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Efficient and Versatile Flow Synthesis of New Nonionic Glucamide Surfactants

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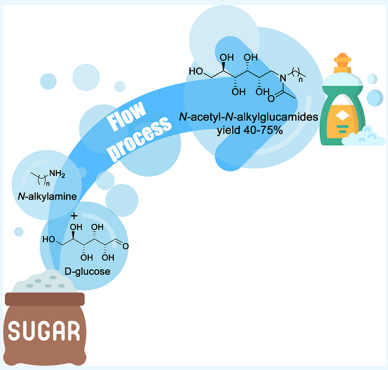
ABSTRACT: Surfactants are virtually used across all industries where they can fulfill a multitude of roles, such as detergents, emulsifiers, and dispersants, as well as wetting, foaming, and flotation agents. *N*-Acyl-*N*-alkyl-D-glucamides are nonionic surfactants that can be synthesized from inexpensive natural resources. They have a broad range of hydrophilic−lipophilic balance (HLB) values, depending on the length of the alkyl chain. This chemical diversity and versatility allow customization of surfactant properties, making these chemicals useful for a diverse range of industrial purposes. In this work, six *N*-acyl-*N*-alkyl-D-glucamides have been prepared by exploiting immobilized scavengers and reagents in a flow-batch mode. Moreover, the interfacial properties (both surface and interfacial tensions) of two selected glucamide-based surfactants were evaluated.



INTRODUCTION

Surfactants are amphiphilic organic compounds characterized by a polar headgroup and a nonpolar chain that are widely used in the pharmaceutical, food, and personal care industries owing to their physicochemical and functional properties.[1−3] In fact, they possess the ability to alter surface and interfacial properties and to self-associate and solubilize themselves in micelles. These properties provide the means to apply surfactants in wettability modification, detergency, and stabilization and destabilization of dispersions, including foams, froths, and emulsions. Their importance in our daily life is reflected in the increased production of these compounds: the surfactants market size is estimated at 18.25 million tons in 2024 and is expected to reach 21.52 million tons by 2029, growing at a compound annual growth rate (CAGR) greater than 3.30% during the forecast period (2024−2029).[4] Most surfactants on the market today are made from nonrenewable resources such as crude oil. Since crude oil stocks may be exhausted, several attempts are being made to replace such petroleum-based compounds with biomass-based alternatives to lower the carbon footprint of surfactant production.[5−11] From a chemical point of view, surfactants can be classified, according to the charge of their polar headgroup, as anionic, cationic, zwitterionic, and nonionic surfactants. Nonionic surfactants represent about 45% of the overall industrial production of surfactants, and among them, surfactants with a sugar headgroup linked with an alkyl chain represent an important class of compounds that can be synthesized from inexpensive natural resources and over a wide range of hydrophilic−lipophilic balance (HLB) values, which result in tunable surfactant properties, depending on carbon chain length and the nature of the sugar headgroup.[12−14] Sugar-based surfactants (i.e., sorbitan esters, sucrose esters, and alkyl polyglycosides) are widely used in a variety of areas such as detergent, medicine, food, personal care products, cosmetics, and agrochemicals, thanks to their properties such as high surface activity, excellent biodegradability, low toxicity, and high environmental and dermatological compatibility.[10] Moreover, important advantages of sugar-based surfactants are that they do not pose significant hazards in terms of acute or chronic toxicity to human health and the environment[15] and can be derived from renewable sources.[16,17] However, traditional chemical syntheses of sugar-based surfactants typically require long synthetic pathways and still rely on toxic reagents and solvents and harsh reaction conditions, resulting in high energy consumption, low regioselectivity, and formation of undesirable byproducts.[18] A biocatalyzed approach could help to overcome these limitations, thanks to its potential for developing more selective and environmentally friendly procedures. Researches

