

A Novel Anisotropic Supramolecular Hydrogel with High Stability over a Wide pH Range

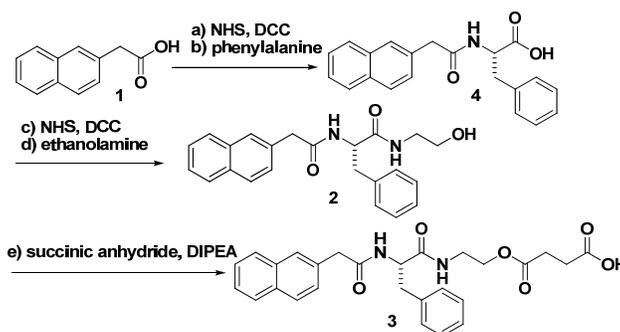
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Supporting Information

A) Materials and Methods

Chemical reagents and solvents were used as received from commercial sources. ^1H NMR and ^{13}C NMR spectra were obtained on Varian Unity Inova 400, MALDI-TOF MS on Finnigan/MAT TSQ7000 Mass Spectrometer system, LC-MS on Waters Acuity ultra PerformaceLC with Waters MICROMASS detector, CD on a JASCO J-810 spectrometer, TEM on Morgagni 268 transmission electron microscope and rheology test on TA ARES-G2 with the parallel plate (diameter = 25 mm).

B) Synthesis



Scheme S1. The synthesis route of **3**.

NapF (**4**): Synthesis of **4** follows the literature method.¹ N,N'-Dicyclohexylcarbodiimide (DCC, 460 mg, 1.1 eq.) was added to 20 mL CHCl_3 solution containing **1** (372 mg, 2.0 mmol) and N-hydroxysuccinimide (NHS, 230 mg, 1 eq.). The reaction mixture was stirred at room temperature for 4 hours. The organic solvent was removed by rotary evaporation and the solid was dissolved in 20 mL of acetone and followed by filtration. Phenylalanine (165mg, 1 eq.) and Na_2CO_3 (95.4mg, 0.9 eq.) were dissolved in 15 mL of DI water and mixed with the acetone solution of NHS activated ester of **1**. The reaction was carried out overnight at room temperature and acetone was evaporated by rotary evaporation. The solution was acidified by HCl (1.0 M) to pH = 3 and the solid was filtered and freeze-dried to give **4**. ^1H NMR of **4** (400MHz, $\text{DMSO}-d_6$) is shown in Page 5.

NapF-ethanolamine (**2**): Synthesis of **3** follows the same procedure as the synthesis of **4** except using ethanolamine (183 mg, 3eq.) instead of phenylalanine and Na_2CO_3 in DI water. After the reaction is completed, acetone was evaporated. The solid was filtered, washed with DI water, and freeze-dried. Flash silica gel chromatography with the eluent (CHCl_3 : MeOH = 150:1) was used to get pure compound **2**. ^1H NMR of **2** (400MHz, $\text{DMSO}-d_6$) is shown in Page 6; HR-MS (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_3^+$ 377.1860, found 377.1676, shown in Page 7.

NapFES (**3**): **2** (376mg, 1 eq.), succinic anhydride (300mg, 3 eq.) and N,N-diisopropylethylamine (DIPEA, 260mg, 2 eq.) were dissolved into 25 mL of chloroform and stirred overnight at room temperature. After the reaction was completed, the organic solvent was evaporated. Flash silica gel chromatography with the eluent (CHCl_3 : MeOH:AcOH = 200:1:0.5) was used to purify the compound **3**. ^1H NMR of **3** (400MHz, $\text{DMSO}-d_6$) is shown in Page 8; ^{13}C NMR (100.5Hz, $\text{DMSO}-d_6$): δ =174.15, 172.78, 172.09, 170.48, 138.45, 134.67, 133.57, 132.36, 129.86, 128.64, 128.27, 128.10, 128.00, 127.91, 126.88, 126.65, 126.11, 63.14, 54.69, 42.87, 40.76, 38.54, 38.21, 29.36, 29.35 ppm, shown in Page 9; HR-MS (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_6^+$ 477.2020, found 477.2339, shown in Page 10.

