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Unusual Rate Enhancement of Bimolecular Dehydrocondensation Forming Amides at the Interface of Micelles of Fatty Acid Salt

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Experimental details including synthesis and characterization of 2, 3, and 6

General methods. ^{1}H and spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are reported as δ values relative to tetramethylsilane as internal standard. Infrared spectra were recorded on a Nicolet FT-IR AVATER 360 spectrometer. Mass spectra were measured on a Waters MassLynx 4.0 (ESI-MS), and a JEOL The MStation JMS-700 (FAB-MS). GC analysis was performed on a Silicon SE-30 (2 m) or OV-17 (2 m). Preparative thin-layer chromatography (PTLC) was performed on Merck precoated silica gel plates.

Preparation of octyl *N,N*-dimethylaminoacetate (2b)

To a suspension of *N,N*-dimethylglycine hydrochloride (2.23g, 0.016 mol), 1-octylalcohol (2.08 g, 0.016 mol), triethylamine (1.62 g, 0.016 mol), and *N,N*-dimethylaminopyridine (0.195 g, 1.6 mmol) in DMF (100 mL) was added 1,3-dicyclohexylcarbodiimide (3.63g, 0.0176 mol) in dry DMF (100 mL) under nitrogen atmosphere. After being stirred for 1 day, the solvent was removed *in vacuo*, and the residue was dissolved in ether. The organic layer was washed successively with $NaHCO_3$, water, and brine, and then dried over $MgSO_4$. The crude mixture was purified by silica gel column chromatography (hexane : AcOEt : Et_3N = 50 : 50 : 1) to give **2b** (2.03 g, 59% yield) .

Colorless liquid; ^{1}NMR($CDCl_3$) δ 0.85 (3H , t, J = 6.9 Hz), 1.21-1.33 (m, 10H), 1.57-1.65 (m,

2H), 2.32 (s, 6H), 3.13 (s, 2H), 4.09 (t, J = 6.8 Hz, 2H); IR (neat) 2928, 1753 cm^{-1}; ESI-MS m/z 216 [$(M+1)^+$]. *Anal*. Calcd for $C_{12}H_{25}NO_2$: C, 66.93; H, 11.70; N, 6.50. Found: C, 66.48; H, 11.53; N, 6.52.

Dodecyl *N,N*-dimethylaminoacetate (2c): 48% yield. Colorless liquid; NMR($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.23-1.31 (m, 18H), 1.59-1.68 (m, 2H), 2.35 (s, 6H), 3.16 (s, 2H), 4.12 (t, J = 6.8 Hz, 2H); IR (neat) 2923, 1749 cm^{-1}; ESI-MS m/z 272 [$(M+1)^+$]. *Anal*. Calcd for $C_{16}H_{33}NO_2$: C, 70.80; H, 12.25; N, 5.16. Found: C, 71.06; H, 11.97; N, 5.31.

Hexadecyl *N,N*-dimethylaminoacetate (2d): 44% yield. Colorless liquid; NMR($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.23-1.30 (m, 26H), 1.59-1.68 (m, 2H), 2.35 (s, 6H), 3.16 (s, 2H), 4.12 (t, J = 6.8 Hz, 2H); IR (neat) 2923, 1742 cm^{-1}; ESI-MS m/z 328 [$(M+1)^+$]. *Anal*. Calcd for $C_{20}H_{41}NO_2$: C, 73.34; H, 12.62; N, 4.28. Found: C, 72.72; H, 12.36; N, 4.28.

General procedure for preparation of alkyl 2-[*N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)-*N,N*-dimethylammonio]acetate trifluoromethanesulfonate (3a-d). [1]

To a solution of 2-hydroxy-4,6-dimethoxy-1,3,5-triazine (HO-DMT; 1.46 g, 9.3 mmol) in dry CH_2Cl_2 (160 mL) was added trifluoromethanesulfonic anhydride (2.89g, 10.2 mmol) and *N,N*-diisopropylethylamine (1.2 g, 9.3 mmol) under nitrogen atmosphere. After being stirred for 1 h, the mixture was washed with water (three times), dried ($MgSO_4$), and concentrated. The resulting reside was dissolved in THF (24 mL), and then, **2** (3.7 mmol) in THF (16 mL) was added. After being stirred for 1 h, the solvent was removed *in vacuo*, and the residue was purified by decantation (hexane and ether) to give **3**.

Ethyl 2-(*N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)-*N,N*-dimethylammonio)acetate trifluoromethanesulfonate (**3a**): 79% yield. Pale yellow crystals; mp 52-56°C; ^{1}NMR ($CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H), 3.79 (s, 6H), 4.17 (s, 6H), 4.21 (q, J = 7.2 Hz, 2H), 5.10 (s, 2H); IR (KBr) 2922, 1765, 1617 cm^{-1}; ESI-MS m/z 271 [$(M-CF_3SO_3)^+$]; *Anal*. calcd for $C_{12}H_{19}F_3N_4O_7S$: C 34.29; H, 4.56; N, 13.33. Found: C, 34.22; H, 4.41; N, 13.47.

Octyl 2-(*N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)-*N,N*-dimethylammonio)acetate trifluoromethanesulfonate (**3b**): 75% yield. Colorless crystals; mp 51-53°C. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.23-1.34 (m, 10H), 1.59-1.67 (m, 2H), 3.79 (s, 6H), 4.14

(t, J = 6.8 Hz, 2H), 4.17 (s, 6H), 5.10 (s, 2H); IR (KBr) 2972, 1741, 1630 cm^{-1}; ESI-MS m/z 355 [$(M\text{-}CF_3SO_3)^+$]. *Anal*. Calcd for $C_{18}H_{31}F_3N_4O_7S$: C, 42.85; H, 6.19; N, 11.10. Found: C, 42.67;H, 5.93; N, 11.16.

