

## Supporting Information for

### **Influence of molecular weight on kinetics release of metronidazole from proline-based polymers prepared by RAFT polymerization**

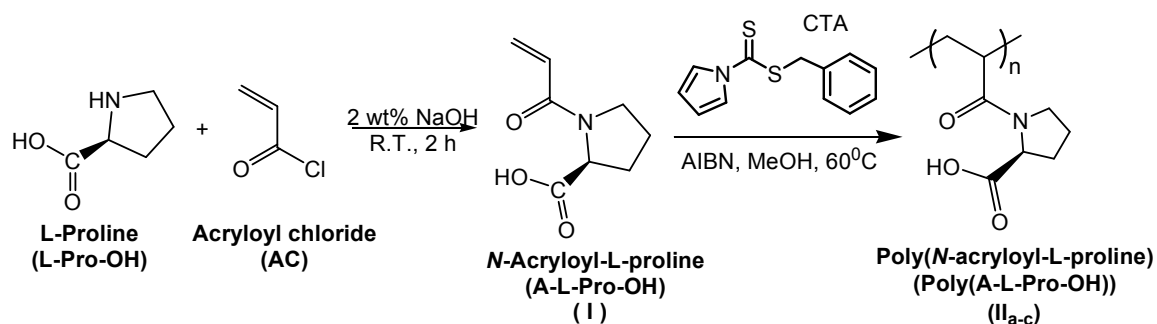
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*Scheme S1.* Synthesis of *N*-acryloyl-L-proline (A-L-Pro-OH) (I) and RAFT polymerization of A-L-Pro-OH.

### Synthesis of proline-based monmer (I)<sup>1</sup>

In two-neck round bottomed flask, L-proline (25.0 g, 217.2 mmol) was dissolved in 50 mL of 2 wt% NaOH and it was kept at 0°C in an ice-bath, and then acryloyl chloride (13.5 mL, 166.2 mmol) was added dropwise. After the addition, the reaction mixture was stirred for 30 min with the temperature raising to room temperature. The mixture was acidified to pH = 1-3 with 6N HCl, and then the stirring was continued for additional 1h at room temperature. The resulting mixture was extracted five times with chloroform (100 mL X 5) and the solution was dried over anhydrous MgSO<sub>4</sub>. The solution was filtered and the solvent was removed under reduced pressure and the resulting residue was purified by recrystallization from cold ethyl acetate to give 7.4 g of A-L-Pro-OH (I) as a white solid (yield =20 %). m.p. = 115-117°C (lit. m.p. = 118-120°C)<sup>2</sup>.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 6.10-6.68 (2H, -CH=CH<sub>2</sub>), 5.68-5.76 (1H, -CH=CH<sub>2</sub>),

4.39-4.92 (1H, >CHCO<sub>2</sub>H), 3.45-3.81 (2H, >NCH<sub>2</sub>-), 1.83-2.39 (4H, -CH<sub>2</sub>CH<sub>2</sub>-) ppm.

<sup>13</sup>C NMR (400 MHz, CD<sub>3</sub>OD): δ 174.1 (-COOH), 165.2 (-CO<sub>2</sub>NH-), 128.4 (-CH=CH<sub>2</sub>), 127.2 (-CH=CH<sub>2</sub>), 59.4 (>CHCO<sub>2</sub>-, *s-cis*), 59.1 (>CHCO<sub>2</sub>-, *s-trans*), 47.1 (>NCH<sub>2</sub>-, *s-cis*), 46.5 (>NCH<sub>2</sub>-, *s-trans*), 31.8 (>CHCH<sub>2</sub>-, *s-cis*), 29.0 (>CHCH<sub>2</sub>-, *s-trans*), 24.8 (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, *s-cis*), 21.8 (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, *s-trans*) ppm.

IR (KBr): 2880 (O-H, carboxylic), 1734 (C=O, carboxylic), 1637 (C=O, amide), 1576 (C=C vinylic), 1457-1097 (C-N) cm<sup>-1</sup>.

