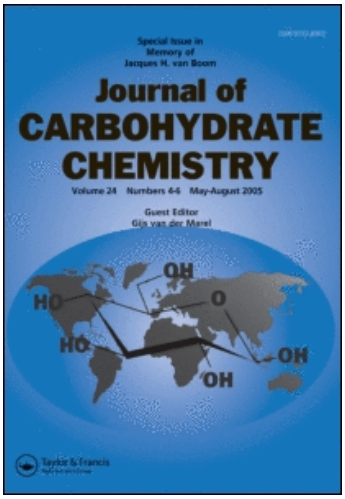

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COMMUNICATION

HYDROPHOBIC EFFECT DRIVEN ESTERIFICATION OF SUCROSE IN AQUEOUS MEDIUM[1]

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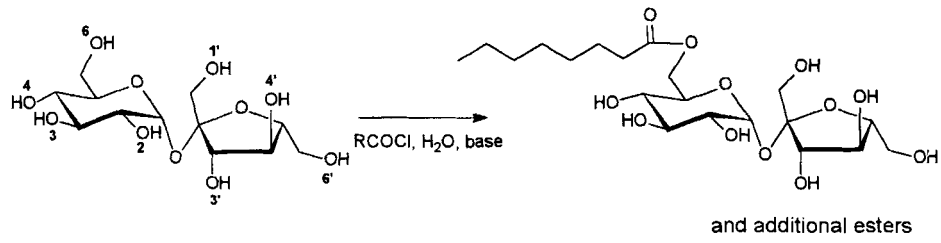
Sucrose is an attractive molecule for chemistry because it is pure, abundant, inexpensive, and produced from renewable sources. Among its derivatives, sucrose esters are valuable targets for the chemical valorization of sugar, either as polymerizable derivatives, surfactants, or non-caloric fat substitutes.[2] But although such potential commercially attractive sucrose derived molecules can be targeted, methods consistent with low-cost sucrose diversification have still to be found. The issue of the solvent being critical, we have been interested in evaluating water as a possible solvent for some transformations of sucrose, and we report herein some preliminary results on the esterification of this sugar in basic aqueous medium.

Esterification of unprotected sucrose is already used for the manufacturing of sucrose fatty esters as emulsifiers.[3] Most of the processes involve the use of aprotic dipolar solvents (DMF or DMSO) difficult to remove after reaction. This strictly limits food applications for which only trace amounts of remaining solvent can be tolerated. Nevertheless, good sucrose conversion and substitution degree control can be obtained, although regioselectivity is nearly random.[4] Regioselective sucrose monoesterifications have been described, notably using the Mitsunobu reaction,[5] thiazolidine-2-thione acyl



Scheme 1

derivatives,[6] with the help of metal salts,[7] or via enzyme catalyzed transesterifications.[8] For the latter examples, the more reactive hydroxyl groups are the primary ones (6, 1', 6') as for reactions depending essentially on steric factors. Reactivity at secondary hydroxyl groups can sometimes prevail, especially at position 2 which is by far the most acidic, to selectively yield 2-substituted sucrose derivatives.[6,9] Competition of hydroxyl groups at positions 1' and 3' on the fructose moiety with the more reactive OH-2 has also been observed, and has been explained on the basis of spectroscopic and theoretical studies.[10] A general trend of sucrose reactivity lies in the fact that OH-2 is involved in hydrogen bonding with OH-1' or OH-3', even in aqueous medium via a bridging water molecule.[11] The interactions between sugar and water are already known to influence the outcome of some chemical reactions.[12] The purpose of the present study is also to see whether these interactions might modify the outcome of a transformation on sucrose itself.

The reaction we investigated was the esterification of sucrose with octanoyl chloride in basic aqueous medium as a model reaction (the fatty acid chlorides are not suitable substrates for industrial conversions) to provide insight into concentration effects on sucrose transformations. Aqueous solutions of sucrose in a concentration range from 10 to 70% (0.4 to 2.7 M) were used while keeping the sugar/acylating agent ratio constant. The yield based on the starting acid chloride quantity (in default) provided information on the relative reactivity of sucrose and water towards the acylating agent, and on the stability of the products. The selectivity of the reaction was followed in terms of substitution degree (SD), and of regiochemistry (for the monoesters).

