

Water-Soluble Cello-Oligomer Surfactants by Mechanochemical Conversion and Sustainable Modification of Cellulose

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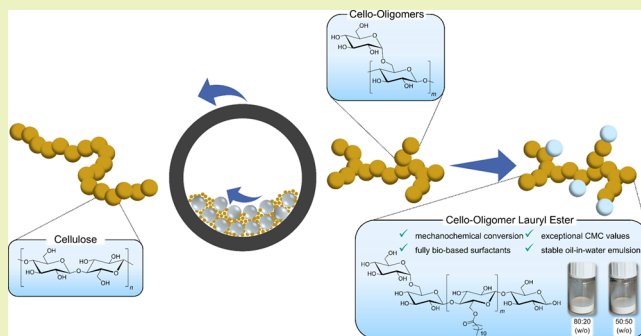
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Supporting Information

ABSTRACT: Surfactants are ubiquitous materials of high industrial and consumer relevance. Carbohydrate-derived surfactants, such as alkyl glucosides or sugar esters, represent more sustainable alternatives to fossil-based systems while maintaining competitive performance. Herein, we report an approach to fully bio-based surfactants derived from cellulose- and fatty acid-based feedstocks. By combining ball-mill-assisted mechanochemical depolymerization of cellulose with subsequent esterification, a versatile surfactant platform with tunable degree of substitution (DS), and thus properties, was established. The resulting amphiphiles exhibit critical micelle concentrations (CMCs) as low as 0.00614 mM indicating high efficiency, forming micellar populations with hydrodynamic diameters of 16–42 nm, as evidenced by dynamic light scattering (DLS) analysis. Performance studies demonstrated excellent emulsifying properties in oil-in-water systems, while cytotoxicity assays revealed comparable or improved cell compatibility relative to conventional alkyl glucosides. Overall, this work provides a sustainable and efficient strategy for the design of highly functional nonionic surfactants, bridging renewable feedstocks with tunable performances without compromising application-relevant properties.

KEYWORDS: bio-based surfactant, ball-mill, cellulose, mechanochemistry, emulsion, sustainability



INTRODUCTION

Surfactants are amphiphilic molecules that orient at interfaces (e.g., oil-water) and reduce surface tension by inhibiting intermolecular interactions.^{1,2} Their structure, comprising hydrophilic as well as lipophilic parts, enables important functional properties, such as emulsification, foaming, and stabilization of biphasic systems.^{3,4} Consequently, surfactants find widespread applications across diverse industries, including food, cosmetics, pharmaceuticals, and material science.^{5–8} Conventional surfactants, especially ionic representatives, are predominantly derived from fossil feedstock (e.g., alkylbenzene sulfonates).⁹ Dependence on fossil-based resources and limited biodegradability contributes to environmental pollution, bioaccumulation, and toxicological issues, including skin and eye irritation.^{10–12} Driven by environmental concerns, nonionic carbohydrate-based surfactants (e.g., sorbitan esters, sucrose esters, or alkyl (poly)glucosides) proved to be more sustainable alternatives due to their renewability, increased biodegradability, and minimized toxicological risks.^{13,14} Sugar fatty acid esters are of particular interest due to their tunable hydrophilic–lipophilic balance (HLB), which can be systematically adjusted *via* the degree of esterification, thereby enabling application-specific properties.¹⁵ In contrast, alkyl (poly)glucosides are well-known as environmentally benign, low-toxicity surfactants that are readily accessible from glucose and fatty alcohols.¹⁶ To

advance sustainability, the use of valuable food-relevant saccharides (e.g., glucose or sucrose) should be replaced by the ubiquitous lignocellulosic feedstock, *i.e.* cellulose-based hydrophilic oligomers (cello-oligomers).¹⁷ Polysaccharides derived from lignocellulosic biomass represent abundant renewable feedstocks with considerable potential to reduce dependence on fossil resources.^{18,19} Their broader utilization, however, is often limited by poor processability arising from low solubility.²⁰ In this context, mechanochemistry overcomes this challenge by enabling the direct transformation of these solid substrates without prior dissolution, while often reducing solvent use, waste generation, energy demand, and process complexity, thereby directly addressing several of the Principles of Green Chemistry.^{21–23} These advantages have established mechanochemistry as one of the fastest-growing areas of synthetic chemistry with increasing industrial relevance.^{24,25} Compared to cost- and resource-intensive chemical or enzymatic approaches,²⁶

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ball-mill-assisted mechanocatalytic depolymerization of cellulose emerged as a promising, cost-efficient, and facile route to the desired oligosaccharide building blocks.^{27,28} Herein, this mechanochemical strategy circumvents the use of harsh reagents or sensitive biocatalysts, thereby minimizing downstream processing and waste generation.^{29,30} Reducing-end modifications (reductive amination, *O*-glycosylation, and *N*-glycosylation) of the resulting carbohydrate-oligomers demonstrate their suitability as hydrophilic head groups for surfactant synthesis, enabling more sustainable alternatives to conventional alkyl (poly)glucosides.^{31–33} To further advance functionality, we report the synthesis of fully bio-based cello-oligomer lauryl ester (COLE) surfactants, combining mechanocatalytic cellulose depolymerization with subsequent selective fatty acid esterification. Variation of the degree of substitution (DS) is possible in contrast to the mentioned reducing-end modifications and enables adjustment of surfactant properties. For instance, CMC values well below conventional carbohydrate-based surfactants were obtained, highlighting the competitive characteristics of these new surfactants. Furthermore, the surfactants demonstrate excellent emulsifying performance in water/sunflower oil biphasic systems, forming stable oil-in-water emulsions (80:20 or 50:50 water/oil), while exhibiting reduced cytotoxicity in relation to the respective CMC compared to conventional alkyl glucosides (octyl, decyl, or dodecyl glucosides).

