

Hydrophobic Effect and Substrate Specificity in Reaction of Thioester and Amine in Water

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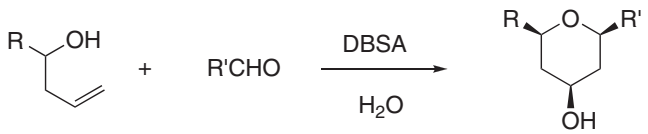
The extent of hydrophobic effect in amidation reaction of alkyl thioester with alkylamine in water was studied. The yield of the products was primarily dependent on the alkyl group of amine. For example, the reaction of *S*-dodecyl dodecanethioate with dodecylamine proceeded in good yield, while the reaction did not occur with cyclohexylamine, piperidine, and dipropylamine. The effect of chain length of *n*-alkylamine was studied to suggest the presence of hydrophobic effect. The yield of amide also depended on the alkyl group of the thioester secondarily, but the effect was smaller than amine.

Organic reactions in aqueous media have been developed recently on account of convenience, harmlessness, and unique chemical behavior.[1] In contrast to reactions in organic solvent, hydrophobic interaction among substrates is thought to be an important factor.[2] Thus, it is essential to study how hydrophobic interaction works in the presence of water. Engberts and co-workers extensively studied hydrophobic effects in aqueous Diels–Alder reactions.[3] Recently, we described the presence of hydrophobic interaction in dodecylbenzenesulfonic acid (DBSA)-promoted Prins-type cyclization (Scheme 1), in which hydrophobic interaction was observed between homoallyl alcohols and the aldehydes.[4]

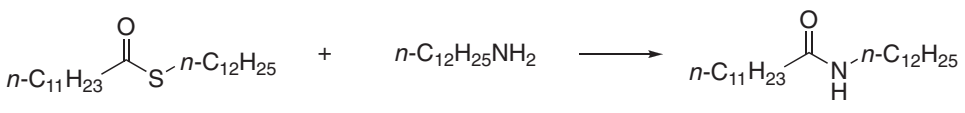
In the present study, we focus on the reaction of thioester with amine yielding amide. Amidation from thioester is a fundamental reaction in not only organic chemistry but also biological chemistry in which all reactions proceed in water.[5] For example, *N*-acetylglucosamine is obtained from glucosamine and acetyl CoA, a thioester which plays important roles in metabolism. In organic chemistry, only a few studies have been reported on the amidation reaction of thioester in water. Kita and co-workers reported reaction of activated thioester (pentafluorophenyl thioester).[6] Kinoshita and Kunieda's group reported formation of polyamino acid and/or diketopiperadine from *n*-alkyl thioester of amino acid in the presence of weak base.[7,8] As a related aqueous organic reaction, esterification from carboxylic acid and alcohol in the presence of DBSA was reported by Kobayashi and co-workers.[9] Here we report that the yield of the products in the amidation reaction from thioester is highly dependent on the alkyl groups.



Scheme 1.

Results and Discussion

Initially, amidation of *S*-dodecyl dodecanethioate (**1a**) with dodecylamine (**2a**) was examined under various conditions, and the results are summarized in Scheme 2 and Table 1. When an aqueous suspension of **1a** and **2a** was refluxed for three hours, *N*-dodecyldodecanamide (**3aa**) was afforded in 75% yield (Entry 1). Since surfactants are often utilized to provide a reaction media dissolving water-insoluble organic materials,[1,9,10] the effect of some surfactants was studied. As a result, the same product **3aa** was obtained (Entries 2–6). However, unexpectedly, the yield of **3aa** was lower when each of hexadecyltrimethylammonium bromide, sodium dodecyl sulfate (SDS), and dodecylpyridinium chloride was used (Entries 2–4), while the reaction with sodium laurate afforded the product in better yield (Entry 5). It was found that ammonium salt of **2a** also acts as surfactant to yield **3aa** (Entry 6). As a reference, the same reaction was also carried out in organic solvent resulting in lower yield in spite of higher temperature (Entry 7) or longer reaction time (Entry 8). These data seem to indicate that the reaction of **1a** and **2a** is more facile in water than in organic solvents, implying the presence of hydrophobic interaction between the alkyl substituents.



1a **2a** **3aa**

Scheme 2.

