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journal or publication title	Angewandte Chemie - International Edition
volume	51
number	8
page range	2080-2083
year	2012-02-27
URL	<a href="http://hdl.handle.net/2297/30350">http://hdl.handle.net/2297/30350</a>

doi: 10.1002/anie.201107706

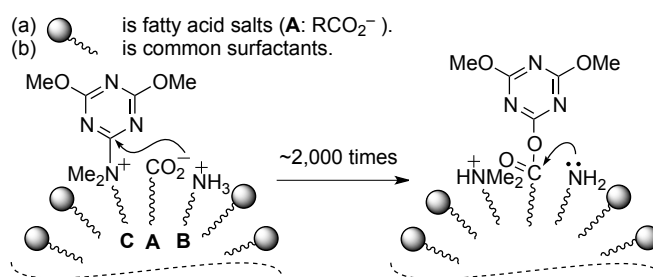
# Substrate-Selective Dehydrocondensation at an Interface of Micelles and Emulsions of Common Surfactants\*\*

Munetaka Kunishima,\* Kanako Kikuchi, Yukio Kawai, Kazuhito Hioki

The utilization of micelles for controlling organic reactions has been attracting considerable attention. The micellar interface is well known as an excellent reaction field for *hydrolysis*.<sup>[1-4]</sup> In spite of this fact, the reverse reaction, i.e., the *dehydrocondensation* of a carboxylic acid and an amine, can also be accelerated in the micellar interface. In fact, we successfully showed that a remarkable rate acceleration for the reaction of aliphatic carboxylic acids **A** and amines **B** by 1,3,5-triazine-based amphiphilic dehydrocondensing agents **C**,<sup>[5]</sup> which are available in water similar to 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM),<sup>[6,7]</sup> occurred up to 2,000 times faster in micelles than in a normal homogeneous molecular dispersion phase (Fig. 1). Because both carboxylic acids and amines generally exist in the ionized state in water at near-neutral pH, these compounds have amphiphilic properties when they possess a long alkyl chain. Thus, when dissolved in water, they can form a molecular assembly, such as micelles, independently or be incorporated into molecular assemblies formed by other surfactants. In this case, the concentration of all reactants in the micelles will significantly increase (local concentration effect). In addition, the charged hydrophilic polar heads, such as carboxylate, ammonio, and triazinylammonio groups, undergoing the reaction should be located at the interface in close proximity to each other (preorientational effect). Thus, the coupling reaction of carboxylic acids and amines using the amphiphilic dehydrocondensing agents can be promoted by the formation of micelles.

However, in our previous study, the reaction rate enhancement was achieved in limited cases where the reactant fatty acid salts, such as laurate, could act as surfactants forming micelles under the reaction conditions (Fig. 1-(a)).<sup>[5]</sup> In fact, no significant rate

acceleration was observed in the reactions using carboxylates with a high critical micellar concentration (cmc), such as octanoate that cannot form micelles under the reaction conditions. In addition, the majority of the carboxylates used in excess to generate micelles must be discarded. If a similar acceleration is realized with lesser number of carboxylates independent of their micelle-forming properties, the reaction becomes synthetically useful. This paper describes the micellar effect of common surfactants other than fatty acid salts on amide formation (Fig. 1-(b)), and investigates the relationship between reactant lipophilicity (carboxylates or amines) and reaction rate acceleration. Selectivity for alkylamines that had not been previously examined will also be discussed.



**Figure 1.** Rate acceleration of dehydrocondensation in micelles.

We examined coupling reactions of aliphatic sodium carboxylates possessing alkyl chains of different lengths (5 mM) and butylamine (20 mM) in the presence of nonionic (4-(1,1,3,3-tetramethylbutyl)phenyl-polyethylene glycol: Triton X-100) and anionic (sodium dodecyl sulfate (SDS), sodium 1-decanesulfonate (DSA)) surfactants under identical conditions (25 °C, 12 h). We employed an amphiphilic condensing agent (**C-1**, 1.5 mM), which was found to realize a large rate acceleration in the fatty acid micellar system previously reported by us.<sup>[5]</sup> The concentration of surfactants was five times their cmc.