■ RESULTS AND DISCUSSION

Water-Soluble Cello-Oligomers by Mechanocatalytic Depolymerization

The mechanocatalytic depolymerization of cellulose presents a sustainable, facile, and cost-efficient alternative to conventional chemical or enzymatic depolymerization approaches for the production of low molecular weight cello-oligomers, enabling a more environmentally benign pathway for the selective access to the desired hydrophilic building blocks.³⁴ Here, H₂SO₄-impregnated (8 mol %) microcrystalline cellulose (MCC) was transferred to a 50 mL stainless steel grinding vessel in combination with a defined number (28) of stainless steel milling balls (*d* = 10 mm) to initiate the mechanocatalyzed glycosidic bond cleavage. H₂SO₄ was employed as a readily available, cost-effective, and ball-mill compatible acid for cellulose impregnation, enabling homogeneous acid distribution and efficient depolymerization. Milling parameters (milling time, cellulose filling degree (Φ = 0.3), milling ball diameter, and rotational speed) were systematically evaluated and optimized for the formation of low molecular weight oligomers.^{27,35} To maximize the fraction of water-soluble cello-oligomers, MCC was processed at 650 RPM in four milling cycles consisting of 15 min effective milling followed by a 10 min cooling interval to suppress the formation of isomerization and dehydration products (fructose, HMF, or furfural) at elevated temperatures (verified *via* HPLC, Supporting Information Figure S6).³⁶ After MeOH-washing to remove residual H₂SO₄, quantitative conversion toward fully water-soluble cello-oligomers with a yield of 84% was achieved (Figure 1 A). Investigations of the molecular cello-oligomer composition *via* HPLC analysis revealed a low percentage of short-chain saccharides (glucose, cellobiose, or cellotriose), besides illustrating a notably narrow distribution of the desired water-soluble cello-oligomers. The predominant

species of this water-soluble fraction can be attributed to oligosaccharides with a degree of polymerization (DP) $\geq$ 5 with more than 93% of the total composition (Figure 1 B (left)).

Moreover, ¹H NMR spectroscopy was utilized to further investigate the average oligomeric structure of the mixture. The reducing end proton signals at 5.22 ppm (α -re *H*₁) and 4.64 ppm (β -re *H*₁) enable both qualitative identification and quantitative characterization of the synthesized oligomers. Comparison of the corresponding integral values reveals an average degree of polymerization (DP) of 4.99 for the oligomeric mixture (Supporting Information, eq S1). The signal emerging at 4.98 ppm indicates the presence of α -1,6-glycosidic linkages (21%) (Supporting Information, eq S2), arising from an equilibrium between re- and depolymerization,³⁷ indicating branching of the linear structure, further enhancing water solubility of the oligomers (Figure 1 B (right)). Finally, ESI-MS data clearly shows different oligomer species (DP = 3–8), peaks being separated by the characteristic repeating unit mass of 162.05 Da (Supporting Information, Figure S4). To improve the sustainability of the proposed depolymerization procedure, a solvent recycling strategy was implemented. Owing to the high cello-oligomer yield, facile hydrolysis of cellulose, and the confirmed absence of significant side-product formation (Supporting Information, Figure S6), solvent consumption during the reaction and purification steps accounts for the largest contribution to the overall *E*-factor. Under the conditions investigated, methanol was intentionally selected as the washing solvent based on its specific purification advantages. In addition to removing residual H₂SO₄, methanol efficiently dissolves undesired glucose and cellobiose side products (Figure 1 A), providing more effective purification compared to other alcohols (*e.g.*, ethanol or 2-propanol). Furthermore, despite its toxicity, methanol is classified as a recommended or preferred solvent, exhibiting favorable life-cycle assessment scores.^{38,39} Thus, methanol represents an effective compromise between purification efficiency and environmental considerations. Simple distillation enabled recovery rates of 92% for diethyl ether, 96% for methanol, and 91% for water (Supporting Information, Table S1), resulting in an overall *E*-factor of 3.03 for the cello-oligomer synthesis (detailed *E*-factor composition in Supporting Information, Figure S21). As water is often neglected in *E*-factor calculation,^{40,41} the *E*-factor without considering water would reduce to 2.41. The recovered solvents exhibited high purity, as confirmed by ¹H NMR spectroscopy (Supporting Information, Figures S22–S24), indicating their potential reuse. Given the low catalytic amounts of H₂SO₄ employed, its recovery was not considered in the present study, constituting less than 2% contribution to the overall *E*-factor.

Water-Soluble COLE Surfactants

In contrast to conventional alkyl (poly)glucosides, the lipophilic moiety of the reported surfactants was introduced *via* selective modification of the hydroxyl groups, thereby substantially expanding the accessible range of the HLB values. Therefore, a transesterification strategy employing cello-oligomers and vinyl laurate (VL) as the acylation agent was used to afford fully bio-based and renewable, water-soluble surfactants (Figure 2 A). The lauric acid-derived ester serves as the preferred acyl donor due to its bio-based availability and ability to provide more precise tunability over a broad HLB range, in contrast to longer alkyl chain analogues with higher lipophilic weight in the HLB value