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The amidation reaction was also examined from ester instead of thioester. Namely, dodecyl laurate (**4**), prepared from dodecyl chloride and dodecanol, was treated under the same reaction conditions as in the case of thioester, but the expected amide **3aa** was hardly afforded (Scheme 3 and Table 1, Entry 9). The amidation did not occur after addition of any surfactant (Entries 10–12).

Alkyl group selection was next studied. To find the difference between substrates having *n*-alkyl and cycloalkyl groups, amidation of thioesters **1b**–**1d**, **5a**, and **5b** was studied with dodecylamine (**2a**) and cyclohexylamine (**2b**) under the same reaction conditions (refluxing in water for 3 h without surfactant). The results are shown in Table 2. A remarkable difference between **2a** and **2b** was observed; namely, amidation did not occur at all from cyclohexylamine (**2b**) (Entries 1, 3, 5, 8, and 10), while the corresponding amides were afforded from **2a**. When a cyclohexyl group is included on the carbonyl side of thioester **1b** and **5b**, the reaction with **2a** proceeded in lower yield (Entries 2 and 6), while the reaction product was afforded in better yield from substrates with an *n*-alkyl group on the carbonyl side (Entries 4 and 9). This indicates that the reactivity strongly depends on the alkyl substituents. The effect was found to be large for amine (R^3) and small for thioester (R^1 and R^2).

Table 1. Amidation Reaction of **1a** or **4** with **2a**[a)]

Entry	Substrates	Solvent	Surfactant[b)]	Time/h	Yield/%[c)]
1	**1a**	H_2O	none	3	75[d)]
2	**1a**	H_2O	$[C_{16}H_{33}NMe_3]Br$	3	6
3	**1a**	H_2O	$C_{12}H_{25}OSO_3Na$	3	11
4	**1a**	H_2O	$[C_5H_5NC_{12}H_{25}]Cl$	3	22
5	**1a**	H_2O	$C_{11}H_{23}COONa$	3	86
6	**1a**	H_2O	$C_{12}H_{25}NH_3Cl$[e)]	3	67
7	**1a**	toluene	none	3	32
8	**1a**	EtOH	none	72	29
9	**4**	H_2O	none	3	0
10	**4**	H_2O	$C_{12}H_{25}OSO_3Na$	3	0
11	**4**	H_2O	$[C_5H_5NC_{12}H_{25}]Cl$	3	0
12	**4**	H_2O	$C_{11}H_{23}COONa$	3	0

a) All reactions were carried out at refluxing temperature. Molar ratio was **1a**/**2a** (or **4**/**2a**) = 1/2.2. b) The molar amount of surfactant was equal to amine. c) Isolated yield of **3aa**. d) The product was obtained in 41% yield when the molar ratio **1a**/**2a** = 1/1.1. e) Approximately half the amount of dodecylamine (**2a**) was protonated by the addition of dilute aqueous HCl. No reaction occurred when 100% **2a** was protonated.

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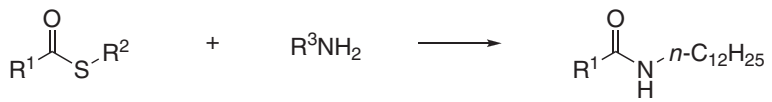
Scheme 3.

The reaction with secondary amine was also examined using **1a**–**1d** and **5a** as the substrates, and the results are listed in Table 3. Here again, *n*-alkylamine was more reactive. Namely, the reaction occurred from dodecylmethylamine (**6a**) giving the corresponding amides **7** (Entries 1, 7, 10, and 13) except from **1b** (Entry 4), while no reaction proceeded from either piperidine (**6b**) (Entries 2, 5, 8, 11, and 14) or dipropylamine (**6c**) (Entries 3, 6, 9, 12, and 15). For the reaction of **1a**, **1b**, **1d**, and **5a**, the yields of the products were lower than the reaction with primary amine. This is probably due to steric hindrance. Only compound **1c** afforded the product in high yield (Entry 10), which is similar to the reaction of **1c** with **2a** (Table 2, Entry 7).