### **Synthesis of poly(*N*-Acryloyl-L-Proline) [Poly(A-L-Pro-OH)] (II<sub>a-c</sub>)**

Poly(A-L-Pro-OH) with different molecular weight were prepared according to the following general procedure described by Mori *et al.*,<sup>1</sup>; Poly(A-L-Pro-OH) was prepared as following; A-L-Pro-OH (I), benzyl 1-pyrrolicarbodithioate (CTA), AIBN were dissolved in dehydrated methanol and were placed in a dry glass ampule equipped with a magnetic stirrer bar, and then the solution was degassed by two freeze-evacuate-thaw cycles, the ampule was flame-sealed off under vacuum, and was stirred at 60°C for 24 h. The characteristic pale red color maintained during the polymerization. The reaction was stopped by rapid cooling with liquid nitrogen.

For the determination of the monomer conversion, the <sup>1</sup>H NMR spectrum of the polymerization mixture collected after the polymerization was measured in CD<sub>3</sub>OD at

room temperature, and the integration of the monomer C=C-*H* resonance at around 5.7 ppm was compared with the sum of N-C-*H* peak intensity of the polymer and the monomer at around 4.2-4.7 ppm.

After removing the solvents by evaporation, a part of the crude sample was employed for methylation without purification, which was directly used for the size-exclusion chromatography (SEC) measurements. For the <sup>1</sup>H NMR measurement, the crude polymer was purified by precipitation from a MeOH solution into a large excess of tetrahydrofuran (THF)/hexane (8/2 vol %) (500 mL), and the resulting product was dried under vacuum at room temperature.

The resulting poly(A-L-Pro-OH) was soluble in basic water (pH=10), methanol, ethanol, DMSO, DMF, and insoluble in neutral water (pH = 7), acidic water (pH = 1), ethyl acetate, THF, chloroform, diethyl ether, hexane.

For SEC measurements, the crude poly(A-L-Pro-OH)s were modified by methylation of the carboxylic acid groups using trimethylsilyldiazomethane according to a method reported previously with a slight modification<sup>1</sup>. In this way, 25 mg of each sample was dissolved in a mixture of methanol/THF (2/1 vol %, to get solubilization at room temperature), overall volume 3.0 mL. The yellow solution of trimethylsilyldiazomethane (0.5 mL, 1.0 mmol, (CH<sub>3</sub>)<sub>3</sub>SiCHN<sub>2</sub>/COOH group in poly(A-L-Pro-OH) = 7/1 molar

ratio) was added dropwise at room temperature into the polymer solution. Upon addition, bubbles appeared and the bright yellow solution became instantaneously pale yellow. After the methylation agent was added completely, the solution was stirred for 30 min at room temperature. After removing the solvents by evaporation, the methylated samples were employed without any purification for the SEC measurements.

### **Poly(A-L-Pro-OH) (II<sub>a</sub>)**

Poly(A-L-Pro-OH) (II<sub>a</sub>) ( $M_n = 6000$ ,  $M_w/M_n = 1.30$ ) was prepared using the following quantities: A-L-Pro-OH (I) (1.5 g, 8.87 mmol), benzyl 1-pyrrolocarbodithioate (CTA) (41.3 mg, 0.18 mmol), AIBN (5.82 mg, 0.04 mmol) and dehydrated methanol (6 mL). Conversion determined by the <sup>1</sup>H NMR spectrum was found to be 55%. The product was dried under vacuum at 55°C to yield 0.98 g, 65%.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 4.4 (1H, >CHCO<sub>2</sub>H), 3.4-4.0 (2H, >NCH<sub>2</sub>-), 2.6 (1H, -CHCH<sub>2</sub>-), 2.2 (2H, >CHCH<sub>2</sub>CH<sub>2</sub>-), 1.8-2.0 (1H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.2-1.5 (2H, -CHCH<sub>2</sub>-) ppm.

IR (KBr): 3479 (O-H, carboxylic), 2957 (C-C, alkane), 1736 (C=O, carboxylic), 1619 (C=O, amide), 1454-1045 (C-N) cm<sup>-1</sup>.

