Supplementary Information to accompany:

Dissipative Assembly of an Ion Transport System.

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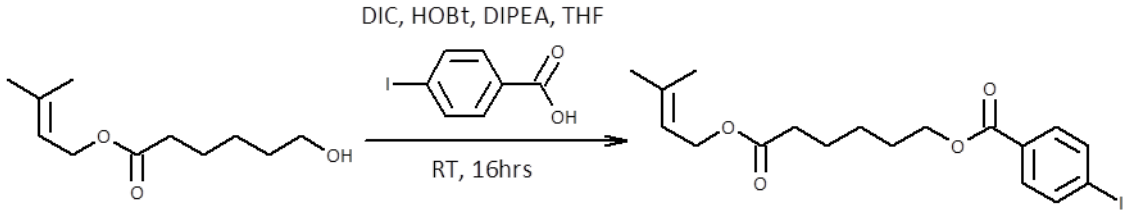
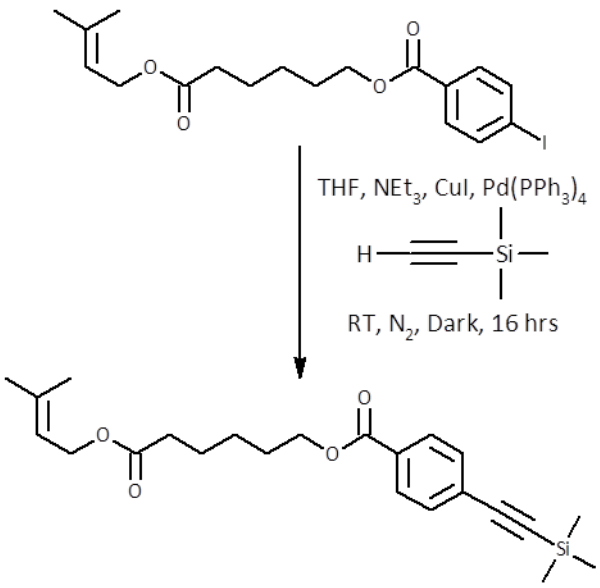
SYNTHESIS

Most chemicals and solvents were used as received from known suppliers. NMR spectra were recorded on a Bruker AC300 (300 MHz ^{1}H and 75 MHz ^{13}C). Chemical shifts are reported relative to tetramethylsilane in ppm. UV spectra were run on a Cary 5 UV-VIS spectrometer in a 10 x 10 mm quartz cell. ESI Mass spectra were recorded on a Waters MicroMass Q-TOF instrument running in both positive and negative ion mode. HPLC was performed using an HP Series 1100 instrument, with either a Macherey-Nagel "Nucleosil" RP C18 analytical (4 mm x 250 mm) or a Grace Davison "Alltima" RP C18 semi-prep (10 mm x 150 mm) column. Solvents used (Acetonitrile, MeOH; HPLC-grade, H_2O; Milipore) were filtered through a Milipore sub-micrometre filter before use. HPLC elution was monitored at various UV wavelengths (typically 254, 280 and 220 nm) and fluorometrically (λEx = 310, λEm = 330 nm). Fluorescence spectra were run on a PTI QM-2 instrument at T = 20^{0}C in 10 x 10 mm quartz cells equipped with a micro stir rod.



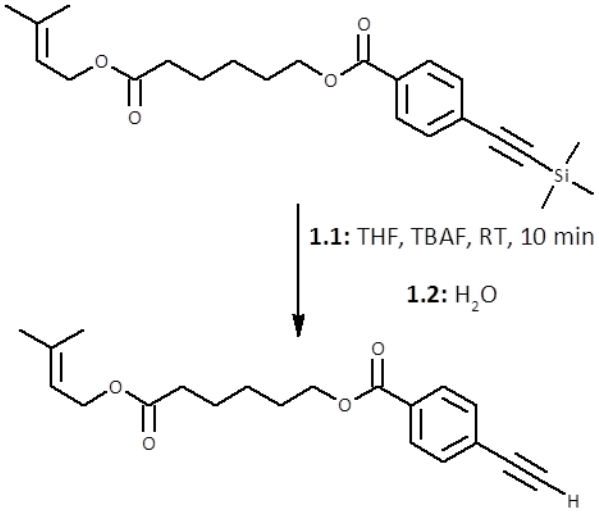
9: 6-[(3-methylbut-2-en-1-yl)oxy]-6-oxohexyl 4-iodobenzoate: 1.4 equivalents of 4-iodobenzoic acid , 1.4 equivalents of HOBt was dissolved into dry THF to which was added in order 1.4 equivalents of HOBt, 1.4 equivalents of DIC, 1.0 equivalent of 3-methylbut-2-en-1-yl 6-hydroxyhexanoate (**8**)[1] and 2.8 equivalents of DIPEA. The reaction was then stirred vigorously at room temperature for 16 hours monitoring by TLC (SiO_2, 2:1 hexanes:Et_2O, UV and vanillin (blue) used for visualization, R_f = 0.54). In the beginning the reaction mixture was clear and colourless but over time a white precipitate was observed to form in the now pale yellow solution. The reaction was worked up by first filtering the reaction mixture through celite and then evaporating the filtrate under vacuum. The resulting light brown oil was dissolved into Et_2O and this resulting solution was washed in order with water, saturated bicarb solution and brine. The organic fraction was dried over Na_2SO_4, filtered and then dried under vacuum. The resulting oil was purified by silica gel column chromatography eluting with 0 - 10% Et_2O in hexanes. Yields 83 - 90% as a pale yellow oil. NMR ($CDCl_3$): **^{1}H** = 7.76 (m, 4H), 5.32 (m, 1H), 4.56 (d, 2H, J= 6Hz), 4.29 (t, 2H, J= 7Hz), 2.32 (t, 2H, J= 7Hz), 1.79-1.65 (m, 11H), 1.42 (m, 2H). **^{13}C** =

173.6, 166.2, 139.2, 137.8, 131.1, 129.9, 118.7, 100.7, 65.2, 61.4, 34.3, 28.5, 25.9, 25.7, 24.8, 18.1.



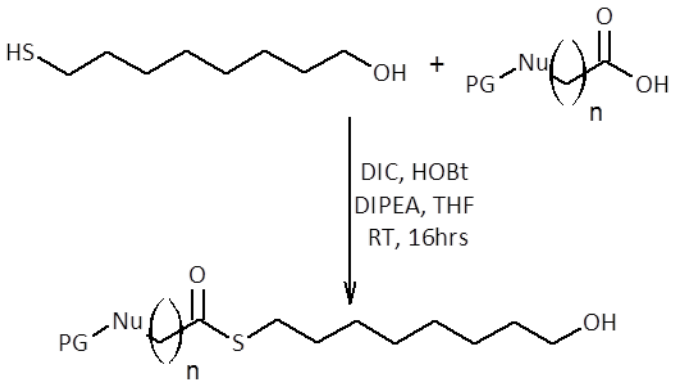
10: 6-[(3-methylbut-2-en-1-yl)oxy]-6-oxohexyl 4-(trimethylsilylethynyl) benzoate: 1.0 equivalent of **9** was dissolved into dry THF, this solution was then degassed and purged with N_2. To this solution was added in order 4.0 equivalents of NEt_3, 0.06 equivalents of CuI, 0.03 equivalents of $Pd(PPh_3)_4$ and 2.0 equivalents of TMS-acetylene. The reaction mixture, a pale yellow solution, was stirred for 16 hours under an atmosphere of N_2 in the dark, monitoring by TLC (SiO_2, 5:1 hexanes:Et_2O, UV and vanillin (teal) used for visualization, R_f = 0.38). Upon completion the reaction mixture appeared as a dark yellow solution with dark orange precipitate. The reaction was worked up by first filtering the reaction mixture through celite and then evaporating the filtrate under vacuum. The resulting yellow semi-solid was then dissolved into Et_2O. This solution was then washed in order with disodium EDTA solution, water, 1M sodium phosphate buffer pH 3 and brine. The organic fraction was dried over Na_2SO_4, filtered and then dried under vacuum. The resulting yellow oil was purified by silica gel column chromatography eluting with 0 - 10% Et_2O in hexanes. Yields 91 - 93% as a yellow oil. NMR ($CDCl_3$): ^{1}**H** = 7.94 (d, 2H, J= 8Hz), 7.50 (d, 2H, J= 8Hz), 5.32 (m, 1H), 4.55 (d, 2H, J= 6Hz), 4.29 (t, 2H, J= 7Hz), 2.33 (t, 2H, J= 7Hz), 1.74 (m, 10H), 1.45 (m, 2H), 0.25 (s, 9H). ^{13}**C** = 173.6, 166.2, 139.1, 131.9, 130.1, 129.5, 127.8, 118.9, 97.7, 65.1, 61.5, 34.3, 28.6, 25.9, 25.7, 24.8, 18.1, 0.03.

11: 6-[(3-methylbut-2-en-1-yl)oxy]-6-oxohexyl 4-ethynylbenzoate: 1.0 equivalents of **10** was dissolved into a minimum amount of dry THF. To this solution was added 1.0 equivalents of a 1.0M solution of TBAF in THF with vigorous stirring. Upon addition of the TBAF the solution went instantly from a pale yellow colour to a dark olive brown. The reaction was monitored by TLC (SiO_2, 2:1 hexanes:Et_2O, UV and vanillin (blue) used for visualization, R_f = 0.53) and found to be complete after 10 minutes. The reaction was worked up by first treating it with a few mL of H_2O during which time the solution turned cloudy pale yellow. The THF was removed from this solution under vacuum to afford a goopy yellow clod in an aqueous solution which was treated with sufficient Et_2O to dissolve the semi-solid resulting in a two phase mixture. The organic fraction was isolated and the aqueous fraction extracted with another portion of Et_2O which was combined with the first organic fraction. The combined organic fraction was then washed with H_2O and then brine after which time it was dried over Na_2SO4, filtered and then dried under vacuum. The resulting yellow oil was then purified using silica gel column chromatography eluting with 0 - 20% Et_2O in hexanes. Yields 63 - 83% as a pale yellow oil. NMR ($CDCl_3$): ^{1}**H** = 7.95 (d, 2H, J= 8Hz), 7.52 (d, 2H, J=8Hz), 5.31 (m, 1H), 4.55 (d, 2H, J= 6Hz), 4.28 (t, 2H, J= 7Hz), 3.22 (s, 1H), 2.32 (t, 2H, J= 7Hz), 1.70 (m, 11H), 1.51 (m, 2H). ^{13}**C** = 173.5, 166.0, 139.2, 132.2, 130.5, 129.5, 126.8, 118.8, 82.9, 80.1, 65.1, 61.4, 34.3, 28.5, 25.9, 25.7, 24.7, 18.1.

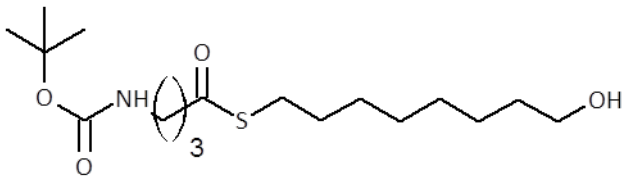


General procedure for the thioester coupling of 8-sulfanyloctan-1-ol (14) with carboxylic acids with protected nucleophiles (12a-d and 13e-f):

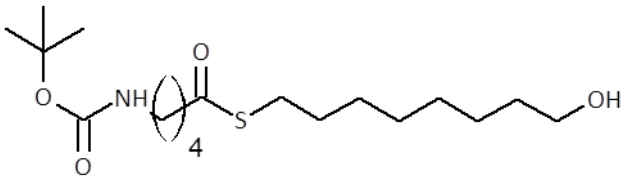
1.0 equivalents of the **carboxylic acid (12a-d or 13e-f)** was dissolved into dry THF and to this solution was added in order 1.0 equivalents of HOBt, 1.0 equivalent DIC, 1.5 equivalents of **14** and 1.0 equivalents of DIPEA. The solution was stirred vigorously at room temperature and after ~15 minutes the formation of DIU was observed as an opalescent white precipitate. The reactions were monitored by TLC chromatography and after 16 hours the reactions were



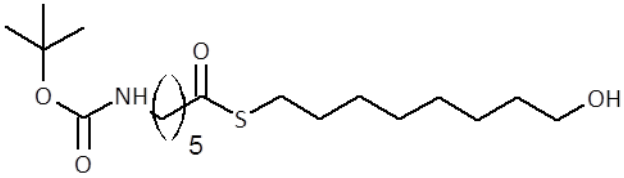
determined to be complete. The reactions were worked up by first vacuum filtering to remove the DIU side product. The filtrates were then evaporated under vacuum to remove the THF and the resulting oils were re-dissolved into Et_2O. The organic solutions were then washed in order with H_2O, 1M sodium phosphate buffer pH~3 and then brine before being dried over Na_2SO_4, filtered and then evaporated under vacuum to remove the organic solvent. The resulting crude oils were then purified using silica gel column chromatography using appropriate conditions.



