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Accelerated Non-Enzymatic Fatty Acid Esterification during Microdroplet Collision: A Method for Enhanced Sustainability

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ABSTRACT: Accelerated non-enzymatic and metal-free "reaction and extraction" of sugar esters at the interface of two immiscible liquid microdroplets is demonstrated. The bimolecular reaction occurs by collision of microdroplets originating from two home-built electrospray sonic ion sources, carrying sugar molecules in water and long-chain fatty acids in toluene, respectively. Our method shows that the rate of reaction is enhanced ~10⁷ times in comparison to the bulk, initiated by ultrasonic activation. Such a high rate of reaction in the microdroplets can be attributed to factors such as surface activity, concentration enhancement, partial solvation, and temperature-assisted dehydration of the species occurring in microdroplets. We provide evidence for an interfacial nucleophilic addition—elimination reaction mechanism. This method of synthesis is extended to 18 similar reactions. Microdroplet synthesis offers a sustainable method for biphasic reactions, eliminating the need for phase transfer reagents and activating agents such as acids/bases, metals, or enzymes.

KEYWORDS: microdroplets, reaction acceleration, mass spectrometry, sugar esters, fatty acids

INTRODUCTION

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Green chemistry is a long-term desire of chemists, and its associated 12 principles are well known.^{1,2} Several unconventional energy sources such as ultrasound, mechanical forces, heat, and photons have been used in chemical synthesis to eliminate hazardous metal catalysts, strong acids, solvents, and reagents, contributing to green chemistry.³ Nevertheless, advancements in developing greener preparative processes are always in high demand for a sustainable future.

Despite decade-long advancements in synthetic procedures for the esterification reaction, an ester C–O bond formation⁴ has always been a challenge chemically.⁵ One of the major limitations is that a reaction between a carboxylic acid and an alcohol is energetically unfavorable due to the low reactivity of the functional groups, and they are altered conventionally by using acid anhydrides⁶ or acid chlorides⁷ or by adding strong inorganic acids to activate the electrophilic C-center of the carboxylic acid.^{8,9} Some of the classic examples are Fischer,¹⁰ Steglich,¹¹ and Yamaguchi esterification reactions.¹² Several such reactions were also performed using transition-metal catalysts.¹³ Fatty acid esters of carbohydrates, called sugar esters (SEs), are commonly synthesized by the reaction of long-chain fatty acids and alcohol-functionalized sugar molecules by lipase enzymes (Scheme 1a).^{14,15} An acyl-enzyme intermediate complex between the fatty acid and lipase is formed first, followed by the binding of alcohol onto this enzyme–substrate complex, leading to a lipase–ester complex, which finally releases the ester and the enzyme.¹⁶ In general, enzyme extraction and purification is an intricate process that involves processes such as fermentation, vacuum filtration, separation, preconcentration, and drying, some of which are energy intensive. The ester products are biosurfactants and are metabolites found in several organisms. Biologically, such

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Scheme 1. Sugar Esterification (a) Catalyzed by Lipase in Cell/Bulk Synthesis vs (b) Accelerated Microdroplet Synthesis

reactions are important because these compounds help in controlling cell adhesion, which affects the growth and localization of the organism.¹⁷ These biosurfactants have a growing demand in comparison to synthetic surfactants due to their lower toxicity and biodegradability. SEs are used in several food, pharmaceutical, and cosmetic industries.^{15,17–19} However, lipase-catalyzed esterification reactions are limited by the choice of the solvent system for making a homogeneous solution for lipids that are soluble in non-polar solvents and sugars soluble in water. To overcome the solution-phase heterogeneity, several ionic liquid-based synthetic protocols have been attempted in the past.^{20–22} Use of a phase transfer catalyst is a general practice in such organic–aqueous mixed phase reactions.²³