C) Hydrolysis product analysis

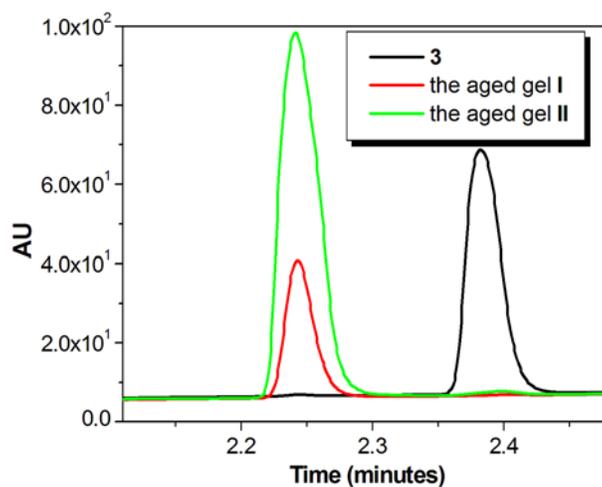


Figure S1. The HPLC trace of **3** and the gels aged for 7 days detected at all wavelengths. From ESI+, the m/z values of the peak at 2.268 minutes and 2.400 minutes are 377.16 and 477.15, respectively; the values are 375.21 and 475.33 from ESI-, respectively.

D) Hydrolysis rate

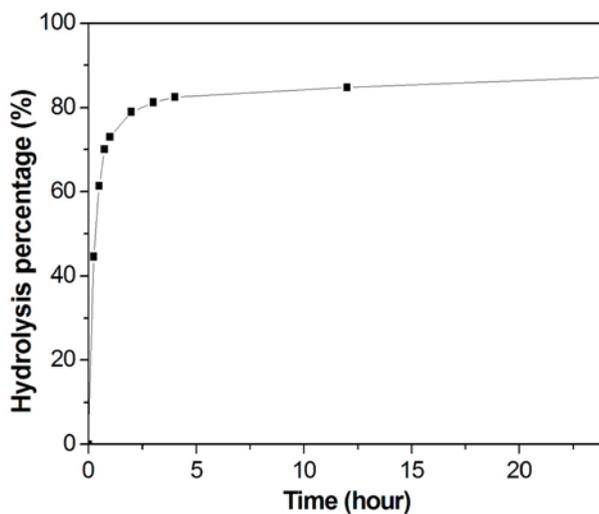


Figure S2. The hydrolysis percentage of **3** to **2** after the addition of 40 mL NaOH (1.0 M) to 1 mL aqueous solution of **3** at the concentration of 0.8% (w/v) with pH=7.5, with the gel formed after the first 15 minutes.

E) Critical gelation concentration (CGC) test

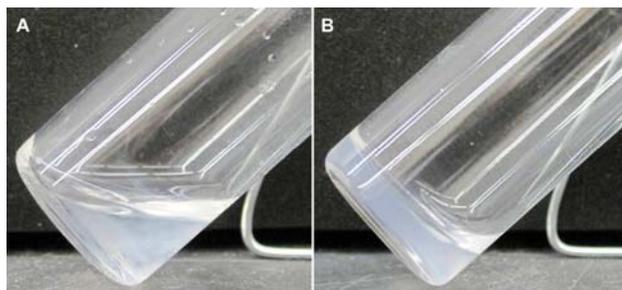


Figure S3. The optical images of the solution of **3** (pH = 7.5, 400 μL) after the addition of 10 μL of aqueous NaOH solution (1.0 M) with (A) [**3**] = 0.12 % (w/v) and (B) [**3**] = 0.16 % (w/v).

F) Dynamic time sweep

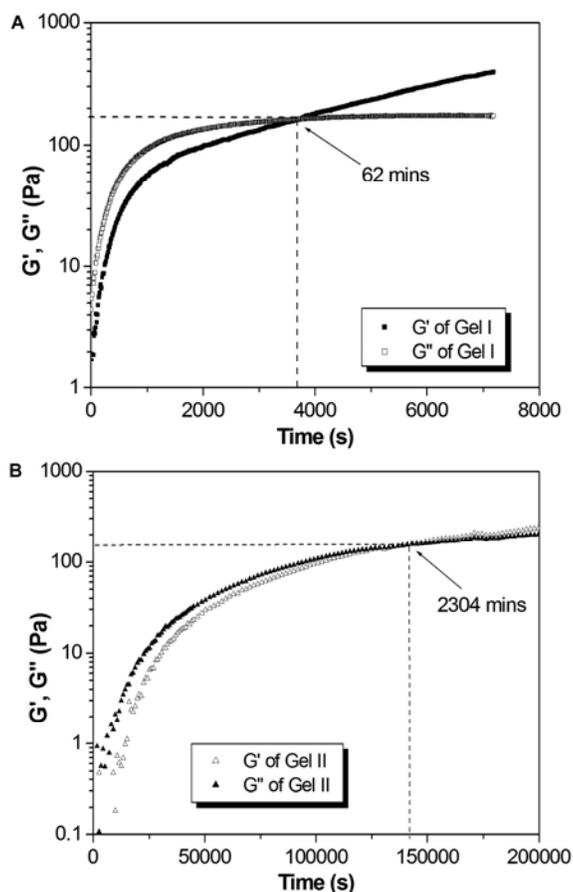


Figure S4. Dynamic time sweep (1% strain and 6.28 rad/s) of the solution of **3** (0.8 % (w/v), pH = 7.5, 800 μL) after (A) the addition of 10 μL of aqueous NaOH solution (1.0 M) and (B) the addition of 10 μL esterase solution (1 U/ μL).