These data indicate that the presence of *n*-alkyl substituents in the amine is essential. Then, the reaction was carried out using **1a**, **1c**, and **1d** with various length of *n*-alkylamines **2c**–**2i** and the results are shown in Table 4. Dramatic chain-length dependence was observed for the reaction of **1c** (Entries 8–14). Namely, the reaction did not occur for **2c** ($n = 6$) but the product was afforded in more than 80% yield for **2e**–**2i** ($n \geq 9$). Chain-length effect was also observed for the reaction of **1a** and **1d**, although the product was obtained in moderate yield for the substrates $n = 9$, 10, and 11. Kawabata and Kinoshita reported that condensation reaction of thioalanine *S*-dodecyl ester affording diketopiperadine takes place after formation of micelle.[7] In the present case, although amine **2a** is not soluble

Table 2. Substituent Effect in the Reaction of Thioester and *prim*-Amine in Water[a)]

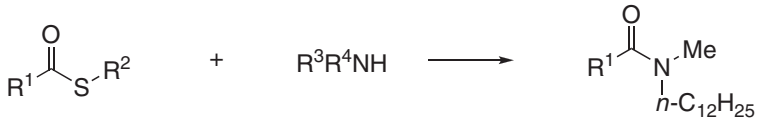


1a-d, 5a,b **2b,a** **3aa,ba,ca,da**

Entry	Substrates	R^1	R^2	R^3	Product	Yield/%[b)]
1	**1a** + **2b**	n-$C_{11}H_{23}$	n-$C_{12}H_{25}$	cyclohexyl	no reaction	—
2	**1b** + **2a**	cyclohexyl	n-$C_{12}H_{25}$	n-$C_{12}H_{25}$	**3ba**	19
3	**1b** + **2b**	cyclohexyl	n-$C_{12}H_{25}$	cyclohexyl	no reaction	—
4	**5a** + **2a**	n-$C_{11}H_{23}$	cyclohexyl	n-$C_{12}H_{25}$	**3aa**	80
5	**5a** + **2b**	n-$C_{11}H_{23}$	cyclohexyl	cyclohexyl	no reaction	—
6	**5b** + **2a**	cyclohexyl	cyclohexyl	n-$C_{12}H_{25}$	**3ba**	48
7	**1c** + **2a**	Me	n-$C_{12}H_{25}$	n-$C_{12}H_{25}$	**3ca**	93
8	**1c** + **2b**	Me	n-$C_{12}H_{25}$	cyclohexyl	no reaction	—
9	**1d** + **2a**	n-C_6H_{13}	n-$C_{12}H_{25}$	n-$C_{12}H_{25}$	**3da**	68
10	**1d** + **2b**	n-C_6H_{13}	n-$C_{12}H_{25}$	cyclohexyl	no reaction	—

a) All reactions were carried out in refluxing water for 3 h. Molar ratio was **1**/**2** (or **5**/**2**) = 1/2.2. b) Isolated yield.

Table 3. Substituent Effect in the Reaction of Thioester and *sec*-Amine in Water[a)]



1a-d, 5a **6a-c** **7aa,ca,da**

Entry	Substrates	R^1	R^2	R^3, R^4	Product	Yield/%[b)]
1	**1a** + **6a**	*n*-$C_{11}H_{23}$	*n*-$C_{12}H_{25}$	Me, *n*-$C_{12}H_{25}$	**7aa**	14
2	**1a** + **6b**	*n*-$C_{11}H_{23}$	*n*-$C_{12}H_{25}$	–$(CH_2)_5$–	no reaction	—
3	**1a** + **6c**	*n*-$C_{11}H_{23}$	*n*-$C_{12}H_{25}$	(*n*-Pr)$_2$	no reaction	—
4	**1b** + **6a**	cyclohexyl	*n*-$C_{12}H_{25}$	Me, *n*-$C_{12}H_{25}$	no reaction	—
5	**1b** + **6b**	cyclohexyl	*n*-$C_{12}H_{25}$	–$(CH_2)_5$–	no reaction	—
6	**1b** + **6c**	cyclohexyl	*n*-$C_{12}H_{25}$	(*n*-Pr)$_2$	no reaction	—
7	**5a** + **6a**	*n*-$C_{11}H_{23}$	cyclohexyl	Me, *n*-$C_{12}H_{25}$	**7aa**	15
8	**5a** + **6b**	*n*-$C_{11}H_{23}$	cyclohexyl	–$(CH_2)_5$–	no reaction	—
9	**5a** + **6c**	*n*-$C_{11}H_{23}$	cyclohexyl	(*n*-Pr)$_2$	no reaction	—
10	**1c** + **6a**	Me	*n*-$C_{12}H_{25}$	Me, *n*-$C_{12}H_{25}$	**7ca**	79
11	**1c** + **6b**	Me	*n*-$C_{12}H_{25}$	–$(CH_2)_5$–	no reaction	—
12	**1c** + **6c**	Me	*n*-$C_{12}H_{25}$	(*n*-Pr)$_2$	no reaction	—
13	**1d** + **6a**	*n*-C_6H_{13}	*n*-$C_{12}H_{25}$	Me, *n*-$C_{12}H_{25}$	**7da**	8
14	**1d** + **6b**	*n*-C_6H_{13}	*n*-$C_{12}H_{25}$	–$(CH_2)_5$–	no reaction	—
15	**1d** + **6c**	*n*-C_6H_{13}	*n*-$C_{12}H_{25}$	(*n*-Pr)$_2$	no reaction	—