15a: TLC conditions - SiO_2, 2:1 hexanes:EtOAc, Hanessian's stain (dark blue) used for visualization, Rf = 0.19. Silica gel column chromatography carried out using 0 - 45% EtOAc in hexanes. Yields 34 - 37% of pale yellow oil. NMR ($CDCl_3$): ^{1}**H** = 4.65 (s, br, 1H), 4.06 (m, 2H), 3.59 (m, 2H), 3.45 (m, 2H), 3.11 (m, 2H), 2.82 (t, 2H, J= 7Hz), 2.55 (t, 2H, J= 7Hz), 1.81 (m, 3H), 1.53 (m, 4H), 1.41 (s, br, 9H), 1.26 (m, 9H). ^{13}**C** = 199.3, 171.3, 156.0, 79.9, 66.3, 62.9, 60.5, 41.3, 39.7, 32.7, 29.6, 29.4, 29.1, 28.9, 28.8, 28.5, 26.1, 25.8, 21.2, 15.5, 14.4.

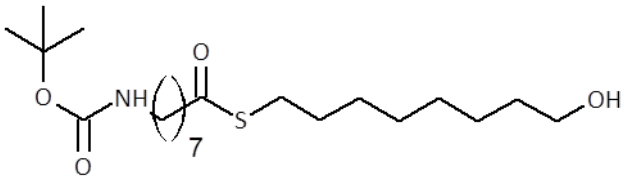


15b: TLC conditions - SiO_2, 1:1 hexanes:EtOAc, Hanessian's stain (dark blue) used for visualization, Rf = 0.43. Silica gel column chromatography carried out using 0 - 40% EtOAc in hexanes. Yield 53% of a white waxy solid. NMR ($CDCl_3$): ^{1}**H** = 4.62 (s, br, 1H), 3.59 (t, 2H, J= 7Hz), 3.08 (m, 2H), 2.80 (t, 2H, J= 7Hz), 2.54 (t, 2H, J= 7Hz), 1.74-1.41 (m, 19H), 1.29 (s, br, 8H). ^{13}**C** = 199.4, 156.3, 79.3, 62.9, 43.6, 32.7, 29.5, 29.4, 29.3, 29.1, 28.9, 28.8, 28.5, 25.8, 22.8.

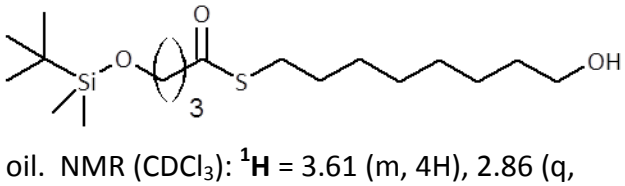


15c: TLC conditions - SiO_2, 2:1 hexanes:EtOAc, Hanessian's stain (dark blue) used for visualization, Rf = 0.23. Silica gel column chromatography carried out using 0 - 40% EtOAc in hexanes. Yield 43% of a clear colourless oil. NMR ($CDCl_3$): ^{1}**H** = 4.56 (s, br, 1H), 3.61 (t, 2H, J= 7Hz), 3.08 (m, 2H), 2.84 (t, 2H, J= 7Hz), 2.52 (t, 2H, J= 7Hz), 1.65-1.24 (m, 30H). ^{13}**C** = 200.0, 156.3, 79.9, 63.0, 44.1, 40.5, 32.9, 29.9, 29.6, 29.3, 29.1, 28.9, 28.8, 28.5, 26.2, 25.8, 25.4, 14.3.

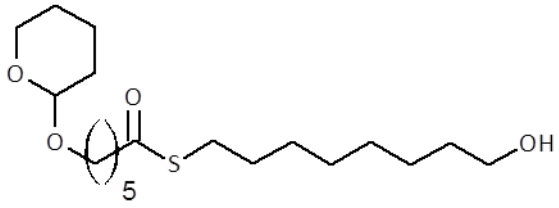
15d: TLC conditions - SiO_2, 2:1 hexanes:EtOAc, Hanessian's stain (dark blue) used for visualization, Rf = 0.29. Silica gel column chromatography carried out using 0 - 40% EtOAc in hexanes. Yield 50% of a white waxy solid. NMR ($CDCl_3$): **^{1}H** = 4.55 (s, br, 1H), 3.59 (t, 2H, J= 7Hz), 3.05 (m, 2H), 2.82 (t, 2H, J= 7Hz), 2.49 (t, 2H, J= 7Hz), 1.84 (s, br, 1H), 1.61-1.28 (m, 32H). **^{13}C** = 200.2, 156.1, 79.1, 63.0, 44.2, 40.6, 32.8, 30.1, 29.6, 29.3, 29.1, 28.9, 28.8, 28.7, 28.5, 26.7, 25.7, 25.7.



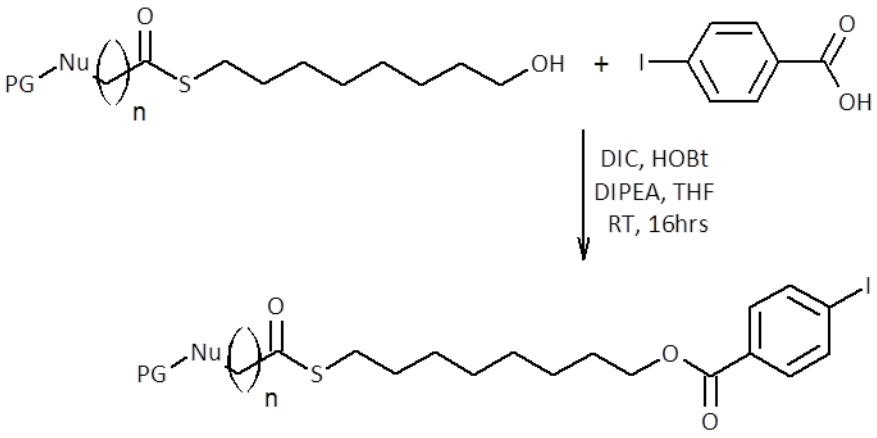
15e: TLC conditions - SiO_2, 2:1 hexanes:EtOAc, Hanessian's stain (dark blue) used for visualization, Rf = 0.36. Silica gel column chromatography carried out using 0 - 25% EtOAc in hexanes. Yield 34% of a clear colourless oil. NMR ($CDCl_3$): **^{1}H** = 3.61 (m, 4H), 2.86 (q, 2H, J= 7Hz), 2.62 (t, 2H, J= 7Hz), 1.86 (p, 2H, J= 7Hz), 1.54 (m, 5H), 1.30 (m, 8H), 0.87 (s, 9H), 0.03 (s, 6H). **^{13}C** = 199.7, 63.1, 61.9, 40.7, 32.8, 29.7, 29.3, 29.2, 28.9, 28.8, 28.7, 26.0, 25.8, 18.5, -5.2.



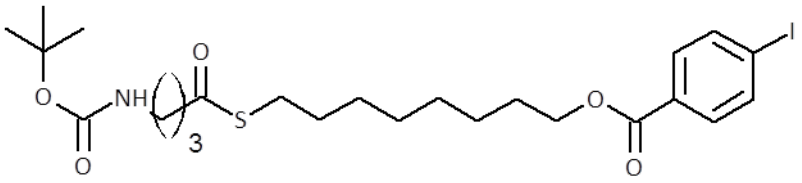
15f: TLC conditions - SiO_2, 2:1 Et_2O:hexanes, Hanessian's stain (dark blue) used for visualization, Rf = 0.30. Silica gel column chromatography carried out using 0 - 60% Et_2O in hexanes. Yield 40% of a white waxy solid. NMR ($CDCl_3$): **^{1}H** = 4.54 (m, 1H), 3.82 (m, 1H), 3.69 (m, 1H), 3.61 (m, 1H), 3.59 (t, 2H, J= 7Hz), 3.46 (m, 1H), 3.34 (m, 1H), 2.85 (t, 2H, J= 7Hz), 2.52 (t, 2H, J= 7Hz), 1.66 (m, 16H), 1.29 (m, 10H). **^{13}C** = 199.8, 99.1, 67.4, 62.8, 62.3, 44.1, 32.8, 30.9, 30.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 28.8, 28.7, 25.9, 25.6, 25.5.



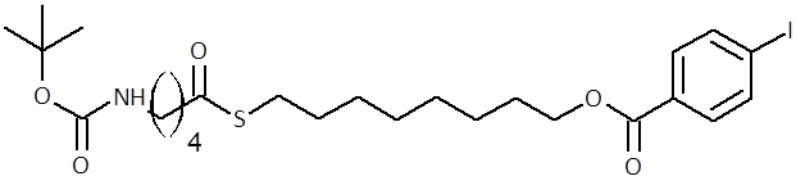
General procedure for the ester coupling of alcohol terminated thioester with protected nucleophile (15a-f) with *p*-iodobenzoic acid:



1.2 equivalents of *p*-iodobenzoic acid was dissolved into dry THF and to this solution was added in order 1.2 eqiuvalents of HOBt, 1.2 equivalents of DIC, 1.0 equivalent of the alcohol terminated thioester **15a-f** and 2.4 equivalents of DIPEA. The reaction was stirred at room temperature and after ~15 minutes the formation of DIU was observed as an opalescent white precipitate. The reactions were monitored by TLC and after 16 hours the reactions were determined to be complete. The reactions were worked up by first vacuum filtering to remove the DIU side product. The filtrates were then evaporated under vacuum to remove the THF and the resulting oils were re-dissolved into Et_2O. The organic solutions were then washed with H_2O, 0.1M sodium phosphate buffer pH~3 and then brine before being dried over Na_2SO_4, filtered and then evaporated under vacuum to remove the organic solvent. The resulting crude oils were then purified using silica gel column chromatography using appropriate conditions.



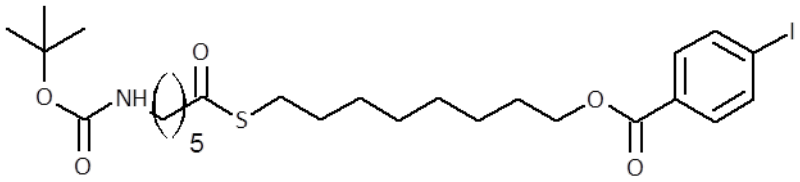
16a: TLC conditions - SiO_2, 2:1 hexanes:EtOAc, UV and Hanessian's stain (dark blue) used for visualization, Rf = 0.69. Silica gel column chromatography carried out using 0 - 50% EtOAc in hexanes. Yield 51% of pale yellow oil. NMR ($CDCl_3$): ^{1}**H** = 7.74 (m, 4H), 4.64 (s, br, 1H), 4.28 (t, 2H, J= 7Hz), 3.13 (m, 2H), 2.84 (t, 2H, J= 7Hz), 2.59 (t, 2H, J= 7Hz), 1.77 (m, 4H), 1.53 (m, 2H), 1.42-1.31 (m, 18H). ^{13}**C** = 199.3, 166.3, 155.9, 137.8, 131.0, 130.2, 100.8, 79.3, 65.4, 41.4, 39.7, 29.6, 29.2, 29.0, 28.9, 28.8, 28.7, 28.5, 26.0.