### **Poly(A-L-Pro-OH) (II<sub>b</sub>)**

Poly(A-L-Pro-OH) (II<sub>b</sub>) ( $M_n = 13300$ ,  $M_w/M_n = 1.34$ ) was prepared using the following

quantities: A-L-Pro-OH (I) ( 1.5 g, 8.87 mmol), benzyl 1-pyrrolicarbodithioate (CTA) (20.6 mg, 0.09 mmol), AIBN (2.91 mg, 0.02 mmol) and dehydrated methanol (6 mL). Conversion determined by the <sup>1</sup>H NMR spectrum was found to be 98%. The product was dried under vacuum at 55°C to yield 1.37 g, 91%.

### **Poly(A-L-Pro-OH) (II<sub>c</sub>)**

Poly(A-L-Pro-OH) (II<sub>c</sub>) ( $M_n = 22600$ ,  $M_w/M_n = 1.37$ ) was prepared using the following quantities: A-L-Pro-OH (I) (1.5 g, 8.87 mmol), benzyl 1-pyrrolicarbodithioate (CTA) (10.3 mg, 0.04 mmol), AIBN (1.45 mg, 0.01 mmol) and dehydrated methanol (6 mL). Conversion determined by the <sup>1</sup>H NMR spectrum was found to be 98%. The product was dried under vacuum at 55°C to yield 1.44 g, 98%.

*Table S1.* Elemental microanalysis of monomers and polymers.

Polymer Code	C (%)		H (%)		N (%)	
	Calc.	Found	Calc.	Found	Calc.	Found
I	56.80	56.44	6.55	6.57	8.28	8.08
II <sub>a</sub>		53.95		6.90		7.40
II <sub>b</sub>	53.88 <sup>a</sup>	53.72	6.73 <sup>a</sup>	7.02	7.86 <sup>a</sup>	7.45
II <sub>c</sub>		54.30		6.85		7.47

<sup>a</sup> Theoretical values for poly(A-L-Pro-OH) with 1/2 H<sub>2</sub>O.

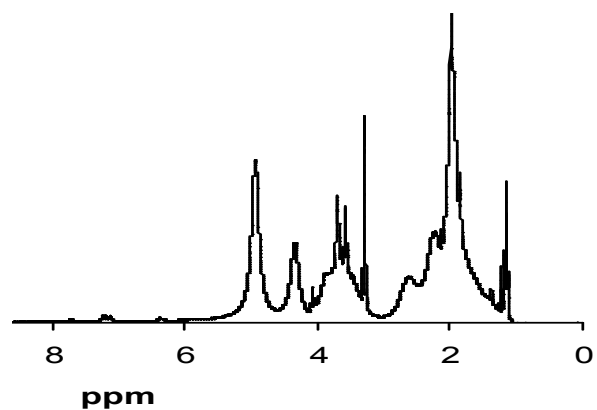


Figure S1.  $^1\text{H}$  NMR spectrum ( $\text{CD}_3\text{OD}$ ) of poly(*N*-acryloyl-L-proline) (Poly(A-L-Pro-OH)).

