

Supplementary Material

The influence of salt additives on the macrocyclic product distributions in double-amidation reactions

G. Pikus, E. Pańniczek, J. Jurczak

*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224
Warsaw, Poland.*

E-mail: jurczak_group@icho.edu.pl

Table of Contents

1. Analytical and spectroscopic data of macrocyclic di- and tetraamides	S2
2. Calibration of HPLC UV-detector	S4

Analytical and spectroscopic data of macrocyclic di- and tetraamides

Diamide **9**: 77% yield; mp. 224-225 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.38 (*br s*, 2H), 7.01-6.85 (*m*, 4 arom. H), 4.48 (*s*, 4H), 3.67 (*m*, 4H), 3.64 (*m*, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 167.2, 146.1, 122.1, 112.5, 69.0, 66.9, 38.4.

Diamide **10**: 75% yield; mp. 175-176 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.36 (*s*, 2H), 7.04-6.95 (*m*, 2H), 6.91-6.82 (*m*, 2H), 4.48 (*s*, 4H), 3.74-3.55 (*m*, 12H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 167.87, 146.75, 122.41, 113.24, 70.20, 69.70, 67.68, 38.69.

Diamide **11**: 29% yield; 125-127 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.25 (*bs*, 2H), 7.03-6.95 (*m*, 2H), 6.94-6.83 (*m*, 2H), 4.57 (*s*, 4H), 3.75-3.33 (*m*, 16H); ¹³C NMR (100 MHz, CDCl₃) δ 168.38, 147.64, 122.88, 114.71, 70.75, 70.68, 69.76, 69.12, 38.97.

Diamide **12**: 40% yield; mp. 134-136 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.49 (*s*, 2H), 7.05-6.96 (*m*, 2H), 6.95-6.85 (*m*, 2H), 4.50 (*s*, 4H), 3.53-3.43 (*m*, 8H), 3.29-3.19 (*m*, 4H), 1.84-1.74 (*m*, 4H), 1.58-1.46 (*m*, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 168.24, 148.38, 123.26, 116.39, 71.12, 70.88, 69.95, 38.71, 28.13, 26.47.

Diamide **13**: 55% yield, 117-118 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (*bs*, 2H), 7.01-6.98 (*m*, 2H), 6.96-6.93 (*m*, 2H), 4.51 (*s*, 4H), 3.57-3.49 (*m*, 16H), 1.85-1.80 (*m*, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 168.28, 148.06, 123.08, 115.79, 70.28, 70.18, 70.15, 69.55, 37.94, 28.42.

Diamide **14**: 25% yield; mp. 230-231 °C; ¹H-NMR (400 MHz, CDCl₃) δ 7.26 (*br s*, 2H), 7.17 (*t*, *J*=8.5 Hz, 1H), 6.67 (*dd*, *J*=8.5 Hz, *J*=2.5 Hz, 2 H), 6.55 (*t*, *J*=2.5 Hz, 1H), 4.65 (*s*, 4H), 3.39-3.59 (*m*, 8H); ¹³C-NMR (100 MHz, CDCl₃) δ 168.5, 158.8, 131.1, 109.0, 102.8, 69.5, 67.7, 38.9.

Diamide **15**: 22% yield; mp. 144-147°C; ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.12 (*m*, 1H), 6.68 (*bs*, 2H), 6.55-6.52 (*m*, 3H), 4.53 (*s*, 4H), 3.51-3.45 (*m*, 8H), 3.41 (*s*, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 168.50, 158.87, 130.50, 107.61, 102.94, 70.71, 69.69, 67.75, 38.87.

Diamide **16**: 29% yield; mp. 125-127 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.26 (*d*, *J*=8.2 Hz, 1H), 7.01 (*s*, 2H), 6.63 (*t*, *J*=2.4 Hz, 1H), 6.59 (*d*, *J*=2.4 Hz, 1H), 6.57 (*d*, *J*=2.4 Hz, 1H), 4.53 (*s*, 4H), 3.65-3.60 (*m*, 4H), 3.57-3.48 (*m*, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 167.95, 158.77, 130.73, 107.43, 105.16, 70.81, 70.69, 69.53, 67.93, 38.52.