a) All reactions were carried out in refluxing water for 3 h. Molar ratio was **1**/**6** (or **5**/**6**) = 1/2.2.
b) Isolated yield.

in water at room temperature, the reaction mixture of **2a** forms a homogeneous suspension in refluxing water. In contrast, **2c** dissolves in water to form a clear solution. Although it is not clear that the reaction of **2a** takes place in micelle, as in the case of Kawabata and Kinoshita's reaction, the two reaction sites, carbonyl of the thioester and the amino group, are believed to come close to each other by the hydrophobic effect.

Alkyl group interaction between the substrates and additional surfactant was also studied. Thioesters **1a**, **1b**, **5a**, and **5b** were refluxed with dodecylamine (**2a**) for 24 h with 1 molar equivalent of surfactant, either sodium dodecylbenzenesulfonate (SDBS) or SDS. The results are summarized in Table 5. The yield of **3aa** from **1a** in SDBS was better than that in SDS (Entries 1 and 2). On the other hand, **3ba** was obtained from **1b** in better yield in SDS than in SDBS (Entries 3 and 4). For substrates **5a** and **5b**, better yield was obtained in SDS than in SDBS (Entries 5–8). These results indicate that the additional surfactant had some interaction with alkyl substituent of the thioester. However, the direction of substrate specificity was opposite to our previous study on acid-promoted Prins-type cyclization in which substrates bearing *n*-alkyl groups afforded the products in better yield in SDS + HCl than in DBSA (Scheme 1).[4] In contrast to the DBSA-catalyzed Prins-type reaction, SDBS is thought to prevent the approach of the two reaction sites, thioester and amine, especially in the case of substrates with cycloalkyl groups. However, detailed explanation of the difference in direction is not made at present, because the reaction conditions are different, namely, the Prins-type reaction is acidic and the present amidation reaction is neutral.

Conclusion

It is obvious that the reaction of thioester with amine in the presence of water depends on the alkyl group. The alkyl group of the amine is more effective than that of the thioester. The other alkyl group such as the thioester or surfactant also affected secondarily. Since substrate-specificity is one fundamental feature of biological reactions, we believe that the present findings may contribute to development of substrate-specific reactions in the presence of water.

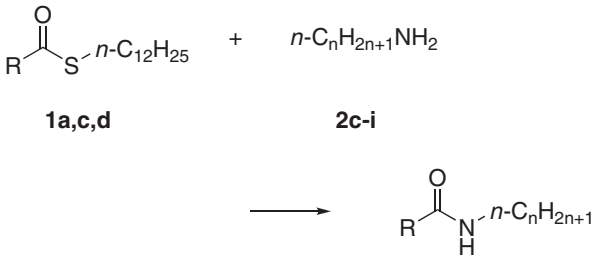
Experimental

General Procedure. Melting points were measured on a Laboratory Devices Mel-Temp apparatus. IR spectra were recorded on a Jasco FT/IR-230 spectrometer. Both ^{1}H and ^{13}C NMR spectra were measured on a Jeol ECX-400P (400 MHz for ^{1}H; 100 MHz for ^{13}C) spectrometer in $CDCl_3$ as the solvent. Chemical shifts were recorded on the δ scale (ppm) with tetramethylsilane as an internal standard. For ^{13}C NMR, the signal of the solvent ($CDCl_3$, 77.0 ppm) was used as the reference. Mass spectra (MS) was obtained on a Jeol SX-102A, CMATE II, JMS-700 MStation, or Shimadzu GCMS-QP5050 mass spectrometer. Analytical TLC was done on precoated TLC plates (Kieselgel 60 F254, layer thickness 0.2 mm). Wakogel C-200 was used for column chromatography.