G) Swelling test

After the gel **I** (400 μL , 0.8 % (w/v)) was aged, 2 mL of HCl solution (1.0 M) was added to the vial containing the gel and the HCl solution was changed every two hours.

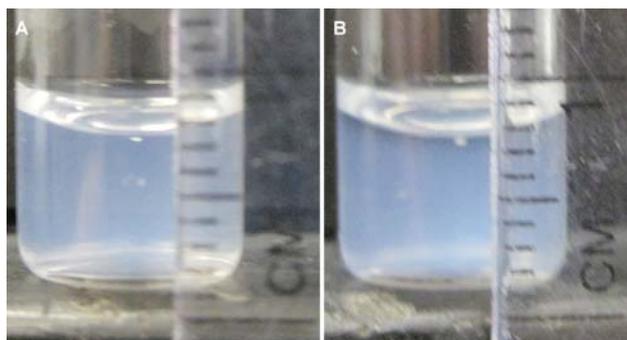


Figure S5. The optical images of the aged gel **I** (400 μ L, 0.8 % (w/v)) before (A) and after (B) the eight hours treatment of HCl solution (1.0 M)

H) The normalized intensities of peaks from CD spectra

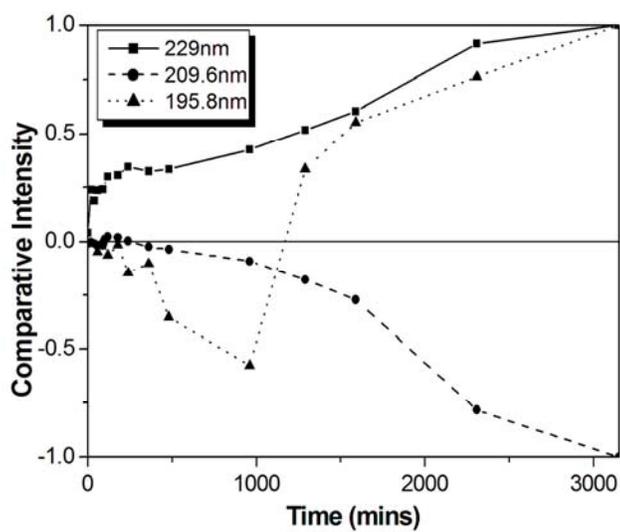
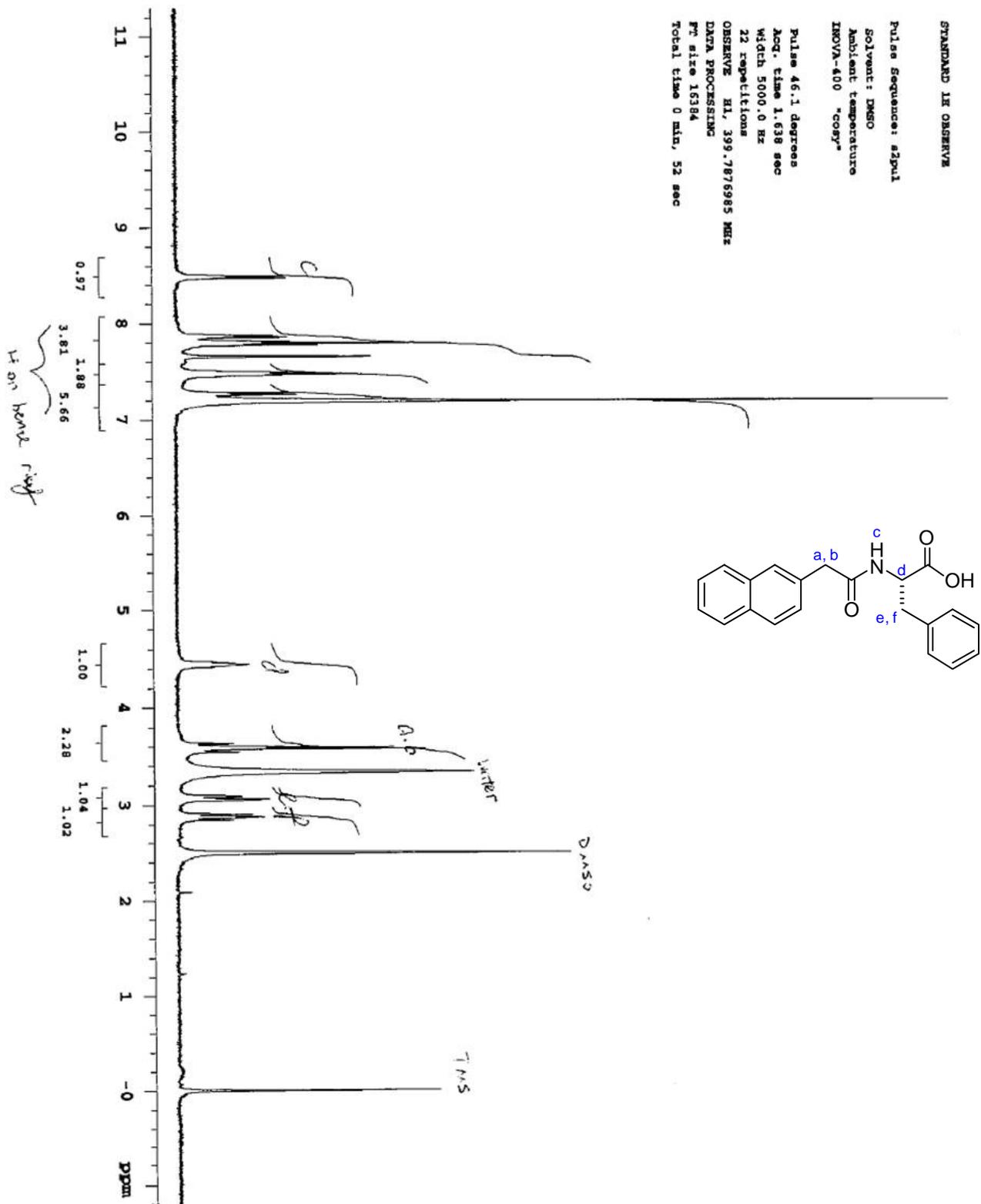
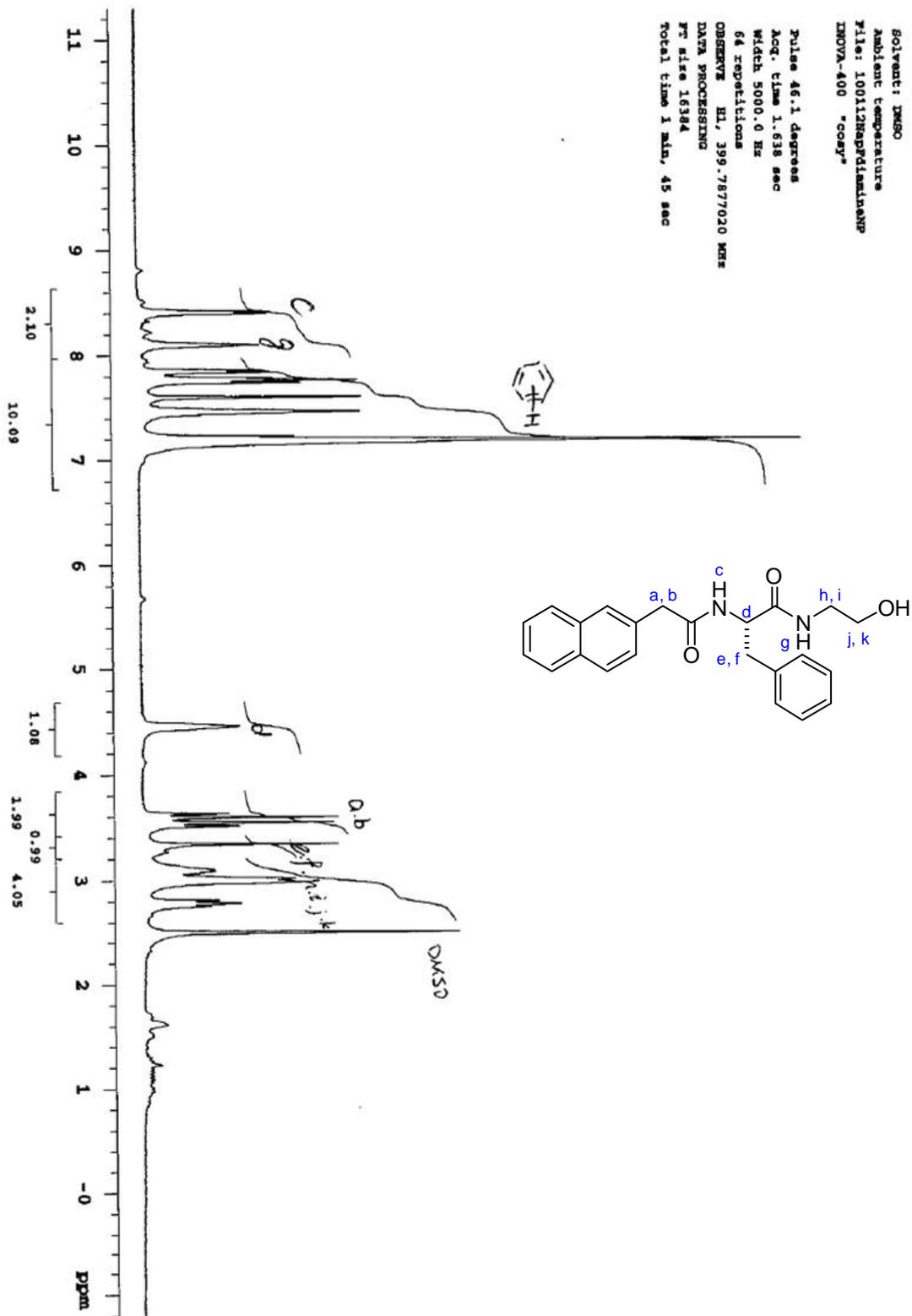


