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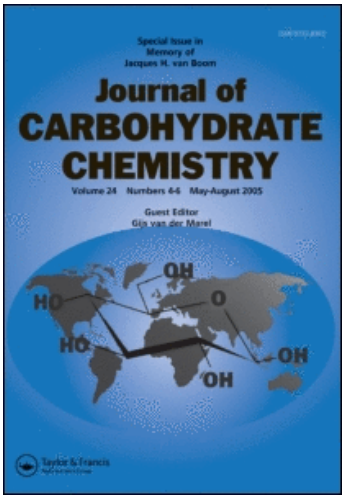

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
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To cite this Article Kretzschmar, Gerhard(2000) 'Large Scale Synthesis and Properties of the Novel Sucrose Aspartate Surfactants', Journal of Carbohydrate Chemistry, 19: 7, 879 — 889
To link to this Article: DOI: 10.1080/07328300008544124
URL: http://dx.doi.org/10.1080/07328300008544124

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J. CARBOHYDRATE CHEMISTRY, 19(7), 879-889 (2000)

LARGE SCALE SYNTHESIS AND PROPERTIES OF THE NOVEL SUCROSE ASPARTATE SURFACTANTS

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Received August 18, 1999 - Final Form May 30, 2000

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ABSTRACT

Sucrose aspartates were synthesised on kg-scales using a simple, high-yielding one-pot procedure from inexpensive sucrose, fatty amines and maleic anhydride and tested for their physical properties. Mostly being derived from renewable resources, these novel biodegradable surfactants provided favourable application properties.

INTRODUCTION

The current world surfactants market today (excluding soap) is in excess of 10 million tons with growth to almost 14 million tons by the year 2005.[1] By far most of these products are made from petrochemicals. However, especially in Europe the use of readily biodegradable ingredients for surfactants – like the alkyl polyglycosides (APGs)[6b] from glucose and palm kernel or coconut oil – have become commercially more important.[2] A large number of approaches have been reported to use carbohydrates, in particular very inexpensive sucrose, as hydrophilic components in surfactants. However, no specific, direct derivatives have became available with high yield and little

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downstream processing.[3] Nevertheless, the production capacities for sucrose fatty acid esters is being increased due to strong demand for these physiologically favourable products, and in particular up to 5000 tons of esters with a high DS value (Degree of Substitution) are used as food emulsifying agents, e.g. in bread, ice-cream, fat substitutes, canned drinks and margarine.[1] The breadth of applications may be varied easily over a wide range of HLB values (Hydrophilic/Lipophilic Balance) by adjusting the DS value and the length of the lipophilic chain, thus providing a host of functional uses in detergents,[4] as dispersing and wetting agents, as adjuvants in delivery systems for active ingredients[5] or in cosmetic formulations.[6] Many investigations have been carried out using the commercially available sucrose laurates.[5] The ongoing interest in overcoming the disadvantages in availability and price as well as the potential broad uses of sugar esters stimulates the design and synthesis of novel carbohydrate-based surfactants. However, a closer look at the respective manufacturing processes reveals that either multi-step reactions,[7a-d] high reaction temperatures (typically up to 110 °C)[7e] or tedious work-up manipulations are required.[7a-e] Therefore, I devised a rewarding new approach towards an inexpensive and high-yielding process that is simple and industrially relevant. This process provides the novel sucrose aspartates **1**, mostly derived from renewable, non-petrochemical resources, and in particular from cheap sucrose and fatty amines. The aspartate moiety was introduced *via* inexpensive maleic anhydride to serve as an activator and linker group for the renewable two main components. Moreover, the anionic aspartate and additional maleate groups in **1b** provided improved water solubility at the same time. This strategy stands in contrast to other approaches being directed to compensate for some solubility problems of sucrose esters, e.g. by additional sulfonation[7a] or oxidation reactions.[7c] Surprisingly, an extensive patent and literature research revealed that these rather simple target compounds **1** have not been explicitly described up to now.[8,17]