Diamide **17**: 42% yield; mp. 103-104 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.49 (*s*, 2H), 7.05-6.96 (*m*, 2H), 6.95-6.85 (*m*, 2H), 4.50 (*s*, 4H), 3.53-3.43 (*m*, 8H), 3.29-3.19 (*m*, 4H), 1.84-1.74 (*m*, 4H), 1.58-1.46 (*m*, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 167.57, 158.55, 130.63, 106.06, 105.82, 71.44, 71.12, 67.29, 39.13, 28.04, 26.46.

Diamide **18**: 40% yield; mp. 117-118 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.53 (*bs*, 2H), 7.27 (*t*, *J*=8.3 Hz, 1H), 6.76 (*t*, *J*=2.4 Hz, 1H), 6.56 (*dd*, *J*=8.4, 2.5 Hz, 2H), 4.47 (*s*, 4H), 3.74-3.57 (*m*, 12H), 3.55-3.42 (*m*, 4H), 1.91-1.75 (*m*, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 167.55, 158.60, 130.67, 106.26, 105.71, 71.99, 70.30, 70.21, 67.42, 39.09, 28.06.

Diamide **19**: 1% yield; 177-179 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.91 (*t*, *J*=5.4 Hz, 2H), 6.81 (*s*, 4H), 4.35 (*s*, 4H), 3.47 (*m*, 4H), 3.32-3.27 (*m*, 4H); ¹³C NMR (100 MHz, DMSO) δ 167.68, 152.04, 115.57, 68.40, 67.54, 38.18.

Diamide **20**: 20% yield; mp. 197-198 °C; ¹H NMR (400 MHz, CDCl₃) δ 6.84 (*s*, 4H), 6.62 (*bs*, 2H), 4.54 (*s*, 4H), 3.53-3.32 (*m*, 8H), 3.20 (*s*, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 168.82, 152.02, 114.98, 69.96, 69.73, 67.51, 38.51.

Diamide **21**: 18% yield; mp. 155-157 °C; ^1H NMR (400 MHz, CDCl_3) δ 6.88 (s, 4H), 6.80 (s, 2H), 4.51 (s, 4H), 3.51-3.43 (m, 8H), 3.42-3.28 (m, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.74, 152.80, 116.13, 70.62, 70.35, 69.63, 68.70, 38.62.

Diamide **22**: 35% yield; mp. 165-167 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.16 (bs, 2H), 6.86 (s, 4H), 4.45 (s, 4H), 3.51-3.29 (m, 8H), 3.18 (bs, 4H), 1.80-1.62 (m, 4H), 1.36-1.25 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.36, 152.75, 116.11, 71.05, 70.41, 68.63, 38.19, 28.49, 26.07.

Diamide **23**: 28% yield; mp. 136-137 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.80 (bt, $J=5.5$ Hz, 2H), 6.89 (s, 4H), 4.42 (s, 4H), 3.45-3.40 (m, 4H), 3.39-3.34 (m, 4H), 3.28 (t, $J=6.3$ Hz, 4H), 3.21-3.12 (m, 4H), 1.66-1.53 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ 167.71, 152.13, 115.68, 69.53, 69.32, 68.82, 67.71, 36.16, 28.61.

Tetraamide **24**: 2% yield; mp. 219-220 °C; ^1H -NMR (400 MHz, CDCl_3), δ 6.97-6.96 (m, 4 arom. H), 6.82-6.81 (m, 4 arom. H), 4.42 (s, 8H), 3.59-3.52 (m, 16H); ^{13}C -NMR (100 MHz, CDCl_3), δ 168.4, 147.6, 123.2, 115.4, 69.3, 69.2, 38.7.

