Reaction of Amphipathic-Type Thioester and Amine with Hydrophobic Effect in Water

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Abstract: The title reaction was studied using sodium 3-(1-oxododec-1-yl)thio- and 3-(1-oxohept-1-yl)thiopropanoate with various chain lengths of amines. The yields of the amides were found to depend on both the chain length of the thioester and that of amine, suggesting the presence of hydrophobic interaction. The amides were obtained in better yields after addition of sodium fluoride. Acylation (dodecanoylation) of some hydrophobic amino acids was also studied to obtain the corresponding amides.

Key words: amines, amides, amino acids, thioesters, hydrophobic effect

Organic reactions in aqueous media have been extensively developed because of convenience, harmlessness and unique chemical behavior.¹ Formation of amides from thioesters and amines is one of the fundamental reactions in biological chemistry. The reaction is one of the practical methods in peptide synthesis.² In aqueous organic chemistry, reaction of activated thioester is also reported.³ Kinoshita and Kunieda's group reported dimerization and polymerization reactions of thioalanine or thioglycine Sdodecyl ester in water in the presence of a weak amine.⁴ We recently reported hydrophobic effect in the reaction of S-dodecyl dodecanethioate (1) or heptanethioate (2) with *n*-alkylamine 3.5 The reaction occurred without the aid of any surfactant or organic solvent, and the yield of the products 4 or 5 depended primarily on the chain length of amine (Scheme 1). Namely, long-chain alkylamine (n >12) afforded the corresponding amide in good yield, while no amide was obtained from amine having shorter alkyl chain (n = 6, 8) or cyclohexylamine.





Since thioesters 1 and 2 are hydrophobic molecules, the above results led us to suspect that hydrophobic interaction was not enough between water-soluble short-chain amines and the water-insoluble thioesters. Thus, we

SYNLETT 2011, No. 14, pp 2035–2038 Advanced online publication: 10.08.2011 DOI: 10.1055/s-0030-1261165; Art ID: U03611ST © Georg Thieme Verlag Stuttgart · New York planned to use amphipathic thioesters 6 and 7, which have both a hydrophobic alkyl chain and a hydrophilic carboxylate moiety, in place of 1 and 2, respectively. Herein we report that the reaction proceeds even with hydrophilic amines including butylamine and cyclohexylamine to yield the corresponding amides.

Each of compounds 6^6 and 7^7 were prepared by acylation of 3-mercaptopropanoic acid with lauroyl chloride or heptanoyl chloride, respectively, followed by titration with NaOH.⁸ Initially, amidation of **6** with amines having various chain length of alkyl group (3a-h) was studied, and the results are summarized in Scheme 2 and Table 1.9 When an aqueous suspension of 6 and octylamine (3c) was stirred for 24 hours at ambient temperature, N-octyldodecanamide (4c) was afforded in 94% yield (entry 3). Shorter amines such as butylamine (3a) and hexylamine (3b) also reacted under the same reaction condition to give 4a and 4b in 45% and 97% yields, respectively (entries 1 and 2). In the previous method involving S-dodecyl dodecanethioate (1), short-chain amines **3b**,**c** did not react at all despite the reaction being carried out under refluxing condition.⁵ Compounds **3d–h** reacted with thioester **6**, affording the corresponding amides 4d-h in good yields (entries 4-8). Cyclohexylamine (3i) also reacted with 6, to give amide 4i albeit in a low yield (entry 9). Since watersoluble amines such as 3a,b,i reacted, it was suggested that the solubility of amine in water is not a main factor to determine the occurrence of the reaction. The low yield of 4i is probably due to steric hindrance.



Compound 7 afforded amides 5a-h after reaction with the corresponding amines under the same reaction conditions (Table 1, entries 10–17). Difference in yields between 6 and 7 was obvious. Namely, the long-chain amines were acylated in moderate yields when reacted with 7 (entries 12–17), while the short-chain amines were acylated in only low yields (entries 10 and 11). The results indicate that the yield of the product depends primarily on the chain length of the thioester, suggesting the presence of hydrophobic interaction. Compound 6 forms micelle un-

der the reaction conditions (CMC = 2.6 mM, determined by electric conductivity method), while 7 dissolves in water to form a clear solution.