Preparation of the Substrates. Compounds **1a** and **5a** were prepared according to literature;[11] compounds **1b**, **1d**, and **5b** to literature.[10] Compound **1c** was obtained by a standard acetylation method (acetic anhydride and pyridine). Compounds **1a**,[10] **1b**,[10] **5a**,[10] **5b**,[12] **1c**,[13] and **4**[14] are known. All amines used in the study are commercially available.

***S*-Dodecyl Heptanethioate (1d).** An oil. IR (neat): 1693 cm^{-1}. ^{1}H NMR: δ 0.88 (6H, t, J = 6.9 Hz), 1.22–1.38 (24H, m), 1.51–1.69 (4H, m), 2.53 (2H, t, J = 7.3 Hz), 2.86 (2H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 77.0 ppm): δ 14.0, 14.1, 22.4, 22.7, 25.7, 28.6, 28.8 (2C), 29.1, 29.3, 29.5, 29.6 (4C),

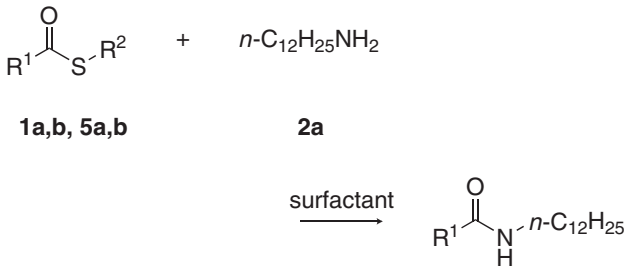
Table 4. Chain-Length Effect in the Reaction of **1a**, **1c**, and **1d** with *n*-Alkylamine[a)]



Entry	Substrates	R	n[b)]	Product	Yield/%[c)]
1	**1a** + **2c**	*n*-$C_{11}H_{23}$	6	—	0
2	**1a** + **2d**	*n*-$C_{11}H_{23}$	8	—	0
3	**1a** + **2e**	*n*-$C_{11}H_{23}$	9	**3ae**	30
4	**1a** + **2f**	*n*-$C_{11}H_{23}$	10	**3af**	36
5	**1a** + **2g**	*n*-$C_{11}H_{23}$	11	**3ag**	50
6	**1a** + **2h**	*n*-$C_{11}H_{23}$	14	**3ah**	99
7	**1a** + **2i**	*n*-$C_{11}H_{23}$	18	**3ai**	90
8	**1c** + **2c**	Me	6	—	0
9	**1c** + **2d**	Me	8	**3cd**	17
10	**1c** + **2e**	Me	9	**3ce**	85
11	**1c** + **2f**	Me	10	**3cf**	84
12	**1c** + **2g**	Me	11	**3cg**	84
13	**1c** + **2h**	Me	14	**3ch**	81
14	**1c** + **2i**	Me	18	**3ci**	92
15	**1d** + **2c**	*n*-C_6H_{13}	6	—	0
16	**1d** + **2d**	*n*-C_6H_{13}	8	—	0
17	**1d** + **2e**	*n*-C_6H_{13}	9	**3de**	46
18	**1d** + **2f**	*n*-C_6H_{13}	10	**3df**	47
19	**1d** + **2g**	*n*-C_6H_{13}	11	**3dg**	44
20	**1d** + **2h**	*n*-C_6H_{13}	14	**3dh**	74
21	**1d** + **2i**	*n*-C_6H_{13}	18	**3di**	99

a) All reactions were carried out in refluxing water for 3 h. Molar ratio was **1**/**2** = 1/2.2. b) The number of carbon atoms in *n*-alkylamine. c) Isolated yield.