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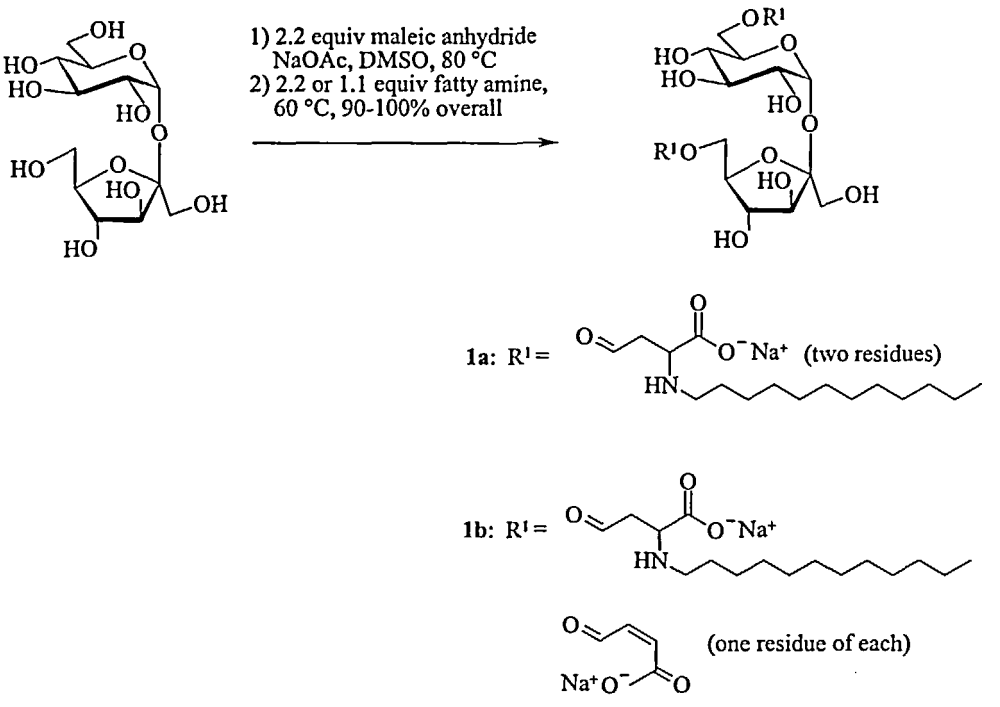
RESULTS AND DISCUSSION

The syntheses of the sucrose aspartates **1** was readily accomplished on kg-scales as outlined in Scheme 1. Either DMSO or DMF could be used with equal success for the



SCHEME 1

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acylation step with maleic anhydride, but DMSO was preferred as a safer and less expensive solvent.[16]

At least 2.2 equivalents of the anhydride and of sodium acetate were required to convert the sucrose completely into the sodium salts of the known maleate ester intermediates[9] which were not isolated. The final products were directly obtained upon reaction with a stoichiometric amount of the respective fatty amine in 90-100% overall yield. In general, the primary hydroxyls at C-6 and C-6′ showed higher reactivity in esterifications of sucrose to give the 6,6′-diesters[10] and reactions at the remaining 1′-hydroxyl group may account for the 10% quantity of maleic anhydride exceeding the 2 equivalents that were needed here. Therefore – anticipating no specific preference for the *Michael* addition of the primary amine – the expected main components of the product mixture are as drawn in Scheme 1. For all practical purposes the inexpensive coconut

Table 1. CMC and σ_{min} values for compounds 1[a]

Compound	CMC [mol/L]	σ_{min} [mN/m]
$C_{12}H_{25}NaSO_4$ (SLS)	$8.6 \cdot 10^{-3}$	37.4
1a	$1.0 \cdot 10^{-3}$	29.7
1b	$4.3 \cdot 10^{-4}$	36.5
water (2x dist.)	-	72.4

a. Measured at 22 °C with a tensiometer according to the method of Du Nouy.[12]

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fatty amine fractions containing predominantly C-12 alkyl chains can be used, whereas for analytical purposes the pure C-12 fatty amine (lauryl amine) has been employed.