Dodecyl 2-(*N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)-*N*,*N*-dimethylammonio)acetate trifluoromethanesulfonate (**3c**): 63% yield. Colorless crystals; mp 52-54˚C. ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.23-1.34 (m, 18H), 1.59-1.68 (m, 2H), 3.80 (s, 6H), 4.14 (t, J = 6.8 Hz, 2H), 4.17 (s, 6H), 5.11 (s, 2H); IR (KBr) 2918, 1764, 1619 cm^{-1}; ESI-MS m/z 411 [$(M\text{-}CF_3SO_3)^+$]. *Anal*. Calcd for $C_{22}H_{39}F_3N_4O_7S$: C, 47.13; H, 7.01; N, 9.99. Found: C, 46.97;H, 7.08; N, 10.04.

Hexadecyl 2-(*N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)-*N*,*N*-dimethylammonio)acetate trifluoromethanesulfonate (**3d**): 44% yield. Colorless crystals; mp 59-61˚C. ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.23-1.33 (m, 26H), 1.59-1.68 (m, 2 H), 3.79 (s, 6H), 4.14 (t, J = 6.8 Hz, 2H), 4.17 (s, 6H), 5.10 (s, 2H); IR (KBr) 2916, 1765, 1612 cm^{-1}. ESI-MS m/z 467 [$(M+1)^+$]. *Anal*. Calcd for $C_{26}H_{47}F_3N_4O_7S \cdot H_2O$: C, 49.20; H, 7.78. Found: C, 49.50; H, 7.61.

General procedure for the kinetic study of stoichiometric reaction between 1 and 3 is described in experimental section in the text.

***N*-Butylbutanamide** (**6A**)[2,3]: Colorless liquid; NMR($CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H), 1.31-1.39 (m, 2H), 1.43-1.52 (m, 2H), 1.62-1.69 (m, 2H), 2.13 (t, J = 7.5 Hz, 2H), 3.22-3.28 (m, 2H), 5.39 (br. s, 1H); IR (neat) 3288, 1649, 1559 cm^{-1}; ESI-MS m/z 144 [$(M+1)^+$].

***N*-Butyloctanamide** (**6B**)[3]: Colorless liquid; NMR($CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H), 1.23-1.40 (m, 10H), 1.43-1.52 (m, 2H), 1.57-1.66 (m, 2H), 2.15 (t, J = 7.6 Hz, 2H), 3.21-3.28 (m, 2H), 5.37 (br. s, 1H); IR (neat) 3288, 1641, 1561 cm^{-1}; ESI-MS m/z 200 [$(M+1)^+$].

***N*-Butyldodecanamide** (**6C**)[4]: Colorless crystals; mp 45-46˚C. (CH_2Cl/hexane). NMR ($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H), 1.20-1.40 (m, 18H), 1.43-1.52 (m,

2H), 1.57-1.67 (m, 2H), 2.15 (t, J = 7.6 Hz, 2H), 3.22-3.28 (m, 2H), 5.36 (br. s, 1H); IR (KBr) 3293, 1633, 1548 cm^{-1}; ESI-MS m/z 256 $[(M+1)^+]$.

***N*-Butyloleamide (6D)**[4]: Colorless liquid; NMR($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H), 1.20-1.40(m, 22H), 1.43-1.52 (m, 2H), 1.58-1.65 (m, 2H), 1.97-2.04 (m, 4H), 2.14 (t, J = 7.6 Hz, 2H), 3.21-3.28 (m, 2H), 5.31-5.40 (m, 3H); ESI-MS m/z 338 $[(M+1)^+]$.

General procedure for the competitive amide-formation.

To a stirred aqueous solution (1.7 mL) containing two kinds of sodium carboxylates **1** (30 μmol each), butylamine hydrochloride (**5**•HCl, 40 μmol) in sodium phosphate buffer (pH 8) was added **3** (6 μmol in 20% aq. MeOH, 0.3 mL) at 25˚C. The initial concentration of reactants in the resulting solution were as follows: **1**: 15 mM (each); **5**: 20 mM; **3**: 1.5 mM; NaPi: 20 mM; and MeOH: 3%. The mixture was stirred at 25°C, and 5M HCl (0.3 mL) was added at a definite time. The resulting mixture was applied to Extrelut® NT (Merck, 2 g) and eluted with AcOEt. The product was quantified by GC (Silicone SE-30 for **6A**, Silicone OV-17 for **6B-D**).

General procedure for the kinetic study of catalytic reaction using 2 and 2-chloro-4,6-dimethoxy-1,3,5-triazine (DMT-Cl).

To a stirred aqueous solution (9.65 mL) containing sodium carboxylate **1** (150 μmol), butylamine hydrochloride (**5**•HCl, 200 μmol), in sodium phosphate buffer (pH 8) was added tertiary amine catalyst **2** (15 μmol dissolved in 0.05 mL MeOH). The reaction was started by addition of, followed by DMT-Cl (150 μmol in 0.3 mL MeOH) at 25˚C. The initial concentration of reactants in the resulting solution were as follows: **1**: 15 mM; **5**: 20 mM; **2**: 1.5 mM; DMT-Cl: 15 mM; NaPi: 200 mM; and MeOH: 3.5%. The mixture was stirred at 25°C, and 5M HCl (0.3 mL) was added at a definite time. The resulting mixture was applied to Extrelut® NT (Merck, 2 g) and eluted with AcOEt. The product was quantified by GC (Silicone OV-17). The pseudo-first-order rate constants were determined from the slopes of liner plots of $\ln([\mathbf{1}]_t/[\mathbf{1}]_0)$ versus time (t).

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