Since the development of electrospray ionization-mass spectrometry (ESI-MS) half a century ago, it has facilitated the advancement of molecular analysis. In ESI, solution-phase neutral molecules are converted to gas phase ions via charged microdroplets. Recently, these charged microdroplets have attracted the interest of many mass spectrometrists from the preparative point of view. This is because of the acceleration of rates of several organic reactions,^{24–31} formation of reactive species,³²⁻³⁴ and alternate reaction pathways³⁵ in such environments compared to similar chemistry in reaction vessels. In addition, microdroplet synthesis is a promising sustainable technique involving low solvent and energy consumption, catalyst-free chemical transformation, and with high atom economy.³¹ Similarly, nanobubbles are becoming important in various aspects of environmental remediation.³ These experiments are mainly performed in electrospray sonic ionization,^{29,35,37–39} nanoelectrospray ionization,^{40,41} paper spray ionization,⁴² and individually levitated droplets.⁴³ Furthermore, the Zare group found that such reactions can also be performed in colliding microdroplets formed from two ESI sources kept at an angle such that the spray plumes intersect each other.^{26,44-47} Many microdroplet reactions were scaled up to prepare gram-scale quantities of products. Methods such as multiplexed electrospray,^{39,45} ultrasonic heated nebulized spray,⁴⁶ and solvent recycling electrospray⁴⁸ have been demonstrated in the literature for large-scale synthesis. A few hypotheses were made in the literature to understand such unique chemistry such as spatial distribution of solute molecules,⁴⁹ existence of a substantial pH gradient,⁵ formation of reactive species,⁵¹ restricted molecular rotations,⁵² high interfacial electric field,⁵³ and partial solvation of molecules.^{31,54} Recently, enzyme-catalyzed hydrolysis of lipids was monitored in microdroplet environments by the Badu-Tawiah group.⁵⁵ All the above studies encouraged us to perform C–O ester bond formation reactions in microdroplets.

In the present work, we have demonstrated a non-enzymatic, fast synthetic method leading to SEs using microdroplet chemistry under ambient conditions at an immiscible aqueous—organic interface, without adding any phase-transfer catalyst. Reaction and extraction were performed simultaneously. We used online MS monitoring to derive a mechanistic understanding of the reaction. Several control experiments were performed by varying parameters such as the spray distance, solvents, external surfactant, and so forth to realize the microdroplet reaction process. The scope of the microdroplet reaction was further tested by extending the synthesis to 18 different SEs.

EXPERIMENTAL SECTION

Microdroplet Collision Experiment. The experimental setup for microdroplet collision is schematically presented in Scheme 2. The reactions were performed using two ESSI sources, which were held at

Scheme 2. Schematic of the Experimental Setup for Ester Bond Formation Reaction by the Collision of Aqueous and Organic Microdroplets Generated by Two ESSI Sources Coupled with a Mass Spectrometer^a



^{*a*}The distance from the collision point to the inlet of the mass spectrometer is given as X, in cm. While the aqueous spray tip is at high voltage, the organic spray tip is grounded.

an angle of 60° in front of the mass spectrometer. We used N₂ as a nebulization gas at 100 psi. To perform the reaction, we sprayed an aqueous solution of sugar (8 mM) at a flow rate of 5 μ L/min at 2.5 kV spray potential of negative polarity through the first ESSI source. Using the second ESSI source, the organic solution of fatty acid (8 mM) was sprayed with N₂ gas at no applied potential. It should be noted that while we chose sugar to dissolve in water in all the experiments, the fatty acids were insoluble in water and we used toluene instead for their dissolution.

MS Experiment. Online MS measurements were performed using a Thermo Scientific LTQ XL mass spectrometer. We used an inlet temperature of 50 °C for most of the reactions otherwise mentioned in the respective places. Tube lens and capillary potentials were set to -35 and -110 V. The sheath gas flow rate was set to zero.

MS Experiment of the Sonicated Bulk Reaction. The aqueous phase was separated from toluene, it was diluted 1000 times with MeOH to quench the reaction, and ESI-MS was performed with a commercial ion source at 5 kV spray potential, 8 psi sheath gas flow rate, -35 V capillary potential, -110 V tube lens potential, and 275 °C inlet temperature for characterizing the intermediate and the product. We chose methanol for dilution to make a homogeneous system for electrospray as both water and toluene are miscible in methanol.

