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Preparation of amphiphilic sucrose carbamates by reaction with alkyl isocyanates in water–alcohol mixtures

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Abstract—The reactivity of sucrose with isocyanates in aqueous media has been studied. Mixtures of water and alcohols allow good conversion of the isocyanates to sucrose carbamates. The influence of the reaction parameters on the selectivity (degree of substitution and regioselectivity) was investigated in the case of long chain isocyanates, which have potential surfactant properties.

The use of carbohydrates as organic raw materials is attractive since some of them are readily available renewable commodities.[1] Sucrose, notably, has been shown to be an interesting substrate, which can be used in many reactions to form functional derivatives such as surfactants, polymerisable compounds, sequestering agents, etc.[2] As part of our work in this field, we have been interested in the use of aqueous media for the chemistry of sucrose.

There are actually not many solvents in which sucrose is reasonably soluble, and water is a better medium compared to polar aprotic solvents in terms of cost and toxicity. We have shown that sucrose, thanks to the peculiar reactivity of some of its OH groups, can react in basic aqueous media with acid chlorides[3] and epoxides,[4] despite their sensitivity to water. We are also involved in studies of the thermotropic liquid crystal behaviour of sucrose derivatives, aimed at establishing relationships between the properties and the molecular structures of these materials. It was notably demonstrated that the position of the chain influences the nature of the thermotropic phases, depending on the possible arrangement of the two monosaccharidic moieties via hydrogen bonding.[5] In order to widen the scope of the aqueous reactivity of sucrose with respect to other electrophilic species, we became interested in the case of isocyanates, which can provide *N*-alkyl sucrose carbamates having different properties (stability, physicochemical behaviour) compared to other amphiphilic sucrose derivatives. We report the preparation of such derivatives in water–alcohol mixtures and the effect of some reaction parameters on the outcome of the reaction in the case of long-chain alkyl isocyanates.

Although the reaction of carbohydrates with diisocyanates is well documented since it is the route to polyurethane materials,[6] the controlled and selective synthesis of *N*-alkylcarbamoyl carbohydrate derivatives is less well studied.[7] In the case of sucrose, Plusquellec and co-workers[8] and Lichtenthaler and co-workers[9] reported the preparation of sucrose carbamates in dipolar aprotic solvents. In pure water, the reaction of sucrose (**1**) with octyl isocyanate (**2a**) in the presence of base led to polysubstituted derivatives, confirming the strong hydrophobic effect-driven behaviour of such systems.[3] In contrast, solvent systems such as water–THF or water–alcohol mixtures were shown to provide good yields of low-substituted sucrose octyl carbamates, which have potentially interesting properties as surface active agents. Alcohol carbamation and isocyanate hydrolysis (as well as the subsequent carbamic acid and urea derivative formation) were observed (Scheme 1),

Keywords: Sucrose; Aqueous medium; Isocyanates; Carbamates; Regioselectivity.

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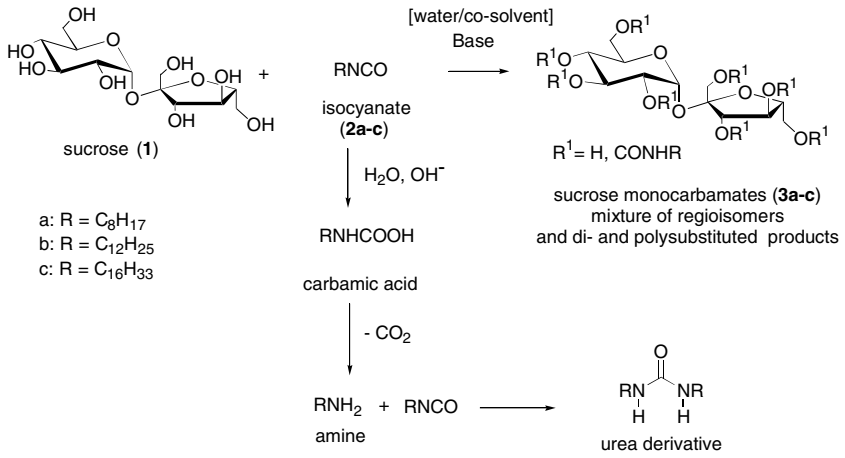