Entry	Thioester	Amine	R′	Product	Yield (%) ^b	
1	6	3a	<i>n</i> -Bu	4a	45	
2	6	3b	$n - C_6 H_{11}$	4b	97	
3	6	3c	$n-C_8H_{17}$	4c	94	
4	6	3d	$n - C_9 H_{19}$	4d	84	
5	6	3e	$n-C_{10}H_{21}$	4e	89	
6	6	3f	$n-C_{11}H_{23}$	4f	93	
7	6	3g	$n-C_{12}H_{25}$	4g	77	
8	6	3h	$n-C_{14}H_{29}$	4h	77	
9	6	3i	cyclohexyl	4i	9	
10	7	3 a	<i>n</i> -Bu	5a	7	
11	7	3b	$n-C_{6}H_{11}$	5b	16	
12	7	3c	$n-C_8H_{17}$	5c	36	
13	7	3d	$n - C_9 H_{19}$	5d	20	
14	7	3e	$n-C_{10}H_{21}$	5e	36	
15	7	3f	$n-C_{11}H_{23}$	5f	45	
16	7	3g	$n-C_{12}H_{25}$	5g	50	
17	7	3h	$n-C_{14}H_{29}$	5h	36	

 Table 1
 Amidation Reaction of Thioester 6/7 with Amine 3^a

^a Each substrate was mixed in distilled H_2O and stirred for 24 h at r.t. Molar ratio of **6/3** or **7/3** = 1:2. Concentration of **6** or **7** = 13 mM. ^b Isolated yield.

The effect of salts was examined with the expectation that the hydrophobic effect would be increased. Sodium chloride and sodium fluoride were individually added to the reaction mixture of thioester **6** with hydrophilic amines **3a,i**, from which the amidation reaction proceeded in low or moderate yields without additive (see Table 1, entries 1 and 9). The results of the salt effect are shown in Table 2. The yield of **4a** or **4i** increased after the addition of sodium chloride or sodium fluoride, the latter of which was a little more effective. Amidation of **7** was also improved by the addition of sodium fluoride to obtain **5** in acceptable yields for synthetic purpose (entries 5–12).

The reactions of **6** with functionalized amine, acylation (dodecanoylation) reaction of glycine and β -alanine hexyl esters **8a** and **8b** were next studied (Scheme 3). Compounds **8a,b** were prepared as triflate from 1-hexanol and glycine or β -alanine, respectively.¹⁰ The reaction of **8a,b** with **6** is summarized in Table 3.¹¹ When **8a** was treated with **6** under the same reaction conditions as described above (r.t., 24 h), the reaction proceeded slowly to give

Entry	Thioester Ami	ne Salt	Product	Yield (%) ^b
1	6 3a	NaCl	4 a	82
2	6 3a	NaF	4 a	89
3	6 3i	NaCl	4i	39
4	6 3i	NaF	4i	59
5	7 3a	NaF	5a	67
6	7 3b	NaF	5b	91
7	7 3c	NaF	5c	88
8	7 3d	NaF	5d	75
9	7 3e	NaF	5e	82
10	7 3f	NaF	5f	83
11	7 3g	NaF	5g	74
12	7 3h	NaF	5h	57

 Table 2
 Salt Effect in the Reaction of Thioester 6/7 and Amine 3^a

^a All the reactions were carried out under the same conditions as mentioned in the footnote a of Table 1. Molar ratio of 6/3 or 7/3 = 1:2. ^b Isolated yield.

amide $9a^{12}$ in 21% yield after one day (entry 1). A similar result was obtained for the reaction of **8b** with **6** giving $9b^{13}$ (entry 2). When sodium fluoride was added (entries 3 and 4) or the reaction temperature was raised to 70 °C (entries 5 and 6), 9a, b were obtained in better yields. In contrast, compound **7** did not react with **8a** at all even after the reaction was heated to 70 °C.