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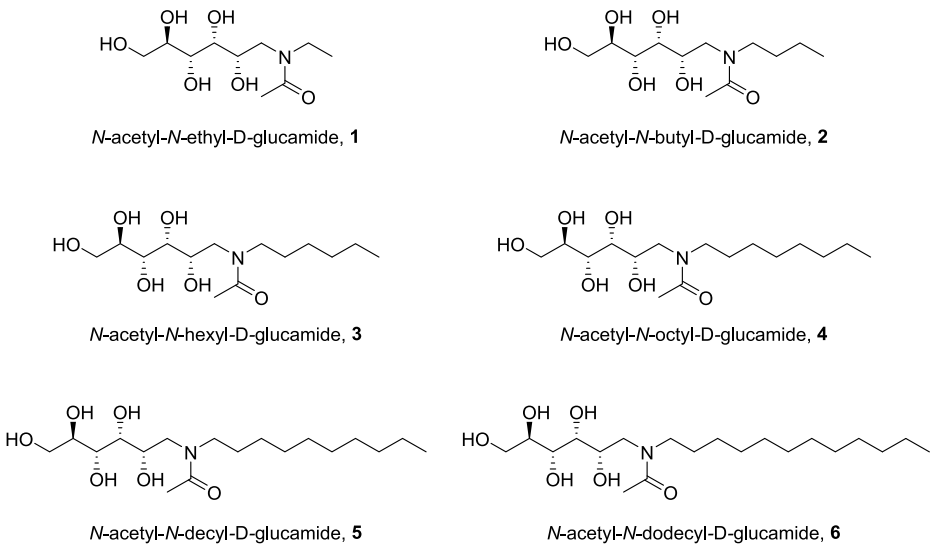
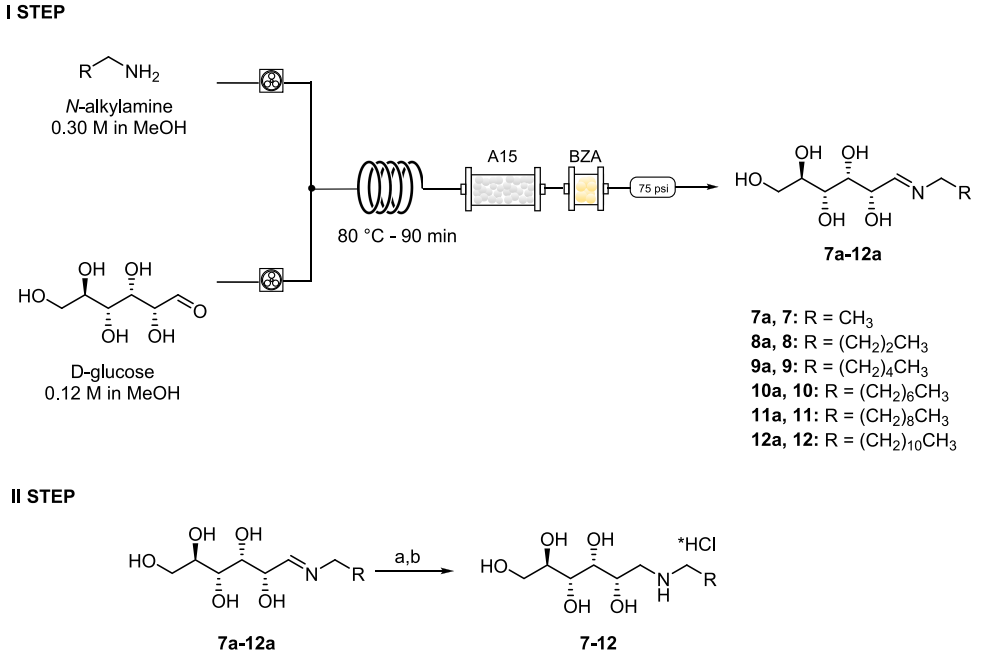


Figure 1. Structures of synthesized glucamides **1**−**6**.

Scheme 1. Synthesis of *N*-Alkyl-D-Glucamines 7−12[a]



[a]Reagents and conditions (II Step): a) immobilized $NaBH_4$ (1.5 equiv), MeOH, r.t., o.n.; b) 4 M HCl in dioxane, MeOH, T = 65 °C to room temperature.

in this field are mainly focused on the esterification of sugars with fatty acids catalyzed by lipases.[19,20] However, the primary challenges in the enzymatic synthesis of sugar-based surfactants are the opposite solubility profile of substrates, low reaction yields, and prolonged reaction times. Among sugar-based surfactants, fatty acid glucamides or *N*-methylglucamides (NMGAs) are increasingly being used due to both their performance and mildness in laundry/dishwasher detergents/personal care products and environmental compatibility. The typical synthesis of NMGAs relies on the reaction between glucose and methylamine to form *N*-methylglucamine, which is further converted into the respective fatty acid amide.[10] The biocatalyzed acylation of *N*-methylglucamine with different acyl donors has been reported both in solvent[21] and *solvent-free* systems.[16] However, the formation of diacylated products was observed, and these reactions are generally very slow (40−50 h). In this context, we proposed an alternative strategy to circumvent the issues mentioned above by combining the efficiency of reductive amination (even with long-chain alkylamines) with the advantages of flow chemistry. A novel protocol for the synthesis of six *N*-acetyl-*N*-alkyl-D-glucamides was designed by exploiting immobilized scavengers and reagents in a flow-batch mode (compounds **1**−**6**, Figure 1). The protocol includes a reductive amination reaction starting from glucose, followed by the acylation of the nitrogen to obtain the desired glucamide. Flow technology offers numerous benefits compared to traditional batch processes, including enhanced heat and mass transfer, improved mixing, reduced reaction times, and increased reactor efficiency and reproducibility. In line with Green Chemistry principles, the