Two representative product mixtures were characterised by electrospray ionisation mass spectrometry (ESI-MS), ^{1}H NMR and elemental analysis. All spectra were well in accord with the proposed main molecular compositions as given in Scheme 1. ESI-MS was complicated by intense cluster ion formation, but the predominant presence of the mono- and disubstituted sucrose aspartates could be confirmed. The average DS values, with respect to the fatty amine moieties, ca. 2 for **1a** and 1 for **1b**, were further established by integration of the ^{1}H NMR spectra and by elemental analysis.

Several simple application assays were performed to establish the utility of the compositions **1a** and **1b**. Their critical micelle concentration (CMC) values were measured in comparison to a standard compound sodium lauryl sulfate (SLS), to describe the relative proportion of the surfactant's monomeric and micellar forms which depend on the balance between hydrophilic repulsion and hydrophobic attraction forces.[12] With regard to some desired application properties for surface-active compounds, the lower substitution degrees ranging from DS 1.1 to DS 2.2 are much preferred. The products **1a** and **1b** were found to reduce the surface tension of water to about 30 mN m^{-1} at a CMC of ca. 1.0 mM. (Table 1).

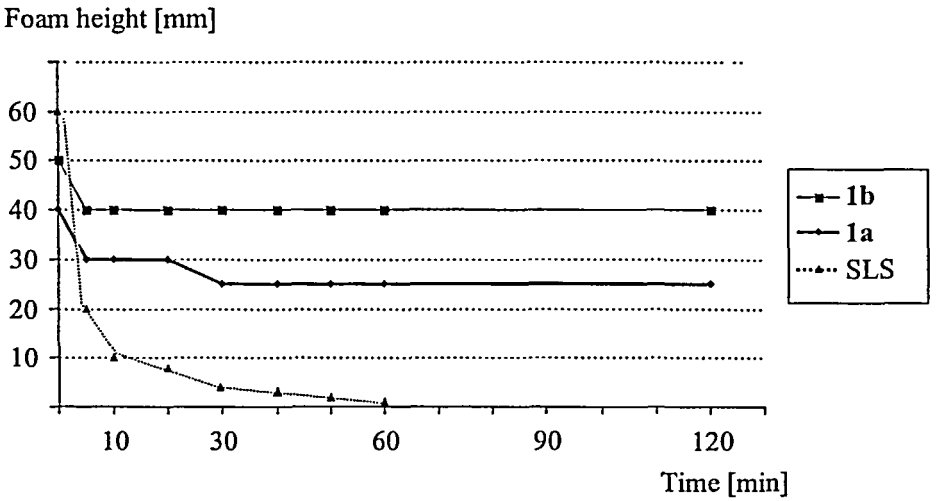

Figure 1. Foam height and stability according to the Ross-Miles test at 25 °C.[7b]

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The Ross-Miles test[7b] was used to measure the foam height and stability that can be achieved with solutions containing the surfactants **1a** or **1b**. From Figure 1 it can be seen that these sucrose aspartates provided excellent foams exceeding the sodium lauryl sulfate standard. After a small decline within 5 minutes, the microporous foams remained virtually stable just until the water disappeared by evaporation.

Other simple standard application assays provided evidence for the sucrose aspartate's ability to improve the solubility of certain active ingredients (Tables 2 and 3).

The sucrose aspartates **1** share a certain hydrolytic lability together with the known surface active fatty acid esters of sucrose, especially at higher temperatures. Figure 2 describes the autohydrolysis of **1a** starting at pH 10.1 due to the two basic functions being present in the molecule. However, in practice and in contrast to conventional sucrose esters, the compounds **1** were just hydrolysed to sucrose and the known[14] amphoteric *N*-alkyl aspartic acids. Hydrolytic lability, of course, is less pronounced with the transacylation products of *N*-methylglucamine and fatty acid methyl esters, but in general higher reaction temperatures and more process steps are required to prepare these products.[11] Furthermore, sucrose is much less expensive than glucose and starches. Estimated total material expenses per kilogram of **1b** are about Euro 1.45 using inexpensive coconut fatty amine fractions (Genamin® types).