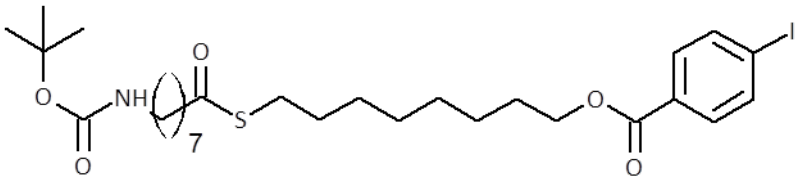
16b: TLC conditions - SiO_2, 5:1 hexanes:EtOAc, UV and Hanessian's stain (dark blue) used for visualization, Rf = 0.27. Silica gel column

chromatography carried out using 0 - 15% EtOAc in hexanes. Yield 89% of pale yellow waxy solid. NMR ($CDCl_3$): **^{1}H** = 7.74 (m, 4H), 4.58 (s, br, 1H), 4.28 (t, 2H, J= 7Hz), 3.09 (m, 2H), 2.87 (p, 2H, J= 7Hz), 2.55 (t, 2H, J= 7Hz), 1.73-1.33 (m, 26H). **^{13}C** = 199.7, 166.1, 156.1, 137.7, 130.9, 129.8, 100.5, 79.1, 65.5, 43.7, 39.9, 29.6, 29.4, 29.2, 29.0, 28.9, 28.7, 28.6, 28.5, 26.1, 22.9.

16c: TLC conditions - SiO_2, 2:1 hexanes:Et_2O, UV and Hanessian's stain (dark blue) used for visualization, Rf = 0.30. Silica gel column chromatography carried out using 0 - 40% Et_2O in hexanes. Yield 84% of pale yellow waxy solid. NMR ($CDCl_3$): **^{1}H** = 7.74 (m, 4H), 4.53 (s, br, 1H), 4.28 (t, 2H, J= 7Hz), 2.09 (m, 2H), 2.84 (t, 2H, J= 7Hz), 2.52 (t, 2H, J= 7Hz), 1.76-1.32 (m, 28H). **^{13}C** = 199.7, 166.3, 156.3, 137.9, 131.1, 130.1, 100.6, 65.4, 44.0, 40.3, 29.9, 29.7, 29.6, 29.2, 29.1, 28.8, 28.7, 28.6, 26.2, 26.1, 25.4, 15.3.

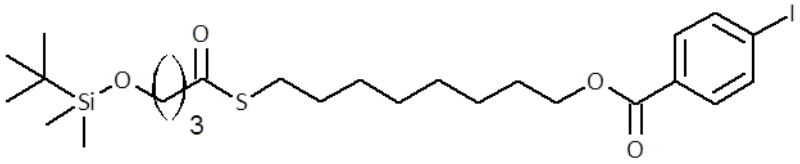


16d: TLC conditions - SiO_2, 5:1 hexanes:EtOAc, and Hanessian's stain (dark blue) used for visualization, Rf = 0.35. Silica gel column chromatography carried out using 0 - 15% EtOAc in hexanes. Yield 99% of pale yellow waxy solid. NMR ($CDCl_3$): **^{1}H** = 7.75 (m, 4H), 4.52 (s, br, 1H), 4.29 (t, 2H, J= 7Hz), 3.09 (m, 2H), 2.85 (t, 2H, J= 7Hz), 2.52 (t, 2H, J= 7Hz), 1.75 – 1.31 (m, 31H). **^{13}C** = 200.3, 166.1, 156.1, 137.7, 132.0, 121.3, 129.8, 125.0, 120.8, 108.3, 100.8, 65.4, 44.1, 40.9, 30.1, 29.7, 29.2, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 26.7, 26.0, 25.8.

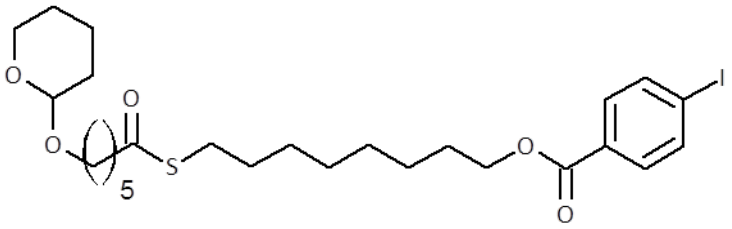


UV

16e: TLC conditions - SiO_2, 11:1 hexanes:acetone, UV and Hanessian's stain (dark blue) used for visualization, Rf = 0.62. Silica gel column chromatography carried out using 0 - 5% Et_2O in hexanes. Yield 92% of clear colourless oil. NMR ($CDCl_3$): **^{1}H** = 7.75 (m, 4H), 4.29 (t, 2H, J= 7Hz), 3.62 (t, 2H, J= 7Hz), 2.86 (t, 2H, J= 7Hz), 2.63 (t, 2H, J= 7Hz),1.85 (p, 2H, J= 7Hz), 1.75 (m, 2H), 1.56 (m, 2H), 1.33 (m, 8H), 0.89 (s, 9H), 0.04 (s, 6H). **^{13}C** = 199.6, 166.2, 137.7, 131.2, 130.2, 100.9, 65.4, 62.0, 40.7, 29.8, 29.3, 29.1, 28.9, 28.7, 28.7, 26.0, 18.6, -5.2.

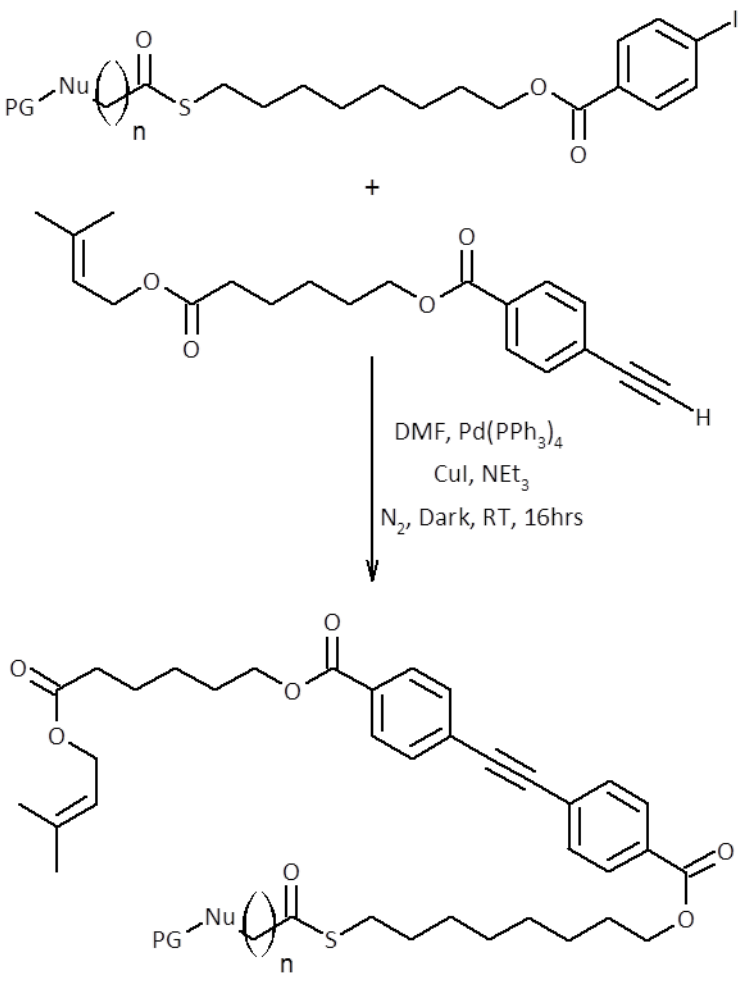


16f: TLC conditions - SiO_2, 11:1 hexanes:acetone, UV and Hanessian's stain (dark blue) used for visualization, Rf = 0.33. Silica gel column chromatography carried out using 0 - 8% acetone in hexanes. Yield 94% of white waxy solid. NMR ($CDCl_3$): **^{1}H** = 7.74 (m, 4H), 4.52 (m, 1H), 4.29 (t, 2H, J= 7Hz), 3.83 (m, 1H), 3.70 (m, 1H), 3.47 (m, 1H), 3.36 (m, 1H), 2.81 (t, 2H, J= 7Hz), 2.53 (t, 2H, J= 7Hz), 1.75- 1.32 (m, 25H). **^{13}C** = 199.6, 266.2, 137.8, 131.2, 130.1, 100.5, 99.1, 67.3, 65.4, 62.4, 44.2, 30.7, 29.6, 29.5, 29.1, 29.0, 28.8, 28.7, 28.6, 25.9, 25.8, 25.6, 25.5, 19.7.

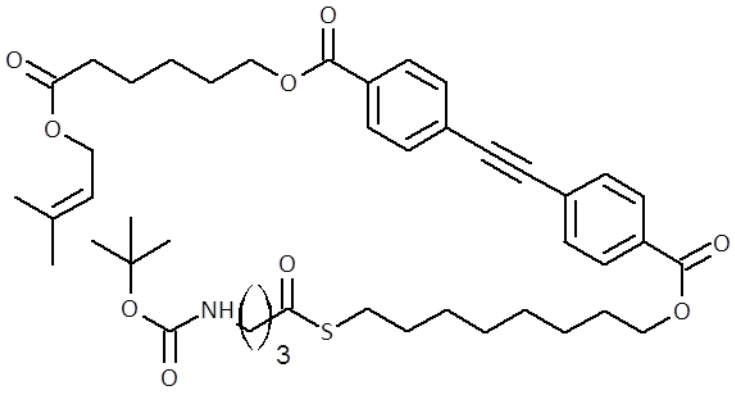


General procedure for the Sonogashira cross-coupling of aryliodide terminated thioester with protected nucleophile (16a-f) with 6-[(3-methylbut-2-en-1-yl)oxy]-6-oxohexyl 4-ethynylbenzoate (11):

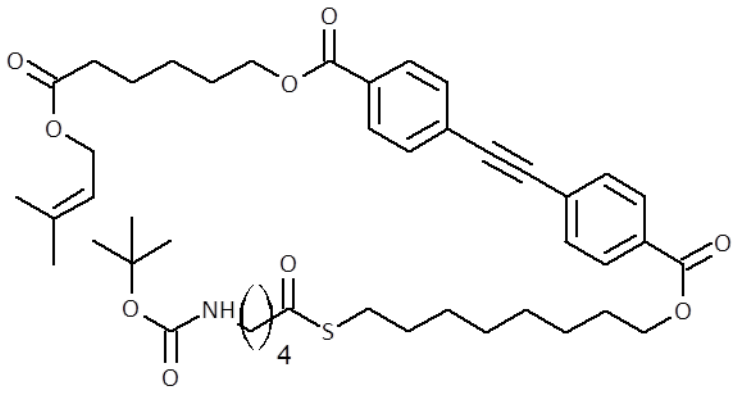
1.0 equivalents of aryliodide terminated thioester **(16a-f)** was dissolved in dry THF and the solution was degassed and then purged with N_2. To his solution under a constants stream of N_2 was added in order 2.4 equivalents of NEt_3, 0.06 equivalents of CuI, 0.03 equivalents of $Pd(PPh_3)_4$ and 1.2 equivalents of **11**. The reaction was then stirred vigorously at room temperature under and inert N_2 atmosphere shielded from light. The reaction was monitored by TLC and after ~16 - 24 hrs was determined to be complete as indicated by complete consumption of the aryl iodide. During the reaction the solutions generally went from clear yellow solutions to orange solutions with visible dark orange precipitates. The reaction was worked up by first vacuum filtering



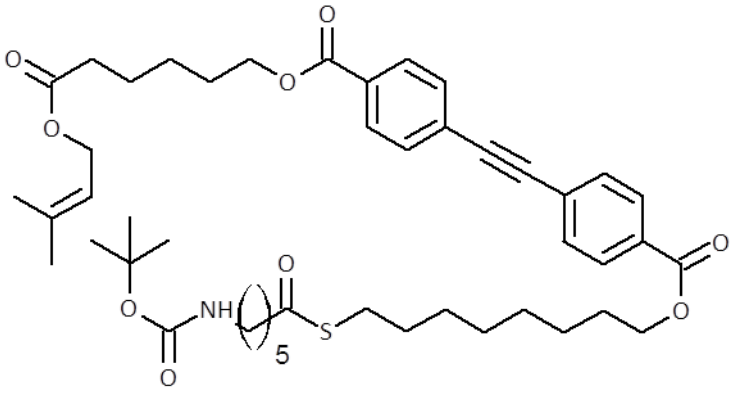
the mixture to remove the dark orange precipitates and the filtrate was then evaporated under vacuum. The resulting sticky solids were then dissolved in Et_2O and the resulting solution washed in order with a solution of disodium EDTA, saturated sodium bicarbonate, H_2O, 0.1M sodium phosphate buffer pH~3 and then brine. The organic fraction was then dried over Na_2SO_4, filtered, evaporated under vacuum and then purified by silica gel column chromatography using conditions appropriate for the compound.