As shown in Table 1, the reactions of sodium hexanoate ( $\text{C}_5\text{H}_{11}\text{COONa}$ ) and sodium octanoate ( $\text{C}_7\text{H}_{15}\text{COONa}$ ) were significantly promoted by the addition of a surfactant. Because these carboxylates do not form micelles under the reaction conditions, the observed rate acceleration is attributed to the micellar effect of the added surfactants. A similar effect of surfactant on the reaction rate was observed with aromatic benzoate. On the other hand, the reaction of sodium laurate ( $\text{C}_{11}\text{H}_{23}\text{COONa}$ ) proceeded in good yield irrespective of the presence or absence of the surfactant. Because the reaction of laurate had already been accelerated by its own micelles,<sup>[8]</sup> an additional surfactant did not have a substantial effect on the reaction rate. A positive relationship between the yield and the carbon chain length of carboxylates reflecting their hydrophobicity would also support the micellar effects on the reactions.

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[\*\*] This work was supported partially by a Grant-in-Aid for Scientific Research (No. 20390007) from Japan Society for the Promotion of Science (JSPS).



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**Table 1.** Effect of surfactants on the yield of *N*-butylalkanamides.

surfactant (concentration)	Yield (%) of amide <b>1</b> (R <sup>1</sup> CO-NHC <sub>4</sub> H <sub>9</sub> ) <sup>[a]</sup>			
	R <sup>1</sup> = C <sub>5</sub> H <sub>11</sub> <b>1b</b>	R <sup>1</sup> = C <sub>7</sub> H <sub>15</sub> <b>1c</b>	R <sup>1</sup> = C <sub>11</sub> H <sub>23</sub> <b>1d</b>	R <sup>1</sup> = Ph <b>1e</b>
none	7	8	75	8
Triton X-100 (1.5 mM)	25	44	74	31
SDS (40 mM)	23	44	88	18
DSA (200 mM)	36	50	89	31

[a] Determined by GC. The initial concentration of reactants: carboxylate: 5 mM; butylamine hydrochloride: 20 mM; **C-1**: 1.5 mM; surfactant: 5 times cmc; and MeOH: 3% (v/v) in sodium phosphate buffer (20 mM, pH 8).

Interestingly, the addition of the cationic surfactant, cetyltrimethylammonium chloride (CTAC, 5 mM), to the reaction of sodium laurate completely depressed amide formation. Because the cmc of CTAC (1.3 mM) is lower than that of laurate,<sup>[8]</sup> CTAC would be the major micelle-forming component. Thus, because cationic micelles are known to promote (enhance the rate of) hydrolysis at their interface by the concentration of anionic hydroxide ions in their diffuse layer,<sup>[11,9]</sup> the amphiphilic dehydrocondensing agent or an activated triazinyl ester intermediate incorporated into the micelles would be exclusively hydrolyzed.

We examined the effect of the surfactant on the substrate selectivity in the competitive reaction between equimolar amounts (5 mM each) of butyrate and other carboxylates with a more lipophilic substituent (Fig. 2). Under these conditions, octanamide

**1c** was obtained with high selectivity (>99%) in the presence of DSA, SDS, or Triton X-100 at their cmc concentrations after 12 h at 25 °C. In the absence of the surfactant, the yield of amides reduced to only 13%, whereas the selectivity was still good (94:6). This is presumably due to a hydrophobic effect, because no micelles could be formed under these conditions. Compared with aliphatic amide **1c**, the yield and selectivity for aromatic carboxamides **1e–1g** were moderately increased by the addition of Triton X-100 (1.5 mM). After several attempts using various conditions, we found that both the selectivity and yield for these reactions were significantly increased by mixing Triton X-100 (1.5 mM) and 1% (v/v) toluene to form an emulsion. It should be noted that the observed high selectivity is attributed to acceleration by interfacial effects because the yield and the selectivity simultaneously increased in the micellar (and emulsion) system.

surfactant	Yield ( <b>1a</b> : <b>1c</b> )
DSA (41 mM)	78 (0.5 : 99.5)
SDS (8 mM)	64 (0.8 : 99.2)
Triton X-100 (0.3 mM)	52 (0.8 : 99.2)
none	13 (6 : 94)

surfactant	Yield ( <b>1a</b> : <b>1e</b> )	Yield ( <b>1a</b> : <b>1f</b> )	Yield ( <b>1a</b> : <b>1g</b> )
Triton X-100 (1.5 mM)	37 (15 : 85)	44 (15 : 85)	50 (13 : 87)
Triton X-100 + 1% (v/v) toluene	62 (4 : 96)	64 (5 : 95)	75 (4 : 96)
none	10 (45 : 55)	14 (41 : 59)	11 (45 : 55)

**Figure 2.** Study of substrate (carboxylate) selectivity: competitive reaction between butyrate and other carboxylates for selective formation of *N*-butylalkanamides (**1a**:**1x**). The initial concentration of reactants: carboxylate: 5 mM each; butylamine hydrochloride: 20 mM; and **C-1**: 1.5 mM.