Table 5. Secondary Alkyl-Group Effect in the Presence of Additional Surfactant[a)]



Entry	Substrates	R^1	R^2	Surfactant	Product	Yield /%[b)]
1	**1a** + **2a**	*n*-$C_{11}H_{23}$	*n*-$C_{12}H_{25}$	SDS	**3aa**	36
2	**1a** + **2a**	*n*-$C_{11}H_{23}$	*n*-$C_{12}H_{25}$	SDBS[c)]	**3aa**	60
3	**1b** + **2a**	cyclohexyl	*n*-$C_{12}H_{25}$	SDS	**3ba**	37
4	**1b** + **2a**	cyclohexyl	*n*-$C_{12}H_{25}$	SDBS	**3ba**	7
5	**5a** + **2a**	*n*-$C_{11}H_{23}$	cyclohexyl	SDS	**3aa**	74
6	**5a** + **2a**	*n*-$C_{11}H_{23}$	cyclohexyl	SDBS	**3aa**	46
7	**5b** + **2a**	cyclohexyl	cyclohexyl	SDS	**3ba**	46
8	**5b** + **2a**	cyclohexyl	cyclohexyl	SDBS	**3ba**	20

a) All reactions were carried out in refluxing water for 24 h with equal molar amount of surfactant. Molar ratio of **1**/**2a** (or **5**/**2a**) = 1/2.2. b) Isolated yield. c) SDBS was prepared from equal molar amount of DBSA and NaOH.

31.4, 31.9, 44.2, 199.9. EI-MS: m/z 145 ($[M - C_{12}H_{25}]^+$), 133 (base, $[M - SC_{12}H_{25}]^+$). HRMS: Found: m/z 314.2651. Calcd for $C_{19}H_{38}OS$: M, 314.2643.

Typical Amidation Procedure. Thioester **1** (0.13 mmol) was added to a stirred mixture of amine **2** (0.27 mmol) in water (10 mL), and the mixture was refluxed for 3 h. After cooling to room temperature, the mixture was extracted with Et_2O. The ethereal layer was washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and the solvent was evaporated. The product was purified by silica gel column chromatography using hexane/AcOEt as eluent. Compounds **3aa**,[15] **3ba**,[16] **3ca**,[17] **3af**,[18] **3ag**,[19] **3ah**,[20] **3ai**,[21] and **3dh**[22] are known. Spectral data of compounds **3cd**, **3ce**, **3cf**, **3cg**, **3ch**, and **3ci** are not given here because these are known simple acetates of the corresponding amine.

***N*-Dodecylheptanamide (3da).** Mp 58.0–59.0 °C. IR (KBr): 1637 cm^{-1}. ^1H NMR: δ 0.88 (6H, t-like, J = 6.9 Hz), 1.22–1.35 (24H, m), 1.44–1.69 (4H, m), 2.15 (2H, t, J = 7.6 Hz), 3.24 (2H, dt, J = 6.0, 7.0 Hz), 5.40 (1H, br). ^{13}C NMR ($CDCl_3$, 77.0 ppm): δ 14.0, 14.1, 22.5, 22.7, 25.8, 26.9, 29.0, 29.3 (2C), 29.5, 29.6 (3C), 29.7, 31.5, 31.9, 37.0, 39.5, 173.0. EI-MS: m/z 297 (M^+). Analysis Found: C, 76.56; H, 13.49; N, 4.49%. Calcd for $C_{19}H_{39}NO$: C, 76.70; H, 13.21; N, 4.71%.

***N*-Nonyldodecanamide (3ae).** Mp 70.5–71.5 °C. IR (KBr): 1637 cm^{-1}. ^1H NMR: δ 0.88 (6H, t-like, J = 6.8 Hz), 1.22–1.35 (28H, m), 1.43–1.66 (4H, m), 2.15 (2H, t, J = 7.5 Hz), 3.24 (2H, dt, J = 6.0, 7.0 Hz), 5.41 (1H, br). ^{13}C NMR ($CDCl_3$, 77.0 ppm): δ 14.1 (2C), 22.6, 22.7, 25.8, 27.0, 29.2, 29.3 (3C), 29.4, 29.5 (2C), 29.6 (2C), 29.7, 31.8, 31.9, 37.0, 39.5, 173.0. EI-MS: m/z 325 (M^+). Analysis Found: C, 77.16; H, 13.61; N, 4.17%. Calcd for $C_{21}H_{43}NO$: C, 77.47; H, 13.31; N, 4.30%.