Dark Field Imaging. A CytoVivaTM microscope was used for collecting the dark-filed image of the droplets. The microscope was equipped with a high-resolution dark-field oil immersion condenser lens. We used a L1090-halogen lamp from International Light Technologies Inc. as a white light source for imaging the droplets. The image was captured using a Dage Excel M cooled CCD camera. The imaging experiment was performed by drop casting the liquid on clean glass slides (SCHOTT nexterion).

RESULTS AND DISCUSSION

Microdroplet Collision and Mass Spectrometry Analysis. Scheme 1 compares the reaction between conventional synthesis and the microdroplet method. Scheme 2 shows the experimental setup for the reaction, where two ESSI sources were held at an angle of 60° in front of the mass spectrometer (detailed discussion on the setup is presented in the Experimental Section). Figure 1a,b shows the negative ion mass spectra of individual reagents collected by electrospraying (-2.5 kV spray voltage) one reagent at a time. Peaks at m/z179 and 281 correspond to deprotonated glucose and oleic acid. The peaks were further confirmed using collision-induced dissociation experiments of the isolated ions (Figure S1). Interestingly, in Figure 1c two additional peaks at m/z 443 and 461 were observed along with the reagent peaks upon spraying both the reagents, as shown in Scheme 2. Note that we did not apply any potential to the oleic acid source, but still observed a peak corresponding to the deprotonated oleic acid $(m/z \ 281)$ probably because of the charge transfer as discussed in detail in the next section. We collected a mass spectrum from the nebulized spray of oleic acid in toluene as well, where no such molecular ion peak at m/z 281 was observed (Figure S2). The two new peaks that appeared in Figure 1c were assigned to the product, glucose-oleate at m/z 443, and the intermediate peak of the esterification reaction at m/z 461. These assignments were further confirmed using the MS/MS spectra of the isolated peaks. The MS/MS spectrum of the product at m/z443 shows neutral losses corresponding to CO₂, CO, and water molecules to give a major peak at m/z 399 and two minor peaks at m/z 415 and 425 (Figure S3a). A few minor peaks in the mass rage of m/z 390 to 330 and two intense peaks at m/z315 and 297 were also observed, and their assignments are shown in Figure S3a. We also observed m/z 281, corresponding to deprotonated oleic acid, which was further



Figure 1. Microdroplet synthesis of glucose/oleic acid ester. (a,b) Negative ion ESSI mass spectra collected individually from 8 mM aqueous solution of glucose and 8 mM solution of oleic acid in toluene. The insets of (a,b) show the molecular structures of the reagents. (c) Mass spectrum collected by spraying both the reagents at a time. Insets of the spectrum represent the microdroplet collision and the zoomed-in spectrum of the selected mass range showing isotopic distributions of the product and the intermediate peaks. The peak at m/z 443 is multiplied five times. The ions at m/z 297 and 313 are oxides of oleic acid. Mass speaks are labeled.

confirmed by the MS/MS/MS spectrum of m/z 281, shown in Figure S3b. Similarly, the MS/MS spectrum (Figure S3c) of the intermediate at m/z 461 shows neutral loss of water molecules to give a base peak at m/z 443 (product peak) and three other peaks at m/z 399, 417, 425, and 433, corresponding to (H₂O + CO₂), CO₂, and 2H₂O and a CO loss from m/z 461. Noticeably, we did not observe polysubstituted products for the reaction, either due to low product ion concentration to undergo further reaction or a short time available for the reaction at the interface or inadequate energy of activation. We observed peaks at m/z 297 and 313, corresponding to mono- and dioxygen-added oleic acid, due to areal oxidation of oleic acid at the droplet surface. Such oxidation might occur due to the presence of airborne ozone.⁵⁶

The conversion ratio (CR), that is, the ratio between the intensity of the product ion or the intermediate species and the sum of the intensities of the product, intermediate, and fatty acid (R) ions gives a rough idea about the yield of the reaction.⁵⁷ Note that we did not consider the intensities for the sugars in this equation. We observed that the intensities of sugar species were invariant with respect to different reaction conditions. This could be due to the fact that the resultant signal intensity of the sugar comprises both sugar from uncollided droplets and unreacted sugar from collided droplets. The calculated CRs of the reagent to intermediate and product are 20 and 1.2%, respectively. However, the absolute yield may vary due to a difference in the ionization efficiency of the species.