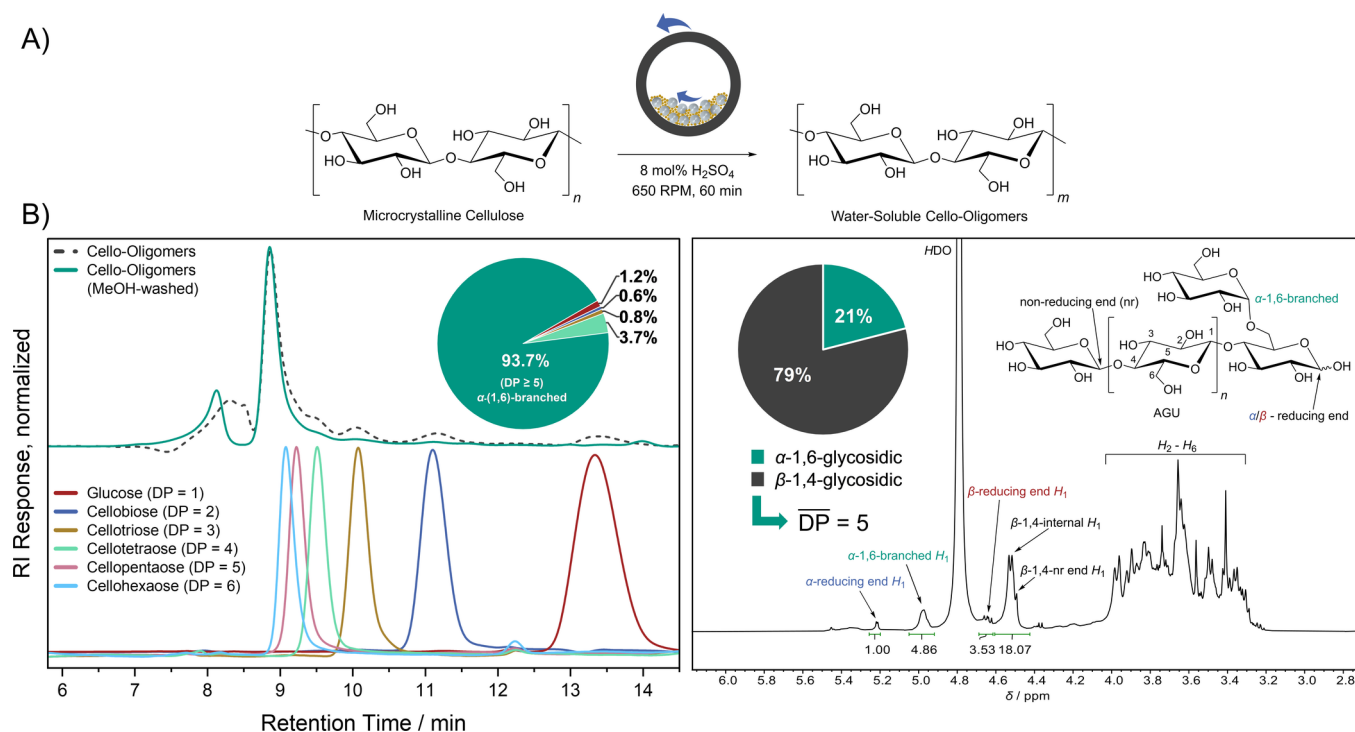


Figure 1. (A) Reaction scheme of the optimized mechanocatalytic depolymerization conditions of cellulose toward water-soluble cello-oligomers. (B) HPLC analysis of the synthesized cello-oligomers and water-soluble cello-oligosaccharide standards (exact DP = 1–6) and the molecular oligomer composition (calculated on the assumption of consistent RI responses (raw data, [Supporting Information Figure S5](#)) throughout the analytes) (left). ^1H NMR analysis (D_2O) of cello-oligomers and the structural investigation of the DP and glycosidic bonds (right).

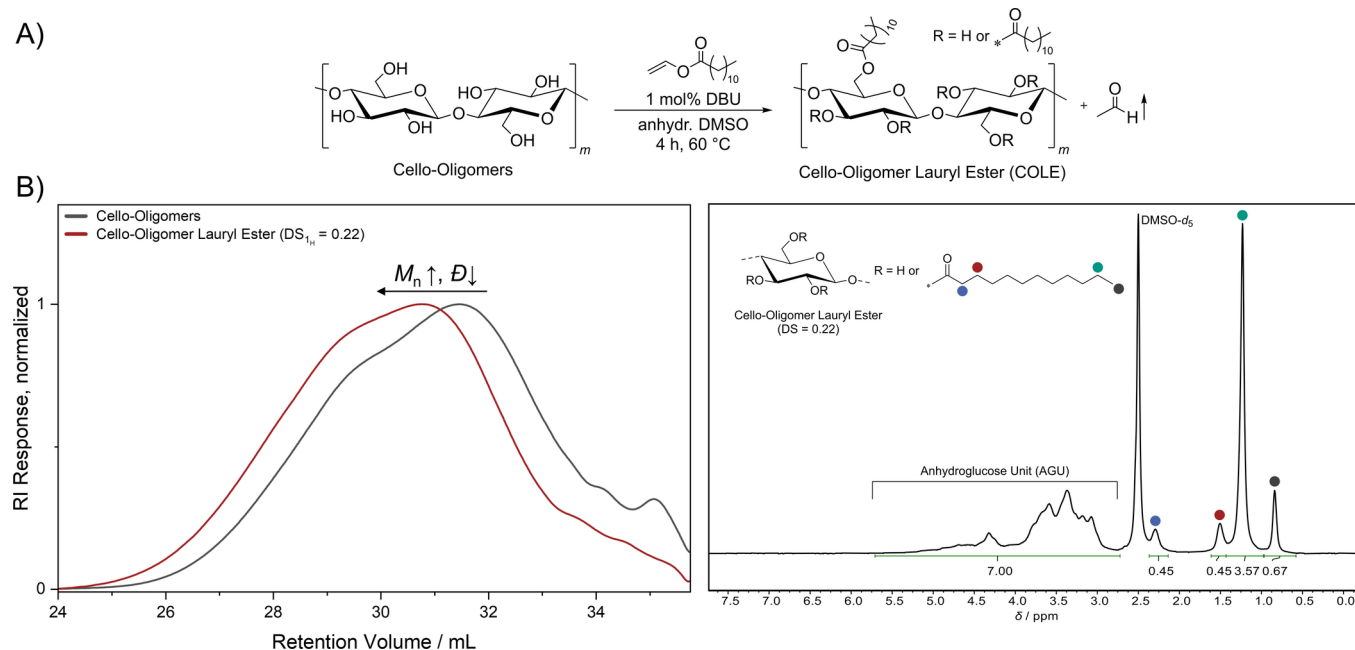


Figure 2. (A) Reaction scheme of the formation of cello-oligomer lauryl esters (COLEs). (B) SEC traces of unmodified cello-oligomers (black) and COLE ($\text{DS}_{\text{IH}} = 0.22$) (red) conducted in DMAc (0.034 wt % LiBr) (left). ^1H NMR spectrum ($\text{DMSO}-d_6 + \text{TFA}$) of COLE ($\text{DS}_{\text{IH}} = 0.22$) for the quantitative DS determination (right).

calculation. Previous studies by Meier *et al.* have highlighted the high efficiency of vinyl esters in transesterification reactions of carbohydrates, driven by the formation and evaporation of acetaldehyde (b.p. 20°C) as a thermodynamic driving force at elevated

temperatures.^{42,43} Accordingly, a reaction temperature of 60°C was employed in the present work. ATR-FTIR spectroscopy was utilized to assess the influence of different catalytic systems (H_2SO_4 , DBU, and 2,6-lutidine) and to monitor the

progression of cello-oligomer esterification (Supporting Information, Figures S15 and S17). For reaction monitoring, ATR-FTIR spectra were normalized to the vibrational band at 1022 cm^{-1} , assigned to the invariant C-O-C acetal bond of the anhydroglucose unit (AGU), to ensure comparability. The increased intensities of the C-H and C=O stretching vibrations at 2922 cm^{-1} and 1727 cm^{-1} , respectively, indicated a pronounced catalytic performance of DBU (1 mol % per -OH group), whereas no conversion could be observed for the other investigated catalyst systems (H_2SO_4 or 2,6-lutidine) (Supporting Information, Figures S15 and S17).

Owing to the co-oligomeric nature of the obtained COLE samples, size exclusion chromatography (SEC) was selected as an initial characterization method. The observed shift of the SEC trace toward lower retention volume, *i.e.* an increased molecular weight (M_n), suggests a higher hydrodynamic radius of the COLEs compared to unmodified cello-oligomers, consistent with successful covalent incorporation of the fatty acid ester moieties (Figure 2 B (left)). Qualitatively, the appearance of high-field signals in the ^1H and ^{13}C NMR spectra, corresponding to alkyl chain resonances, further confirms the successful synthesis of the cello-oligomer-based surfactants. In addition, DOSY NMR experiments were conducted to further verify the covalent incorporation of the acyl moieties into the oligomer backbone, as evidenced by identical diffusion coefficients observed for both the AGU-related and fatty acid ester proton resonances (Supporting Information, Figures S18–S20).