Scheme 1. Reaction of sucrose with alkyl isocyanates.

but depending on the nature of the alcohol, these processes were more or less competitive compared to sucrose functionalization, as seen by a modulation of the yield of sucrocarbamates. More hindered alcohols such as isopropanol and *tert*-butanol gave better conversion of low-substituted products, the water–isopropanol system providing a slightly higher mono/di-substitution ratio, as a result of a better homogeneity of the reaction media. It is interesting to observe that sucrose carbamates could be formed in the presence of ethanol or even methanol, although in lower yield due to extensive competitive alcohol carbamation. Results are reported in Table 1.[10] In isopropanol–water, *N*-dodecyl and *N*-hexadecyl derivatives could also be obtained.

The monosubstituted sucrose octyl carbamates **3a** were compared to octyl esters and octyl carbonates of sucrose with respect to their stability to basic conditions (Fig. 1). This showed that the carbamate linkage was much more resistant, widening the potential of such derivatives as surfactants in more aggressive formulations. The regioselectivity of the reaction in water/co-solvent media was also compared with the case of ester and carbonate formation in aqueous media, [3] as well as the reaction of isocyanate in DMF. The increased stability of the carbamate function resulted in an increased regioselectivity in all cases, the regioisomeric distribution being a complex balance between relative kinetic reactivity of the eight alcohol functions of sucrose and the rate of intramolecular migrations. As is now well established in sucrose chemistry,[2–4,11] major functionalisation was observed at 2-OH, 3′-OH and 1′-OH (see Scheme 2 for sucrose numbering). In aqueous medium, the reaction was slightly less selective. The derivatives substituted at 4-OH and 4′-OH were present in larger amounts than in DMF, consistently with much slower migration rates compared to esters and carbonates (Fig. 2). The precise position of the functionalisation was assessed by full characterisation of pure derivatives purified from a mixture of regioisomers of **3a** by preparative HPLC. Consistent chemical shift changes compared to unprotected sucrose were observed in the ^{1}H and ^{13}C NMR spectra.[12] The high selectivity for monosubstitution also results in a simpler mixture of disubstituted products obtained in hydroalcoholic medium, in which the 3′,4′-dicarbamate **4** (Scheme 2) is the major isomer (it was not formed in the DMF-mediated reaction).[13]

In conclusion, we have shown that isocyanates can react with sucrose in water in the presence of a co-solvent to provide low-substituted *N*-alkylcarbamoylsucrose in good yield and regioselectivity. Water/isopropanol appears to be the best system, which balances medium homogeneity and competitive alcohol carbamation.

Table 1. Reaction of sucrose and octyl isocyanate in water/co-solvent media[a,10]

Co-solvent	*t* (h)	Mono[b] (%)	Di[b] (%)	Mono + di[b] (%)
—[c]	2	5	4	9
THF	3	31	27	58
Isopropanol	1	36	22	58
tert-Butanol	3	29	29	58
EtOH	3	31	14	45
MeOH	5	12	0	12
2-Butanol[d]	3	8	14	22
1-Butanol[d]	5	2	8	10

[a] Conditions: [sucrose] = 10% in weight in the mixture of solvents; [isocyanate] = [NaOH] = 0.5 equiv; rt; co-solvent (1/1) with water (w/w).
[b] Conversion ratio of isocyanate to sucrose carbamate determined by HPLC.
[c] Pure water, initial pH = 12.9 (NaOH).
[d] Not fully homogeneous.

