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Synthesis in water of amphiphilic sucrose hydroxyalkyl ethers

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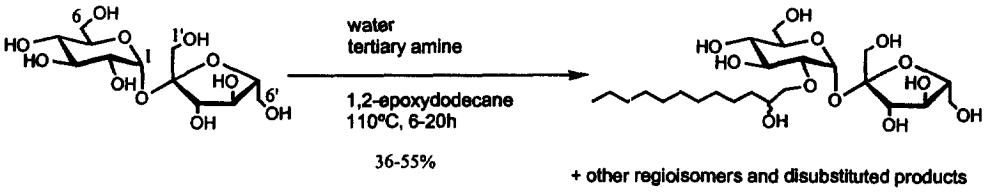
Abstract: We describe the preparation of amphiphilic hydroxyalkylsucrose ethers from unprotected sucrose in water and we show that among the monosubstituted products, the 2- and 1'- regioisomers account for 60% of the mixture. The high reactivity of these positions is thus confirmed in water as it is in dipolar aprotic solvents. A careful analysis also show evidence of the formation of oligomerisation products as by-products.

Keywords: surfactants, carbohydrates, etherification, epoxide

This work is part of a project which aims at developing new synthetic methods based on the direct transformation of renewable organic raw materials such as sugar without organic solvents [1]. Industrial interest for amphiphilic sucrose hydroxyalkylethers in detergents or cosmetics has led to several methods of preparation, most of them using DMSO as the solvent [2,3], while only a few have been described without any solvent [4]. In contrast to sucrose esters, ethers can resist harsh alkaline conditions, which can be taken as an advantage to extend their field of application. Syntheses in water must deal with the concurrent nucleophilicity of water and with the non-miscibility of the reagents which dramatically decreases the reactivity [5,6].

In order to understand both the chemical and interfacial phenomena occurring in the heterogeneous reaction of unprotected sucrose with 1,2-epoxydodecane in water (scheme 1), a first requirement was to obtain quite fair yields and a satisfactory analytical method [7]. In this Letter, we describe our preliminary results concerning the chemical, analytical and regiochemical aspects of this reaction.



Scheme 1

Preliminary attempts showed that using potassium hydroxide as the basic catalyst for the reaction between the epoxide and an aqueous solution of sucrose (80% w/w) at 110°C did not transform the epoxide (table 1, entry 1) or gave mainly the product of hydrolysis (entry 2) when cetyltrimethylammonium bromide (CTAB) was added as a surfactant catalyst. In contrast, using a tertiary amine [4b,6,8] such as N-methylmorpholine (NMM) or dimethylbutylamine, the desired sucrose ethers were obtained in an overall yield of 36%

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to 47% for the mono- and di-substituted derivatives, depending on the sucrose/epoxide ratio (entries 3-4-5-6). The global yield of monosubstituted and disubstituted products could be improved up to 55 % by the addition of CTAB (entries 7-8-9).

Tri- and tetra-substituted derivatives are also produced and can be observed by mass spectroscopy [7]. Other constituents of the reaction mixture, identified by n.m.r., mass spectroscopy and t.l.c. analysis are the 1,2-dodecanediol and its oligomers (up to 4 units) with epoxydodecane, formed in the oil phase [9,10]. The addition products of N-methylmorpholine on one or two epoxide molecules, giving surfactant ammonium salts have also been detected in the polar part of the reaction mixtures [6,11,12]. Such competitive reactions account for the limitation of the sucroether yields, in addition to the non-quantified tri- and tetra-substituted products.

Better yields and faster reaction rates have been obtained in the presence of CTAB probably because of the reduction of the side reactions in the oil phase, owing to the better emulsification between the aqueous and the oil phase and to the acceleration of the etherification reaction of sucrose by cationic micellar catalysis [13,14,15]. Reaction time dependence on the amine could be due to different partition between water and oil phase or to pKa differences.