Upon addition of trifluoroacetic acid (TFA), the acyl moiety density relative to the cello-oligomer unit can be quantified by ^1H NMR, enabling determination of the respective degree of substitution (DS) (Figure 2B (right), Supporting Information eq S3). Here, we focused on water-soluble surfactants with high HLB values, and thus a set of water-soluble COLEs with low degrees of substitution (DS = 0.07–0.22) was synthesized and further investigated (Table 1).

The surfactants were obtained in moderate yields by precipitation into acetone, followed by dialysis against deionized water to remove excess vinyl laurate and potential salt residues, with conversions reaching up to 90% (Table 1). Besides the moderate yields, this represents valuable improvements in terms of sustainability and resource-efficiency compared to conventional alkyl (poly)glucoside syntheses, which typically require a significant excess of the fatty alcohol component coupled with distillation recovery processes.⁴⁵ To quantify the environmental impact of the COLE synthesis, an additional COLE (DS = 0.18) with an intermediate DS between COLE (DS = 0.11) and COLE (DS = 0.22) was synthesized and its *E*-factor determined. Under the optimized reaction conditions, COLE (DS = 0.18) was obtained in a yield of 72% at 96% conversion. As a result, solvent consumption constituted the predominant contribution to the overall *E*-factor, making solvent recovery a key

factor in minimizing the environmental impact. Distillation enabled recovery rates of 97% for DMSO and 86% for acetone, resulting in an *E*-factor of 12.3 for the COLE (DS = 0.18) synthesis (detailed *E*-factor composition in Supporting Information, Figure S25). Owing to the low catalytic amount of DBU employed, its nonrecovery contributes only 0.26% to the overall *E*-factor, thus, its recycling was not further pursued. Nevertheless, recovery of both DBU and the formed side product acetaldehyde may be feasible upon scale-up and acetone recovery and yield would also likely improve, in line with related approaches reported by Meier and co-workers.⁴³

Micellar and Self-Assembly Properties of COLE Surfactants

The critical micelle concentration (CMC) of the synthesized COLEs was determined using the pyrene fluorescence method.⁴⁶ Fluorescence spectra were recorded over a surfactant concentration range of 0.001–2.56 mM at a constant pyrene concentration (1 μM) in aqueous solution. The fluorescence data indicate a strong correlation between CMC and DS of the COLEs (Figure 3 A). Notably, even the lowest substituted COLE (DS = 0.07) exhibited a low CMC of 0.0525 mM, significantly below reported values for established alkyl glucoside (*e.g.*, octyl, decyl, dodecyl glucoside) and within the range of recently reported ball mill-derived oligosaccharide analogues, demonstrating efficient surface activity of the prepared surfactants at highly dilute concentrations.^{32,47} An increase in DS led to a pronounced further decrease in CMC, reflecting enhanced amphiphilic character and surfactant practicality. For COLE (DS = 0.22), a CMC value as low as 0.00614 mM was determined, underlining the self-assembly behavior at low concentrations (Figure 3 A). This general structure–property relationship is consistent with literature reports of comparable alkyl or acyl polyglucoside surfactants, where variation of alkyl chain length results in reduced CMC (*e.g.*, 19.0 mM for C8 to 0.180 mM for C12 alkyl cellobioside or 105 mM for C5 to 0.08 mM for C11 acyl glucosides), while in the herein presented system, similar tunability at significantly lower CMC values can simply be achieved through variation of the DS.^{48,49}

Dynamic light scattering (DLS) measurements were performed to investigate the self-assembly behavior of the surfactants in aqueous solution at concentrations above the respective CMC (2.5-fold CMC). Due to the sensitivity of the intensity-weighted particle size distribution (PSD) to minor fractions of micelle aggregates, the volume-weighted PSD more accurately reflects the hydrodynamic micelle diameter of the predominant population. Thus, to assess the actual average particle size of the forming micelles, the investigation of the volume-weighted PSD was preferred. The volume-weighted PSDs generally display a narrow diameter distribution for all investigated systems, indicating a predominant particle

Table 1. Synthesized COLEs per Used Equivalents of Vinyl Laurate (VL) and Respective Degree of Substitution (DS), Conversion, Yield, and HLB Value

sample	equiv. VL	DS _{1H}	conversion / %	yield ^a / %	HLB value ^b
COLE (DS = 0.07)	0.100	0.070	70	52	18.6
COLE (DS = 0.11)	0.125	0.113	90	54	17.8
COLE (DS = 0.22)	0.250	0.223	89	47	16.1

^aCalculated based on the determined DP and DS_{1H} (SI, eqs S4–S7). ^bHLB values were calculated based on the Griffin method for nonionic surfactants (SI, eq S8).⁴⁴