**Table 2.** Study of amine selectivity in micelles: effect of alkyl chain length of carboxylates and/or condensing agents on competitive reactions between decylamine and butylamine.

Run <sup>[a]</sup>	R <sup>1</sup> COONa	Condensing agents <b>C</b>	Surfactant (100 mM)	Time	Yield <sup>[b]</sup>	Ratio <sup>[b]</sup> <i>N</i> -decylamide ( <b>2</b> ) : <i>N</i> -butylamide ( <b>1</b> )
1	C <sub>11</sub> H <sub>23</sub>	<b>C-1</b>	TritonX-100	4 h	76%	<b>2d</b> : <b>1d</b> = 98.7 : 1.3
2	C <sub>11</sub> H <sub>23</sub>	<b>C-1</b>	DSA	4 h	32%	<b>2d</b> : <b>1d</b> = 49 : 51
3	C <sub>7</sub> H <sub>15</sub>	<b>C-1</b>	TritonX-100	12 h	69%	<b>2c</b> : <b>1c</b> = 98.9 : 1.1
4	C <sub>3</sub> H <sub>7</sub>	<b>C-1</b>	TritonX-100	12 h	19%	<b>2a</b> : <b>1a</b> = 90 : 10
5	C <sub>3</sub> H <sub>7</sub>	<b>C-1</b>	none	12 h	6%	<b>2a</b> : <b>1a</b> = 54 : 46
6	C <sub>3</sub> H <sub>7</sub>	<b>C-2</b>	TritonX-100	12 h	6%	<b>2a</b> : <b>1a</b> = 42 : 58
7	C <sub>3</sub> H <sub>7</sub>	<b>C-2</b>	none	12 h	9%	<b>2a</b> : <b>1a</b> = 49 : 51

[a] The initial concentration of reactants: carboxylate: 5 mM; amine hydrochloride: 10 mM each; **C**: 1.5 mM; surfactant: 100 mM; and MeOH: 3% (v/v) in sodium phosphate buffer (20 mM, pH 8). [b] Determined by GC.

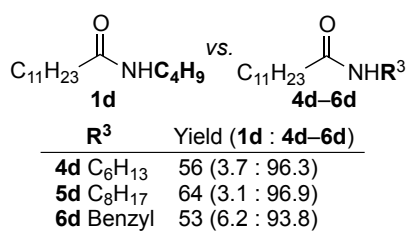
Next, we examined the effect of the alkyl chain length of *amines* on the reaction selectivity in the micellar system. Competitive

reactions between decylamine and butylamine with carboxylic acids were carried out. When a mixture of equimolar amounts of these

amines was treated with laurate and **C-1** in the presence of Triton X-100 (100 mM), *N*-decyldecanamide **2d** was obtained predominantly over *N*-butyldecanamide **1d** in 98.7:1.3 (Table 2, run 1). Interestingly, the yield of amides reduced to 32%, and the selectivity was completely lost when DSA was substituted for Triton X-100 (run 2). As it is reported that the  $pK_a$  of indicators possessing a dissociative proton, such as bromothymol blue, shifts toward the less-acidic side (higher  $pK_a$ ) in anionic micelles,<sup>[10]</sup> the acidity of decylammonium at the micellar interface would become lower than that of butylammonium in an aqueous phase. Since the ionized ammonium ion **B** (Fig. 1) must dissociate to the nonionized amine prior to its attack on the triazinyl ester in the final step of amide formation, the micellar effect of DSA could prevent the dissociation of the decylammonium ion to decylamine, and thus could reduce the rate of formation of *N*-decylamide. As a result, these effects would be responsible for the observed low yield and low selectivity for this reaction. The unfavorable effect of anionic micelles of DSA on reactions between amines and carboxylic esters has been observed and reported previously.<sup>[11]</sup>