Figure S6. The normalized intensities of the peaks at 229 nm, 209.6nm and 195.8 nm of the CD spectra at different time points.

^1H NMR of **4** (400MHz, DMSO- d_6)



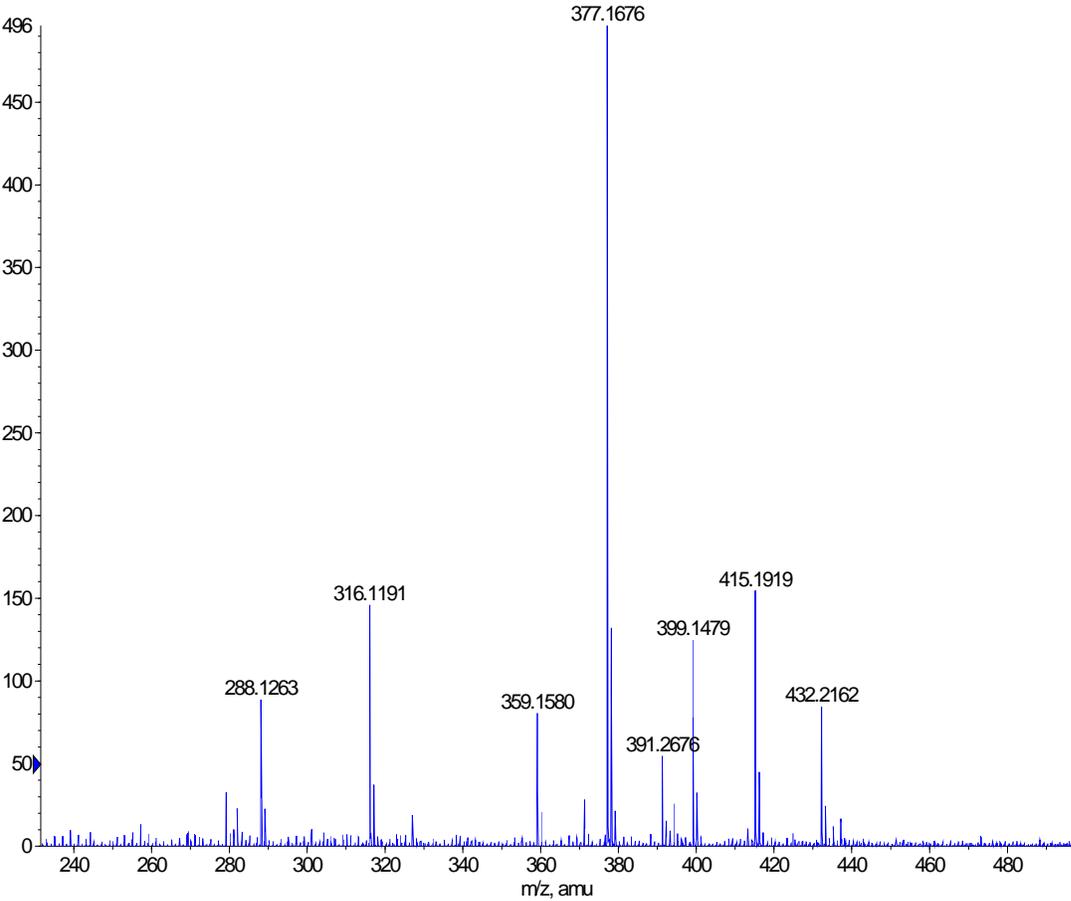
^1H NMR of 2 (400MHz, DMSO- d_6)