Mechanistic Understanding of Simultaneous Microdroplet Reaction-Extraction of SEs. Based on the above understanding and previous studies on microdroplet chemistry, we suggest that the sugar anion formed at the air/water interface of the aqueous microdroplet attains a specific orientation, by which the anionic alkoxide maximizes charge distribution (Scheme 3, blue droplets) and minimizes

Scheme 3. Mechanistic Understanding of the Microdroplet Collision-Esterification Reaction a



"The schematic demonstrates different steps involved in the collision, reaction, extraction, and product formation of the glucose/oleic acid esterification reaction on the surface of a microdroplet. The blue and the red color represent the aqueous and toluene droplets, respectively.

electrostatic repulsion. Such a charge distribution at the air/ liquid interface has been reported previously.58 This interfacial alkoxide anion acts as a strong nucleophile. On the other hand, the long-chain hydrophobic hydrocarbon part of the fatty acid, dissolved in organic microdroplets, will be at the core of the droplet due to the hydrophobic-hydrophobic interactions, whereas the hydrophilic carboxylic acid groups will occupy the interface to minimize the hydrophobic-hydrophilic repulsion energy (Scheme 3, red droplets). Strong interfacial concentration of molecules is one such reason for reaction acceleration in confined volumes.⁴⁹ Microdroplets undergo rapid desolvation, and the molecules at the interface are partially solvated, which help them overcome the activation barrier due to solvation. The recent experimental and computational results from Cooks et al. support such a limited solvation at the air/liquid interface of microdroplets.^{59,60} Herein, we proposed a process involving interfacial molecular enrichment, specific molecular orientation, and partial solvation, for the C-O coupling reaction in microdroplets. These factors give more accessibility to the alkoxide nucleophile to attack the electrophilic C-center of the carboxylic acid on the interface, while two droplets are colliding with each other. However, such a nucleophilic addition in the bulk is limited by liquid-liquid phase separation, low nucleophilicity of the hydroxyl group, low electrophilicity of the carboxylic group, solvation of the reagents, and so forth, and consequently lipid esterification requires enzymatic activation. The microdroplet environment helps in overcoming such constraints to achieve chemical bond formation in the absence of an enzyme. Such a nucleophilic attack between the sugar and the fatty acid leads to the formation of a new C–O covalent bond (i.e., intermediate, m/z 461) at the aqueous organic interface between the two colliding droplets. In other words, the tetrahedral intermediate (Scheme 4a) forms due to the nucleophilic addition, creating a bridge between two flying droplets. Scheme 4b displays a schematic view of the overall reaction mechanism.

On the other hand, we propose a competitive reaction pathway to explain the ionization of oleic acid during microdroplet collision, schematically shown in Scheme S1. This represents a proton transfer from the carboxylic acid in the organic microdroplet to the alkoxide group of the sugar in

Scheme 4. Understanding the Reaction Mechanism at the Interface of Two Droplets; (a) Schematic View of the Tetrahedral Intermediate Formed by the Nucleophilic Addition of the Alkoxide Group to the Carboxylic Group at the Interface of Two Droplets of Immiscible Liquids; (b) Reaction Mechanism of the Formation of Neutral Glucose-Oleate Ester





Figure 2. Esterification in bulk vs ultrasonicated toluene-in-water droplet. (a) Dark-field microscopy (DFM) of toluene microdroplets containing oleic acid in aqueous glucose solution. Moving droplets of different sizes were observed (white squares). One of the droplets is focused and a zoomed-in image of the same is shown in the inset. (b) Comparative mass spectra of the aqueous part of the reaction mixture after phase separation and dilution with methanol. Reaction was performed at 3, 15, and 30 min of ultrasonication. Insets show an expanded mass range, and the intermediate at m/z 461 is marked.