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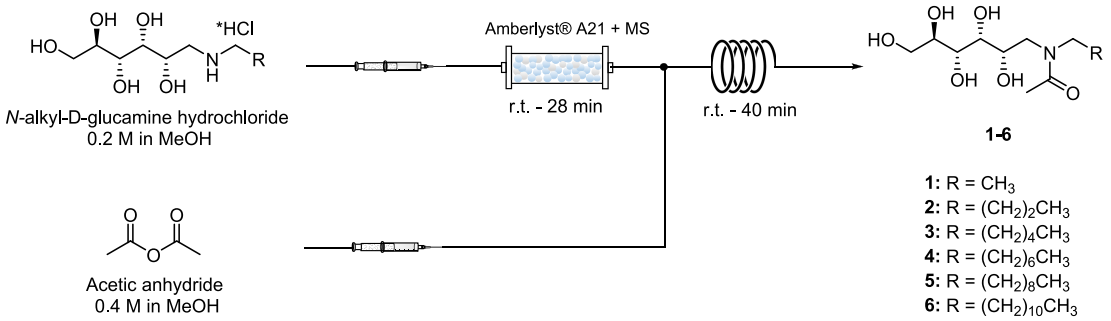
Scheme 2. Flow Synthesis of *N*-Alkyl-D-Glucamides 1−6



smaller footprints of flow reactors, along with more cost-effective solvent and reagent usage and the possibility to perform in-line workups and purifications, make this technology environmentally friendly. Additionally, flow technology is easily scalable and ensures safety.[22,23] Finally, the ability to reduce both the surface and interfacial tension of compounds **4** and **5** (having an HLB of 13.2 and 12.2, respectively) has been evaluated.[24]

RESULTS AND DISCUSSION

First, we focused on the synthesis of glucose-based amines **7**−**12** through a reductive amination reaction (Scheme 1). The reaction was preliminarily studied in batch, using *N*-ethylamine as a model amine and $NaBH_4$ as a reducing agent. The reaction requires an excess of *N*-ethylamine (i.e., 5 equiv) to obtain the full conversion of glucose (6 h, refluxing in methanol in a sealed tube). Then, after the mixture cooled to 0 °C, $NaBH_4$ was added, and the mixture was stirred at room temperature overnight. After this time, the suspension was quenched with water, and the organic solvent together with the amine were removed under vacuum. The crude product was then purified by ion-exchange chromatography using Amberlite IR-120 (H^+) and lyophilized. The batch protocol led to the isolation of the desired *N*-ethyl-D-glucamine **7** in moderate yield (40%). The use of a large excess of *N*-ethylamine was necessary to lead the reaction to completion, but in this case, due to the low boiling point of the amine, the excess was then easily removed under vacuum. However, this purification procedure was not as versatile for all the target *N*-alkyl-D-glucamines, and, in the case of high-boiling-point amines, the products were difficult to isolate in a pure form, being contaminated by the amine. Therefore, a novel flow-batch protocol integrated with an in-line purification procedure was designed for the synthesis of the desired glucamines **7**−**12** with the aim of increasing the efficiency, productivity, and safety of the protocol. Indeed, there is a high demand for effective flow-based methodologies for the majority of common reactions. In this case, flow chemistry also offers a significant advantage by reducing exposure to toxic chemicals such as *N*-alkylamines. In fact, the continuous flow system confines the reagents within a closed system, minimizing the risk of exposure, and the small volumes used in flow chemistry reduce the potential hazards associated with handling larger quantities of toxic substances in batch processes. Specifically, a solution of glucose in MeOH and a solution of *N*-ethylamine in MeOH were pumped into a 20 mL heated reactor coil. A back-pressure regulator was used to pressurize the system, and the reaction outcome, containing the imino-derivative **7a**, was collected in a flask. Keeping the temperature constant at 65 °C, and using a 1:1 ratio of glucose/*N*-ethylamine, an increase in the residence time from 30 to 90 min (i.e., 30, 45, 60, 90 min) showed a progressive improvement in the conversion of glucose (determined by ^1H NMR) to the imino-derivative **7a**. The optimal conversion (c) was achieved at 90 min (c = 55%). Then, the reaction temperature was varied between 65 and 80 °C (i.e., 65, 75, 80 °C). The highest conversion was reached at 80 °C (degree of conversion = 68%). Then, different molar ratios of glucose to *N*-ethylamine were also tested (1:2, 1:2.5, 1:3). The optimized experimental conditions led to the full conversion of the starting material by using 2.5 equiv of *N*-ethylamine in only 90 min of residence time, at 80 °C (Scheme 1, Step I). The reaction outcome, containing the imino-compound, was flowed through an unpowered Omnifit column reactor packed with the resin Amberlyst 15 (H^+), functionalized with strongly acidic groups, followed by a second glass column reactor containing Quadrapure BZA, functionalized with a benzylamine moiety. These resins acted as scavengers to catch unreacted amine and glucose, respectively, avoiding further work-up procedures and manual handling, thus increasing safety.