Incorporation of carboxylates and the dehydrocondensing agent into the micellar phase would also be essential for selective formation of *N*-alkylamides. In the reaction of octanoate, which does not form micelles independently, the selectivity and the yield were retained by extending the reaction time to 12 h (run 3). When butyrate was employed, the yield of amides reduced to 19%, while the selectivity of *N*-decylamide **2** was still significantly high (run 4). However, the selectivity was almost lost in the absence of the surfactant (run 5). In the case of hydrophilic dehydrocondensing agent **C-2** possessing a short alkyl chain (ethyl group), no selectivity was observed irrespective of the presence or absence of Triton X-100 even though decylamine could be incorporated into micelles (runs 6 and 7). Interestingly, in spite of the involvement of the same intermediate triazinyl butyrate, the amine selectivity in micelles varied when different condensing agents were employed (runs 4 and 6). When amphiphilic **C-1** was used, the activated triazinyl butyrate could be formed in the micellar phase where it is attacked mainly by decylamine in the same phase. On the contrary, because the reaction using hydrophilic **C-2** gives the activated ester in the aqueous phase, there is no advantage with decylamines incorporated into micelles.

We further examined the amine selectivity in competitive reactions between butylamine and other more lipophilic amines under the same conditions using **C-1** and Triton X-100 (Fig. 3). Interestingly, hexylamine, which has only two additional methylene groups in the alkyl chain, showed 96% selectivity. An aromatic benzylamine also reacted with good selectivity.



**Figure 3.** Study of amine selectivity in micelles: competitive reaction between butylamine and other amines in the synthesis of *N*-alkyldecanamides.

We next examined a competitive reaction between mixtures of two types of carboxylates and amines, each including substrates

with both long- and short-chain alkyl groups (Table 3). As it can be expected that four unique amides should be formed in equal amounts in a common molecular dispersion phase, the reaction proceeded with no significant selectivity in methanol. In contrast, the amide **2d** resulting from the coupling reaction of laurate and decylamine, both of which have a long alkyl chain, was obtained exclusively (97% selectivity, 64% yield) by conducting the reaction in the micellar system with Triton X-100. The other three amides were generated in very limited quantities.

Finally, we determined that the reaction site (1,3,5-triazinyl group) of amphiphilic dehydrocondensing agent **C-1** employed in the present work was located at the micellar interface and not in the hydrophobic core region of micelles by the UV absorption study. Because the dehydrocondensing agent is susceptible to hydrolysis, particularly at the micellar interface, an amphiphilic quaternary anilinium salt (*N*-dodecyl-*N,N*-dimethyl-3-methoxyanilinium iodide) was employed as a model compound simulating the structure of **C-1**.<sup>[12]</sup> On the basis of this study, we concluded that the reacting site is located at the interface or in the palisade layer of micelles (supporting information); therefore, the observed rate enhancement of lipophilic substrates can be attributed to the micellar effect.

In summary, we clarified the effect of surfactants on amide formation using amphiphilic 1,3,5-triazine-based coupling agents. Cationic surfactants, such as quaternary ammonium salts, completely inhibit the reaction by promoting the hydrolysis of the coupling agents or reactive intermediates. Both nonionic and anionic surfactants dramatically promote the reaction of carboxylates and the amphiphilic dehydrocondensing agents by generation of micelles. Anionic surfactants, however, suppress the nucleophilic attack of amines, which are incorporated into micelles, on the activated triazinyl esters that are in close proximity and cause a decrease in the amine selectivity. As a result, nonionic surfactants are the most suitable for the acceleration of both steps of the reaction involving the attack of carboxylates and amines at the micelle surface.

To extend its synthetic applications, we are currently studying the reaction at higher substrate concentrations and exploring reaction conditions that support the use of various carboxylic acids other than the fatty acids.

**Table 3.** Dual selective reactions between two types of carboxylates and amines, each including substrates with both long- and short-chain alkyl groups.