the aqueous droplet, leaving the anion of the fatty acid detected in the mass spectrum (m/z 281, Figure 1c). Due to such charge transfer across the water/toluene interface, both the droplets become negatively charged. Lee et al. found that the propulsion force by dry N₂ during nebulization accelerate droplets to attain a high speed in air.⁴⁴ Therefore, electrostatic repulsion and momentum exchange during high speed collision between the two droplets in air will push them apart from each other and subsequently create a choice for the intermediate species to travel to either of the droplets.⁶¹ It has previously been reported that microdroplet provides aqueous organic biphasic reactions that require no phase transfer catalyst.^{45,62} However, whether the reaction occurs at the interface of the two droplets or they undergo a reaction followed by coalescence is not understood well. We proposed that during microdroplet collision, the intermediate species get extracted by the aqueous droplets preferentially. Such extraction of the analyte from one droplet to the other, termed as extractive electrospray ionization, was previously reported by Cooks et al.⁶³ This may be understood as the hydrogen bond strength between the hydroxyl unit of the sugar part of the intermediate and water is higher than the interaction energy between the long-chain hydrocarbon and toluene. This is also evident from the solvent dependency experiment and the infrared (IR) spectroscopy experiments (see below). Finally, subsequent loss of a water molecule from the intermediate leads to the formation of the product ester.

Monitoring Bulk Reactions. A bulk reaction was performed by mixing a toluene solution of oleic acid (8 mM) with glucose in water (8 mM) at a 1:1 (v/v) ratio. Due to the immiscibility of the two solvents, immediate phase separation occurred in the bulk. Upon examination of both the aqueous and organic phases using MS, we found that the reaction does not occur by mixing, in the bulk. However, we noticed the presence of oleic acid in the aqueous phase as evident from the mass spectrum (Figure S4a). Interestingly, the reaction does occur, but got stopped at the stage of intermediate formation (m/z 461) during ultrasonication for 1 min (Figure S4b), but no product (m/z 443) was observed. Sonication leads to water-in-oil and oil-in-water droplets,

which could drive the reaction. This was evident from the IR spectroscopy, DFM, and MS results. Figure S5 shows the ATR-IR spectrum of the aqueous phase of the reaction mixture, in which we observed peaks corresponding to CH stretch, asymmetric and symmetric stretches of CH_2 , and C=Ostretch at 3010, 2926, 2854, and 1707 cm⁻¹, respectively. Two peaks at 693 and 725 cm⁻¹ were also observed due to the out of plane C-H bending of toluene. We suspected that oleic acid present in water and as a solvated species in toluene microdroplets made a heterogeneous system. To observe these toluene microdroplets, we performed DFM of the water sample. Figure 2a shows the DFM image of three individual droplets immersed in water. In the mass spectrum of the sonicated mixture (Figure S4b), we found a deprotonated peak of oleic acid at m/z 281 along with a deprotonated peak of glucose at m/z 179 and an intermediate peak at m/z 461 with very low intensity.

Above findings led us to perform time-dependent reactions of oil-in-water microdroplets by sonicating the reaction mixture in an ultrasonicator (see the experimental section). Figure 2b(i–iii) shows the mass spectra of the aqueous phase after 3, 15, and 30 min of ultrasonication. We observed $\sim 1\%$ of the intermediate peak intensity relative to oleic acid upon 3 min of sonication, which got intensified three times upon 30 min of sonication. We found no increase in relative signal intensity of the intermediate upon further sonication. The spectrum shows the intermediate at m/z 461 and not the product at m/z 443 as the reaction was performed in bulk water. Note that m/z 443 is a result of elimination of water from m/z 461. In the bulk reaction, removal of water needs a strong dehydrating agent and therefore its absence in ultrasonication is not surprising. This observation indicates that microdroplet promotes efficient dehydration from the reaction site. Comparing the intermediate ion yield of "15 min sonicated bulk reaction" with the microdroplet reaction, we calculated the apparent acceleration factor (AAF). A qualitative estimation of AAF can be made by taking a ratio between the time taken by the product to reach the same CR in both bulk and microdroplet conditions.⁶⁴ Note that the AAF was calculated by keeping X at 1 cm for microdroplet reaction.