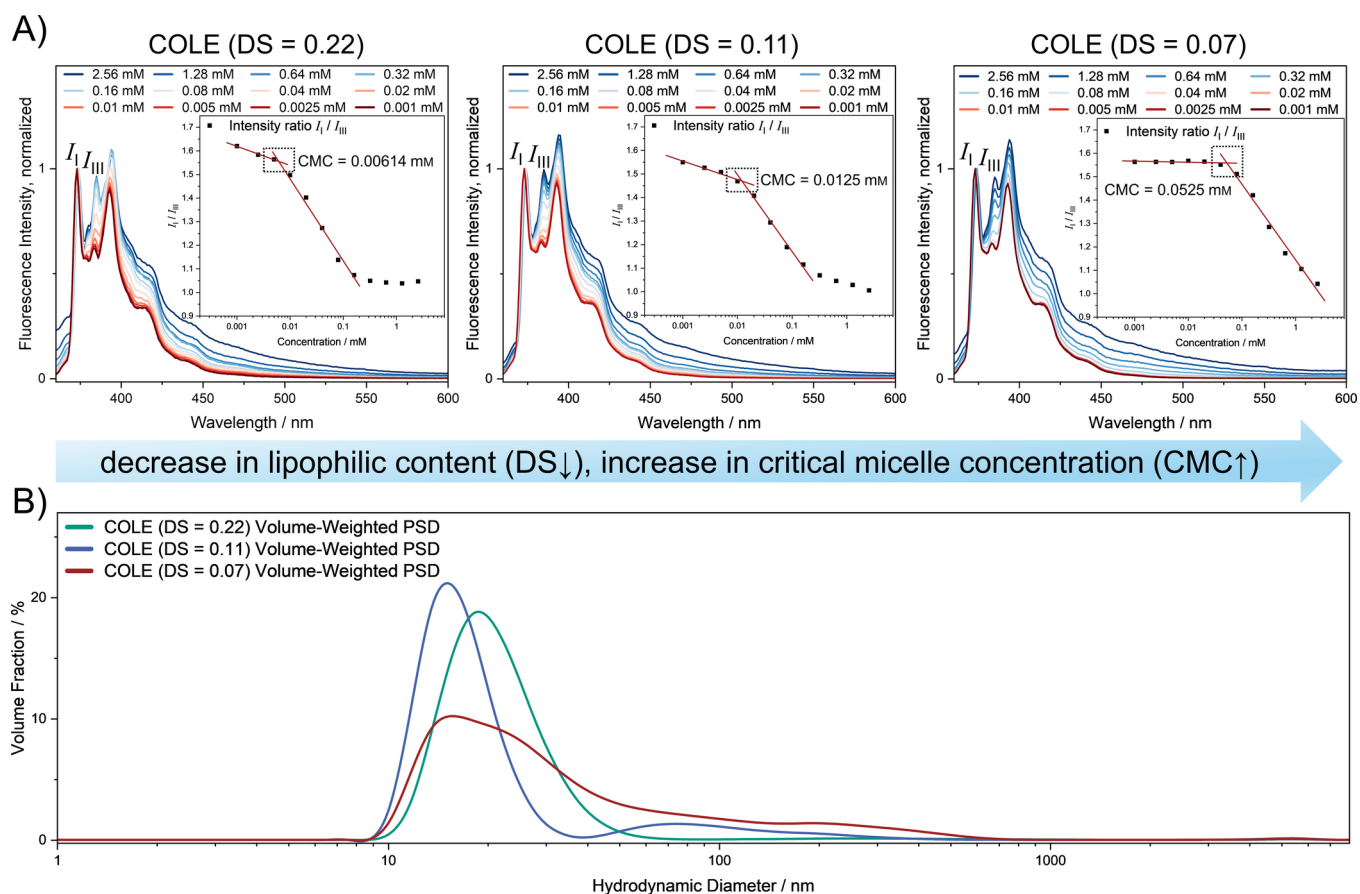


Figure 3. (A) Fluorescence spectra of 1 μ M aqueous pyrene solutions at different surfactant concentrations for the CMC determination of the respective COLE. (B) DLS measurements for analysis of the hydrodynamic diameter (volume-weighted PSD) at 2.5-fold CMC of the respective COLE surfactant.

population with a hydrodynamic diameter in the range of 16–42 nm, respectively, accounting for 85–99% of the total population (Figure 3 B). DLS data further indicate that increasing the lipophilic content (higher DS) results in the formation of smaller hydrodynamic diameter and less dispersed micelles, whereas lower DS values are associated with increased micellar aggregation, as indicated by the broadening of the size distribution and shift toward aggregates (Figure 3, B (red)). The observed behavior may be partly attributed to a higher fraction of unmodified cello-oligomers present in surfactant mixtures of lower DS, which show pronounced aggregation, as evidenced by DLS measurements of the pure cello-oligomers (Supporting Information, Figure S29). The best-performing surfactant, *i.e.*, COLE (DS = 0.22), showed an average diameter of 16 nm for 89% of the total population. The *z*-average hydrodynamic diameter remained largely independent of surfactant concentration, whereas dispersity decreased slightly with increasing concentration (2.5–10-fold CMC), indicating a literature-known trend of growing aggregation of the actual micellar populations at higher surfactant concentrations, thus narrowing the intensity-weighted dispersity (Supporting Information, Figure S28).⁵⁰

Optical Microscopy Analysis of Water/Oil Emulsions Stabilized by COLE Surfactants

Water/oil emulsions were prepared at different mixing ratios to evaluate the emulsifying properties of the COLEs. The

surfactant (1.5% w/V) was dissolved in deionized water, the oil phase (food-grade sunflower oil) was added, and the mixture was homogenized using a sonicator (Branson Sonifier Cell Disruptor B15, 60 W, 40 kHz) with continuous pulsing for three minutes in an ice bath. Preliminary tests revealed no difference in performance to commercial sorbitan olivate as an emulsifier, *i.e.*, both the commercial standard and the herein investigated COLEs with low DS stabilized the emulsion for more than 4 weeks.

COLE (DS = 0.11) was selected as a representative surfactant due to its intermediate HLB value to evaluate the general emulsifying behavior. Optical micrographs were acquired after ten minutes of equilibration. For the stable emulsion systems (Figure 4 A (80:20 and 50:50, water/oil)), optical microscopy revealed well-dispersed, predominantly spherical droplets, indicating stabilization by the nonionic surfactants at the water–oil interface. A high number density of droplets in the submicron to low micrometer range (0.2–1.6 μ m) was observed (Figure 4 B (left, middle)), comparable to the stabilizing properties of sucrose or lactose lauryl ester systems (80:20, water/oil).⁵¹ The uniform and homogeneous distribution reflects efficient emulsification, while the large interfacial area enables effective surfactant coverage, suppressing coalescence, thus stabilizing the emulsions. In contrast, the less stable emulsion (20:80, water/oil) displayed a drastically lower droplet number density and broader size distribution, with a predominant