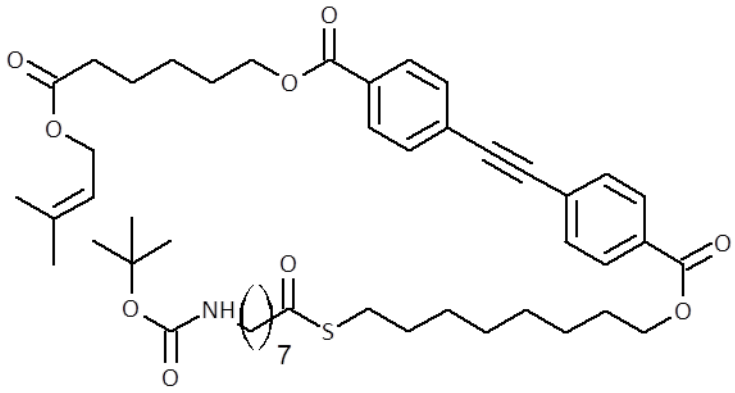
17a: TLC conditions - SiO_2, 1:1 hexanes:Et_2O, UV and vanillin stain (green) used for visualization, Rf = 0.33. Silica gel column chromatography carried out using 0 - 50% Et_2O in hexanes. Yield 87% of a waxy pale yellow solid. NMR ($CDCl_3$): ^{1}**H** = 8.02 (dd, 4H, J= 8Hz), 7.59 (d, 4H, J= 8Hz), 5.30 (m, 1H), 4.57 (s, br, 1H), 4.56 (d, 2H, J= 6H), 4.31 (m, 4H), 3.14 (m, 2H), 2.86 (t, 2H, J= 7Hz), 2.58 (t, 2H, J= 7Hz), 2.34 (t, 2H, J= 7Hz), 1.86-1.69 (m, 15H), 1.56-1.34 (m, 21H). ^{13}**C** = 199.3, 173.7, 165.9, 155.9, 139.2, 131.8, 130.4, 129.6, 127.4, 118.7, 91.4, 65.5, 65.3, 61.5, 41.4, 39.8, 34.3, 29.6, 29.2, 29.1, 28.9, 28.8, 28.8, 28.6, 26.1, 25.9, 25.8, 24.8.



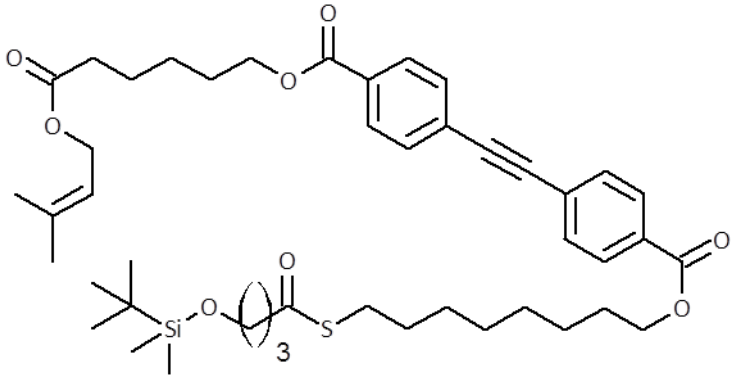
17b: TLC conditions - SiO_2, 1:1 hexanes:Et_2O, UV and vanillin stain (green) used for visualization, Rf = 0.29. Silica gel column chromatography carried out using 0 - 50% Et_2O in hexanes. Yield 94% of a waxy pale yellow solid. NMR ($CDCl_3$): ^{1}**H** = 8.01 (dd, 4H, J= 8, 1Hz), 7.58 (d, 4H, J= 8Hz), 5.32 (m, 1H), 4.55 (d, 3H, J= 6Hz), 3.11 (m, 2H), 2.84 (t, 2H, J= 7Hz), 2.55 (t, 2H, J= 7Hz), 2.33 (t, 2H, J= 7Hz), 1.74 (m, 14H), 1.54-1.33 (m, 24H). ^{13}**C** = 199.6, 173.6, 166.1, 156.0, 139.1, 131.7, 130.4, 129.8, 127.5, 118.7, 91.4, 65.1, 61.4, 43.5, 40.4, 34.2, 29.7, 29.4, 29.3, 29., 28.9, 28.8, 28.7, 28.5, 26.0, 25.9, 25.7, 25.0, 18.1, 15.4.



17c: TLC conditions - SiO_2, 1:1 hexanes:Et_2O, UV and vanillin stain (green) used for visualization, Rf = 0.39. Silica gel column chromatography carried out using 0 - 40% Et_2O in hexanes. Yield 59% of a waxy pale yellow solid. NMR ($CDCl_3$): ^{1}**H** = 8.01 (dd, 4H, J= 8, 1Hz), 7.58 (d, 4H), 5.32 (m, 1H), 4.55 (d, 3H, J= 6Hz), 4.29 (m, 4H), 3.08 (m, 2H), 2.84 (t, 2H, J= 7Hz), 2.52 (t, 2H, J= 7Hz), 2.33 (t, 2H, J= 7Hz), 1.74 (m, 14H), 1.42 (m, 26H). ^{13}**C** = 199.6, 173.7, 166.1, 155.9, 139.1, 131.7, 130.4, 130.3, 129.6, 127.4, 118.7, 91.5, 65.4, 65.1, 61.4, 44.0, 40.5, 34.3, 29.9, 29.6, 29.2, 29.0, 28.8, 28.7, 28.7, 28.5, 26.0, 25.9, 25.7, 25.4, 24.7, 18.5.



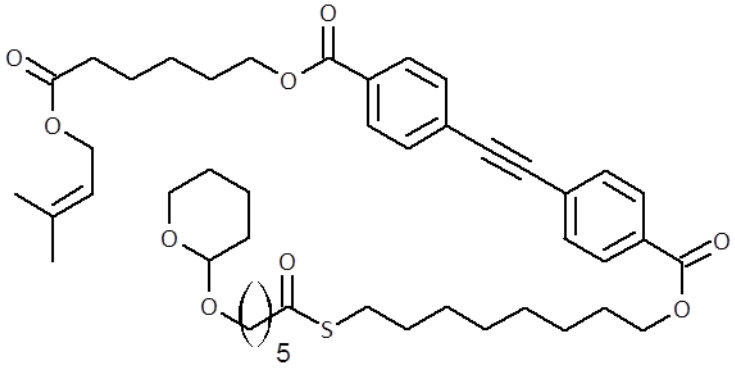
17d: TLC conditions - SiO_2, 1:1 hexanes:Et_2O, UV and vanillin stain (green) used for visualization, Rf = 0.28. Silica gel column chromatography carried out using 0 - 50% Et_2O in hexanes. Yield 85% of a waxy pale yellow solid. NMR ($CDCl_3$): ^{1}**H** = 8.01 (d, 4H, J= 8Hz), 7.58 (d, 4H, J= 8Hz), 5.32 (m, 1H), 4.55 (d, 3H, J= 7Hz), 4.31 (m, 4H), 3.06 (m, 2H), 2.84 (t, 2H, J= 7Hz), 2.51 (t, 2H, J= 7Hz), 2.33 (t, 2H, J= 7Hz), 1.70 (m, 14H), 1.67-1.28 (m, 29H). ^{13}**C** = 199.9, 173.6, 165.8, 156.5, 138.9, 131.7, 130.4, 129.7, 127.3, 118.5, 91.6, 65.2, 65.1, 61.3, 44.2, 40.6, 34.2, 30.0, 29.7, 29.2, 29.1, 29.0, 28.9, 28.8, 28.7, 28.5, 26.7, 26.0, 25.9, 25.7, 25.7, 17.9.



17e: TLC conditions - SiO_2, 9:1 hexanes:acetone, UV and vanillin stain (green) used for visualization, Rf = 0.23. Silica gel column chromatography carried out using 0 - 50% Et_2O in hexanes. Yield 93% of a waxy pale yellow solid. NMR ($CDCl_3$): ^{1}**H** = 8.02 (dd, 4H, *J*= 8, 2Hz), 7.59 (d, 4H, *J*= 8Hz), 5.33 (m, 1H), 4.57 (d, 2H,

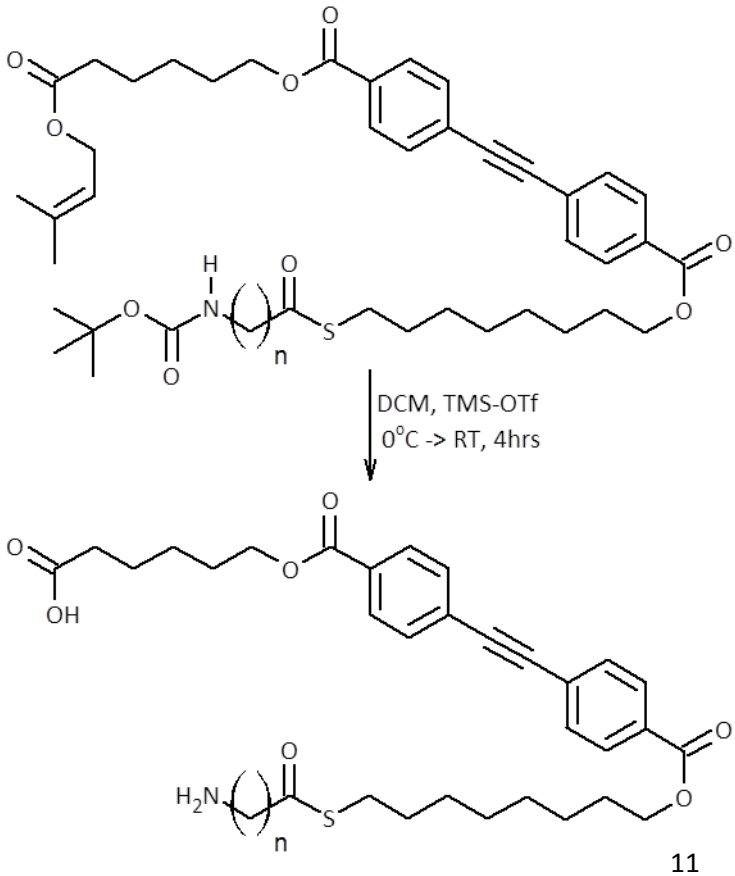
J= 6Hz), 4.32 (m, 4H), 3.62 (t, 2H, *J*= 7Hz), 2.86 (t, 2H, *J*= 7Hz), 2.63 (t, 2H, *J*= 7Hz), 2.35 (t, 2H, *J*= 7Hz), 1.88-1.60 (m, 14H), 1.35 (m, 13H). **^{13}C** = 199.2, 173.7, 166.1, 139.7, 131.7, 130.5, 118.8, 91.6, 65.4, 61.9, 61.5, 40.6, 34.4, 29.7, 29.3, 29.1, 28.9, 28.8, 28.8, 28.7, 28.6, 26.1, 25.9, 25.8, 24.9, 18.5, -5.2.

17f: TLC conditions - SiO_2, 1:1 hexanes:Et_2O, UV and vanillin stain (green) used for visualization, Rf = 0.29. Silica gel column chromatography carried out using 0 - 50% Et_2O in hexanes. Yield 94% of a waxy pale yellow solid. NMR ($CDCl_3$): **^{1}H** = 8.01 (dd, 4H, *J*= 8Hz), 7.58 (d, 2H, *J*= 8Hz), 5.32 (m, 1H), 4.55 (m, 3H), 4.29 (m, 4H), 3.82 (m, 1H), 3.71 (m, 1H), 3.46 (m, 1H), 3.36 (m, 1H), 2.84 (t, 2H, *J*= 7Hz), 2.51 (t, 2H, *J*= 7Hz), 2.33 (t, 2H, *J*= 7Hz), 1.69 (m, 18H), 1.34 (m, 21H). **^{13}C** = 199.7, 172.9, 166.3, 138.9, 132.1, 130.4, 130.0, 127.5, 118.7, 99.0, 91.4, 67.3, 65.4, 65.0, 62.4, 61.0, 44.1, 34.3, 30.8, 29.5, 29.4, 29.2, 29.0, 28.8, 28.5, 26.0, 25.9, 25.8, 25.7, 25.6, 25.5, 24.7.