C <sub>3</sub> H <sub>7</sub> COONa	C <sub>4</sub> H <sub>9</sub> NH <sub>3</sub> Cl	$\xrightarrow[\text{25 } ^\circ\text{C, 1 h}]{\text{C-1}}$	C <sub>3</sub> H <sub>7</sub> CONHC <sub>4</sub> H <sub>9</sub>	<b>1a</b>
			C <sub>3</sub> H <sub>7</sub> CONHC <sub>10</sub> H <sub>21</sub>	<b>2a</b>
C <sub>11</sub> H <sub>23</sub> COONa	C <sub>10</sub> H <sub>21</sub> NH <sub>3</sub> Cl		C <sub>11</sub> H <sub>23</sub> CONHC <sub>4</sub> H <sub>9</sub>	<b>1d</b>
			C <sub>11</sub> H <sub>23</sub> CONHC <sub>10</sub> H <sub>21</sub>	<b>2d</b>
Solvent <sup>[a]</sup>		Yield (%)	Ratio ( <b>1a</b> : <b>2a</b> : <b>1d</b> : <b>2d</b> )	
MeOH		22	31 : 26 : 18 : 25	
H <sub>2</sub> O/Triton X-100 (200 mM) <sup>[b]</sup>		64	0.5 : 0.9 : 1.5 : 97.1	

[a] Reaction was conducted with 1.5 mM of **C-1**, 5 mM of each carboxylate, and 20 mM of each amine hydrochloride. [b] Reaction was conducted in sodium phosphate buffer (100 mM, pH 8).

## Experimental Section

**General procedure for dual selective reactions between two types of carboxylates and amines in micelles.** To a stirred aqueous solution of sodium phosphate buffer (pH 8, 1.85 mL) containing sodium butyrate and laurate (10 μmol for each carboxylate), the hydrochlorides of butylamine and decylamine (20

$\mu\text{mol}$  for each amine), and Triton X-100 (0.5 M) was added the condensing agent **C-1** (20 mM in 40% aqueous MeOH, 150  $\mu\text{L}$ ) at 25 °C. The initial concentration of reactants in the resulting solution was as follows: carboxylates: 5 mM each; amines: 10 mM each; **C-1**: 1.5 mM; Triton X-100: 200 mM; and MeOH: 3%(v/v) in sodium phosphate buffer (20 mM, pH 8). The mixture was stirred at 25 °C for 12 h, and 5 M HCl (0.3 mL) was added. The resulting mixture was applied to Extrelut® NT (Merck, 2 g) and eluted with AcOEt. The produced amide was quantified by GC.

*N*-Decyldodecanamide (**2d**). Colorless crystals; mp 64-66 °C ( $\text{CH}_2\text{Cl}_2/\text{hexane}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.9$  Hz, 6H), 1.22-1.31 (m, 30H), 1.43-1.52 (m, 2H), 1.57-1.66 (m, 2H), 2.14 (t,  $J = 7.6$  Hz, 2H), 3.23 (td,  $J = 7.1, 5.8$  Hz, 2H), 5.38 (s, 1H); IR (KBr) 3314, 1636  $\text{cm}^{-1}$ ; ESI-MS  $m/z$  340 [(M+1) $^+$ ].

Received: ((will be filled in by the editorial staff))

Published online on ((will be filled in by the editorial staff))

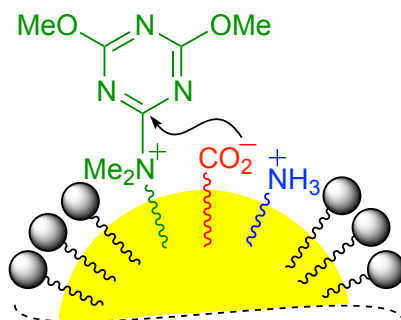
**Keywords:** amides · micelles · emulsion · condensation · interfaces

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**Micellar Effect**

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Substrate-Selective  
Dehydrocondensation at an Interface of  
Micelles and Emulsions of Common  
Surfactants



Dehydrocondensation using an amphiphilic 1,3,5-triazinylammonium-based coupling agent was accelerated by the interfacial effect of micelles and emulsions of common surfactants. The reaction of carboxylates was promoted by both anionic and nonionic surfactants, while the reaction of amines was promoted by only a nonionic surfactant. In competitive studies, high selectivities for more lipophilic substrates were observed in micelles or emulsions.

**Table 1.** Effect of surfactants on the yield of *N*-butylalkanamides.

[a] Determined by GC. The initial concentration of reactants: carboxylate: 5 mM; butylamine hydrochloride: 20 mM; **C-1**: 1.5 mM; surfactant: 5 times cmc; and MeOH: 3% (v/v) in sodium phosphate buffer (20 mM, pH 8).