Table 2. Assay to measure the surfactant's ability to solubilise Sudan Red B in water at the given concentrations.

	extinction coefficient [516 nm]		
% (w/w)	caprylate[a]	**1a**	**1b**
0.0	0.000	0.000	0.000
0.3	n.d.	0.0495	0.0253
0.6	0.0654	0.0997	0.0571
1.2	0.1513	0.1603	0.1003

a. Caprylate refers to oxidised sucrose caprylate.[7c]

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Table 3. Assay to measure the ability of **1a** to solubilise α-tocopherol in water.

	extinction coefficient
1a [mg]	[290 nm]
0	0.0115
75	0.6997
150	0.9005
300	0.9819

In summary, it is expected that the novel sucrose aspartates **1** described here may provide a viable, sound alternative to some other specialty surfactants currently being used in many industrial applications. Due to the simplicity of the overall chemical process described here there should be no serious technical hurdles to perform these reactions in larger vessels.

EXPERIMENTAL

General. Thin-layer chromatography (TLC) was carried out on precoated Kieselgel 60 F_{254} plates (0.25 mm thickness, E. Merck). Spots were visualised by

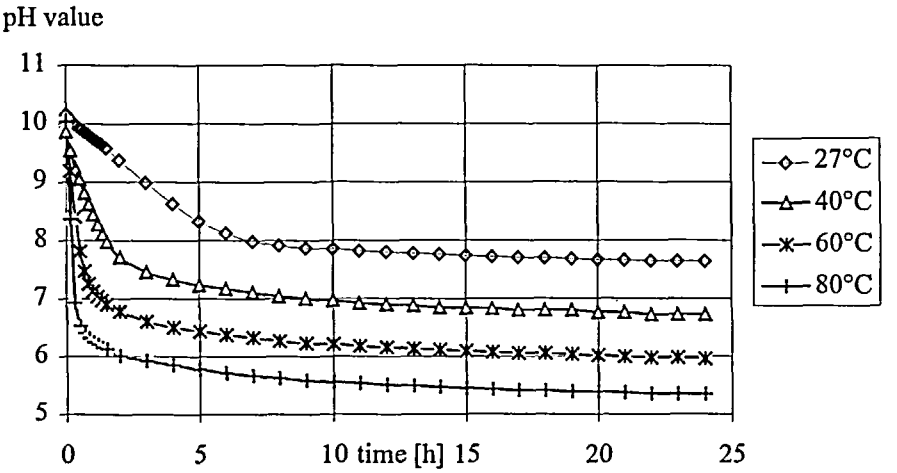

Figure 2. Autohydrolysis of **1a** in water (3% w/w) in dependence of the temperature.

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spraying the plates with sulfuric acid/anisaldehyde reagent, followed by heating. NMR spectra were recorded on a Bruker WT 400 (400 MHz). NMR chemical shifts are given as δ-values with reference to tetramethylsilane (TMS) as an internal standard, if not otherwise noted. Mass spectra were recorded on a Finnigan/MAT LCQ (ion trap spectrometer) using electrospray ionisation (ESI). CMC and σ_{min} values were measured using a tensiometer from Lauda (Lauda-Königshofen, type TD1). UV spectra were recorded on a CARY 1 instrument from Varian. IR spectra were recorded using the neat substances on a Perkin Elmer FT-IR spectrometer (Paragon 1000) using an ATR unit.

Synthesis of 1a. Sucrose (600.0 g, 1.752 mol) was dissolved in anhydrous dimethyl sulfoxide (DMSO, 1.5 L) at 80 °C. Sodium acetate (316.3 g, 3.86 mol, 2.2 equiv) and then maleic anhydride (378.1 g, 3.86 mol, 2.2 equiv, in portions) were added and the mixture was stirred for 2 h at 80 °C. TLC monitoring (1-propanol/ acetic acid/water = 80/12/3 v/v/v) indicated that the sucrose was completely consumed. ^1H NMR analysis of a sample showed a very small amount of residual maleic anhydride (6.30 ppm) and the two maleate protons (5.90 and 6.70 ppm) of the maleate sucrose being formed.