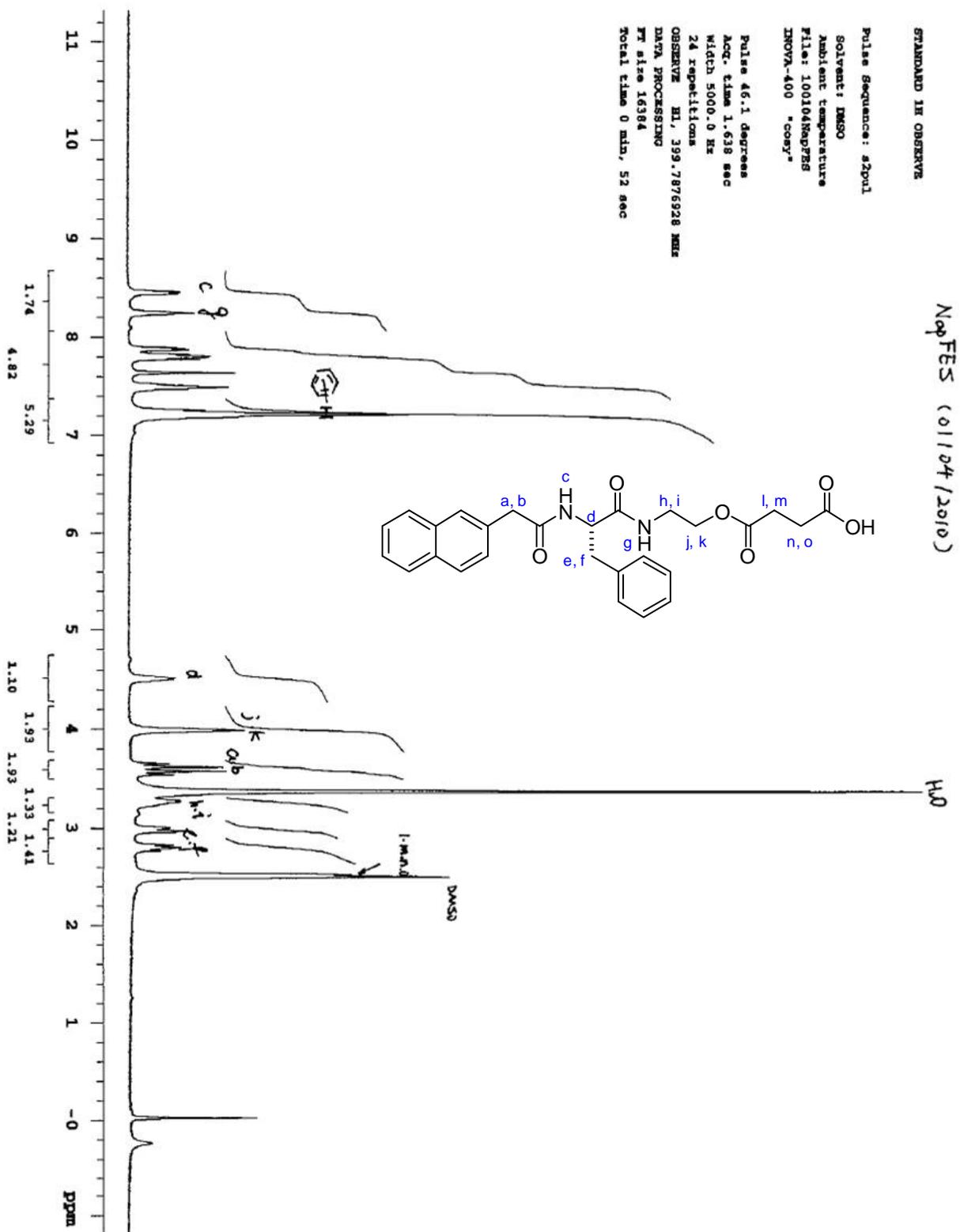
MALDI-TOF MS of 2

+TOF MS: 0.983 to 1.283 min from Sample 14 (ZF-NapF-NH-(CH2)-OH, MW=376) of xu08...
a=3.63143134049316690e-004, t0=5.71760890399418710e+001