Then, immobilized $NaBH_4$ 10% *w*/*w* on an alumina support was added to the collected solution at room temperature, and the reaction mixture was stirred overnight. The choice to use $NaBH_4$ on an alumina support guaranteed improved safety and greatly simplified work-up procedures. In fact, after completion, the reaction mixture was filtered under vacuum, and the resulting solution was dried under reduced pressure. The obtained crude was dissolved in MeOH under heating, and then, 4 M HCl in dioxane was added to obtain the product as an insoluble hydrochloride salt (Scheme 1, Step II). All *N*-alkyl-D-glucamine hydrochloride **7**−**12** were successfully isolated in moderate to good yields (40−75%). The optimal yields were observed for medium-chain alkyl lengths (i.e., hexyl and octyl; yield = 65% and 75%, respectively), while shorter (butyl) and longer alkyl chains (decyl and dodecyl) resulted in lower yields (yield = 40%, 60%, and 45%, respectively).

First attempts to synthesize *N*-acyl-*N*-alkyl-D-glucamides **1**−**6** in batch were made by using *N*-ethyl-D-glucamine hydrochloride **7** as a model starting material. Vinyl acetate was employed as an acyl donor in the presence of Amberlite IRA 400 (OH^-) as a base, and the reaction mixture was refluxed for 48 h. Unfortunately, the reaction proceeded very slowly, leaving most of the starting material unreacted. Therefore, a biocatalyzed approach starting from the free base was investigated by using immobilized *Candida antarctica* lipase B (imm-CaLB) or immobilized lipase from *Thermomyces lanuginosus* (imm-TLL) in a water/vinyl acetate biphasic system (95/5% *v*/*v*) at 45 °C for 24 h. Only with imm-CaLB,

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the reaction led to the formation of the desired product but in a very low yield (<5%). Increasing the temperature (70 °C) and extending the reaction time (72 h) were not beneficial; again, a very low conversion was observed. A classical coupling reaction was tested by using DCC and DMAP, but the reaction again resulted in being very slow, leaving most of the starting glucamine **7** unreacted and leading to a complex mixture in which only traces of the product were tentatively detected. Finally, a new approach was exploited, by using acetic anhydride as an acyl donor in the presence of Amberlyst A21 as a supported base in dry MeOH. The product was isolated in 90% yield after stirring at room temperature for 5 h under nitrogen. On this basis, a flow protocol was developed (Scheme 2).

A solution of *N*-alkyl-D-glucamine hydrochloride **7** in dry MeOH was pumped by a syringe pump in a packed-bed column reactor containing a 1:1 mixture *w*/*w* of Amberlyst A21 and molecular sieves. Then, the exiting solution encountered a second flow stream of acetic anhydride in dry MeOH (stock solution kept at 0 °C), and the resulting mixture was flowed in a 10 mL unpowered reactor coil with a residence time of 40 min. *N*-Acetyl-*N*-alkyl-D-glucamides **1**−**6** were successfully isolated in quantitative yield without any further purification after solvent evaporation.

Only compounds **4** and **5** were used for surface and interfacial tension measurements because compounds **1**, **2**, and **3** (i.e., *N*-acetyl-*N*-ethyl-, *N*-acetyl-*N*-butyl-, and *N*-acetyl-*N*-hexyl-D-glucamide, respectively) have short alkyl chains, which hinder efficient stabilization of the water−air or oil−water interfaces, thus limiting the emulsifying properties of these glucamides. Compound **6** (*N*-acetyl-*N*-dodecyl-D-glucamide) was excluded because its HLB value of around 11 is borderline, indicating that the compound may exhibit partial solubility in both oil and water. Moreover, compounds **4** and **5** possess HLB values (HLB_4 = 13.2, HLB_5 = 12.2) similar to that of *N*-methylglucamides with C_{12}−C_{14} alkyl chains, a class of glucose-derived surfactants produced industrially and currently used as liquid dishwashing agents and liquid detergents.[10,25] Specifically, the ability of compounds **4** and **5** to reduce the air/water (Milli-Q) surface tension (γ) and the sunflower oil/water (Milli-Q) interfacial tension (IFT) was assessed using a Gibertini tensiometer, following the du Noüy ring method,[26] at increasing surfactant concentrations (from 0.05 to 3.0 mM). Figure 2 depicts the reduction in both surface and interfacial tension values as the concentration of *N*-acetyl-*N*-alkyl-D-glucamides increases. Compounds **4** and **5** significantly reduced the air/water surface tension (violet curves) from 72.8 to below 40.0 mN m^{-1}, with a plateau observed at 1.0 mM. This behavior is comparable to that of the commercially used nonionic surfactant Tween 80.[27] Additionally, *N*-acetyl-*N*-decyl-D-glucamide (compound **5**) resulted in lower γ values compared to compound **4**. The CMC values for both compounds are approximately in the range between 0.2 and 0.6 mM. Notably, for compound **4**, the CMC is roughly 2−3 times higher than that of the surfactant with the longer alkyl chain (compound **5**), as expected. Similar CMC values (1.6 and 4.8 mM) were obtained in the case of undecanoyl-[28] and decyl-*N*-methylglucamide,[29] respectively. For IFT measurements, a similar decreasing trend was observed (blue lines in Figure 2) for both samples. Particularly, *N*-acetyl-*N*-octyl-D-glucamide (compound **4**) reduced the sunflower oil/water IFT from 26 mN m^{-1}, the value without surfactants, to 3.9 mN m^{-1} at 3.0 mM. In contrast, compound **5** achieved a similar IFT reduction (3.4 mN m^{-1}) at a lower concentration of 1.0 mM and reached a plateau value of approximately 1.0 mN m^{-1} at 1.5 mM. The superior ability of compound **5** to reduce both surface and interfacial tensions is likely attributed to its longer alkyl chain, indicating higher surfactancy compared to compound **4**.

