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 $\delta$ 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 (2.23 g, 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 (3.63 g, 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$_3$N = 50 : 50 : 1) to give $2b$ (2.03 g, 59% yield). Colorless liquid; $^1$NMR(CDCl$_3$) $\delta$ 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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_2\)Cl\(_2\) (160 mL) was added trifluoromethanesulfonic anhydride (2.89g, 10.2 mmol) and N,N-disopropylethylamine (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 residue 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; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 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\(_3\)SO\(_2\)]+]; Anal. calcd for C\(_{12}\)H\(_{19}\)F\(_3\)N\(_2\)O\(_5\): 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\(_3\)) \(\delta\) 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-CF\(_3\)SO\(_3\))^\(\cdot\)]. Anal. Calcd for C\(_{19}\)H\(_{31}\)F\(_3\)N\(_4\)O\(_7\)S: 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. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 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-CF\(_3\)SO\(_3\))^\(\cdot\)]. Anal. Calcd for C\(_{22}\)H\(_{39}\)F\(_3\)N\(_4\)O\(_7\)S: 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. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.88 (t, \(J = 6.8\) Hz, 3H), 1.23-1.33 (m, 26H), 1.59-1.68 (m, 2H), 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\(_3\)N\(_4\)O\(_7\)S·H\(_2\)O: 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.

\(\text{N-Butylbutanamide (6A)}^{[2,3]}\): Colorless liquid; NMR(CDCl\(_3\)) \(\delta\) 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)^\(+\)].

\(\text{N-Butyloctanamide (6B)}^{[3]}\): Colorless liquid; NMR(CDCl\(_3\)) \(\delta\) 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)^\(+\)].

\(\text{N-Butyldodecanamide (6C)}^{[4]}\): Colorless crystals; mp 45-46°C. (CH\(_2\)Cl/hexane). NMR (CDCl\(_3\)) \(\delta\) 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)⁺].

\( \text{N-Butyloleamide (6D)}^{[4]} \): Colorless liquid; NMR(CDCl₃) 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([I]₀/[I]₀) versus time (t).

**References**