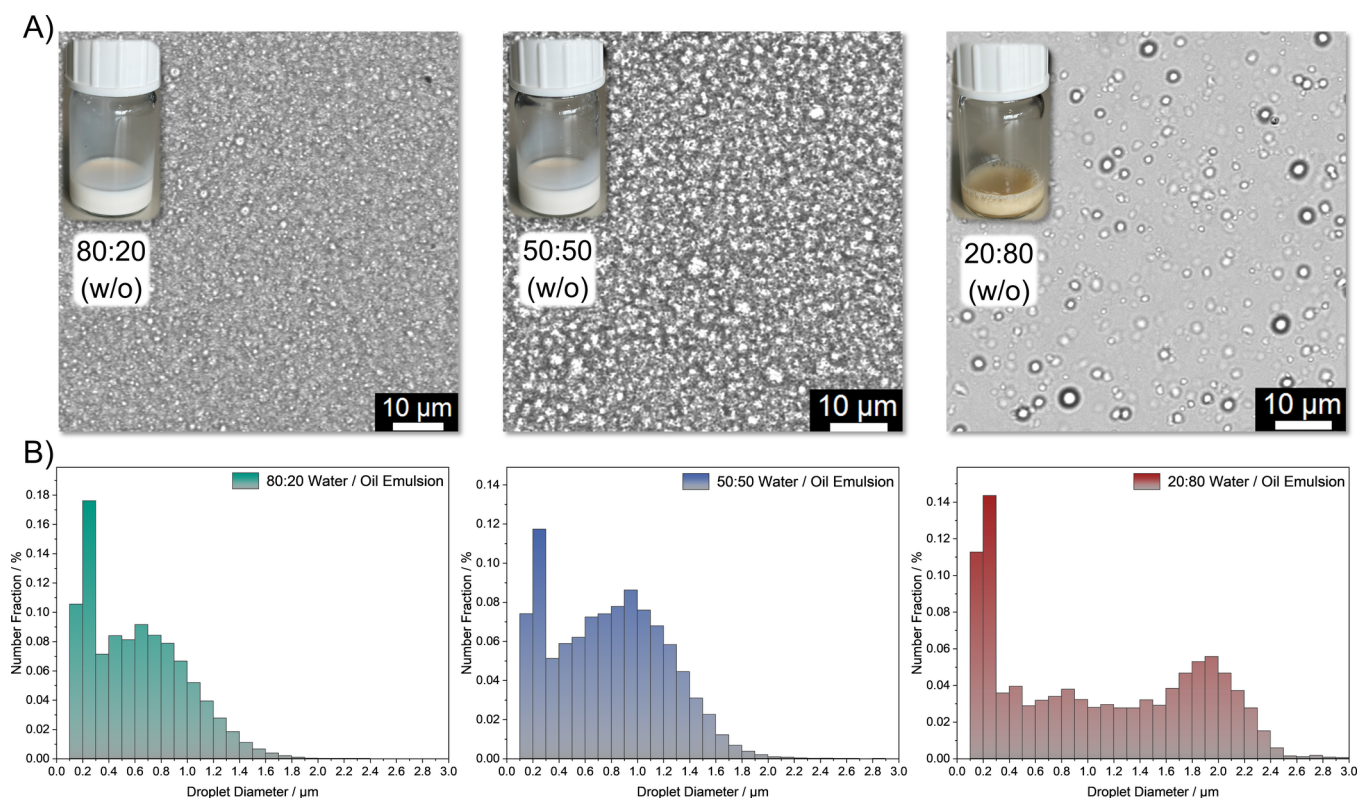


Figure 4. (A) Optical micrograph excerpts of water/sunflower oil emulsions at different mixing ratios, emulsified with COLE ($DS = 0.11$). (B) Droplet diameter distribution of the prepared emulsions, based on optical micrograph analysis (detailed explanation in [Supporting Information](#)).

droplet population of 1.8 to 2.4 μm (Figure 4 B (right)). The formation of larger droplets indicates the occurrence of coalescence, reducing the total interfacial area. Therefore, a clear correlation between the droplet morphology and emulsion stability was observed. Emulsions with smaller, more densely packed droplets demonstrated superior stability of more than 6 months (e.g., 50:50, water/oil emulsion), whereas the oil-rich 20:80 system began to separate within hours. These findings suggest that the reported nonionic surfactants are particularly effective at stabilizing water-continuous oil-in-water emulsions. The use of sunflower oil (food-grade) as the oil phase further highlights the applicability of these surfactants to complex, real-world systems beyond simple alkane-based models. Consequently, the systems investigated herein closely resemble conventional oil-in-water emulsions found in everyday formulations, including cosmetic creams, lotions, or vegan mayonnaise-type products.

Biocompatibility of the COLE Surfactants

To assess the biocompatibility of the synthesized COLE surfactants, their effect on the metabolic activity of HeLa cells was evaluated using a standard MTT colorimetric assay. The results indicate a strong dependency of cell viability on the DS of the surfactants, with the unsubstituted cello-oligomers exhibiting the highest biocompatibility, evidenced by an IC_{50} value of 0.929 mM. An increase in the DS led to a significant, concentration-dependent decrease in cell viability, with IC_{50} values ranging from 0.818 mM for the lowest substituted COLE ($DS = 0.07$) to 0.361 mM for the highest substituted COLE ($DS = 0.22$) (Figure 5).

This trend mirrors the behavior of commercially available surfactants (C8 – C12 alkyl glucosides) used as benchmarks ([Supporting Information, Figure S33](#)), although the COLE surfactants generally maintained a more favorable toxicity profile. The increased toxicity of highly functionalized derivatives can likely be attributed to the amphiphilic nature of these molecules, as surfactants with high hydrophobicity tend to interact more strongly with the phospholipid bilayer of the cell membrane. At critical concentrations, these amphiphiles cause membrane permeabilization through the insertion of hydrophobic chains into the lipid bilayer, leading to leaky membranes and a loss of cellular homeostasis.⁵² Furthermore, interactions with membrane-bound proteins can result in protein denaturation, disrupting essential cellular transport processes, while in extreme cases, the surfactants may cause the solubilization of membrane lipids, leading to complete cell lysis and rupture.⁵³ Consequently, while the introduction of hydrophobic groups is essential to achieve the desired amphiphilic properties for high-performance surfactant applications, there is a distinct trade-off with biological safety. Due to their significantly reduced CMCs, COLE surfactants require generally lower surfactant concentrations for given applications compared to conventional alkyl glucosides, thereby further minimizing the cytotoxic influence.

CONCLUSIONS

A concept for the sustainable synthesis of application-adaptable, fully bio-based surfactants from cellulose- and fatty acid-derived feedstocks was developed. Ball-mill-assisted mechanochemical

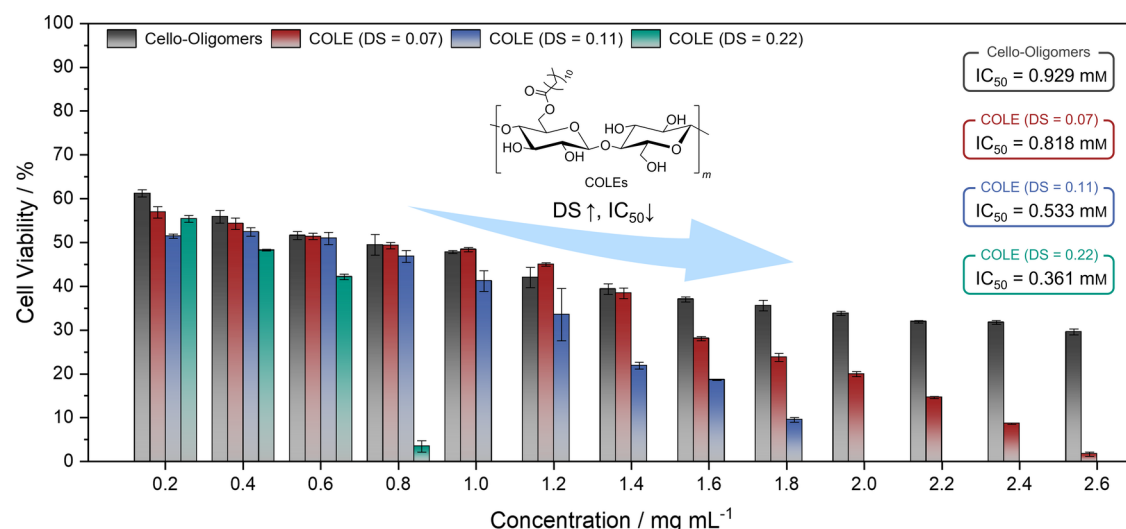


Figure 5. Concentration-dependent cytotoxicity of COLE surfactants assessed by MTT assay ($n = 3$). Bars represent mean normalized cell viability $\pm$ standard deviation (SD) at tested concentrations. IC_{50} values were calculated from dose–response curves as the concentration reducing viability to 50% of untreated control.