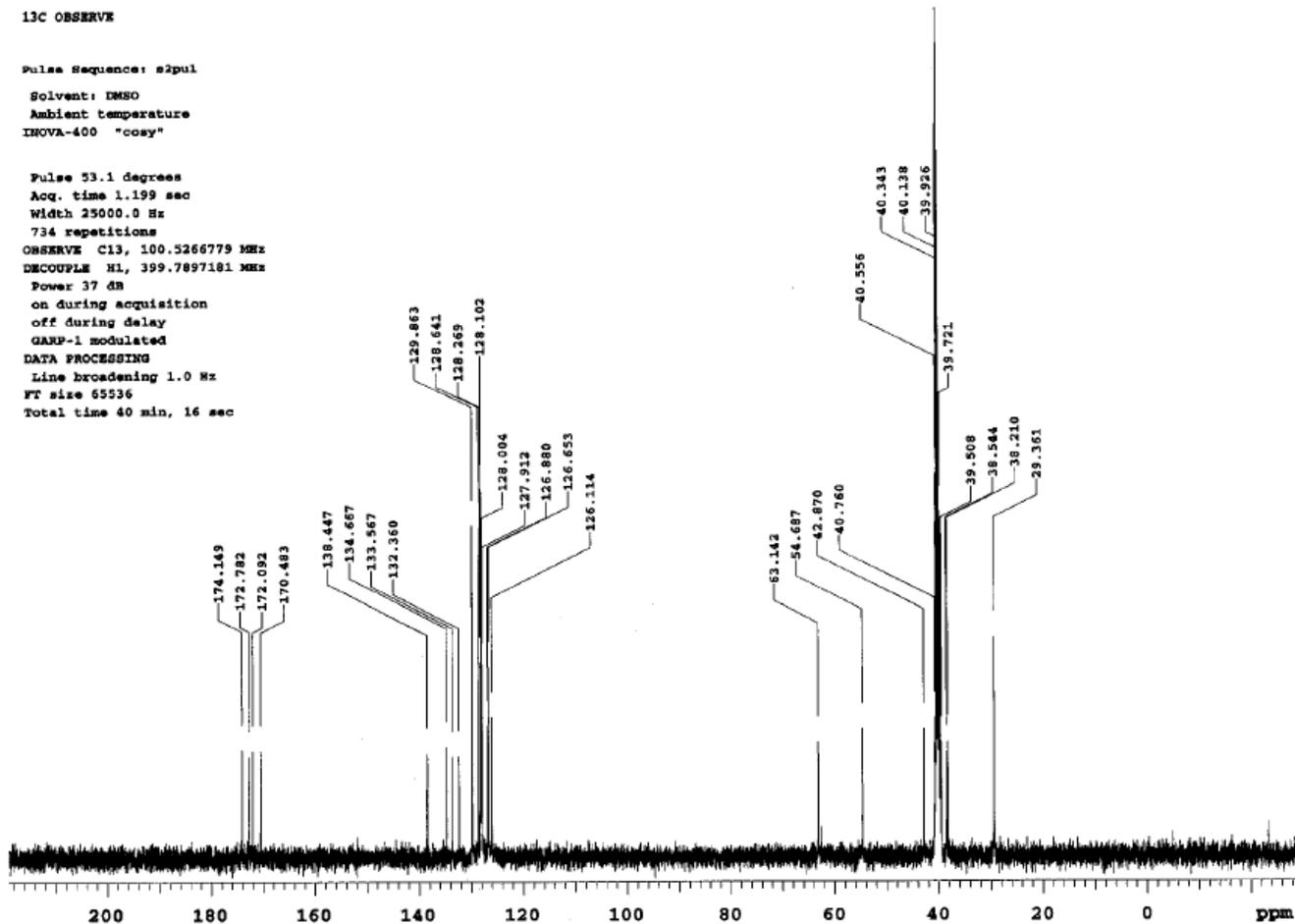
Max. 496.3 counts.