Then Genamin® 12 R 100 D (747.0 g, 4.03 mol 2.3 equiv, based on $C_{12}H_{27}N$ from Clariant AG, Division Tenside, Gendorf, Germany, >90% C-12, lot number

106504710) was added and stirring continued for 3 h at 80 °C, whereby some solid material started to precipitate. The diluted reaction mixture (DMSO, 0.5 L) was cooled to down to 60 °C and decanted under stirring into ethyl acetate. The precipitate was filtered, washed with ethyl acetate and dried in vacuo at 60 °C to give 1.77 kg; 97.8% on a mass basis, 99.6% on a molar basis, DS = 2.2 [$C_{47.2}H_{83.6}Na_{2.2}N_{2.2}O_{17.6}$; 1014.2 g/mol].

For analytical purposes, the synthesis was repeated using pure *n*-dodecylamine (Merck, >98%). ^1H NMR analysis in $CDCl_3/CD_3OD$ showed quite broad signals. Integrations were consistent with a DS of ca. 2.0: δ = 1.85 (t, CH_3), 1.25 (m, C_9H_{18}), 2.6-3.3 (m, CH_2NCHCH_2), 2.30-5.40 (sucrose).

Elemental analysis: N (found) 2.7% (calcd 2.9% for DS = 2.0 and 3.0% for DS = 2.2), Na (found) 4.2% (calcd 4.8% for DS = 2.0 and 4.9% for DS = 2.2).

ESI-MS (negative mode): $[M_1\text{-}H]^-$ = 624 (M_1: $C_{28}H_{51}NO_{14}$; 625); $[M_2\text{-}H]^-$ = 907 (M_2: $C_{44}H_{80}N_2O_{17}$; 908); $[2M_1\text{-}H]^-$ = 1249; $[(2M_1\text{-}2H+Na]^-$ = 1271; ESI-MS (positive mode): $[M_1+H]^+$ = 626; $[M_1+Na]^+$ = 648; $[M_2+H]^+$ = 909; $[2M_1+H]^+$ = 1251; IR: 2918, 2849, 1734, 1637, 1560, 1396, 1135, 1051, 993, 855, 720, 650 cm^{-1}.

Synthesis of 1b. The intermediate sucrose maleate was prepared as described above. Genamin® 12 R 100 D (373.6 g, 2.01 mol 1.15 equiv, based on $C_{12}H_{27}N$, from Clariant AG, Division Tenside, Gendorf, Germany, >90% C-12, lot number 106504710) was added and stirring continued for 3 h at 80 °C, whereby some solid material started to precipitate. The diluted reaction mixture (DMSO, 0.5 l) was cooled to 60 °C and decanted under stirring into ethyl acetate. The precipitate was filtered, washed with ethyl acetate and dried in vacuo at 60°C to give 1.29 kg (89.8% on a mass basis; 90.9% on a molar basis for DS = 1.1 (corresponding to $C_{34}H_{53.9}Na_{2.2}N_{1.1}O_{17.6}$; 810.3 g/mol).

For analytical purposes, the synthesis was reproduced using pure *n*-dodecylamine (Merck, >98%). ^1H NMR ($CDCl_3/CD_3OD$) was consistent with DS ca. 1.0 based on integrations of maleate protons (5.90 and 6.70 ppm), CH-sucrose and the N-dodecyl protons.

IR: 3263, 2921, 2850, 1718, 1578, 1560, 1406, 1134, 1050, 993, 854, 670, 602 cm^{-1}.