Scheme 3

Table 3 Amidation of Thioester **6** with Glycine or β -Alanine Hexyl Esters^a

EntrySubstrateTemperatureTime (h)AdditiveProductYield ($(\%)^b$ 18ar.t.24-9a2128br.t.24-9b3838ar.t.24NaF9a8448br.t.24NaF9b8058a70 °C18-9a6568b70 °C18-9b79							
18ar.t.24 $-$ 9a2128br.t.24 $-$ 9b3838ar.t.24NaF9a8448br.t.24NaF9b8058a70 °C18 $-$ 9a6568b70 °C18 $-$ 9b79	Entry	Substrate	Temperature	Time (h)	Additive	Product	Yield (%) ^b
2 8b r.t. 24 - 9b 38 3 8a r.t. 24 NaF 9a 84 4 8b r.t. 24 NaF 9b 80 5 8a 70 °C 18 - 9a 65 6 8b 70 °C 18 - 9b 79	1	8a	r.t.	24	_	9a	21
3 8a r.t. 24 NaF 9a 84 4 8b r.t. 24 NaF 9b 80 5 8a 70 °C 18 - 9a 65 6 8b 70 °C 18 - 9b 79	2	8b	r.t.	24	-	9b	38
4 8b r.t. 24 NaF 9b 80 5 8a 70 °C 18 - 9a 65 6 8b 70 °C 18 - 9b 79	3	8a	r.t.	24	NaF	9a	84
5 8a 70 °C 18 - 9a 65 6 8b 70 °C 18 - 9b 79	4	8b	r.t.	24	NaF	9b	80
6 8b 70 °C 18 – 9b 79	5	8a	70 °C	18	-	9a	65
	6	8b	70 °C	18	-	9b	79

^a Molar ratio of 6/8 = 1:2.

^b Isolated yield.



Scheme 4

 Table 4
 Amidation of Thioester 6 with Some Hydrophobic Amino

 Acid Hexyl Esters^a
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Entry	Substrate R (parent amino acid)		Product	Yield (%) ^b	
1	10a	Me ₂ CH (valine)	11a	69	
2	10b	Me ₂ CHCH ₂ (leucine)	11b	61	
3	10c	MeEtCH (isoleucine)	11c	83°	
4	10d	Bn (phenylalanine)	11d	73	

^a All the reactions were carried out at 70 °C for 18 h. Molar ratio of 6/10 = 1:2.

^b Isolated yield.

^c Epimerization was not observed.

Similarly, hydrophobic amino acid hexyl esters 10a-d were acylated to afford the corresponding amides $11a-d^{14-17}$ in good yields (Scheme 4 and Table 4). These results suggest that amphipathic-type thioester is a useful acylating agent of amino acid derivative in water. The lower reactivity of amino acid derivative, in comparison to alkylamine, is probably due to low nucleophilicity of the amino group. The *pK*a value of the amino group in amino acid is generally lower than that in alkylamine.

In conclusion, various chain lengths of amines were acylated by amphipathic thioester 6 or 7 in water. The yields of the amides were dependent primarily on the chain length of the thioester. In contrast to the previous method using *S*-alkylthioester 1 or $2,^5$ amides were successfully synthesized from hydrophilic short-chain amines. The present method will be useful in the acylation of amines in water.