***N*-Nonylheptanamide (3de).** Mp 44.0–45.0 °C. IR (KBr): 1637 cm^{-1}. ^1H NMR: δ 0.88 (6H, t-like, J = 6.8 Hz), 1.22–1.36 (18H, m), 1.43–1.67 (4H, m), 2.15 (2H, t, J = 7.5 Hz), 3.24 (2H, dt, J = 6.0, 7.0 Hz), 5.47 (1H, br). ^{13}C NMR ($CDCl_3$, 77.0 ppm): δ 14.0, 14.1, 22.5, 22.7, 25.8, 26.9, 29.0, 29.2, 29.3, 29.5, 29.7, 31.5, 31.8, 36.9, 39.5, 173.0. EI-MS: m/z 255 (M^+). Analysis Found: C, 75.02; H, 13.19; N, 5.33%. Calcd for $C_{16}H_{33}NO$: C, 75.23; H, 13.02; N, 5.48%.

***N*-Decylheptanamide (3df).** Mp 54.0–55.0 °C. IR (KBr): 1639 cm^{-1}. ^1H NMR: δ 0.88 (6H, t-like, J = 6.7 Hz), 1.23–1.36 (20H, m), 1.44–1.67 (4H, m), 2.15 (2H, t, J = 7.5 Hz), 3.24 (2H, dt, J = 6.0, 7.0 Hz), 5.51 (1H, br). ^{13}C NMR ($CDCl_3$, 77.0 ppm): δ 14.0, 14.1, 22.5, 22.6, 25.8, 26.9, 28.9, 29.3 (2C), 29.5 (2C), 29.6, 31.5, 31.8, 36.9, 39.4, 173.1. EI-MS: m/z 269 (M^+). Analysis Found: C, 75.58; H, 12.98; N, 4.95%. Calcd for $C_{17}H_{35}NO$: C, 75.77; H, 13.09; N, 5.20%.

***N*-Undecylheptanamide (3dg).** Mp 55.0–56.0 °C. IR (KBr): 1637 cm^{-1}. ^1H NMR: δ 0.88 (6H, t-like, $J = 6.9$ Hz), 1.22–1.35 (22H, m), 1.44–1.67 (4H, m), 2.15 (2H, t, $J =$ 7.5 Hz), 3.24 (2H, dt, $J = 6.0$, 7.0 Hz), 5.53 (1H, br). ^{13}C NMR ($CDCl_3$, 77.0 ppm): δ 14.0, 14.1, 22.5, 22.6, 25.8, 26.9, 29.0, 29.3 (2C), 29.5, 29.6 (3C), 31.5, 31.9, 36.9, 39.4, 173.0. EI-MS: m/z 283 (M^+). Analysis Found: C, 76.24; H, 13.36; N, 4.86%. Calcd for $C_{18}H_{37}NO$: C, 76.26; H, 13.16; N, 4.94%.

***N*-Octadecylheptanamide (3di).** Mp 78.0–79.0 °C. IR (KBr): 1637 cm^{-1}. ^1H NMR: δ 0.88 (6H, t-like, $J = 6.8$ Hz), 1.23–1.35 (36H, m), 1.44–1.66 (4H, m), 2.15 (2H, t, $J =$ 7.5 Hz), 3.23 (2H, dt, $J = 6.0$, 7.0 Hz), 5.53 (1H, br). ^{13}C NMR ($CDCl_3$, 77.0 ppm): δ 14.0, 14.1, 22.5, 22.7, 25.8, 26.9, 29.0, 29.3 (2C), 29.5, 29.6 (3C), 29.7 (7C), 31.5, 31.9, 36.9, 39.4, 173.0. EI-MS: m/z 381 (M^+). Analysis Found: C, 78.44; H, 13.54; N, 3.63%. Calcd for $C_{25}H_{51}NO$: C, 78.67; H, 13.47; N, 3.67%.