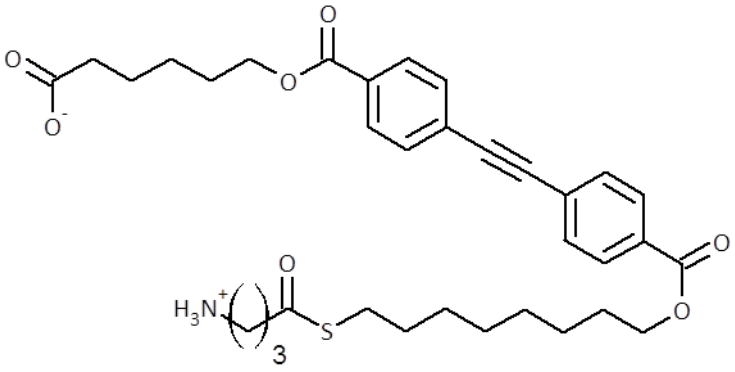


General procedure for the *t*-Boc and Pre deprotection of the doubly protected amine terminated compounds (17a-d):

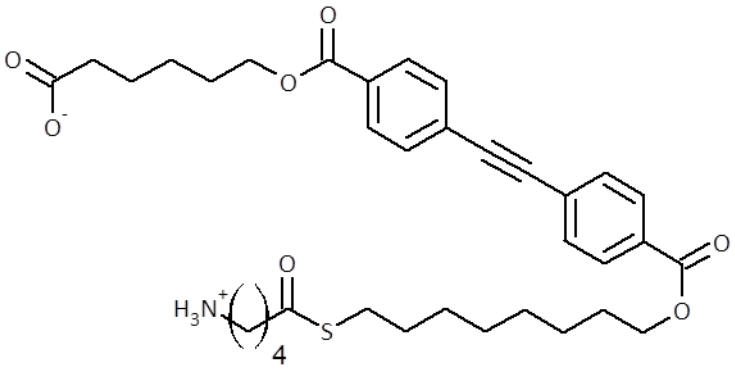
1.0 equivalent of doubly protected amine terminated compound **(17a-d)** was dissolved in DCM and cooled to 0°C. To this solution was added 1.25 equivalents of TMSOTf and the reaction was allowed to warm to room temperature over the course of 4 hours. The reaction was monitored by TLC (SiO_2, 2:1 hexanes:EtOAc, UV used for visualization) to determine completion by disappearance of the spot due to starting material. Note that the products were all of insufficient



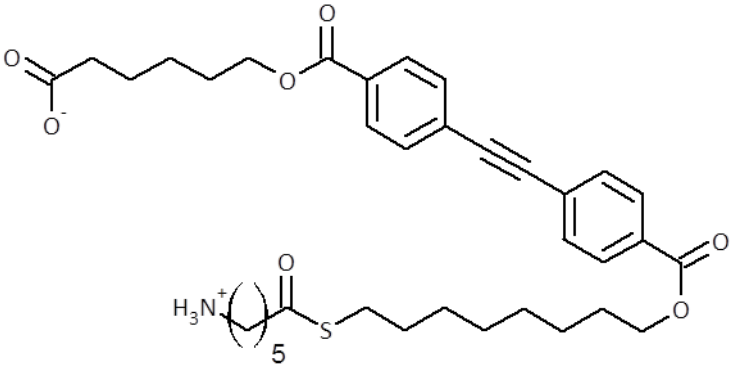
mobility to be resolved from the baseline. Upon completion the reaction was worked up by first reducing the volume by half using a stream of N_2 after which the mixture was slowly diluted by a factor a five using hexanes. This diluted solution was then cooled in the freezer for a few hours to facilitate the precipitation of the final deprotected products. All products were purified via preparatory HPLC using a C18 column and eluting with 0 - 5% MeOH in acetonitrile.



18a: Yield 80% of a waxy pale yellow solid. NMR (CD_3CN): ^{1}**H** = 8.06 (dd, 4H, *J*= 8, 2Hz), 7.70 (d, 4H, *J*= 8Hz), 6.39 (t, 3H, *J*= 9H), 4.34 (m, 4H), 3.06 (m, 2H), 3.00 (t, 2H, *J*= 7Hz), 2.73 (t, 2H, *J*= 7Hz), 2.35 (t, 2H, *J*= 7Hz), 1.98 (m, 4H), 1.79-1.39 (m, 19H). ^{13}**C** = 199.5, 175.2, 166.5, 132.6, 131.5, 130.4, 127.9, 91.9, 65.9, 65.1, 41.0, 40.5, 34.1, 30.2, 29.7, 29.3, 29.0, 26.6, 26.2, 25.1, 23.4.

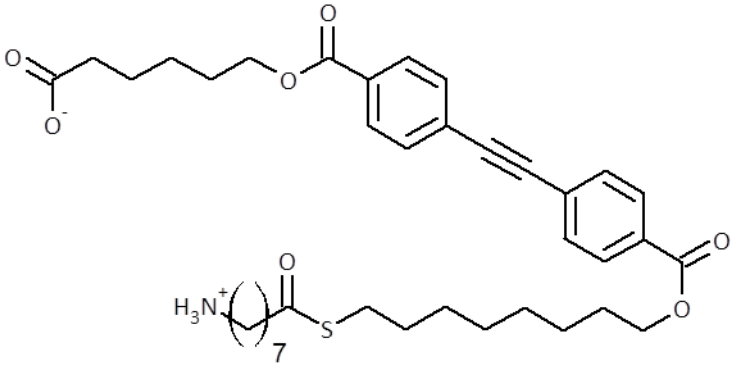


18b: Yield 42% of an off white waxy solid. NMR (d6-acetone): ^{1}**H** = 8.06 (d, 4H, J= 8Hz), 7.71 (d, 4H, J= 8Hz), 7.63 (br s, 3H), 4.33 (q, 4H, J= 7Hz), 3.27 (m, 2H), 2.87 (t, 2H, J= 7Hz), 2.66 (t, 2H, J= 7Hz), 2.34 (t, 2H, J= 7Hz), 1.98-1.25 (m, 22H). ^{13}**C** = 198.9, 174.6, 166.1, 132.6, 131.5, 130.4, 127.9, 91.9, 65.9, 65.7, 43.7, 41.1, 34.1, 30.5, 29.7, 29.2, 27.3, 26.7, 26.3, 25.3, 22.9.



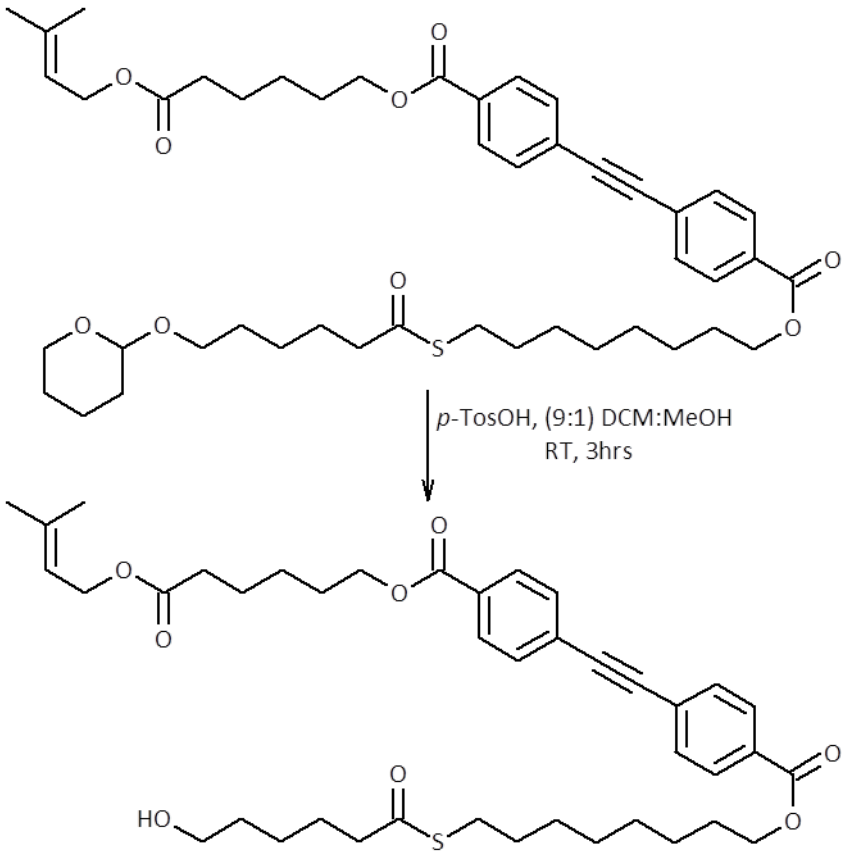
18c: Yield 64% of an off white waxy solid. NMR (d6-DMSO): ^{1}**H** = 7.98 (d, 4H, *J*= 8Hz), 7.72 (d, 4H, *J*= 8Hz), 7.57 (s, br, 3H), 4.27 (s, 4H), 2.79 (m, 3H), 2.50 (m, 3H), 2.23 (m, 2H), 1.79-1.28 (m, 27H). ^{13}**C** = 198.6, 17.5, 165.1, 131.8, 129.9, 129.4, 126.3, 91.2, 64.9, 43.1, 33.6, 29.2, 28.5, 28.3, 28.1, 27.9, 26.7, 26.6, 25.1, 24.5, 24.2, 23.9.

18d: Yield 42% of an off white glassy solid. NMR (d6-acetone): **^{1}H** = 8.05 (d, 2H, *J*= 8Hz), 7.70 (d, 2H, *J*= 8Hz), 7.55 (s, br, 2H), 4.32 (m, 4H), 3.24 (m, 2H), 2.86 (t, 2H, *J*= 7Hz), 2.57 (t, 2H, *J*= 7Hz), 2.36 (t, 2H, *J*= 7Hz), 1.80-1.36 (m, 27H). **^{13}C** = 199.2, 174.6, 166.0, 132.5, 131.4, 130.3, 127.8, 91.9, 65.5, 44.3, 41.4, 34.0, 30.4, 29.0, 27.9, 26.7, 26.2, 25.2.