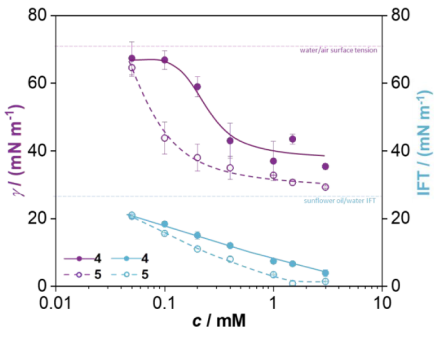

Figure 2. Water/air surface tension (violet curves) and sunflower oil/water interfacial tension (IFT, bluish curves) values at increasing concentrations of compounds **4** and **5**.

CONCLUSIONS

Surfactants play a significant role in various industries, and nowadays, there is an increasing demand for sustainable alternatives to petroleum-based compounds. Biomass-derived surfactants, such as glucamides, represent environmentally friendly substitutes due to their low toxicity and excellent biodegradability and compatibility.

By employing flow technology, we effectively address challenges associated with traditional batch processes, such as reaction time, safety, and purification. The integration of immobilized scavengers and reagents further simplifies the synthetic pathway, resulting in improved yields, safety, and reduced environmental impact. The successful isolation of *N*-acyl-*N*-alkyl-D-glucamides **1**−**6** without extensive purification, which are usually time- and solvent-consuming steps, underscores the potential of this technology for efficient surfactant production. While the initial reactions were conducted on a small scale, we successfully synthesized compounds **4** and **5** on a gram scale, thereby validating the scalability of our protocol and demonstrating that the flow synthesis method can be effectively scaled up, supporting its broader applicability. As the global demand for eco-friendly products continues to grow, the adoption of such innovative synthetic strategies will be crucial in meeting both consumer needs and environmental standards. The interfacial features of both compounds **4** and **5** were evaluated, showing the superior properties of *N*-acyl-*N*-decyl-D-glucamide **5**. Specifically, the ability of compound **5** to reduce the surface tension by around 60% and the IFT by more than 90% indicated its excellent surfactant features.

Overall, this work contributes to ongoing efforts to develop renewable and safe surfactants for industrial applications, paving the way for a more sustainable future in the surfactant industry.

EXPERIMENTAL SECTION

Materials and Methods. Reagents and solvents were obtained from commercial suppliers and were used without further purification. NMR spectra were recorded on a Varian

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Gemini 300 MHz and a Varian Mercury 400 MHz spectrometer using the residual signal of the deuterated solvent as an internal standard. ^{1}H chemical shifts (δ) are expressed in ppm and coupling constants (J) in hertz (Hz). The reductive amination of glucose for the synthesis of imines **7a−12a** was performed using a Vaportec EasyMedChem V-3 flow reactor equipped with a 20 mL coiled tube reactor with static mixers and an Omnifit glass column (6.6 mm i.d. × 150 mm length). Pressure was controlled using back-pressure regulators. Appropriate personal protective equipment was used. Experiments were conducted in a well-ventilated fume hood, and alkylamines were stored in tightly sealed containers and handled with care to prevent spills and accidental exposure. The synthesis of *N*-acetyl-D-glucamides **1−6** was carried out by using Asia Flow Chemistry Syringe pumps (Syrris) equipped with an Omnifit glass column (10 mm i.d. × 100 mm length) and a 10 mL coiled tube reactor. Analytical thin-layer chromatography (TLC) was carried out by using commercially available silica gel 60 F_{254} aluminum sheets; spots were further detected by using a dilute alkaline solution of $KMnO_4$ or a solution of ninhydrin in EtOH. HR-MS instrument: Q-ToF Synapt G2-Si (Waters, Milford, MA, USA); source type: electrospray ionization; data processing: MassLynx V4.2 software (Waters).