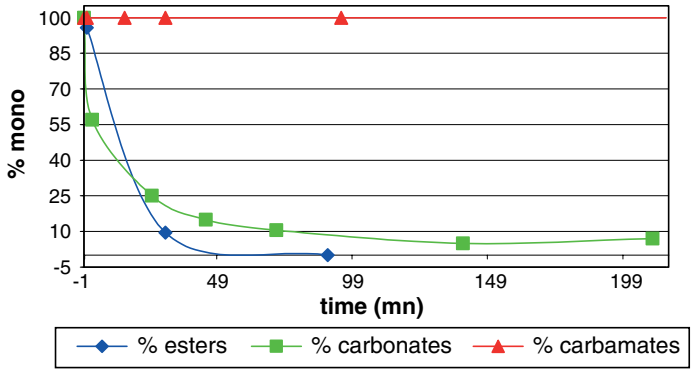
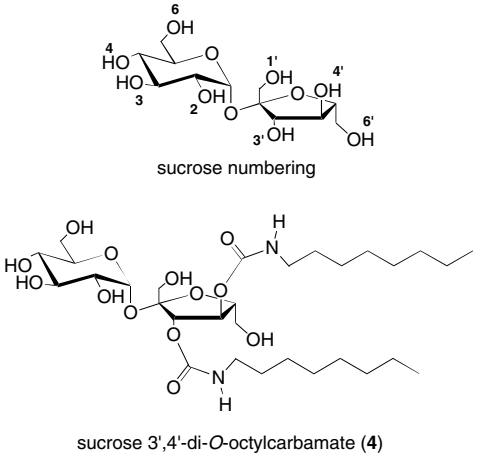


Figure 1. Comparison of the stability to hydrolysis in aqueous basic conditions of mono-*O*-octylcarbamates, octyl esters and octylcarbonates of sucrose (rt [sucrose derivative]$_{initial}$ = 50 mg/mL, NaOH: 1 equiv).



Scheme 2.

Increased regioselectivity and slower migrations compared to esters or carbonates led to more defined mixtures from which pure materials could be obtained by preparative HPLC. The study of the physicochemical properties (in particular the thermotropic liquid crystal properties) of these materials is in progress.

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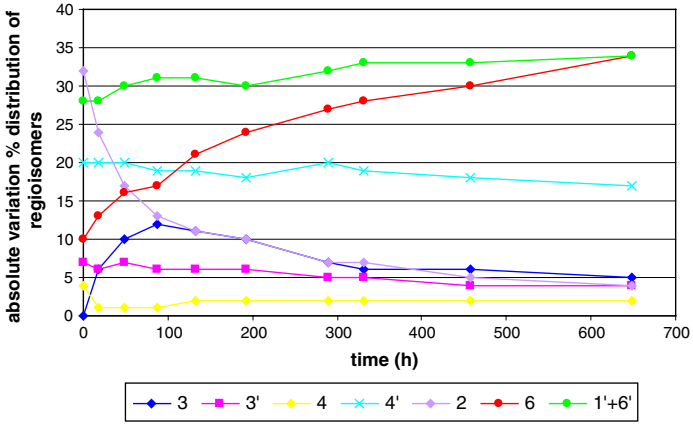

Figure 2. Evolution of the distribution of regioisomers of mono-*O*-octylcarbamates of sucrose (**3a**) in basic aqueous medium (rt [**3a**]$_{initial}$ = 50 mg/mL, NaOH: 1 equiv).