The acylation of sucrose by octanoyl chloride at pH 10 (10N NaOH, pH-stat) in water at various concentrations was studied. The results reported in Table 1 indicate first that even in aqueous medium, acceptable yields of sucrose esters could be obtained.[13]

Table 1. Influence of sucrose/water ratio on ester distribution using NaOH as the base.[a]

sucrose concentration (w/w %)	monooctanoates (%)	dioctanoates (%)	trioctanoates and over (%)	global yield (%)
40	12	11	19	42
50	10	10	30	50
60	4	8	50	62
70	1	2	65	68

a. Reactions conducted at 15 °C at pH 10 (pH-stat 10 N NaOH) with 0.25 equiv of octanoyl chloride (reaction time: 1 h).

Logically, yields increase when the reaction is performed at low water content, as water is responsible for the competitive reactions, i.e. hydrolysis of the acid chloride and the saponification of sucrose esters. However, it was verified that the base promoted cleavage of the ester function in sucrose monooctanoates was much slower in concentrated aqueous sucrose solutions as compared to pure water. More interestingly, the substitution degree distribution is strongly dependent on the concentration of sucrose in water. Indeed, at high starting sucrose concentrations, the reaction gave essentially polyesters (having an average SD of 4), in reasonable yields. The formation of higher esters is presumably driven by the tendency of hydrophobic chains placed in an aqueous environment to aggregate, a tendency which can be referred to as the hydrophobic effect. Therefore, the increase of the SD when using more concentrated sucrose solutions is consistent with the known ability of sucrose to be a water structure strengthener, thus increasing the hydrophobic effect. To confirm our hypothesis, the reaction was performed using dimethylaminopyridine (DMAP) as the base, known to promote efficiency in acylations by involving an acylpyridinium intermediate (Table 2). Again, ester yields increase with increasing starting sucrose concentration, ultimately giving high conversions to sucrose fatty chain esters. However, unlike precedently, all kinds of esters (in terms of SD) are formed, without disfavoring low substituted esters at high concentration. Thus, by forcing the reaction to occur via an ionic pathway, the fatty chain is more easily incorporated in the aqueous phase, making the transformation probably less sensitive to the hydrophobic effect. The reaction is also much faster using DMAP, even when using a catalytic amount (10%) together with NaOH at pH 10 (Table 3). Then, even dilute

Table 2. Influence of sucrose/water ratio on ester distribution using DMAP as the base.[a]

sucrose concentration (w/w %)	monooctanoates (%)	dioctanoates (%)	trioctanoates and over (%)	global yield (%)
40	30	20	23	73
50	35	21	31	87
60	42	15	35	92
70	45	13	40	98

a. Reactions conducted at room temperature using 2 equiv of DMAP and 0.25 equiv of octanoyl chloride (reaction time: 10 min).

Table 3. Influence of sucrose/water ratio and of temperature on ester distribution using catalytic DMAP and NaOH as the base.[a]

sucrose conc. (w/w %)	monooctanoates (%)		dioctanoates (%)		trioctanoates and over (%)		global yield (%)	
	25 °C	0 °C	25 °C	0 °C	25 °C	0 °C	25 °C	0 °C
10	52	62	11	8	9	12	72	82
20	39	49	24	20	22	24	85	93
30	28	32	24	23	34	39	86	94
40	22	26	21	24	50	46	93	96
50	21	21	22	22	52	53	95	96
60[b]	19	-	22	-	54	-	95	-

a. Reactions conducted at pH 10 (pH-stat 10 N NaOH) using 0.01 equiv of DMAP and 0.1 equiv of octanoyl chloride (reaction time: 15 min). b. Results not available because of solubility limit.

sucrose solutions could be used, giving a fair esterification yield at room temperature (72%) compared to trace amounts without catalysis. In this case, the selectivity is again in favour of polyesters at high concentrations, probably because the hydrophobic effect driven polyesterification is faster and can thus compete with the DMAP catalyzed reaction. Lowering the temperature from 25 to 0 °C led to a decrease in the average substitution degree of the polyester fraction obtained from concentrated solutions. Lowering the reaction temperature also resulted in a higher monoester content in the case

of a 10% solution (89% molar, 85% weight), for which an 82% yield of crude sucrose ester mixture having an average SD of 1. 2 could be isolated.

In conclusion, we have shown that the acylation of sucrose by octanoyl chloride in basic aqueous medium can be directed towards the formation of variously substituted esters by chosing the sucrose content of the starting aqueous solution. The natural tendency of the reaction is to yield more substituted esters when increasing the sugar concentration, suggesting that this acylation is driven by the hydrophobic effect. Monoesters can be obtained from a more dilute solution by forcing the reaction to proceed via a less hydrophobic intermediate. Experiments building on these findings are in progress in our laboratory.