*Continuous Synthesis of N-Alkyl-D-glucamine Hydrochloride **7−12***. a) A solution of glucose (1 equiv, 1.4 mmol, 0.12 M) in MeOH (11.6 mL) and a solution of *N*-alkyl-amine (2.5 equiv, 3.5 mmol, 0.30 M) in MeOH (11.6 mL) were mixed in a T-piece and pumped into a 20 mL reactor coil with a total flow rate of 0.222 mL min^{-1} (R_t: 90 min) at 80 °C. A 75 psi BPR was applied to the system. Then, the exiting solution was flowed through an unpowered Omnifit column reactor packed with Amberlyst 15 (H^+, 2.0 g), followed by an Omnifit column reactor packed with Quadrapure BZA (loading: 20 mg/g; 1.0 g), both prewashed with MeOH. MeOH was employed as the flow stream.

b) The resulting solution was collected in a round-bottom flask, cooled to 0 °C, and then, immobilized $NaBH_4$ 10% *w/w* on alumina support (1.5 equiv) was added.[30] The mixture was stirred at room temperature overnight. Then, the suspension was filtered under vacuum to remove immobilized $NaBH_4$. The solvent was evaporated under reduced pressure, and the resulting crude was dissolved in MeOH at reflux. Then, the mixture was cooled to 0 °C, and 4 M HCl in dioxane was added dropwise up to pH = 5. The desired product was obtained as a white precipitate that was recovered through filtration under vacuum.

*N-Ethyl-D-glucamine Hydrochloride (**7**)*. Yield: 60%; white solid; ^{1}H NMR (300 MHz, D_2O) δ 3.89−3.84 (m, 1H), 3.77−3.72 (m, 2H), 3.71−3.67 (m, 1H), 3.64−3.58 (m, 2H), 2.75−2.66 (m, 3H), 2.63−2.59 (m, 1H), 1.12 (t, J = 9.0 Hz, 3H). ^{13}C NMR (75 MHz, D_2O) δ: 71.0, 70.9, 70.8, 70.6, 62.7, 50.0, 42.8, 13.4. HR-MS calcd for $C_8H_{20}NO_5$ $[M + H]^+$: 210.1341; found: 210.1341.

*N-Butyl-D-glucamine Hydrochloride (**8**)*. Yield: 40%; white solid; ^{1}H NMR (300 MHz, D_2O) δ 3.84−3.82 (m, 1H), 3.69−3.57 (m, 3H), 3.55−3.45 (m, 2H), 2.82−2.66 (m, 4H), 1.50−1.30 (m, 2H), 1.28−1.16 (m, 2H), 0.76 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, D_2O) δ 70.8, 70.7, 70.6, 69.8, 62.7, 49.8, 47.9, 29.2, 19.4, 12.9. HR-MS calcd for $C_{10}H_{24}NO_5$ $[M + H]^+$: 238.1654; found: 238.1651.

*N-Hexyl-D-glucamine Hydrochloride (**9**)*. Yield: 65%; white solid; ^{1}H NMR (300 MHz, D_2O) δ 4.05−3.95 (m, 1H), 3.76−3.70 (m, 3H), 3.59−3.50 (m, 2H), 3.19−2.98 (m, 4H), 1.70−1.57 (m, 2H), 1.35−1.18 (m, 6H), 0.78 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, D_2O) δ 70.9, 70.7, 70.5, 68.2, 62.7, 49.4, 47.9, 30.4, 25.3, 25.2, 21.7, 13.3. HR-MS calcd for $C_{12}H_{28}NO_5$ $[M + H]^+$: 266.1967; found: 266.1963.

*N-Octyl-D-glucamine Hydrochloride (**10**)*. Yield: 75%; white solid; ^{1}H NMR (400 MHz, D_2O) δ 4.05−3.95 (m, 1H), 3.73−3.67 (m, 3H), 3.66−3.50 (m, 2H), 3.20−2.90 (m, 4H), 1.63−1.54 (m, 2H), 1.30−1.15 (m, 10H), 0.74 (t, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, D_2O) δ 71.1, 70.8, 70.6, 68.3, 62.8, 49.5, 48.0, 31.1, 28.2, 28.2, 25.8, 25.4, 22.1, 13.5. HR-MS calcd for $C_{14}H_{32}NO_5$ $[M + H]^+$: 294.2280; found: 294.2280.