depolymerization of cellulose provided water-soluble cello-oligomers as hydrophilic building blocks in high yields (84%), while minimizing competitive side reactions. Structural analyses by HPLC, ^1H and ^{13}C NMR, ATR-FTIR, and mass spectrometry revealed narrow oligomer distribution with an average degree of polymerization (DP) of 5. Subsequent fatty acid esterification yielded a series of water-soluble cello-oligomer derivatives (COLEs) with conversions of up to 90%. Investigation of the micellar and self-assembly behavior revealed CMCs values as low as 0.00614 mM (COLE (DS = 0.22)), highlighting the high efficiency of the surfactants at low concentrations. DLS analysis further showed predominant micelle population with hydrodynamic diameters of 16–42 nm for the analyzed COLE surfactants. The applicability of the synthesized surfactants was assessed in application relevant oil-in-water systems (water and food-grade sunflower oil), yielding stable emulsions over several months. Cytotoxicity studies additionally revealed that the amphiphiles combine competitive surfactant performance with enhanced cell compatibility in relation to the respective CMC compared to conventional alkyl glucosides. Building on the established COLE platform, future work could expand on the demonstrated tunability of the DS to tailor the amphiphilic properties of individual COLEs toward specific applications and more application-relevant properties, such as experimentally determined HLB values or cloud points, thereby further expanding the scope of this versatile surfactant concept.

EXPERIMENTAL SECTION

Materials

Acetone (Thermo Scientific, $\geq 99.8\%$), cellobiose (Carl Roth, $\geq 98\%$), cellotriose (Megazyme, $>95\%$), cellotetraose (Megazyme, $>90\%$), cellopentaose (Megazyme, $>95\%$), cellohexaose (Megazyme, $>95\%$), decyl β -D-glucopyranoside (decyl glucoside, BLD Pharm, 98%), deuterium oxide (D_2O , Eurisotop, 99.90%), N,N -dimethyl acetamide (DMAc, Sigma, anhydrous 99.8%), dimethyl sulfoxide- d_6 (DMSO- d_6 , Eurisotop, 99.80%), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, Tokyo

Chemical Industry, $<98\%$), dodecyl β -D-glucopyranoside (dodecyl glucoside, BLD Pharm, 98%), formic acid (Honeywell Fluka, $\geq 98\%$), α -D-glucose (Aldrich, 96%), lithium bromide (LiBr, Acros Organics, 99+%), 2,6-lutidine (Sigma Aldrich, 98%), microcrystalline cellulose (MCC, Sigma Aldrich), octyl β -D-glucopyranoside (octyl glucoside, BLD Pharm, 96%), pyrene (Sigma-Aldrich, 98%), sulfuric acid (H_2SO_4 , Fisher Chemical, $\geq 95\%$), trifluoroacetic acid (TFA, Acros chemicals, extra pure 99%), and vinyl laurate (VL, Tokyo Chemical Industry, $>99.0\%$) were used without further purification. Only deionized water was used. Other solvents used were HPLC or analytical-grade.

Synthesis of Cello-Oligomers by Mechanocatalytic Depolymerization of Cellulose

Microcrystalline cellulose (MCC, 5.00 g, 30.8 mmol, 1.00 equiv.), 95% sulfuric acid (H_2SO_4 , 0.254 g, 2.46 mmol, 8 mol %), and 75 mL diethyl ether were combined in a round-bottom flask and stirred for 1 h at room temperature. Afterward, the solvent was removed under reduced pressure to achieve uniform sulfuric acid impregnation of cellulose. For the mechanocatalytic depolymerization, 28 grinding balls (stainless steel, $d = 10$ mm) were placed into a grinding bowl (stainless steel, 50 mL), 5.00 g of impregnated MCC was added, and the grinding process was initiated. The mechanocatalytic depolymerization was carried out on a Retsch PM 200 planetary ball mill device in grinding cycles of 15 min at 650 RPM, followed by 10 min breaks to prevent overheating. After an effective milling time of 60 min (four cycles), the cello-oligomers were dissolved in 30 mL of deionized water, precipitated in 150 mL methanol, filtered, and dried under vacuum (10 mbar) at 65 °C. The final product was obtained as a white powdery solid with a yield of 84% (4.33 g, 26.1 mmol) (calculated based on the average molecular weight of the repeating unit based on the DP according to ^1H NMR (Supporting Information, eqs S4 and S5).

ATR-FTIR: $\nu / cm^{-1} = 3653\text{--}3001$ ($\nu(O-H)$), 2976–2826 ($\nu(C-H)$), 1014 ($\nu(C-O)_{AGU}$). ^1H NMR (400 MHz, D_2O): $\delta / ppm = 5.22$ (d, $J = 3.8$ Hz, α -re, 1H), 4.98 (br s, α -1,6, 1H), 4.65 (d, $J = 8.0$ Hz, β -re, 1H), 4.52 (d, $J = 8.2$ Hz, β -1,4, 1H), 4.51–4.49 (m, β -nr, 1H), 3.98–3.21 (m, AGU, 6H). ^{13}C NMR (126 MHz, D_2O): $\delta / ppm = 102.30$, 99.23, 95.85, 78.19, 75.93, 75.43, 74.77, 73.96, 72.88, 71.53, 71.17, 69.40, 60.49, 59.82.