Tetraamide **25**: 5% yield; mp. 198-199 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ^1H NMR (400 MHz, DMSO) δ 8.01 (t, $J=5.4$ Hz, 4H), 7.10-6.91 (m, 8H), 4.52 (s, 8H), 3.48-3.42 (m, 12H), 3.36-3.25 (m, 12H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 167.83, 147.68, 122.15, 115.13, 69.43, 68.72, 68.37, 38.19.

Tetraamide **27**: 8% yield; mp. 185-187 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.27-7.16 (m, 6H), 6.57-6.53 (m, 6H), 4.44 (s, 8H), 3.47-3.36 (m, 24H), 1.79-1.78 (m, 8H), 1.59 (bs, 8H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 168.10, 147.79, 123.01, 115.47, 70.77, 69.30, 69.19, 37.52, 29.15, 26.30.

Tetraamide **28**: 6% yield; mp. 122-124 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.40 (bt, $J=5$ Hz, 4H), 7.00-6.97 (m, 4H), 6.92-6.89 (m, 4H), 4.51 (s, 8H), 3.53-3.52 (m, 24H), 3.45 (dd, $J_1=12.5$ Hz, $J_2=6.5$ Hz, $J_3=6.0$ Hz, 4H), 1.80 (dt, $J_1=12.5$ Hz, $J_2=6.5$ Hz, $J_3=6.0$ Hz, 4H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 168.10, 147.79, 123.01, 115.47, 70.77, 69.30, 69.19, 37.52, 29.15, 26.30.

Tetraamide **29**: 4% yield; mp. 257-259 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.92 (t, $J=5.5$ Hz, 4H), 7.16 (t, $J=8.1$ Hz, 2H), 6.63-6.45 (m, 6H), 4.43 (s, 8H), 3.44 (t, $J=5.4$ Hz, 8H), 3.33- 3.23 (m, 8H); ^{13}C NMR (100 MHz, DMSO) δ 167.58, 158.72, 129.91, 107.61, 101.93, 68.46, 66.99, 38.17.

Tetraamide **30**: 6% yield; mp. 213-214 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.95 (t, $J=5.5$ Hz, 4H), 7.19 (t, $J=8.2$ Hz, 2H), 6.61-6.51 (m, 6H), 4.44 (s, 8H), 3.50-3.40 (m, 16H), 3.34- 3.22 (m, 8H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 167.53, 158.73, 129.95, 107.61, 101.96, 69.47, 68.74, 66.98, 38.25.

Tetraamide **32**: 18% yield; mp. 150-153 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.21-7.16 (m, 6H), 6.57-6.53 (m, 6H), 4.44 (s, 8H), 3.47-3.36 (m, 24H), 1.79-1.76 (m, 8H), 1.59 (bs, 8H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 167.72, 158.71, 130.51, 107.90, 102.99, 70.58, 69.75, 67.67, 37.85, 28.90, 26.40.

Tetraamide **33**: 3% yield; mp. 157-158 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.21 (t, $J=8.2$ Hz, 2H), 7.16 (bt, $J=5.3$ Hz, 4H), 6.63-6.51 (m, 6H), 4.44 (s, 8H), 3.64-3.49 (m, 24H), 3.48-3.35 (m, 8H), 1.79 (p, $J=6.4$, 5.6 Hz, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.85, 158.74, 130.48, 107.86, 103.02, 70.36, 70.22, 69.82, 67.60, 37.43, 28.94.