*N-Decyl-D-glucamine Hydrochloride (**11**)*. Yield: 60%; white solid; ^{1}H NMR (300 MHz, CD_3OD) δ 4.08−4.00 (m, 1H), 3.84−3.75 (m, 2H), 3.73−3.61 (m, 3H), 3.18−3.12 (m, 2H), 3.02−2.95 (m, 2H), 1.75−1.63 (m, 2H), 1.45−1.20 (m, 14H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ: 71.5, 70.7, 70.7, 68.5, 63.2, 49.5, 47.7, 31.6, 29.1, 29.0, 28.9, 28.8, 26.2, 25.8, 22.3, 13.0. HR-MS calcd for $C_{16}H_{36}NO_5$ $[M + H]^+$: 322.2593; found: 322.2594.

*N-Dodecyl-D-glucamine Hydrochloride (**12**)*. Yield: 45%; white solid; ^{1}H NMR (300 MHz, DMSO-d_6/D_2O) δ 3.88−3.82 (m, 1H), 3.59−3.54 (m, 2H), 3.50−3.36 (m, 3H), 3.05−3.00 (m, 1H), 2.94−2.81 (m, 3H), 1.57−1.50 (m, 2H), 1.22 (s, 18H), 0.82 (t, J = 6 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6/D_2O) δ 71.5, 70.6, 70.4, 68.6, 63.5, 49.4, 47.3, 31.7, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 26.3, 25.5, 22.5, 14.4. HR-MS calcd for $C_{18}H_{40}NO_5$ $[M + H]^+$: 350.2906; found: 350.2906.

*Flow Synthesis of N-Acetyl-N-alkyl-D-glucamides **1−6***. A stock solution of the proper *N*-alkyl-D-glucamine hydrochloride **7−12** (1 equiv, 0.75 mmol, 0.20 M) in MeOH (3.75 mL) was prepared and pumped by a syringe pump through an unpowered Omnifit packed-bed column reactor (V = 3.5 mL; R_t = 28 min) containing a mixture of Amberlyst A21 beads (1.2 g) and molecular sieves (1.2 g). Then, the resulting solution encountered a second flow stream containing a solution of acetic anhydride (2 equiv, 1.5 mmol, 0.40 M, kept at 0 °C) in MeOH (3.75 mL), and they were flowed through a 10 mL unpowered reactor coil (R_t = 40 min). The pump's flow rate was 0.125 mL min^{-1} each. The resulting solution was collected in a round-bottom flask, and the solvent was evaporated under reduced pressure to obtain the desired compounds **1−6**.

*N-Acetyl-N-ethyl-D-glucamide (**1**)*. Quantitative yield; white solid; Rf: 0.32 (DCM/MeOH 8.8:1.2); ^{1}H NMR (300 MHz, D_2O, mixture of rotamers) δ 3.95−3.86 (m, 1H), 3.72−3.66 (m, 2H), 3.64−3.59 (m, 1H), 3.58−3.52 (m, 2H), 3.43−3.26 (m, 4H), 3.23−3.11 (m, 1H), 2.03 and 2.01 (s, 3H), 1.06 and 0.97 (t, J = 6 Hz, 3H). ^{13}C NMR (75 MHz, D_2O, mixture of rotamers) δ 174.4 and 174.2, 71.7 and 71.4, 70.9, 70.4, 70.2 and 70.1, 62.5, 50.8 and 48.1, 45.0 and 41.4, 20.9 and 20.3, 12.4, and 11.5. HR-MS calcd for $C_{10}H_{21}NO_6$ Na $[M + Na]^+$: 274.1267; found: 274.1266.

*N-Acetyl-N-butyl-D-glucamide (**2**)*. Quantitative yield; white solid; Rf: 0.20 (DCM/MeOH 9:1); ^{1}H NMR (300 MHz, D_2O, mixture of rotamers) δ 3.92−3.87 (m, 1H), 3.70−3.61 (m, 2H), 3.60−3.47 (m, 3H), 3.42−3.28 (m, 3H), 3.15−3.03 (m, 1H), 2.01 (s, 3H), 1.54−1.33 (m, 2H), 1.28−1.08 (m, 2H), 0.80−0.72 (m, J = 3H). ^{13}C NMR (75 MHz, D_2O, mixture of rotamers) δ 174.4 and 174.2, 71.7 and 71.4, 70.9, 70.2 and 70.1, 62.5, 51.0, 48.5 and 46.1, 29.6 and 28.5, 21.7, 20.9 and 20.5, 19.4 and 19.2, 13.0, and 12.9. HR-MS calcd for $C_{12}H_{25}NO_6Na$ $[M + Na]^+$: 302.1580; found: 302.1584.