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- (7) Compound 7: IR (KBr): 1684, 1566, 1425 cm^{-1. 1}H NMR as carboxylic acid (CDCl₃): $\delta = 0.88$ (t, J = 6.4 Hz, 3 H), 1.21–1.37 (m, 6 H), 1.59–1.70 (m, 2 H), 2.55 (t, J = 7.5 Hz, 2 H), 2.69 (t, J = 6.9 Hz, 2 H), 3.11 (t, J = 6.9 Hz, 2 H). ¹³C NMR as carboxylic acid (CDCl₃): $\delta = 14.0$, 22.4, 23.5, 25.5, 28.6, 31.4, 34.2, 44.0, 177.2, 199.3. MS (FAB): m/z = 263 [M + Na]⁺, 241 [M + H]⁺. HRMS (FAB): m/z [M + H]⁺ calcd for C₁₀H₁₈O₃NaS: 241.0874; found: 241.0865.
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- (9) **Typical Procedure for the Amidation Reaction**: Thioester **6** (0.065 mmol) was added to a stirred mixture of amine **3** (0.13 mmol) in H_2O (5 mL), and the mixture was stirred at r.t. for 24 h. The mixture was extracted with Et_2O , and the ethereal layer was washed with aq NaHCO₃ solution, and dried over Na₂SO₄. After evaporation of the solvent, the product was purified by silica gel column chromatography using hexane–EtOAc as eluent.
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- (11) An aqueous solution of NaOH (0.5 M, 0.26 mL) was added in the reaction of **8** triflate (0.13 mmol) with **6** (0.065 mmol).
- (12) Compound **9a**: mp 60–61 °C. IR (KBr): 3315, 1739, 1647, 1552, 1213 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.88$ (t, J = 7.0 Hz, 3 H), 0.89 (t, J = 7.0 Hz, 3 H), 1.23–1.39 (m, 22 H), 1.55–1.69 (m, 4 H), 2.24 (t, J = 7.4 Hz, 2 H), 4.04 (d, J = 5.0 Hz, 2 H), 4.15 (t, J = 6.7 Hz, 2 H), 5.94 (br, 1 H). ¹³C NMR (CDCl₃): $\delta = 14.0$, 14.1, 22.5, 22.7, 25.4, 25.6, 28.4, 29.2, 29.3 (2 × C), 29.4, 29.6 (2 × C), 31.3, 31.9, 36.4, 41.3, 65.7, 170.3, 173.2. EIMS: m/z = 341 [M⁺], 201, 118. HRMS: m/z [M + H]⁺ calcd for C₂₀H₄₀NO₃: 342.3008; found: 342.3002.
- (13) Compound **9b**: mp 45–46 °C. IR (KBr): 3296, 1732, 1639, 1552, 1186 cm⁻¹. ¹H NMR (CDCl₃): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 0.89 (t, *J* = 6.2 Hz, 3 H), 1.22–1.37 (m, 22 H), 1.55–1.69 (m, 4 H), 2.15 (t, *J* = 7.5 Hz, 2 H), 2.53 (t, *J* = 5.9 Hz, 2 H), 3.52 (q, *J* = 5.9 Hz, 2 H), 4.09 (t, *J* = 6.8 Hz, 2 H), 6.07 (br, 1 H). ¹³C NMR (CDCl₃): δ = 14.0, 14.1, 22.5, 22.7, 25.6, 25.7, 28.5, 29.3 (3 × C), 29.5, 29.6 (2 × C), 31.4, 31.9, 34.0, 34.7, 36.8, 173.0, 173.2. EIMS: *m*/*z* = 355 [M⁺], 215, 132. HRMS: *m*/*z* [M + H]⁺ calcd for C₂₁H₄₂NO₃: 356.3165; found: 356.3134.
- (14) Compound **11a**: oil. IR (NaCl): 3307, 1736, 1651, 1539, 1198 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.88$ (t, J = 6.8 Hz, 3 H), 0.89 (t, J = 6.8 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 7.0 Hz, 3 H), 1.22–1.39 (m, 22 H), 1.59–1.69 (m, 4 H), 2.10–2.21 (m, 1 H), 2.23 (t, J = 7.7 Hz, 2 H), 4.07–4.18 (m, 2 H), 4.58 (dd, J = 4.6, 8.8 Hz, 1 H), 5.94 (br d, J = 9.0 Hz, 1 H). ¹³C NMR (CDCl₃): $\delta = 14.0$, 14.1, 17.7, 18.9, 22.5, 22.7, 25.6, 25.7, 28.5, 29.2, 29.3 (2 × C), 29.5, 29.6 (2 × C), 31.3, 31.4, 31.9, 36.8, 56.8, 65.4, 172.4, 173.0. EIMS: m/z = 383 [M⁺], 254. HRMS: m/z [M + H]⁺ calcd for C₂₃H₄₆NO₃: 384.3478; found: 384.3478.
- (15) Compound **11b**: oil. IR (NaCl): 3288, 1741, 1651, 1543, 1192 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.88$ (t, J = 6.8 Hz, 3 H), 0.89 (t, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.3 Hz, 3 H), 0.95 (d, J = 6.0 Hz, 3 H), 1.23–1.39 (m, 23 H), 1.46–1.72 (m, 6 H), 2.21 (t, J = 7.5 Hz, 2 H), 4.12 (t, J = 5.8 Hz, 2 H), 4.65 (dt, J = 5.0, 8.7 Hz, 1 H), 5.84 (br d, J = 8.0 Hz, 1 H). ¹³C NMR (CDCl₃): $\delta = 14.0, 14.1, 22.1, 22.5, 22.7, 22.8, 24.9, 25.5, 25.6, 28.4, 29.2, 29.3 (2 × C), 29.5, 29.6 (2 × C), 31.3, 31.9, 36.6, 41.9, 50.6, 65.5, 172.8, 173.4. EIMS: <math>m/z = 397$ [M⁺], 268, 86. HRMS: m/z [M + H]⁺ calcd for C₂₄H₄₈NO₃: 398.3634; found: 398.3616.