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13. A typical experiment consisted in adding neat octanoyl chloride (8.78 mmol, 1.5 mL) using an automatic syringe (0.1 mL/min flow rate) to a stirred 60% w/w sucrose aqueous solution (sucrose: 88 mmol, 30g, water: 20g) adjusted to pH 10 with 10N NaOH (pH-stat or manually). Reactions were monitored by TLC using a 56:20:20:4 mixture of dichloromethane, methanol, acetone and water as the eluent. After neutralization by adding 0.5N hydrochloric acid, water was added in order to get a less viscous solution, and the crude sucrose esters could be extracted with 1-butanol (2 or 3x 30 mL). After evaporation of the solvent, flash chromatography (same solvent as for TLC) allowed isolation first of the more substituted esters, then the diesters, and finally the monoesters. The average substitution degree was determined by comparing integration for the alkyl chain and sugar regions in ^{1}H NMR spectra (d_6-DMSO). Monoesters could be further purified by semi-preparative HPLC (nucleosil NH_2, 0.5" Ø, 93/7 MeCN/water, 7 mL/min, RI detection) and identified by ^{1}H and ^{13}C NMR spectroscopy. Sucrose reference data (D_2O, 50.32 Mhz) δ 104.1 (C-2'), 92.6 (C-1), 81.8 (C-5'), 76.8 (C-3'), 74.4 (C-4'), 73.0 (C-3), 72.8 (C-5), 71.5 (C-2), 69.7 (C-4), 62.8 (C-1'), 61.8 (C-6'), 60.5 (C-6); 2-*O*-octanoyl sucrose: 176.5 (C=O), 104.4 (C-2'), 90.1 (C-1), 81.9 (C-5'), 75.9 (C-3'), 74.3 (C-4'), 73.0 (C-2), 72.8 (C-5), 70.8 (C-3), 69.7 (C-4), 62.8 (C-1'), 61.5 (C-6'), 60.5 (C-6), 34.2, 31.5, 28.7, 28.6, 24.6, 22.5, 13.9 (alk); 3-*O*-octanoyl sucrose: 176.8 (C=O), 104.3 (C-2'), 92.6 (C-1), 81.9 (C-5'), 76.9 (C-3'), 75.4 (C-3), 74.5 (C-4'), 72.8 (C-5), 69.9 (C-2), 68.0 (C-4), 62.8 (C-1'), 61.8 (C-6'), 60.5 (C-6), 34.6, 31.7, 28.9, 28.8, 25.0, 22.6, 14.0 (alk); 3'-*O*-octanoyl sucrose: 176.4 (C=O), 103.7 (C-2'), 92.0 (C-1), 82.3 (C-5'), 77.5 (C-3'), 73.4 (C-4'), 72.8 (C-3), 72.6 (C-5), 71.4 (C-2), 69.5 (C-4), 63.3 (C-1'), 62.2 (C-6'), 60.5 (C-6), 34.2, 31.4, 28.6, 28.4, 24.8, 22.4, 13.8 (alk); 4'-*O*-octanoyl sucrose: 175.8 (C=O), 104.6 (C-2'), 92.7 (C-1), 80.1 (C-5'), 76.4 (C-4'), 75.1 (C-3'), 73.0 (C-3), 72.9 (C-5), 71.5 (C-2), 69.5 (C-4), 62.7 (C-1'), 61.6 (C-6'), 60.4 (C-6), 34.2, 31.3, 28.5, 28.4, 24.7, 22.4, 13.8 (alk). Esterification position was determined through shift effects analysis [see K. Yoshimoto, Y. Itatani, K. Shibata and Y. Tsuda, *Chem. Pharm. Bull.*,**28**, 208 (1980)], and confirmed by ^{1}H NMR. 4-*O*-Octanoyl sucrose could not be identified because of fast octanoyl migration to position 6. For NMR data of primary mono-*O*-octanoyl sucrose, see: K. Baczko, C. Nugier-Chauvin, J. Banoub, P. Thibault and D. Plusquellec, *Carbohydr. Res.*, **269**, 79 (1995); G. Carrea, S. Riva and F. Secundo, *J. Chem. Soc., Perkin Trans. 1*, 1057 (1989); C. Chauvin and D. Plusquellec, *Tetrahedron Lett.*,**32**, 3495 (1991).