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N-Acetyl-N-hexyl-D-glucamide (**3**). Quantitative yield; white solid; Rf: 0.20 (DCM/MeOH 9:1); ^{1}H NMR (300 MHz, D_2O, mixture of rotamers) δ 3.94−3.88 (m, 1H), 3.72−3.66 (m, 2H), 3.64−3.49 (m, 2H), 3.41−3.28 (m, 2H), 3.16−2.94 (m, 1H), 2.89−2.84 (m, 1H), 2.02 (s, 3H), 1.60−1.41 (m, 2H), 1.27−1.15 (m, 7H), 0.74 (t, J = 6 Hz, 3H). ^{13}C NMR (75 MHz, D_2O, mixture of rotamers) δ 174.6 and 174.4, 71.7 and 71.4, 70.9 and 70.4, 62.5, 50.2, 48.5, 46.3, 39.4, 30.7 and 30.3, 26.5 and 26.3, 25.4 and 25.1, 21.8 and 21.6, 20.5, 13.2, and 13.1. HR-MS calcd for $C_{14}H_{28}NO_6$ $[M - H]^-$: 306.1917; found: 306.1917.

N-Acetyl-N-octyl-D-glucamide (**4**). Quantitative yield; colorless oil; Rf: 0.30 (DCM/MeOH 9:1); ^{1}H NMR (300 MHz, CD_3OD, mixture of rotamers) δ 4.01−3.93 (m, 1H), 3.80−3.74 (m, 1H), 3.73−3.63 (m, 4H), 3.57−3.48 (m, 2H), 3.45−3.38 (m, 2H), 2.13 (s, 3H), 1.64−1.53 (m, 2H), 1.31 (s, 10H), 0.90 (t, J = 9 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD, mixture of rotamers) δ 172.5, 72.8, 71.7 and 71.0, 70.1 and 69.6, 63.2, 50.8 and 50.1, 48.4 and 48.2, 47.4, 47.2, 47.0 and 46.7, 45.8, 31.5, 29.2 and 28.8, 26.8 and 26.4, 22.2, 12.9. HR-MS calcd for $C_{16}H_{32}NO_6$ $[M - H]^-$: 334.2230; found: 334.2236.

N-Acetyl-N-decyl-D-glucamide (**5**). Quantitative yield; colorless oil; Rf: 0.30 (DCM/MeOH 9:1); ^{1}H NMR (300 MHz, CD_3OD, mixture of rotamers) δ 4.02−3.93 (m, 1H), 3.80−3.74 (m, 1H), 3.73−3.65 (m, 4H), 3.63−3.52 (m, 1H), 3.57−3.48 (m, 2H), 2.15 and 2.11 (s, 3H), 1.64−1.53 (m, 2H), 1.30 (s, 15H), 0.89 (t, J = 9 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD, mixture of rotamers) δ 172.8 and 172.5, 72.9 and 72.2, 71.6 and 71.5, 71.4, 69.9, 69.3, 63.2 and 63.0, 50.9, 49.9, 31.6, 29.3 and 29.2, 29.1 and 29.0, 28.1, 26.8 and 26.6, 26.4, 22.3, 20.5 and 20.0, 13.0. HR-MS calcd for $C_{18}H_{36}NO_6$ $[M - H]^-$: 362.2543; found: 362.2550.

N-Acetyl-N-dodecyl-D-glucamide (**6**). Quantitative yield; colorless oil; Rf: 0.30 (DCM/MeOH 9:1); ^{1}H NMR (300 MHz, CD_3OD, mixture of rotamers) δ 4.02−3.93 (m, 1H), 3.79−3.74 (m, 1H), 3.72−3.60 (m, 4H), 3.57−3.53 (m, 2H), 3.45−3.39 (m, 2H), 2.13 (s, 3H), 1.64−1.51 (m, 20H), 0.91 and 0.87 (t, J = 9 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD, mixture of rotamers) δ 172.6 and 172.5, 72.8, 72.0, 71.7 and 71.5, 71.1, 70.2, 69.6, 63.3, 50.8, 50.1, 31.6, 29.3, 29.1 and 29.0, 28.1, 26.9, 26.6, 26.4, 22.3, 20.5 and 19.9, 12.9. HR-MS calcd for $C_{20}H_{40}NO_6$ $[M - H]^-$: 390.2856; found: 390.2848.

Surface and Interfacial Tension Measurements. The air/water (Milli-Q) surface tension (γ) and the sunflower oil/water (Milli-Q) interfacial tension (IFT) reduction ability of *N*-acetyl-*N*-alkyl-D-glucamides **4** and **5** were assessed at increasing surfactant concentrations (from 0.05 to 3.0 mM) at 25 ± 1 °C by using a Gibertini tensiometer, according to the du Noüy ring method.[6,8] Prior to measurements, several parameters (i.e., the platinum ring, the radius, and the liquid density) were introduced in the software to set up the method according to the Harkins−Jordan correction. All samples were equilibrated for 1 h before both surface and IFT analyses. Surface and IFT values were reported as average values on five different replicates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c09871?goto=-supporting-info.

^{1}H NMR, ^{13}C NMR, and HRMS spectra of compounds **1**−**12** (PDF)

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Notes

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