Entry	Base	Additive	Reaction time (h)	Sugar/ epoxide (mol/mol)	Monoethers (%)	Diethers (%)	Mono + Diethers (%)	Dodecanediol (%)
1	KOH	no	22	2/1	0	0	0	0
2	"	CTAB	21	"	14	traces	-	56
3	NMM	no	20	1/1	18	20	38	14
4	"	"	15	2/1	26	18	44	11
5	"	"	11	4/1	28	8	36	12
6	Me_2NBu	"	6	2/1	30	17	47	7
7	NMM	CTAB	4	"	36	19	55	7
8	"	"	4	4/1	38	15	53	6
9	Me_2NBu	"	3	2/1	35	17	52	6

Table 1: Yields of sucroetherification based on epoxide consumption in several reaction conditions (note 7).
NMM = N-methylmorpholine; CTAB = cetyltrimethylammonium bromide.

In order to assess the ability of such heterogeneous and aqueous media to change or even to improve the regioselectivity [15], full characterisation of the monosubstituted product regioisomers has been achieved [16]. It shows again a great predominance of the 2 and 1'-substituted products [5,17,18] for about 60% of the mixture. The relative quantities of the regioisomers are: 2 (34%)- 1' (25%)- 4' (12%)- 3' (11%)- 6' (6%)- 4 (5%)- 6 (5%)- 3 (2%) similar to those obtained for the reaction performed in DMSO, under the same experimental conditions. This high reactivity of the OH-2 and OH-1' in water was already seen in the preparation of sucrose esters and carbonates [5]. This is consistent with the persistence of the intrinsic stereoelectronic reactivity of each hydroxyl group in spite of the high temperature and a different solvation [17]. In our case, neither the use of different solvents nor the presence of a microheterogeneous organized medium (micellar or liquid crystals) has changed the regioselectivity.

Having in hands all the monosubstituted regioisomers after careful separation, as couples of epimers at the α-hydroxyalkyl linkage, some additional informations on the hydrogen bonding of sucrose (in solution at room temperature) can be drawn from the HPLC and NMR data (table 2). Only in the case of the OH-2 substituted ethers, a different retention time was observed between the two epimers in HPLC. Moreover, the ^{13}C n.m.r. chemical shifts of the α-hydroxy carbon of the fatty chain is changed (+1 ppm) whereas it is constant for all the other isomers. When the OH-2 is substituted, the formation of the O-2...HO-1' hydrogen bond cannot

occur as usual, then inducing substantial changes of the conformation and of the behavior [19]. In agreement with classical results in basic medium, only terminal opening of the epoxide ring was observed.

Regio-isomer	Retention time (§)	δ C6 (ppm)	δ C6'	δ C1'	δ C4	δ C2	δ C3	δ C5	δ CHOH (#)	δ C4'	δ C3'	δ OCH_2 (#)	δ C5'	δ C1	δ C2'
6' a, b	30 (min)	61.1 61.2	**73.0**	62.1	70.0 70.1	70.6 70.8	73.0	73.2	71.7	75.3 75.4	77.2	75.8 76.1	80.1 80.3	92.6	104.2
1' a, b	27	60.8	62.3	**71.2**	69.8	70.7	73.1	73.2	71.7	74.0	77.6	76.5 76.7	81.8	93.1	103.8
6 a, b	23	**70.4**	62.1	62.5d	70.0 70.3	70.6	73.1	72.2	71.6	74.3	77.3	76.5	81.9	92.7	104.2
4' a, b	21	60.7	62.2	63.2	69.6	71.1	73.1	73.1	71.6	**83.5**	77.3 77.5	75.3 75.7	81.6 81.9	92.8	104.9
2 a	19	61.0	62.6	62.9	70.0	**81.0**	71.3	73.0	**72.8**	74.5	77.7	77.0	81.9	90.6	104.2
2 b	18	61.0	62.7	62.7	70.2	**80.6**	70.5	73.0	**72.6**	74.5	77.5	76.6	81.9	90.7	104.3
3' a, b	16	60.7	62.7	63.2	69.7	70.8 71.0	73.3	72.8	71.7	73.9 74.1	**85.1** **85.5**	76.2 76.6	82.0	92.6	104.4
4 a, b	15	61.0d	61.9	62.9	**78.8** **79.6**	71.0	73.2 73.3	72.3	71.7	74.5	77.0	77.6 78.0	81.9	92.5	104.3
3 a, b	12	60.8	62.1	62.8	69.7	71.4	**82.7d**	72.8	71.7	74.5	76.9	77.4d	81.9	92.5	104.2
sucrose		61.0	61.8	62.8	69.7	71.5	73.0	72.9		74.5	76.9		81.8	92.6	104.1