Figure 3. Factors that influence droplet reactions. (a) Distance vs CR plot. (b) Comparative CR of the intermediate at different solvent compositions. (c) Schematic illustration of the microdroplet interfaces at close proximity, showing surfactant-induced reaction barrier for nucleophilic addition. (d) Mass spectrum of the reaction mixture containing SDS (peak at m/z 265) in the aqueous phase. Green, blue, and orange shades indicate the peak positions for deprotonated glucose, deprotonated acid, and intermediate species, respectively.

As there is no product peak observed in the sonication experiments, an exact AAF could not be calculated. However, a qualitative understanding can be made by comparing the intensities of the intermediate species at m/z 461. We found that the glucose/oleic acid reaction shows very high AAF (approx 10⁷). It should be noted that this value does not include factor such as the effects of ultrasonic cavitation for the bulk reaction.

Distance Effect. The distance from the point of crossing of two ESI plumes to the inlet of the mass spectrometer is considered as the effective microdroplet reaction zone.³⁰ Microdroplet reactions are known to be influenced by this distance, X (Scheme 2). In our experiment, a change in the distance shows a dramatic effect on the signal intensity for the intermediate species. However, the product peak intensity was varying slightly. Figure 3a shows the distance versus CR for both the intermediate and the product. The distance was varied from 0.3 to 4 cm. We observed that upon increasing the distance, the intensities of both the intermediate and the product peaks increase exponentially. A stack of mass spectra at different distances is shown in Figure S6, where a clear increase in the intensity of m/z 461 is noticed. It suggests that droplets are not only colliding at the point-of-intersection, but collisions may occur during the entire length of flight, all the way toward the inlet of the mass spectrometer. We infer that this effect could be either due to increased collision frequency resulting from the increased number of droplets or due to the fact that smaller droplets have more concentration enhancement at their interfaces, which shifts the reaction toward the intermediate.

Effect of Different Solvent Systems. The interfacial reaction mechanism was further tested by varying solvent polarity. Experiments were conducted by dissolving oleic acid in three different solvent systems; methanol, toluene, and chloroform. Figure S7 shows the mass spectra of microdroplet

reactions between oleic acid in these three solvents and glucose in water. The reaction was performed by keeping X at 1 cm and 50 °C inlet temperature. One would expect better ionization for the polar intermediate in polar methanol than non-polar toluene and chloroform, which are non-friendly to electrospray.⁶⁵ However, we found that by changing the organic solvent from non-polar toluene to polar and protic methanol, the reactivity reduces. As a result, we observed low signal intensity of the intermediate in methanol than in toluene, as shown in Figure 3b. Methanol as an acyl receptor could also react with fatty acid to form methyl ester, which can be viewed as a competitive reaction to reduce the relative intensity of the intermediate (m/z 461). However, we have not observed any methyl ester of the fatty acid, which may be used to neglect the possibility. We assessed that a reduction in chemical reactivity of oleic acid in methanol is due to better solvation of the acidic head group at the droplet interior, which eventually makes the sp²-C center inaccessible to undergo nucleophilic addition. We also found that chloroform works similar to toluene due to its non-polar nature.