General Procedure for the Synthesis of COLE

Cello-oligomers (100 mg, 0.602 mmol, 1.00 equiv.) were stirred in 5 mL of anhydrous DMSO until a homogeneous solution was obtained. Afterward, the reaction mixture was heated to 60 °C, and the respective amount of vinyl laurate (VL) was slowly added, followed by the addition of DBU (2.75 mg, 2.70 μ L, 0.0181 mmol, 1 mol % per –OH group). After the reaction mixture was stirred for 4 h, the solvent was reduced *via* vacuum distillation (95 °C, 5 mbar) to 1 mL, precipitated into 5 mL acetone, and filtered. The solid was submerged in 20 mL of deionized water and dialyzed against water (mixed cellulose ester membrane with a MWCO of 100–500 Da) for 2 days. After filtration to remove undissolved residues, the water was evaporated under reduced pressure, and the obtained solid was dried under vacuum (10 mbar, 65 °C) to afford the final product as a beige powdery solid. Yields were calculated based on the DS_{1H} according to Supporting Information eqs S6 and S7 (Table 1).

Analytic Methods

Infrared Spectroscopy (IR). ATR-FTIR measurements were conducted using a Bruker Alpha-p spectrometer with ATR technology in a range of $\nu = 400\text{--}4000\text{ cm}^{-1}$. Each measurement consisted of one background measurement and one absorbance measurement with 24 scans at a resolution of 4 cm^{-1} at room temperature.

Nuclear Magnetic Resonance Spectroscopy (NMR). NMR spectroscopy was performed using a Bruker Avance DPX 400 spectrometer (400 MHz for ^1H NMR) or Bruker Avance DPX 500 (126 MHz for ^{13}C) at a constant temperature of 298 K. For sample preparation, 5–25 mg of the samples were dissolved in deuterated solvents and mixed until homogeneous. ^1H NMR spectra were recorded at 400 MHz with 16–64 scans (delay time $d_1 = 1.00\text{ s}$), and ^{13}C NMR spectra were recorded at 126 MHz with 1024–16384 scans (delay time $d_1 = 1.00\text{ s}$). The chemical shifts (δ) were reported in parts per million (ppm) relative to the chemical shift of tetramethylsilane ($\delta = 0.00\text{ ppm}$) and referenced to the solvent signals of ^1H : DMSO- d_6 at 2.50 ppm or HDO at 4.79 ppm; ^{13}C : DMSO- d_6 at 39.52 ppm.

Electrospray Ionization-Mass Spectrometry (ESI-MS). ESI experiments were recorded on a Q-Exactive (Orbitrap) mass spectrometer (Thermo Fisher Scientific) equipped with a HESI II probe. Formic acid was added to the analytes to improve ionizability. The spectra were interpreted by peaks of protonated molecules $[\text{M} + \text{H}]^+$ and adducts such as $[\text{M} + \text{Na}]^+$. All peaks are indicated with their mass-to-charge ratio (m/z).

Size Exclusion Chromatography (SEC). SEC measurements were performed on an Agilent Technologies 1260 Infinity II equipped with a Mixed-C 5 μm and Mixed-E 3 μm Agilent column, and a differential refractive index detector. The eluent used was DMAC containing 0.034 wt % LiBr. The number-average molar mass (M_n), the weight-average molar mass (M_w), and the dispersity ($\bar{D} = M_w / M_n$) of the samples were determined using a calibration of poly(methyl methacrylate) (PMMA) standards ranging from 800 to $2.2 \times 10^6\text{ Da}$. The samples were dissolved in the eluent at a concentration of 2 mg / mL and filtered through a 0.20 μm filter.

High-Performance Liquid Chromatography (HPLC). HPLC analyses of the cello-oligomers were performed using an Agilent 1260 Series HPLC equipped with a refractive index detector (RID) and a Hi-Plex Ca (7.7 $\times$ 300 mm, 8 μm) chiral column (Agilent Technologies) with an 8 μm guard column (Agilent Technologies). 10–20 μL of the resulting analyte was injected into the HPLC instrument and analyzed with an isocratic water flow of 0.60 mL / min, a column oven temperature of 80 °C, and a constant RID temperature of 55 °C.

Fluorescence Spectroscopy. Fluorescence experiments were recorded on a FluoroMax Plus spectrometer (HORIBA Scientific) at a constant temperature of 20 °C and corrected by subtraction of a water blank spectrum. The analytes were excited at 334 nm, and the emission spectra were recorded in the range of 360–600 nm with 1 nm increments using quartz cuvettes. The entrance and exit slits were

fixed at 3 nm for each measurement. For the CMC determination, a 1 mM pyrene solution in acetone was prepared; 30 μL of this solution was added to an open screw vial, and the solvent evaporated until dry. Afterward, 30 mL of deionized water was added and stirred overnight to ensure a homogeneous 1 μM aqueous pyrene stock solution. The respective surfactant was dissolved in the 1 μM pyrene stock solution and further diluted to the desired concentrations, while maintaining the pyrene concentration constant.

Dynamic Light Scattering (DLS). DLS measurements were conducted on a Nanoseries ZetaSizer (Malvern, United Kingdom) device equipped with a He-Ne laser (633 nm). For sample preparation, the analyte was dissolved in deionized water and passed through a 0.45 μm syringe filter. All measurements were performed in deionized water at room temperature; each run was conducted in triplicates, and an average value was determined.

Optical Microscopy. Micellar solutions were visualized using a Leica DM IL LED microscope. Briefly, 10 μL of a water/oil emulsion was pipetted onto a glass slide and covered with a coverslip. Images were acquired using a 40-fold objective.

MTT Assay. For quantitative determination of the toxicity of the respective substance, 100 μL of a cell suspension ($1.0 \times 10^5\text{ cells/mL}$) is seeded per well into a 96-well plate (Cellstar 96 Well Cell Culture Plate). The cells are then incubated for 24 h at 37 °C and 5% CO_2 atmosphere. After incubation, the medium is aspirated and replaced with 100 μL of the respective test solution in the growth medium. Each test substance is examined in triplicate. In addition, three wells are provided for the negative and positive controls. Afterward, the plate is incubated for a further 72 h at 37 °C and 5% CO_2 atmosphere. To prepare the negative control, 5 μL of Triton X-100 is added to three untreated wells. Next, 15 μL of MTT reagent is added to all 60 wells and the plate is incubated for 4 h at 37 °C. After incubation, 100 μL of stopping solution is added to lyse the cells. Absorbance is measured after further incubation overnight at 37 °C and 5% CO_2 using a SpectraMax iD3 microplate reader at a wavelength of 595 nm. The HeLa cells are obtained from the Leibniz Institute DSMZ (DSMZ-German Collection of Microorganisms and Cell Cultures).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscchemeng.6c00688>.

Calculation of relevant parameters (DP, content of α -1,6-glycosidic bonds, DS, yields, and HLB values), synthesis details and data of cello-oligomers and COLEs, DLS data, optical micrographs and micrograph analysis, and MTT assay of alkyl glucosides (PDF)

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Notes

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