Tetraamide **34**: 10% yield; mp. 251-252 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.92 (t, *J*=5.5 Hz, 4H), 7.16 (t, *J*=8.1 Hz, 2H), 6.63-6.45 (m, 6H), 4.43 (s, 8H), 3.44 (t, *J*=5.4 Hz, 8H), 3.33-3.23 (m, 8H); ¹³C NMR (100 MHz, DMSO) δ 167.64, 152.04, 115.56, 68.39, 67.55, 38.17

Tetraamide **35**: 11% yield; mp. 200-201 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.91 (bs, 4H), 6.87 (s, 8H), 4.39 (s, 8H), 3.46-3.40 (m, 8H), 3.33-3.22 (m, 8H); ¹³C NMR (100 MHz, DMSO) δ 167.85, 152.20, 115.62, 69.50, 68.74, 67.60, 38.23

Tetraamide **36**: 2% yield; mp. 162-163 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.91 (bs, 4H), 6.87 (s, 8H), 4.44 (s, 8H), 3.47-3.45 (m, 8H), 3.41-3.38 (m, 16H), 3.27-3.23 (m, 8H); ¹³C NMR (100 MHz, DMSO) δ 167.85, 152.20, 115.62, 69.50, 68.74, 67.60, 39.50, 38.23.

Tetraamide **37**: 6% yield; mp. 170-172 °C; ¹H NMR (400 MHz, CDCl₃) 7.52 (bs, 4H), 6.85 (s, 8H), 4.41 (s, 8H), 3.50-3.43 (m, 16H), 3.36-3.34 (m, 8H), 1.81-1.76 (m, 8H), 1.58-1.56 (m, 8H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 168.07, 152.46, 115.89, 70.88, 70.01, 68.23, 37.95, 28.83, 26.34.

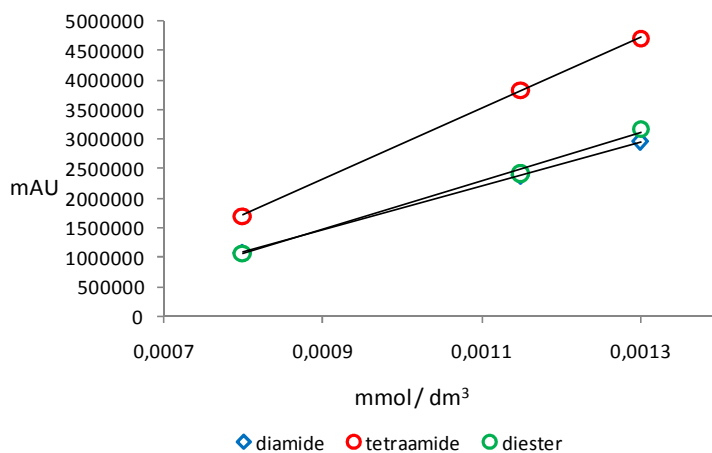
Tetraamide **38**: 4% yield; mp. 138-140 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.22 (bs, 4H), 6.86 (s, 8H), 4.40 (s, 8H), 3.61-3.54 (m, 24H), 3.47-3.34 (m, 8H), 1.83-1.78 (m, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 168.10, 152.43, 115.89, 70.35, 70.21, 70.10, 68.15, 37.56, 28.82.

Calibration of HPLC UV-detector

We prepared three-component mixtures in methanol containing one diester, one diamide and one tetraamide in equal molar concentration of 0.80, 1.15, 1.30 mM. Each mixture was analyzed by HPLC using reversed-phase column Bionacom Velocity C18-2, 4.6 x 250 mm, grain size 5 μm, λ=195 nm, gradient: 25% → 50% acetonitrile in water t=30 min. The results of these experiments were used to determine linear dependence between UV-detector data and concentration (Table 1, Figure 1).

Table S1. Calibration data

Mixed compounds	Concentration [mM]	averaged UV-detector data		
		diamine	tetraamide	ester
29 + 30 + 7	0.80	1083699	1702793	1083533
35 + 35 + 8	1.30	2958070	4717045	3190803
15 + 16 + 6	1.15	2375623	3835689	2404382

**Figure S1**

Based on these data we have calculated correlation coefficients for concentration of 1.2 mM: diamide 1.000, tetraamide 1.593 ± 0.007 , diester 1.014 ± 0.034 what have been used to determined reaction mixtures quantitatively.