Effect of the Surfactant. The interfacial reaction mechanism was further investigated by manipulating the surface of the aqueous droplet. To do so, we added a surfactant to the glucose solution. The surfactant will occupy the droplet surface, which will prevent the alkoxide group to come to the air/water interface to make a nucleophilic attack. Figure 3c shows a schematic of this concept. We used 0.1 mM sodium dodecyl sulfate (SDS) along with 8 mM of glucose solution in water for the reaction. Figure 3d presents the mass spectrum of the oleic acid/glucose reaction with SDS. In the mass spectrum of SDS-added reaction mixture, we observed a significant loss of signal intensity for glucose at m/z 179. We also observed peaks corresponding to SDS at m/z 265 after sodium loss. However, peaks corresponding to the intermediate and the product were missing in the full mass



Figure 4. Effect of temperature in the interfacial microdroplet reactions. (a) Normalized intensity of the intermediate $(m/z \ 461)$ and the product $(m/z \ 443)$ vs temperature plot, showing sigmoidal growth of both the intermediate and the product intensity at 120 and 193 °C, respectively. Temperature dependency of the rate of formation of the intermediate (b) and the product (c) and their corresponding activation energies. (d) Schematic diagram of the energy profile of the reaction based on the temperature-dependent experiment.

spectrum. This suggests that the reaction does not occur upon droplet collision, which further supports our interfacial nucleophilic addition—elimination mechanism upon droplet collision.

Temperature Effect. From our previous studies and existing literature, we understood that microdroplet reactions are significantly influenced by temperature.^{40,66} Part of this is due to the increased rate of desolvation of the droplets,⁶⁷ dehydration from the reaction site,40 and need of some activation energy.⁶⁶ To understand the effect of temperature on the rate of the reaction, an experiment was performed by varying the temperature of the inlet of the mass spectrometer from 50 to 400 °C during the reaction. Figure S8 shows a stack of the mass spectra collected with increasing inlet temperature alone while keeping all other parameters of the setup constant. We noticed a significant increment in signal intensity for both the intermediates and the product, with increasing temperature. Figure 4a,b displays relative intensity-temperature traces for the intermediate and the product. Note that we did not consider the change in the signal intensity of glucose as we used glucose in the electrospray ion source. Hence, it is expected that glucose intensity will increase with temperature due to enhanced droplet-to-gas phase ion transfer at elevated temperatures (Figure S9a). Hence, the signal intensity for glucose is not restricted to its interfacial concentration. The CR-temperature profile shows that the signal intensity of both the intermediate and the product follows a sigmoidal curve with increasing temperature. However, a noticeable difference in saturation temperature was observed for both of them. While the intermediate peak rises to the highest intensity at 152 °C, the product reached its saturation at 225 °C. We speculated that this additional 73 °C is required to eliminate a

water molecule from the intermediate and pull it from the reaction site at the air/water interface. However, one can expect that this process would be inefficient and be perturbed by the presence of water molecules coming from the droplet, according to Le Chatelier principle. As a result, we get a low product yield.

We observed loss of signal intensity for the intermediate peak after 245 °C. Partly, this is due to the intermediate to product conversion. However, some of the intermediates also undergo the newly formed C-O bond cleavage at higher temperature, which eventually regenerates the reagents. This can be seen in the temperature profile for the oleic acid peak (Figure S9b). The peak reduces significantly up to 150 °C and then starts increasing and saturates around 245 °C. This suggests that the reaction is reversible in microdroplets and such an equilibrium can be controlled by controlling the rate of desolvation. Considering the bulk reaction and the time associated with it, a plot of inverse temperature versus reaction rate gave us the corresponding activation energies for the formation of the intermediate and the product. Figure 4b,c shows the overall activation energies required for the conversion of reagents to the intermediate and subsequently to the product, which are 56 and 125 kJ/mol, respectively. The reaction is accelerated at the liquid-liquid interface of two immiscible microdroplets due to the generation of the active nucleophile, partial solvation, and specific orientation of these reactants, as shown in Scheme 3. The temperature of the inlet helps in overcoming such activation barriers. Based on the estimated activation energies, in Figure 4d, we present a schematic of the energy profile of the reaction.