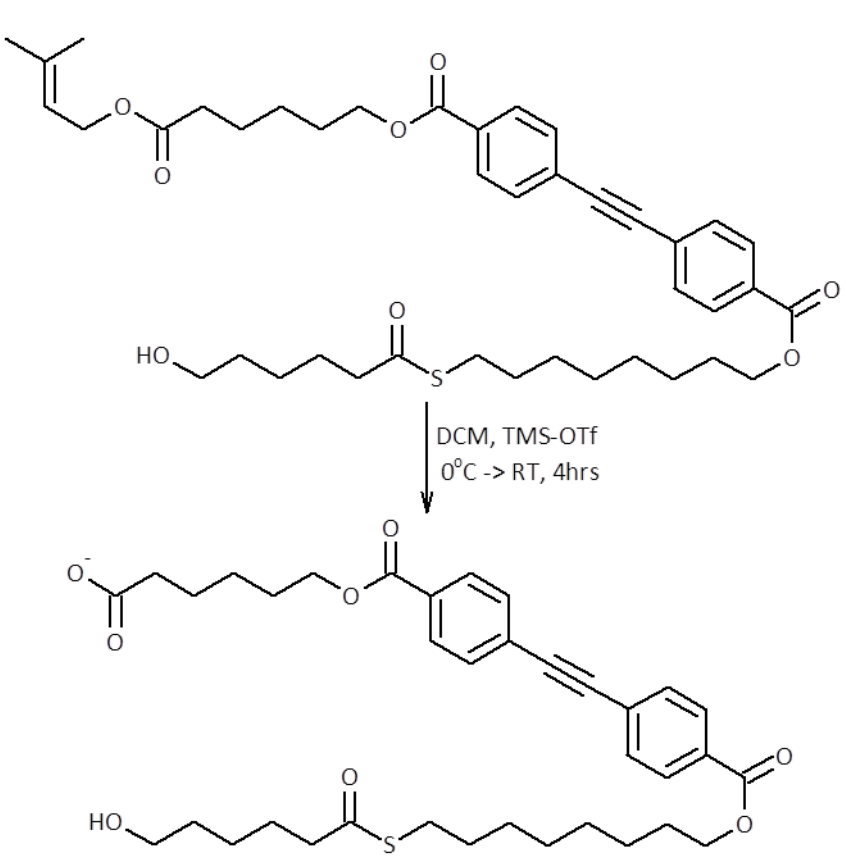
19f:

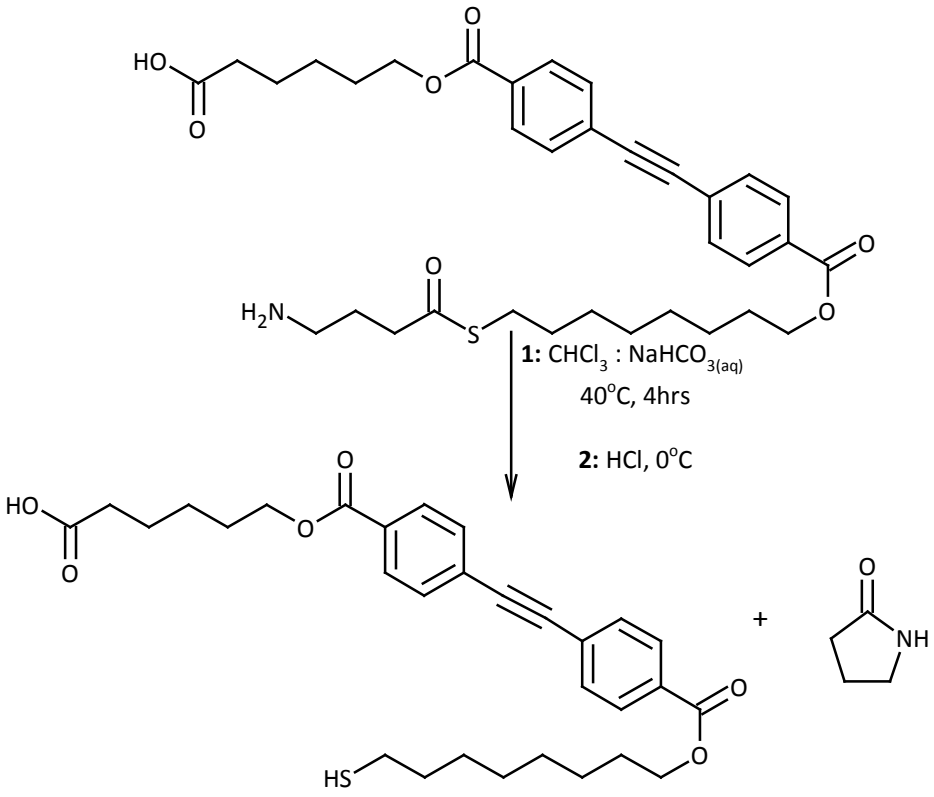
Step 1: 1.0 equivalent of **17f)** was dissolved in 9:1 DCM: MeOH and to the resulting solution was added 0.20 equivalents of *p*-TosOH. The reaction was stirred vigorously for 3 hours while monitoring by TLC (SiO_2, 2:1 hexanes:acetone, UV and vanillin (purple) used for visualization, Rf = 0.38). The reaction was worked up by diluting by a factor of 5 using DCM. This solution was then washed with H_2O and brine before being dried over $MgSO_4$, filtered and then dried under vacuum. The crude material was purified by silica gel column chromatography eluting with 0 - 25% acetone in hexanes. Yield 86% of a pale yellow waxy solid. NMR ($CDCl_3$): **^{1}H** = 8.01 (dd,4H, *J*= 8, 2Hz), 7.58 (d, 4H, *J*= 8Hz), 5.32 (m, 1H), 4.56 (d, 2H, *J*= 7Hz), 4.31 (m, 4H), 3.62 (m, 2H), 2.84 (t, 2H, *J*= 7Hz), 2.54 (t, 2H, *J*= 7Hz), 2.36 (t, 2H, *J*= 7Hz),



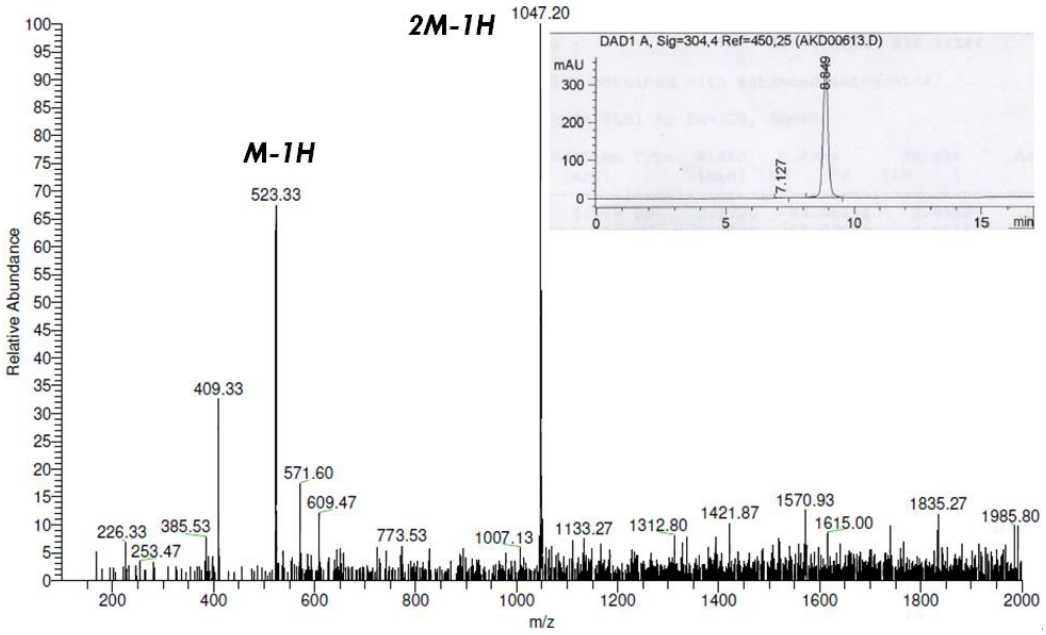
1.74 (m, 14H), 1.45 (m, 18H). **^{13}C** = 199.5, 173.4, 165.9, 139.2, 131.8, 130.3, 129.7, 127.4, 118.7, 91.4, 65.2, 65.4, 62.7, 61.4, 44.1, 34.2, 32.2, 29.7, 29.2, 29.0, 28.9, 28.7, 28.5, 26.0, 25.8, 25.7, 25.5, 25.2, 24.7, 18.0.

Step 2: 1.0 equivalent of the previous product was dissolved in dry DCM and cooled to 0°C to which was added 1.1 equivalents of TMSOTf. The reaction was then allowed to stir for 4 hours while gradually warming to room temperature. The reaction was monitored by TLC (SiO_2, 2:1 hexanes:acetone, UV used to visualize, Rf = 0.27). The reaction was worked up by first adding several drops of glacial acetic acid and then diluting the reaction by a factor of 10 using dry DCM. The resulting solution was then washed with H_2O and brine before being dried over $MgSO_4$, filtered and dried under vacuum. The resulting brown solid was dissolved in a minimum amount of DCM to which was added Et2O until the formation of a fine white precipitate was observed at which point the solution was put in the freezer for a few hours. This precipitate was then filtered off and then dried under vacuum to afford the final product. Yield 24% of an off-white waxy solid. The product was further purified via preparatory HPLC using a C18 column and eluting with 0 - 5% MeOH in acetonitrile as required for studies. NMR ($CDCl_3$): **^{1}H** = 8.01 (dd,4H, J= 8, 2Hz), 7.58 (d, 4H, J= 8Hz), 5.32 (m, 1H), 4.56 (d, 2H, J= 7Hz), 4.31 (m, 4H), 3.62 (m, 2H), 2.84 (t, 2H, J= 7Hz), 2.54 (t, 2H, J= 7Hz), 2.36 (t, 2H, J= 7Hz), 1.74 (m, 14H), 1.45 (m, 18H). **^{13}C** = 199.5, 173.4, 165.9, 139.2, 131.8, 130.3, 129.7, 127.4, 118.7, 91.4, 65.2, 65.4, 62.7, 61.4, 44.1, 34.2, 32.2, 29.7, 29.2, 29.0, 28.9, 28.7, 28.5, 26.0, 25.8, 25.7, 25.5, 25.2, 24.7, 18.0.

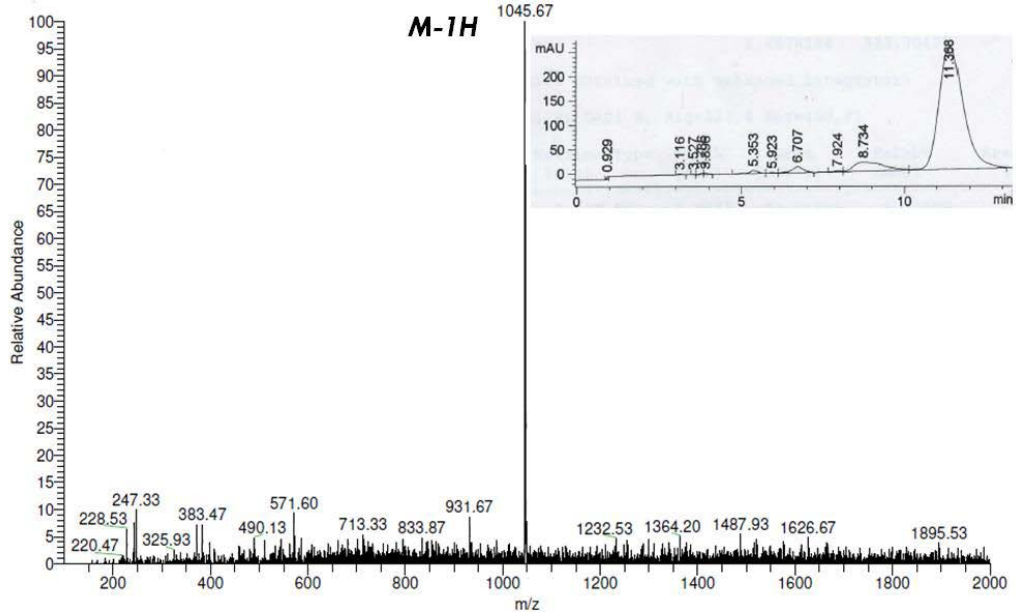




20: All solvents used were bubbled with argon gas. Under inert atmosphere of argon, 1.0 equivalent of **18a** (50mg, 0.0784mmol) was added to 3mL of a saturated bicarbonate solution. This solution was gently stirred and heated to 50°C for 24 hours; a white cloudy solution formed after the reactant had dissolved. The solution was cooled to room temperature then to 0°C in an ice bath. At 0°C with vigorous stirring, 5mL of argon chloroform was added and the solution was acidified to pH 2 with 5M hydrochloric acid. The organic fraction was separated and dried with sodium sulfate. The solution was dried under argon gas once to determine the crude yield of the reaction (14.8mg, 36%) and redissolved into chloroform solution and stored in the freezer. NMR (d6-acetone): ^{1}**H** = 8.06 (d, 4H, J= 8Hz), 7.71 (d, 4H, J= 8Hz), 7.63 (br s, 3H), 4.33 (q, 4H, J= 7Hz), 3.27 (m, 2H), 2.87 (t, 2H, J= 7Hz), 2.66 (t, 2H, J= 7Hz), 2.34 (t, 2H, J= 7Hz), 1.98-1.25 (m, 22H). ^{13}**C** = 198.9, 174.6, 166.1, 132.6, 131.5, 130.4, 127.9, 91.9, 65.9, 65.7, 43.7, 41.1, 34.1, 30.5, 29.7, 29.2, 27.3, 26.7, 26.3, 25.3, 22.9.