**Table 2.** Study of amine selectivity in micelles: effect of alkyl chain length of carboxylates and/or condensing agents on competitive reactions between decylamine and butylamine.

[a] The initial concentration of reactants: carboxylate: 5 mM; amine hydrochloride: 10 mM each; **C**: 1.5 mM; surfactant: 100 mM; and MeOH: 3% (v/v) in sodium phosphate buffer (20 mM, pH 8). [b] Determined by GC.

**Table 3.** Dual selective reactions between two types of carboxylates and amines, each including substrates with both long- and short-chain alkyl groups.

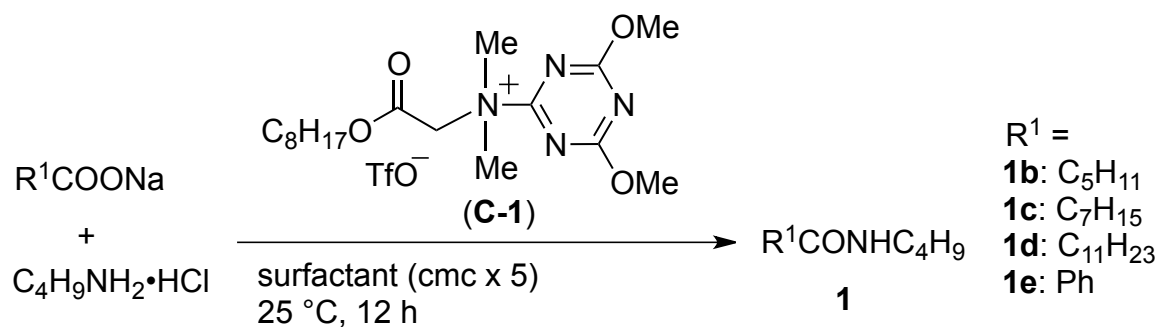
[a] Reaction was conducted with 1.5 mM of **C-1**, 5 mM of each carboxylate, and 20 mM of each amine hydrochloride. [b] Reaction was conducted in sodium phosphate buffer (100 mM, pH 8).

**Figure 1.** Rate acceleration of dehydrocondensation in micelles.

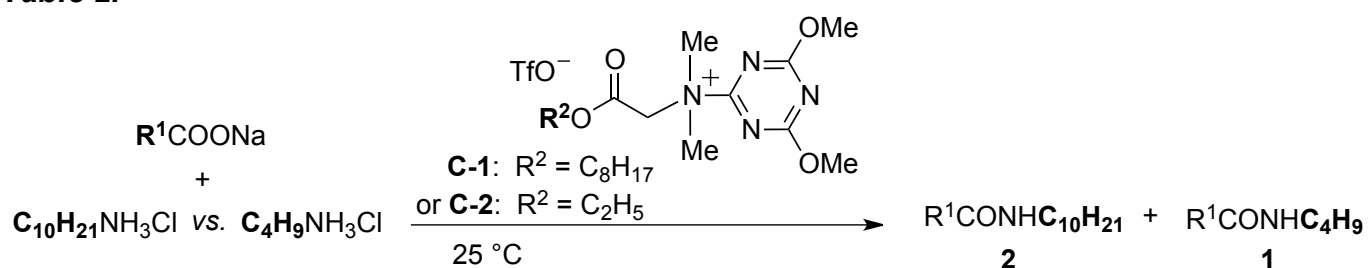
**Figure 2.** Study of substrate (carboxylate) selectivity: competitive reaction between butyrate and other carboxylates for selective formation of *N*-butylalkanamides (**1a:1x**). The initial concentration of reactants: carboxylate: 5 mM each; butylamine hydrochloride: 20 mM; **C-1**: 1.5 mM.

**Figure 3.** Study of amine selectivity in micelles: competitive reaction between butylamine and other amines in the synthesis of *N*-alkyldodecanamides.