Scope of the Microdroplet Reaction of Sugar Esterification. This systematic study of the microdroplet

Scheme 5. General Reaction Scheme along with the Structures of the SEs Synthesized in This Work (a-r) and the Percentage Intensities of the Intermediate or Product Peaks Relative to Their Corresponding Fatty Acid Peaks



reaction mechanism led us to extend the esterification reaction by changing both the sugar and the fatty acid. We chose 6 different sugars, 3 different acids, and all possible combinations to perform 18 reactions. Scheme 5 summarizes the results of all the reactions, where we report the relative intensities (i.e., the ratio between the intermediate or product and the corresponding fatty acids) of the product and the intermediates, considering 150 °C inlet temperature for microdroplet reactions. The product yield is always less in comparison to the intermediate yield, and that can be understood by the relative signal intensities (Figures S10-S26). Interestingly, we observed only monosubstituted products. Esterification at multiple sites of the sugar has not been observed primarily because of the low concentration of the product ester. In addition, we found that the reaction rate is high for glycerol. This could be due to the small size of the reactant, which helps it to overcome the steric effect for nucleophilic addition. Interestingly, glycerol/caproic acid combination gave the highest CR for the intermediate peak. However, the low reactivity of ethylene glycol could be due to its smallest size, which restricts it to attain a specific orientation at the surface in

favor of the reaction. On the other hand, sugars with similar functionality show similar reactivity.

Qualitative Sustainability Assessment. A qualitative assessment of sustainability was performed to determine the greenness of the method. Sugars and fatty acids are biomolecules, and their reactions do not lead to any toxic byproducts. In comparison to the conventional esterification synthesis, herein, no catalysts including strong acids/bases, metals, or enzymes were used. This biphasic microdroplet collision method allows zero use of the phase transfer catalyst as well. The microdroplet method involves a minimal solvent volume along with 100% solvent recovery as demonstrated in the literature. The process involves direct formation of a solid crude product from solution-phase reagents. In microdroplet synthesis, unreacted reagents can also be reused easily after separation and extraction as limited chemical species were used in the reaction. The method also shows low energy wastage because we used electrical energy directly as an input for the reaction to proceed, while conventional methods utilize electrical energy in the form of heat, ultrasound, microwave, or photons. This resulted in net dissipation of energy during each conversion. Therefore, the reaction presents the use of

CONCLUSIONS

In summary, we demonstrated a sustainable method of accelerating interfacial chemistry between analytes dissolved in two immiscible liquids, which is cumbersome in the conventional process due to the requirement of a phase transfer catalyst and agitation. In this work, bimolecular sugarlipid esterification occurs efficiently with two-step nucleophilic addition and water elimination, which completely eliminates the need for conventional lipase enzymes, leading to improved sustainability. However, understanding the reaction mechanism in such a microdroplet environment through spectroscopy is a scope of further investigation. We utilized online MS to detect the species formed during the reaction. We have shown evidence for an interfacial microdroplet mechanism. Our understanding of reaction acceleration in microdroplets stands on a combination of four major mechanisms: (i) interfacial enrichment, (ii) partial solvation of molecules, (iii) specific orientations of the reagents at the interface, and (iv) dehydration at the reaction site. Concepts (i) and (ii) have been understood previously through theory and experiments. However, the current work provides strong evidence for (iii) and (iv). A specific molecular orientation was demonstrated by the surfactant and solvent effects. Dehydration at the reaction site was observed directly from the temperature effects. An analogy between ultrasonic and microdroplet experiments also indicates the same. Successful esterification reactions using a minimal amount of reagents is demonstrated. Moreover, these studies are also important in understanding interfacial chemistry that can occur in electrospray microdroplets. In fact, such enhanced chemical reactivity in aerosols can have profound implications in cellular, atmospheric, and prebiotic chemistries. Improved product yield and enhanced conversion efficiency are in the scope of our future work.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.2c02070.

MS and MS/MS of the reagent, intermediate, and product; IR of the reaction mixture; and MS and MS/MS of several other reactions (PDF)

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Author Contributions

P.B. and T.P. designed and performed the experiments. P.B., J.S.K., and S.D. helped in performing reactions and microscopy of droplets. P.B. wrote the initial draft of the paper with input from all the authors. The project was conceived under the supervision of T.P.

Notes

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ABBREVIATIONS

ESI MS, electrospray ionization mass spectrometry; SE, sugar esters; CR, conversion ratio; AAF, apparent acceleration factor.

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