ESI-MS (negative mode): $[M_1\text{-}H]^-$ = 722 (M_1: $C_{32}H_{53}NO_{17}$; 723); $[M_2\text{-}H]^-$ = 820 (M_2: $C_{36}H_{55}NO_{20}$; 821); instead of mass 907 ($C_{44}H_{80}N_2O_{17}$; 908) as for **1a**, here

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mass $[M_3\text{-}H]^-$ = 1103 (M_3: $C_{52}H_{84}N_2O_{23}$; 1104) appeared which would incorporate two further maleate residues).

Elemental analysis: C (found) 51.9% (calcd 50.3%) N (found) 2.1% (calcd 1.9%) Na (found) 5.8% (calcd 6.2%) Percentages were calculated for the composition $C_{34}H_{53.9}Na_{2.2}N_{1.1}O_{17.6}$ (810.3 g/mol) which corresponds closely to the main component as drawn with formula **1b**.

Application Testing by Physicochemical Measurements

Surface Activity. The critical micelle concentrations (CMC) and surface tensions (σ_{min}) were measured according to the ring-method from De Nouy[12] (ASTM D 971, DIN 53914, results see Table 1).

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Foam Height and Stability. The Ross-Miles test (ASTM D1173-53) was used to measure the foam height and stability of **1a,b** in comparison with sodium lauryl sulfate (SLS).[7b] Briefly, 200 mL of a 0.1% solution of surfactant contained in a pipette with a 2.9 mm i.d. orifice was allowed to fall 90 cm onto 50 mL of the same solution contained in a cylindrical vessel maintained at 25 °C. The height of the foam produced in the cylindrical vessel was read immediately after all the solution was run out of the pipette (initial foam height IFH at t= 0) and then again after the given amounts of time. By using this method, the data shown in Figure 1 were provided.

Compounds 1 in general created microporous foams providing a non-irritating, very pleasant skin feeling.

Solubilisation Assays. Solutions containing 0.075 g, 0.150 g and 0.300 g of **1a** or **1b** in 25 mL water and 12.5 mg of Sudan Red B were sonicated at 20 °C. The suspension was centrifuged for 70 min at 7500 U/min and filtered through a membrane (regenerated cellulose, 0.2 μm). The extinction coefficient of the clear solution was determined at 516 nm wavelength (1 cm cuvette) compared to a blank sample obtained from 12.5 mg Sudan Red B in 25 mL water (Table 2). In a similar manner the ability of **1a** to solubilise α-tocopherol[13] (vitamin E, 12.5 mg) in water (25 mL) was determined (Table 3). In a neat formulation, 50 mg of tocopherol could be completely absorbed in 150 mg of **1a**.

Autohydrolysis in Water. The pH decrease of a 3% (w/w) solution of **1a** in water at different temperatures was measured using a pH electrode. The data are plotted in Figure 2.

Biodegradability. Compound **1a** was tested in an external laboratory[15] and found to be easily biodegradable under aerobic conditions. The modified *Sturm* test according to OECD guideline 301B showed a CO_2-mineralisation degree of 66.3% after 28 days at 22 °C, sodium acetate being used as a control (63%). The *Sapromat* test according to DIN V 54900 (part II, procedure 1) showed an O_2-mineralisation degree of 66.6% after 28 days at 22°C, Avicel® being used as the control (81%).

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ACKNOWLEDGEMENT

The author thanks M. Rheinschmitt for his careful technical assistance.

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of the maleate esters. Another application (*DE Patent* 2739343, abandoned, Bayer AG) suggested the preparation of related compounds by transesterifications of *N*-alkylaspartates with sucrose. However, no analytical evidence was provided there for the formation of sucrose aspartates. By reproducing the procedures described there, some careful analysis unambiguously revealed the formation of other products in our hands.

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15. Some more detailed test results are available upon request from the author.
16. The Expert Working Group of the International Conference on Harmonisation (including the USFDA) has classified DMSO in the safest group of solvents. DMSO can be recycled and is used as a reaction solvent by many pharmaceutical manufacturers.
17. A patent application covering the present inventions has been filed: PCT/EP/99/01619.

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