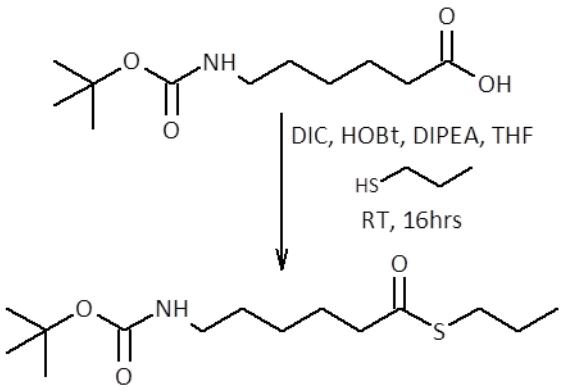


HPLC (acetonitrile, 1.5 mL/min, fluorescence trace excited at 304 nm and detected at 450 nm) and negative ESI-MS (0.1mM in 0.1% ammonia in acetonitrile) **20** as prepared. Major component elution time: 8.85min.

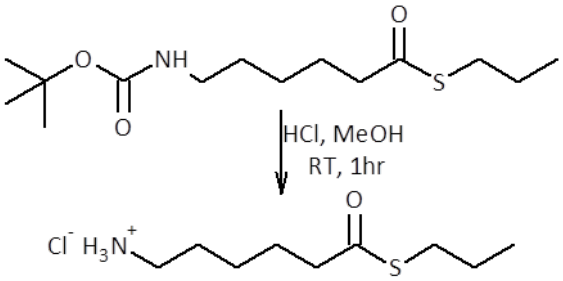


HPLC and negative ESI-MS (conditions as above) for a sample of **20** following 16 hours exposure to air. Major component elution time: 11.37min.

21: 6-oxo-6-(propylsulfanyl)hexan-1-amonium chloride



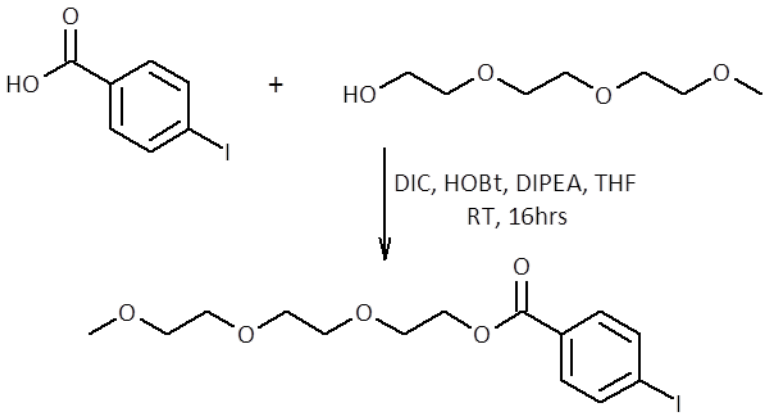
Step 1: 1.0 equivalent of **6-[(tert-butoxycarbonyl)amino]hexanoic acid (3-14)** was dissolved into dry THF and to this solution was added in order 1.5 equivalents of HOBt, 1.5 equivalents of DIC, 1.5 equivalents of propanethiol and 1.5 equivalents of DIPEA. The reaction was stirred vigorously for 16 hours while monitoring by TLC (SiO_2, 2:1 hexanes:Et2O, Hanessian's stain (blue) used for visualization, Rf = 0.46). The reaction was worked up by first vacuum filtering to remove the DIU side product. The filtrate was then dried under vacuum and the resulting oil was dissolved in Et_2O. This solution was washed with H_2O and brine before being dired over Na_2SO_4, filtered and dried under vacuum. The resulting crude product was purified by silica gel column chromatography eluting with 0 - 30% Et_2O in hexanes. Yield 97% as a pale yellow oil. NMR ($CDCl_3$): ^{1}**H** = 4.56 (s, br, 1H), 3.02 (s, br, 2H), 2.84 (td, 2H, *J*= 7, 1Hz), 2.52 (td, 2H, *J*= 7, 1Hz), 1.62-1.30 (m, 18H), 0.90 (td, 3H, *J*= 6, 1Hz). ^{13}**C** = 199.4, 155.9, 79.0, 44.0, 40.4, 30.8, 29.9, 28.6, 26.2, 25.5, 22.9, 13.5.



Step 2 **:** 1.0 equivalents of the previous product was dissolved in MeOH and to this solution was added 2.0 equivalents of HCl as a 2M aqueous solution. The reaction was stirred vigorously for 1 hour at room temperature. The reaction was worked up by evaporating the solvent under vacuum to afford a waxy off white solid. This solid was triturated with 1:1 hexane:Et_2O before being vacuum filtered. The resulting solids were dried further under vacuum. Yield 98% as a white crystalline solid. NMR ($CDCl_3$): ^{1}**H** = 8.14 (br, s, 3H), 2.9 (br, s, 2H), 2.78 (t, 2H, *J*= 7Hz), 2.52 (t, 2H, *J*= 7Hz), 1.76 (m, 2H), 1.64 (m, 2H), 1.52 (p, 2H, *J*= 7Hz), 1.39 (m, 2H), 0.90 (t, 3H, *J*= 7Hz). ^{13}**C** = 199.3, 43.7, 39.8, 30.7, 33.0, 27.0, 25.8, 25.0, 13.4.

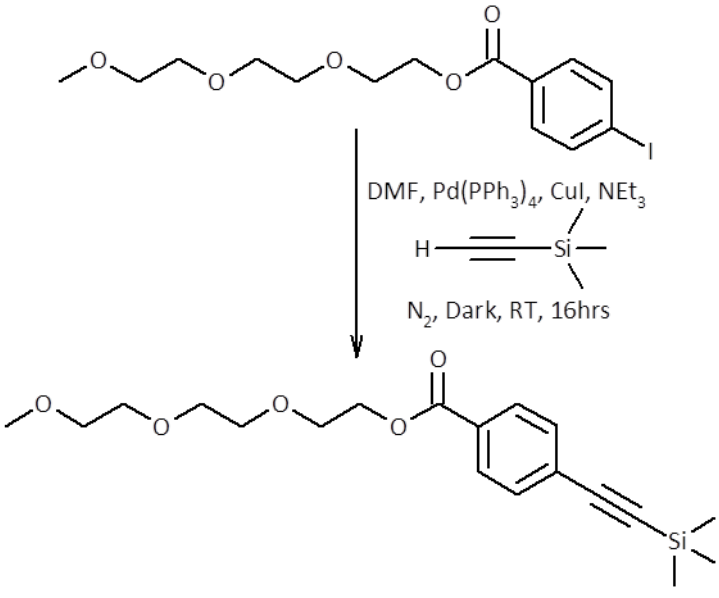
Synthesis of an HPLC chromophore standard (compound 22)

2-[2-(2-methoxyethoxy)ethoxy] ethyl 4-iodobenzoate:

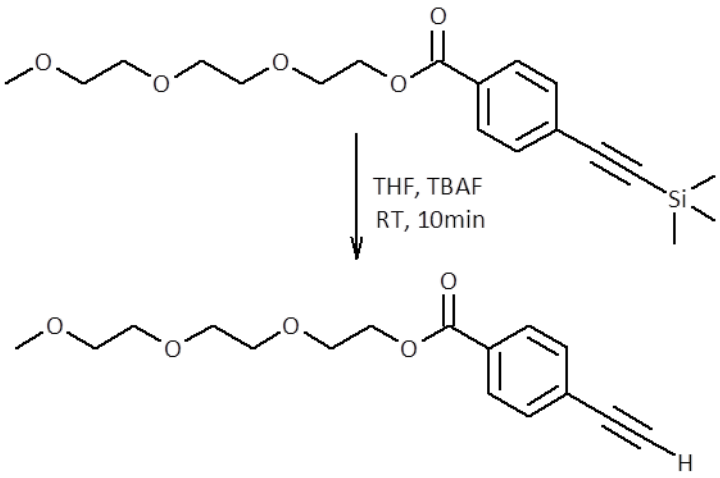


1.0 equivalent of *p*-iodobenzoic acid was dissolved into dry THF. To this solution was added in order 1.2 equivalents of HOBt, 1.2 equivalents of DIC, 1.2 equivalents of triethylene glycol monomethyl ether and 2.4 equivalents of DIPEA. The reaction was then stirred vigorously for 16 hours while being monitored by TLC (SiO_2, 1:1 hexanes:EtOAc, UV used for visualization, Rf = 0.41). Upon completion of the reaction as indicated by the loss of the spot due to the starting material (**3-8**) on the TLC plate, the reaction was worked up by first vacuum filtering to remove the solid diisopropyl urea (DIU) side product. The filtrate was then dried under high vacuum before being dissolved into Et_2O. This Et_2O was washed with H_2O and brine before being dried over Na_2SO_4, filtered and then dried under high vacuum. The resulting crude material was purified by silica gel column chromatography eluting with 0 - 50% EtOAc in hexanes. Yield 88% as a white waxy low melting solid. NMR ($CDCl_3$): ^{1}**H** = 7.72 (m, 4H), 4.42 (m, 2H), 3.77 (m, 2H), 3.61 (m, 6H), 3.48 (m, 2H), 3.31 (s, 3H). ^{13}**C** = 165.9, 137.7, 131.1, 129.5, 100.7, 71.8, 70.6, 69.1, 64.4, 59.1.

2-[2-(2-methoxyethoxy) ethoxy] ethyl 4-trimethylsilyl-ethynylbenzoate: 1.0 equivalents of the previous product was dissolved into dry THF and the resulting solution was purged under N_2. To this solution was added in order under a stream of nitrogen 4.0 equivalents of NEt_3, 0.05 equivalents of $Pd(PPh_3)_4$, 0.10 equivalents of CuI and 2.0 equivalents of TMS-acetylene. The reaction was allowed to stir at room temperature, in the dark and under a stream of N_2 for 16 hours. The reaction was monitored by TLC (SiO2, 1:1 hexanes:EtOAc, UV used for visualization, Rf = 0.52). The reaction was worked up by first

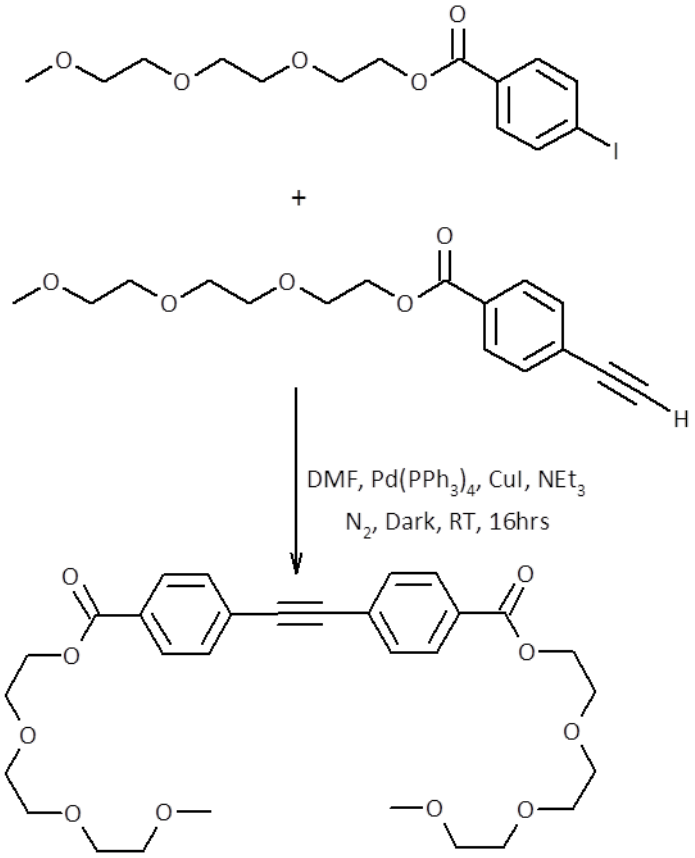


removing the solvent under vacuum to afford dark yellow sticky solid which was treated with Et_2O. The resulting cloudy mixture was vacuum filtered and the filtrate washed with a solution of disodium EDTA, H_2O and brine before being dried over Na_2SO_4, filtered and then dried under vacuum. This crude product was purified by silica gel column chromatography eluting with 0 - 80% Et_2O in hexanes. Yield 98% as a pale orange oil. NMR ($CDCl_3$): **^{1}H** = 7.96 (d, 2H, *J*= 8Hz), 7.49 (d, 2H, *J*= 8Hz), 4.45 (t, 2H, *J*= 6Hz), 3.81 (t, 2H, *J*= 6Hz), 3.65 (m, 6H), 3.51 (m, 2H), 3.35 (s, 3H), 0.24. **^{13}C** = 166.0, 132.3, 129.5, 127.9, 103.8, 97.3, 72.1, 70.6, 69.3, 64.4, 59.1, -0.1.