***N*-Dodecyl-*N*-methyldodecanamide (7aa).** A mixture of stereoisomers. Mp 32.5–33.5 °C. IR (KBr): 1630 cm^{-1}. ^1H NMR: δ 0.88 (6H, t-like, $J = 6.9$ Hz), 1.20–1.35 (34H, m), 1.46–1.67 (4H, m), 2.28 (2H × 1/2, t, $J = 7.6$ Hz), 2.29 (2H × 1/2, t, $J = 7.6$ Hz), 2.90 (3H × 1/2, s), 2.96 (3H × 1/2, s), 3.24 (2H × 1/2, t, $J = 7.6$ Hz), 3.34 (2H × 1/2, t, $J =$ 7.6 Hz). ^{13}C NMR ($CDCl_3$, 77.0 ppm): δ 14.1 (2C), 22.7 (2C), 25.1 (1/2C), 25.5 (1/2C), 26.7 (1/2C), 26.9 (1/2C), 27.3 (1/2C), 28.5 (1/2C), 29.3–29.6 (12C), 31.9 (2C), 33.0 (1/2C), 33.3 (1/2C), 33.7 (1/2C), 35.3 (1/2C), 47.7 (1/2C), 50.0 (1/2C), 172.9 (1/2C), 173.0 (1/2C). EI-MS: m/z 381 (M^+), 225 ($[M - Me - C_{10}H_{21}]^+$). Analysis Found: C, 78.51; H, 13.48; N, 3.62%. Calcd for $C_{25}H_{51}NO$: C, 78.67; H, 13.47; N, 3.67%.

***N*-Dodecyl-*N*-methylacetamide (7ca).** A mixture of stereoisomers. An oil. IR (neat): 1650 cm^{-1}. ^1H NMR: δ 0.88 (3H, t-like, $J = 6.6$ Hz), 1.21–1.35 (18H, m), 1.46–1.61 (2H, m), 2.07 (3H × 1/2, s), 2.09 (3H × 1/2, s), 2.91 (3H × 1/2, s), 2.98 (3H × 1/2, s), 3.25 (2H × 1/2, t, $J = 7.6$ Hz), 3.34 (2H × 1/2, t, $J = 7.6$ Hz). ^{13}C NMR ($CDCl_3$, 77.0 ppm): δ 14.0, 21.1 (1/2C), 21.8 (1/2C), 22.6, 26.6 (1/2C), 26.8 (1/2C), 27.2 (1/2C), 28.2 (1/2C), 29.2–29.6 (6C), 31.8, 33.1 (1/2C), 35.9 (1/2C), 47.4 (1/2C), 50.8 (1/2C), 170.2. EI-MS: m/z 241 (M^+), 226 ($[M - Me]^+$). HRMS: Found: m/z 241.2403. Calcd for $C_{15}H_{31}NO$: M, 241.2406.

***N*-Dodecyl-*N*-methylheptanamide (7da).** A mixture of stereoisomers. An oil. IR (neat): 1650 cm^{-1}. ^1H NMR: δ 0.88 (6H, t-like, $J = 6.6$ Hz), 1.20–1.36 (24H, m), 1.46–1.66 (4H, m), 2.28 (2H × 1/2, t, $J = 7.7$ Hz), 2.30 (2H × 1/2, t, $J = 7.7$ Hz), 2.91 (3H × 1/2, s), 2.96 (3H × 1/2, s), 3.24 (2H × 1/2, t, $J = 7.7$ Hz), 3.34 (2H × 1/2, t, $J = 7.6$ Hz). ^{13}C NMR (Me_4Si, 0.0 ppm): δ 14.1 (2C), 22.7 (2C), 25.2 (1/2C), 25.6 (1/2C), 26.8 (1/2C), 26.9 (1/2C), 27.3 (1/2C), 28.5 (1/2C), 29.3–29.7 (7C), 31.9 (2C), 33.1 (1/2C), 33.3 (1/2C), 33.7 (1/2C), 35.3 (1/2C), 47.7 (1/2C), 50.0 (1/2C), 172.9 (1/2C), 173.1 (1/2C). EI-MS: m/z 254 ($[M - C_4H_9]^+$), 226 ($[M - C_6H_{13}]^+$). HRMS: Found: m/z 311.3179. Calcd for $C_{20}H_{41}NO$: M, 311.3188.

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