Table 2: ^{13}C NMR chemical shifts (ppm) [20] of mono-*O*-(2*RS*-hydroxydodecyl)-sucrose in D_2O at 75 MHz (the chemical shifts of the last ten fatty chain carbons are not reported; § = retention time in min, for semi-preparative HPLC [16]; # = first and second carbon of the fatty chain; d = unresolved splitted peaks). a and b account for the formation of two epimers due to the fatty chain second carbon.

From these results, sucrose hydroxyalkylethers can be prepared in moderate to fair yields in an aqueous medium despite the competitive hydrolysis of the epoxide. Hydrolysis and side reactions can be reduced by the addition of ammonium surfactants and important changes in reaction rates were observed depending on the additive or on the amine used. Further physicochemical and kinetic investigations are in progress in our laboratory in order to determine the role of additional surfactants and microheterogeneous organisation of the medium on the reaction.

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[7] **Typical procedure**: sucrose 1 eq. (4.00 g), water (1.00 g, 80% aqueous sucrose solution), epoxydodecane 0.5 eq. (1.07 g), base 0.14 eq. (e.g. 0.17 g of N-methylmorpholine or dimethylbutylamine) are poured together in an 5 ml aluminium-teflon-sealed vial and allowed to react at 110°C for 6-24 h hours under a strong magnetic stirring at 750 min^{-1}. For surfactant catalyzed experiments, 0.50 g CTAB is added to the reaction mixture. Reaction with triethylamine works more slowly. Determination of the yields were made by HPLC analysis on a analytical C8-grafted column, eluted with MeOH/H_2O 82/18, 0.8 ml/min and confirmed in several cases on isolated products. They are identical (^1H NMR, HPLC NH_2) to authentic samples prepared in DMSO. **LSIMS mass spectroscopy, NBA+LiCl,** after coarse purification: Apolar fraction: 209, 393, 537, 721, 901 (triethers, 25), 1085 (tetraethers, 5); diether fraction: 209, 537, 717 (diethers), 901 (triethers, 15); monoether fraction: 470 (20), 533 (monoethers, 25), 717 (diethers, 2). **Microanalysis of authentic samples: monoethers** (flash chromatography purification, lyophilised samples): measured C:52.91, H:8.72; calculated for [$C_{24}H_{46}O_{12}$+1H_2O] C:52.93, H: 8.88. Analysis of the water content by the Karl-Fischer method: 2% by weight. **Diethers** (inverse-phase HPLC purification): measured C: 60.21, H: 9.89, calculated for [$C_{36}H_{70}O_{13}$+0.3H_2O] C: 60.36, H: 9.93.

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[9] **LSIMS mass spectroscopy of oligomers** (crude reaction mixture without sugar), NBA+LiCl: 393, 470 (25), 577 (70), 654 (12), 761 (2). T.l.c characterisation or flash chromatography purification: ethyl acetate/hexane 3/7, Rf = 0.3 (M=386), Rf = 0.5 (M=570), Rf = 0.8 (M= 754).