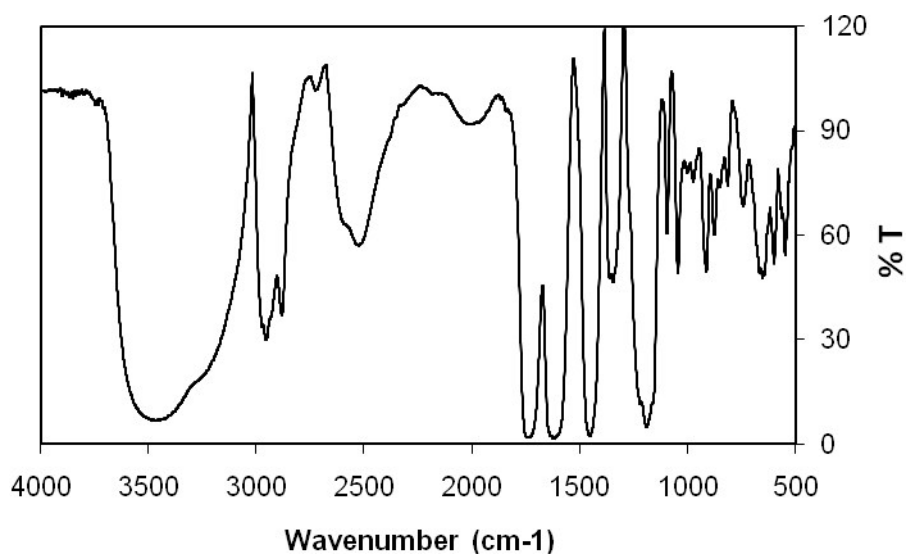
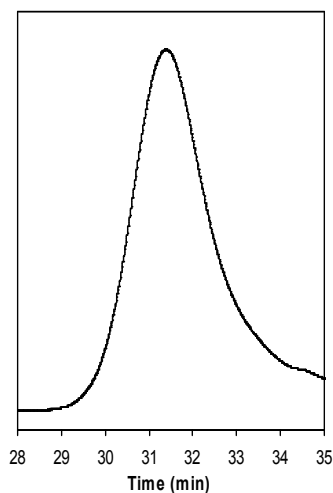
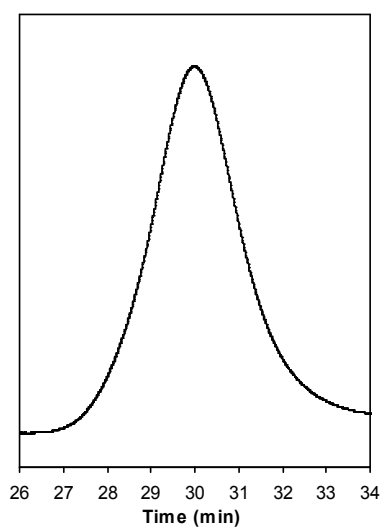


Figure S2. FT-IR spectrum of poly(*N*-acryloyl-L-proline) (Poly(A-L-Pro-OH)).

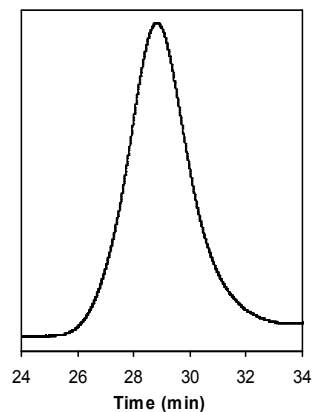


*Figure S3.* SEC trace (RI detector, DMF with 10mM LiBr) of the methylated sample of poly(A-L-Pro-OH) (II<sub>a</sub>),  $M_n = 6000$ ,  $M_w/M_n = 1.30$ , conversion = 55%, obtained at  $[M]/[CTA]/[AIBN] = 250/5/1$ , in methanol at 60°C for 24 h.



*Figure S4.* SEC trace (RI detector, DMF with 10mM LiBr) of the methylated sample of poly(A-L-Pro-OH) (II<sub>b</sub>),  $M_n = 13300$ ,  $M_w/M_n = 1.34$ , conversion = 98%, obtained at  $[M]/[CTA]/[AIBN] = 500/5/1$ , in methanol at 60°C for 24 h.





*Figure S5.* SEC trace (RI detector, DMF with 10mM LiBr) of the methylated sample of poly(A-L-Pro-OH) (II<sub>c</sub>),  $M_n = 22600$ ,  $M_w/M_n = 1.37$ , conversion = 98%, obtained at  $[M]/[CTA]/[AIBN] = 1000/5/1$ , in methanol at 60°C for 24 h.

## REFERENCES

1. H. Mori, I. Kato, M. Matsuyama, T. Endo, *Macromolecules*. **2008**, *41*, 5604.
2. M.P. Bueno, C.A. Cativiela, J.A. Mayoral, A. Avenoza, *J. Org. Chem.* **1991**, *56*, 6551.