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- (16) Compound **11c**: oil. IR (NaCl): 3300, 1738, 1653, 1537, 1192 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.88$ (t, J = 6.9 Hz, 3 H), 0.89 (t, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.93 (t, J = 7.2 Hz, 3 H), 1.22–1.40 (m, 24 H), 1.58–1.72 (m, 4 H), 1.83–1.94 (m, 1 H), 2.22 (t, J = 7.6 Hz, 2 H), 4.11 (dt, J = 10.7, 6.7 Hz, 1 H), 4.14 (dt, J = 10.7, 6.7 Hz, 1 H), 4.62 (dd, J = 4.6, 8.5 Hz, 1 H), 5.97 (br d, J = 8.5 Hz, 1 H). ¹³C NMR (CDCl₃): $\delta = 11.6, 14.0, 14.1, 15.4, 22.5, 22.7, 25.2, 25.5, 25.7, 28.5, 29.2, 29.3 (2 × C), 29.5, 29.6 (2 × C), 31.3, 31.9, 36.8, 38.1, 56.1, 65.4, 172.3, 172.8. EIMS: <math>m/z = 397$ [M⁺], 268, 86. HRMS: m/z [M + H]⁺ calcd for C₂₄H₄₈NO₃: 398.3634; found: 398.3647.
- (17) Compound **11d**: mp 45–46 °C. IR (KBr): 3326, 1732, 1645, 1523, 1209 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.88$ (t, J = 6.6 Hz, 3 H), 0.90 (t, J = 6.0 Hz, 3 H), 1.23–1.38 (m, 22 H), 1.52–1.68 (m, 4 H), 2.17 (t, J = 7.6 Hz, 2 H), 3.11 (dd, J = 5.8, 14.0 Hz, 1 H), 3.14 (dd, J = 6.0, 14.0 Hz, 1 H), 4.04–4.15 (m, 2 H), 4.90 (dt, J = 7.7, 6.0 Hz, 1 H), 5.90 (br d, J = 8.0 Hz, 1 H), 7.08–7.34 (m, 5 H). ¹³C NMR (CDCl₃): $\delta = 14.0$, 14.1, 22.5, 22.7, 25.5, 25.6, 28.4, 29.2, 29.3 (2 × C), 29.4, 29.6 (2 × C), 31.3, 31.9, 36.6, 38.0, 52.9, 65.7, 127.0, 128.5 (2 × C), 129.3 (2 × C), 136.0, 171.8, 172.6. EIMS: m/z = 431 [M⁺], 232, 120. HRMS: m/z [M + H]⁺ calcd for C₂₇H₄₆NO₃: 432.3478; found: 432.3491.

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