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[16] **HPLC conditions for separation of the monoether regioisomers**: direct-phase semi-preparative NH_2-grafted column, elution with acetonitrile/ water 88/12, 20 ml/min gives 9 peaks beetween 12 and 31 min. **RMN ^1H** (300 MHz, D_2O, exept aliphatic signals): **6' a,b**: 5.39 (d, 1H, 2.5 Hz, H_1), 4.19 (d, 1H, 8 Hz, $H_{3'}$), 4.0 (m, 2H, $H_{4'}$, $H_{5'}$), 3.95-3.71 (m+t, 7H, $J_{3,4}$ = 9.2 Hz, $2H_6$, $2H_{6'}$, H_5, H_3), 3.68 (br.s, 2H, $H_{1'}$), 3.55 (br.dd, 2H, 9.5 Hz, 2.5 Hz, H_2), 3.44 (m, 2H, H_4). **1' a,b**: 5.43 (m, 1H, H_1), 4.23 (m, 1H, $H_{3'}$), 4.11 (br.t, 1H, $H_{4'}$), 3.95-3.65 (m, 10H), 3.65-3.3 (m, 4H). **6 a,b**: 5.40 (d, 1H, 2.2 Hz, H_1), 4.21 (d, 1H, 8.5 Hz, $H_{3'}$), 4.10 (br.t, 1H, 8.5 Hz, $H_{4'}$), 3.95 (m, 1H), 3.92-3.7 (m, 7H, $J_{3,4}$ = 9 Hz), 3.66 (br.s, 2H, $H_{1'}$), 3.55 (br.dd, 2H, 2.2 Hz, 10.5 Hz, H_2), 3.5-3.3 (m+dd, 2H, 5.5 Hz, 9 Hz, H_4). **4' a,b**: 5.44 (m, 1H, H_1), 4.34 (t, 1H, 4.5 Hz, $H_{4'}$), 4.0-3.7 (m, 9H), 3.67 (br.s, 2H, $H_{1'}$), 3.65-3.4 (m+t+dd, 4H, $J_{4,3}$ = $J_{4,5}$ = 8.5 Hz, $J_{2,1}$ = 3.7 Hz, H_2, H_4). **2 a**: 5.52 (br.s, 1H, H_1), 4.21 (d, 1H, 8.5 Hz, $H_{3'}$), 4.09 (t, 1H, 8.5 Hz), 4.0-3.7 (m, 9H), 3.7-3.53 (m, 3H), 3.48 (t, 1H, 9.2 Hz, H_4), 3.37 (br.d, 1H, 9.9 Hz, H_2). **2 b**: 5.53 (br.s, 1H, H_1), 4.21 (d, 1H, 8.5 Hz, $H_{3'}$), 4.07 (t, 1H, 8.5 Hz, $H_{4'}$), 3.95-3.5 (m, 12H), 3.46 (t, 1H, 9 Hz, H_4), 3.35 (br.d, 1H, 9.5 Hz, H_2). **3' a,b**: 5.43 (m, 1H, H_1), 4.19 (dt, 1H, 7.5 Hz, 3.7 Hz, $H_{3'}$), 4.04 (t, 1H, 5.5 Hz, $H_{4'}$), 3.95-3.6 (m, 12H), 3.55 (dd, 1H, 10 Hz, 4 Hz, H_2), 3.45 (t, 1H, 9 Hz, H_4). **4 a,b**: 5.44, 5.41 (2s, 1H, H_1), 4.21 (d, 1H, 8.5 Hz, $H_{3'}$), 4.04 (t, 1H, 8.5 Hz, $H_{4'}$), 4.0-3.4 (m, 13H), 3.32 (t, 1H, 6.5 Hz, H_4). **3 a,b**: 5.41 (br.s, 1H, H_1), 4.22 (d, 1H, 8.5 Hz, $H_{3'}$), 4.06 (t, 1H, 8.5 Hz, $H_{4'}$), 4.0-3.4 (m, 14H).

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