the Generation of Sucrose-Containing Monomer Libraries. In *Microwave heating* Chandra, U., Ed. InTech: Croatia, 2011, Chapter 14.