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10. Typical procedure used for the preparation of sucrose carbamates: to a stirred solution of sucrose (5 mmol, 1.71 g, 1 equiv) in a mixture of water/co-solvent (1/1 in weight) at room temperature was added sodium hydroxide (2.5 mmol, 0.1 g, 0.5 equiv) and octyl isocyanate (2.5 mmol, 0.4 g, 0.5 equiv). The reaction was considered finished when the analytical yield of mono- and dicarbamates of sucrose determined by HPLC remained constant over 30 min. The solution was neutralised with 0.5 M aqueous HCl solution and the crude mixture was evaporated to dryness and submitted to silica gel chromatography (as a solid mixture adsorbed on silica gel). Two fractions were isolated: di-*O*-octylcarbamates of sucrose ($R_f = 0.30$–0.55); mono-*O*-octylcarbamates of sucrose (**3a**, $R_f = 0.10$–0.25). Eluent for the TLC and flash chromatography: dichloromethane/methanol/acetone/water (67/15/15/3). HPLC: for monosubstituted products: Nucleosil NH_2 column with CH_3CN/water (86/14), flow 0.8 mL/min, RI detection and for disubstituted products Nucleosil C_8 column with methanol/water (78/22), flow rate 0.8 mL/min. Competitive carbamation of the alcohol (co-solvent) and/or hydrolysis to urea could be estimated on the same column. Polysubstitution, when present, was estimated by TLC (distinctive less polar spots).
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12. Data for mono-*O*-octylcarbamate sucrose derivatives. Elemental analysis for $C_{21}H_{39}O_{12}N{\cdot}1.4H_2O$: Calcd: C, 48.3; H, 8.1; N, 2.7. Found: C, 48.3; H, 7.9; N, 2.8. ^1H NMR (500 MHz, D_2O), ^{13}C (75 MHz, D_2O) NMR and 2D NMR (COSY, HSQC and HMBC) of pure or partially separated regioisomers (semi-preparative HPLC) allowed the identification of some isomers. Consistent effects on chemical shifts were observed in ^1H (ca. +1 ppm for the proton on the carbon atom involved in the carbamate linkage) and in ^{13}C NMR (ca. +1 to 2 ppm for the carbon atom directly connected to the carbamate function, and ca. −2 to 3 ppm for the neighbouring carbon atoms). Mono-4-*O*-octylcarbamate of sucrose: ^1H NMR (500 MHz, D_2O) δ (ppm): 0.80 (m, 3H, CH_3–(CH_2)–); 1.23 (br s, 10H, 5-(CH_2)–); 1.43 (m, 2H, –CH_2–(CH_2–NH–)); 3.05 (m, 2H, –CH_2–(NH)–); 3.54–3.65 (m, 5H, $2H_{1'}$, $2H_6$ and H_2); 3.70–3.84 (m, 3H, $H_{5'}$ and $2H_{1'}$); 3.86 (t, 1H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H_3); 3.92 (m, 1H, H_5); 3.98 (t, 1H, $J_{3',4'} = J_{4',5'} = 8.5$ Hz, $H_{4'}$); 4.15 (d, 1H, $J_{3',4'} = 8.5$ Hz, $H_{3'}$); 4.53 (t, 1H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H_4); 5.38 (d, 1H, $J_{1,2} = 3.5$ Hz, H_1); ^{13}C NMR (125 MHz, C_5D_5N) δ (ppm): 12.7 (CH_3); 21.2, 25.5, 27.9, 28.0, 28.7, 30.4, 39.8 ($7CH_2$); 60.3 (C6); 61.5 (C6′); 62.8 (C1′); 71.0 (C3); 71.2 (C4); 71.5, 71.8 (C5′ and C2); 74.0 (C4′); 77.7 (C3′); 81.8 (C5′); 91.5 (C1); 104.4 (C2′); 158.0 (C=O). Mono-2-*O*-octylcarbamate of sucrose: ^1H NMR (500 MHz, D_2O) δ (ppm): 0.82 (m, 3H, CH_3–(CH_2)–); 1.26 (s large, 10H, 5-(CH_2)–); 1.46 (m, 2H, –CH_2–(CH_2–NH–)); 3.07 (m, 2H, –CH_2–(NH)–); 3.36 (d, $J = 12$ Hz, 1H, $H_{1'b}$); 3.49 (d, $J = 12$ Hz, 1H, $H_{1'a}$); 3.52 (m, 1H, $J_{3,4} = J_{4,5} = 9.8$ Hz, H_4); 3.76 (m, 6H, $2H_6$, $2H_{6'}$, H_5 and $H_{5'}$); 3.87 (t, 1H, $J_{3,4} = J_{4,5} = 9.8$ Hz, H_3); 3.99 (d, 1H, $J_{3',4'} = J_{4',5'} = 8.5$ Hz, $H_{4'}$); 4.18 (d, 1H, $J_{3',4'} = 8.5$ Hz, $H_{3'}$); 4.43 (dd, 1H, $J_{1,2} = 3.5$ Hz and $J_{2,3} = 10.1$ Hz, H_2); 5.44 (d, 1H, $J_{1,2} = 3.5$ Hz, H_1); ^{13}C NMR (75 MHz, D_2O) δ (ppm): 14.2 (CH_3); 23.0–43.3 ($7CH_2$); 60.6 (C6); 61.5 (C1′); 62.7 (C6′); 69.7 (C4); 70.8 (C3); 72.8 (C5); 73.5 (C2); 74.2 (C4′); 76.0 (C3′); 82.0 (C5′); 90.4 (C1); 104.4 (C2′); 157.5 (C=O). Mono-3′-*O*-octylcarbamate of sucrose: ^1H NMR (500 MHz, D_2O) δ (ppm): 0.80 (m, 3H, CH_3–(CH_2)–); 1.23 (br s, 10H, 5-(CH_2)–); 1.44 (m, 2H, –CH_2–(CH_2–NH–)); 3.07 (m, 2H, –CH_2–(NH)–); 3.38 (t, 1H, $J_{3,4} = 9.5$ Hz, H_4); 3.47 (dd, 1H, $J_{1,2} = 3.5$ Hz and $J_{2,3} = 9.8$ Hz, H_2); 3.55–3.65 (m, 2H, $2H_{1'}$); 3.61 (t, 1H, $J_{2,3} = J_{3,4} = 9.8$ Hz, H_3); 3.70–3.83 (m, 5H, $2H_{6'}$ and $2H_6$ at H_5); 4.00 (m, 1H, $H_{5'}$); 4.21 (t, 1H, $J_{3',4'} = J_{4',5'} = 7.9$ Hz, $H_{4'}$); 5.12 (d, 1H, $J_{3',4'} = 7.9$ Hz, $H_{3'}$); 5.37 (d, 1H, $J_{1,2} = 3.5$ Hz, H_1); ^{13}C NMR (75 MHz, D_2O) δ (ppm): 14.0 (CH_3); 22.7, 26.7, 29.2(2), 29.4, 31.8, 41.1 ($7CH_2$); 60.5 (C6); 62.3 (C6′); 63.1 (C1′); 69.6 (C4); 71.4 (C2); 72.9 (C5 at C4′); 73.7 (C3); 77.0 (C3′); 81.9 (C5′); 93.1 (C1); 103.0 (C2′); 158.0 (C=O).
13. Same methods as in Refs. [10] and [12]. Major isomer, Di-3′,4′-*O*-octylcarbamate of sucrose: MS (HR, LSIMS): Calcd for $C_{30}H_{56}O_{13}N_2Na$: 675.3680. Found: 675.3681. ^1H NMR (500 MHz, CD_3OD) δ (ppm): 0.89 (m, 6H, $2CH_3$–(CH_2)–); 1.30 (br s, 20H, 18-(CH_2)–); 1.48 (m, 4H, 2-CH_2–(CH_2–NH–)); 3.09 (m, 4H, 2-CH_2–(NH)–); 3.36 (t, 1H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H_4); 3.41 (dd, 1H, $J_{1,2} = 3.5$ Hz and $J_{2,3} = 9.8$ Hz, H_2); 3.56 (d, 1H, $J = 12.3$ Hz, $H_{1'a}$); 3.61 (d, 1H, $J = 12.3$ Hz, $H_{1'b}$); 3.62 (t, 1H, $J_{2,3} = J_{3,4} = 9.8$ Hz, H_3); 3.70–3.92 (m, 5H, H_5, $2H_6$ at $2H_{6'}$); 3.99 (m, 1H, $H_{5'}$); 5.25 (t, 1H, $J_{3',4'} = J_{4',5'} = 7$ Hz, $H_{4'}$); 5.36 (d, 1H, $J_{3',4'} = 7$ Hz, $H_{3'}$); 5.45 (d, 1H, $J_{1,2} = 3.5$ Hz, H_1); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm): 13.4(2) (CH_3); 22.7–41.0 ($14CH_2$); 61.5 (C6); 62.0 (C6′); 63.8 (C1′); 70.4 (C4); 72.2 (C2); 73.4 (C5); 73.8 (C3); 75.4 (C4′); 76.8 (C3′); 81.7 (C5′); 92.4 (C1); 104.4 (C2′); 156.7 and 156.8 2 (C=O).