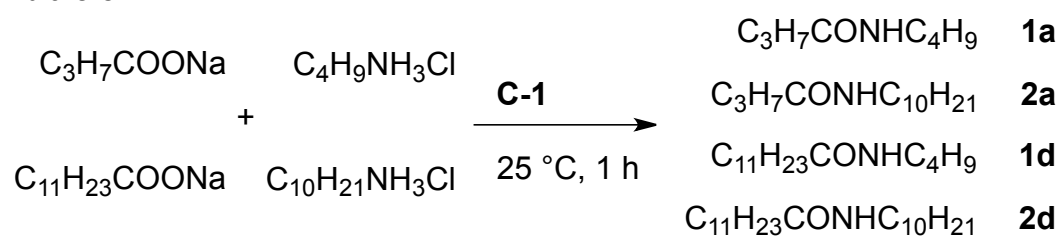
**Table 1.**



**Table 2.**





**Table 3.**

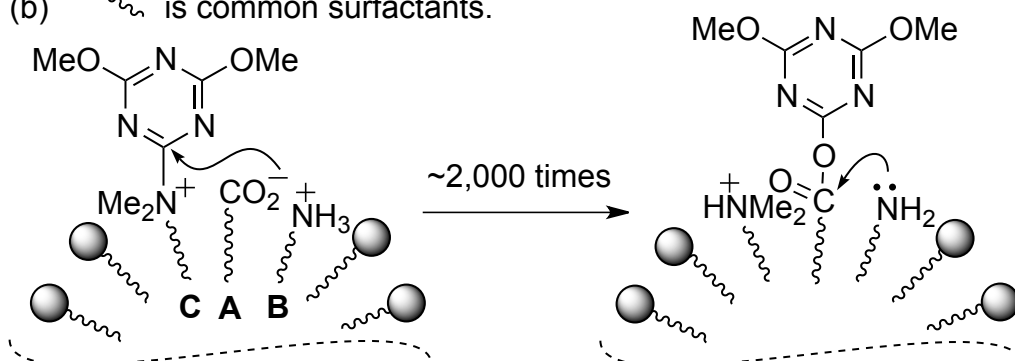




**Figure 1.**

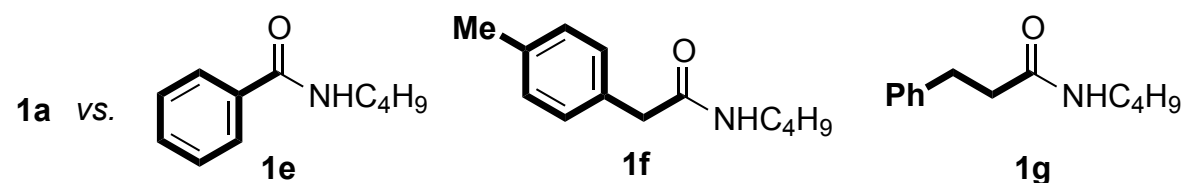
(a)  is fatty acid salts (**A**:  $\text{RCO}_2^-$ ).

(b)  is common surfactants.



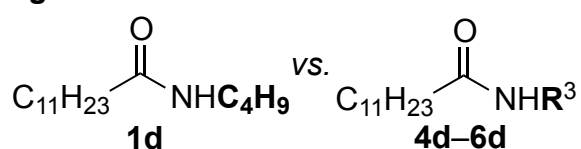
**Figure 2.**

surfactant	Yield ( <b>1a</b> : <b>1c</b> )
DSA (41 mM)	78 (0.5 : 99.5)
SDS (8 mM)	64 (0.8 : 99.2)
Triton X-100 (0.3 mM)	52 (0.8 : 99.2)
none	13 (6 : 94)



surfactant	Yield ( <b>1a</b> : <b>1e</b> )	Yield ( <b>1a</b> : <b>1f</b> )	Yield ( <b>1a</b> : <b>1g</b> )
Triton X-100 (1.5 mM)	37 (15 : 85)	44 (15 : 85)	50 (13 : 87)
Triton X-100 + 1% (v/v) toluene	62 (4 : 96)	64 (5 : 95)	75 (4 : 96)
none	10 (45 : 55)	14 (41 : 59)	11 (45 : 55)

**Figure 3.**



$\text{R}^3$	Yield ( <b>1d</b> : <b>4d-6d</b> )
<b>4d</b> $\text{C}_6\text{H}_{13}$	56 (3.7 : 96.3)
<b>5d</b> $\text{C}_8\text{H}_{17}$	64 (3.1 : 96.9)
<b>6d</b> Benzyl	53 (6.2 : 93.8)