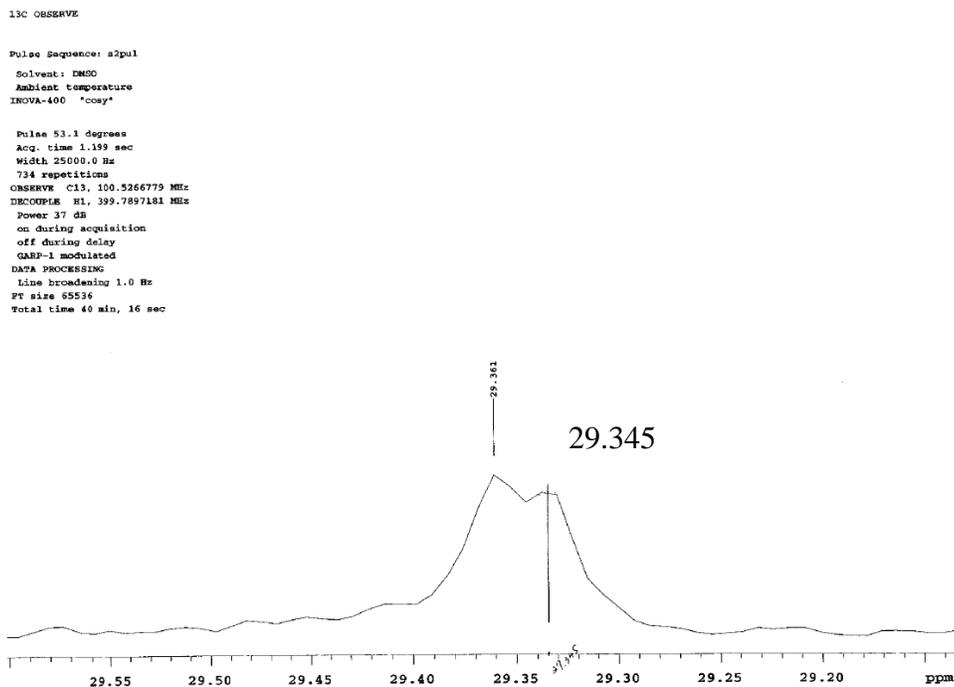
^1H NMR of **3** (400MHz, DMSO- d_6)



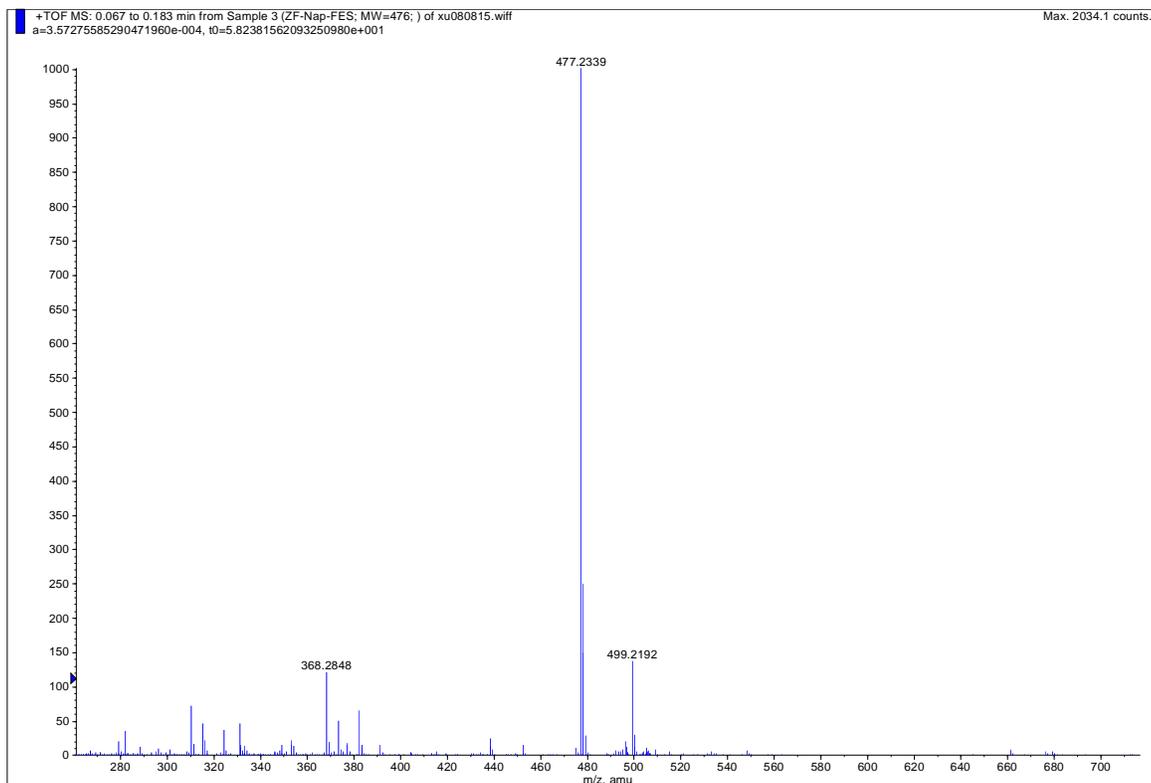
¹³C NMR of 3 (100.5MHz, DMSO-d₆)



Enlargement of 29ppm-30ppm



MALDI-TOF MS of 3



(1) Yang, Z. M.; Liang, G. L.; Ma, M. L.; Gao, Y.; Xu, B. *J. Mater. Chem.* **2007**, *17*, 850-854.