2-[2-(2-methoxyethoxy)ethoxy]ethyl 4-ethynylbenzoate: 1.0 equivalent of the previous product was dissolved in dry THF and then cooled to 0°C. To this solution was added 1.0 equivalent of TBAF as a 1M solution in THF with vigorous stirring. The reaction immediately went inky black blue. The reaction was monitored by TLC (SiO_2, 1:2 hexanes:Et_2O, UV used for visualization, Rf = 0.29). After ~5 minutes the reaction was complete and worked up by first adding a drop of AcOH causing the colour to fade slightly. The reaction was diluted by a factor of 5 using Et_2O and the resulting solution was washed with H_2O and brine before being dried over Na_2SO_4, filtered and then dried under vacuum. The crude material was purified using silica gel column chromatography eluting with 0 - 75% EtOAc. Yield 60% as a pale yellow oil. NMR ($CDCl_3$): **^{1}H** = 7.97 (dd, 2H, *J*= 8, 2H), 7.50 (d, 2H, *J*= 8Hz), 4.45 (t, 2H, *J*= 7Hz), 3.80 (t, 2H, *J*= 7Hz), 3.59 (m, 6H), 3.49 (m, 2H), 3.33 (s, 3H), 3.23 (s, 1H). **^{13}C** = 166.3, 132.2, 130.2, 129.6, 126.9, 82.8, 80.2, 72.1, 70.5, 69.2, 64.5, 59.1.

Chromophore standard (22): 1.0 equivalent of the iodide above was dissolved in dry THF and the resulting solution purged with N_2. To this solution was added in order 2.1 equivalents of NEt_3, 0.03 equivalents of $Pd(PPh_3)_4$, 0.06 equivalents of CuI, and 1.1 equivalents of the alkyne above The reaction was allowed to stir vigorously in the dark under N_2 for 16 hours. The reaction was monitored by TLC (SiO_2, 2:1 hexanes:acetone, UV used for visualization, Rf = 0.23). Upon completion the reaction was worked up by first removing the solvent under vacuum to afford a mass of sticky orange solid. This solid was treated with Et_2O resulting in a cloudy orange solution which was vacuum filtered. The filtrate was then washed with a solution of disodium EDTA, H_2O and then brine before being dried over Na_2SO_4, filtered and then dried under vacuum. The resulting orange oil was purified by silica gel column chromatography eluting with 0 - 30% acetone in hexanes. Yield 96% as a pale orange oil. NMR ($CDCl_3$): **^{1}H** = 8.01 (d, 4H, *J*= 8Hz), 7.56 (d, 4H, *J*= 8Hz), 4.45 (m, 4H), 3.81 (m, 4H), 3.69 (m, 4H), 3.59 (m, 12H), 3.48 (m, 4H), 3.30 (m, 6H). **^{13}C** = 166.1, 131.7, 129.9, 129.7, 127.4, 91.4, 71.9, 70.7, 70.6, 69.1, 64.4, 59.1.



HPLC DETERMINATION OF CHAIN SHORTENING REACTION

HPLC (acetonitrile; 1.5 mL/min; C18 semi-preparative column) gave retention times of 4.0 min for **18a-d**. The chromophore standard **22** prepared above had a retention time of 6.7 minutes under these conditions. The alcohol **19f** requires a higher flow rate for acceptable peak shape (acetonitrile, 2.0 mL/min; C18 semi-preparative column; retention time 8.6 min); the standard **22** eluted at 4.7 minutes under these conditions. A UV/Visible spectroscopy calibration curve of the standard compound **22** in acetonitrile was also obtained. It was found to have two absorbance maxima at 305 and 323 nm with extinction coefficients of 43500 and 39400 $L \cdot cm^{-}$

^{1}mol^{-1} respectively. These values corresponded closely to literature values reported for structurally related compounds[2].

With the retention times and spectroscopic properties of the standard compound characterized the HPLC based studies of compound stability were carried out. Experiments were carried out by purifying small samples of **18a-d** and **19f** which were then diluted and the concentrations of these determined from the intensity of their UV/Visible absorbance spectra. To these solutions were added a known quantity of the standard compound as well as any additional reagents such as basic catalysts. The mixtures were then analyzed by HPLC at varying time intervals in order to monitor changes in the ratio of the integration of the peaks due to the full length compounds versus the standard compound. Representative data are plotted in Figure S1. More basic conditions could not be explored with this analytical method.

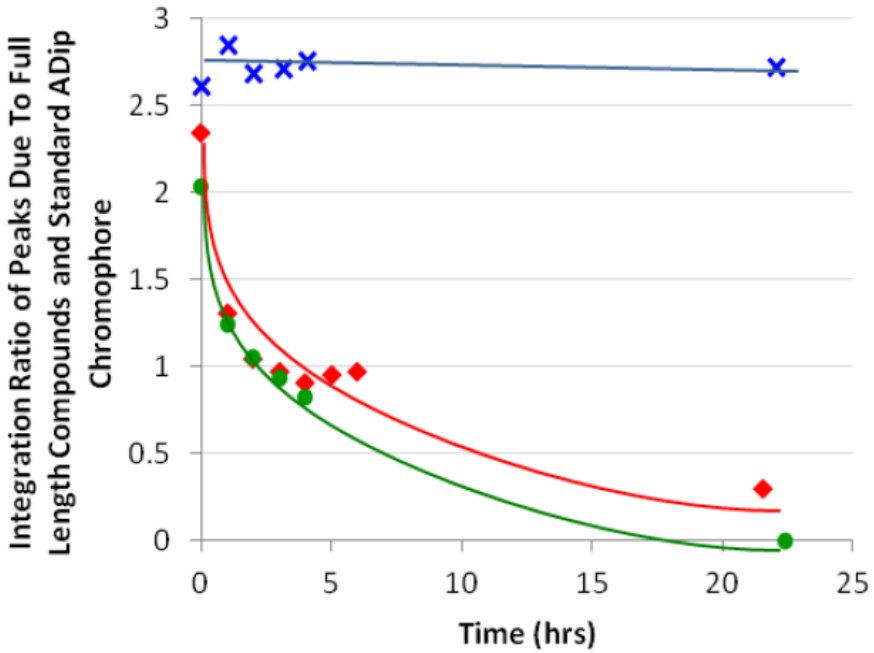


Fig S1: Decomposition of **18c** (red diamond, green circle) and **19f** (blue x) in acetonitrile-water (99:1 vol%) with (green circle, blue x) or without (red diamond) added di-isopropyl ethyl amine (2.2 eq.) as a function of time.

NMR DETERMINATION OF THIOESTER EXCAHNGE AND CHAIN SHORTENING REACTIONS

NMR spectroscopy allows the use of more basic conditions than possible for the HPLC studies but require higher quantities of material. We also wished to explore aqueous conditions where the hydrophobic effect would aggregate full length compounds. We therefore focussed on the reactivity of **21** in D_2O/DMSO (1:3) in which it is soluble to approximately 0.1M. In order to investigate the thioester exchange reaction an appropriate thiol was required to exchange with

the 1-propanethiol. Benzyl thiol was selected as the proton signals from this compound are minimally interfering with the proton signals of **21** and the benzylic protons reflect thiol-thioester cleanly.

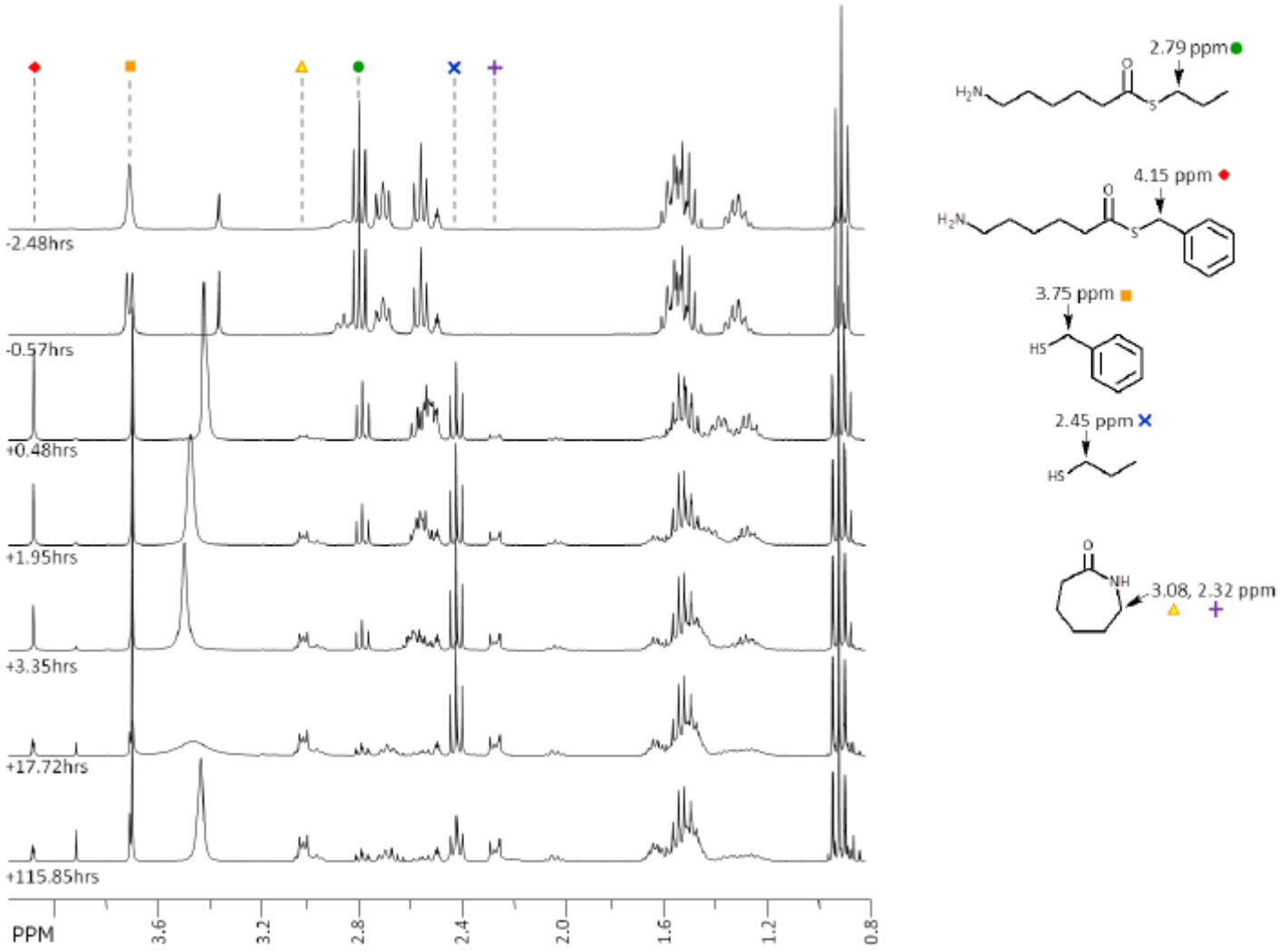


Fig S-2: Time dependent proton NMR of a mixture of **21** and benzyl thiol in DMSO d_6 containing 2.0 equivalents of NaOD (DMSO:D_2O = 3:1). Reported times are relative to the addition of base. Note that thioester exchange reaches its maximum within the first 30 minutes following base addition. Note the slow appearance of a singlet at 3.9 ppm corresponding to the slow air oxidation to produce a benzyl-containing disulfide.

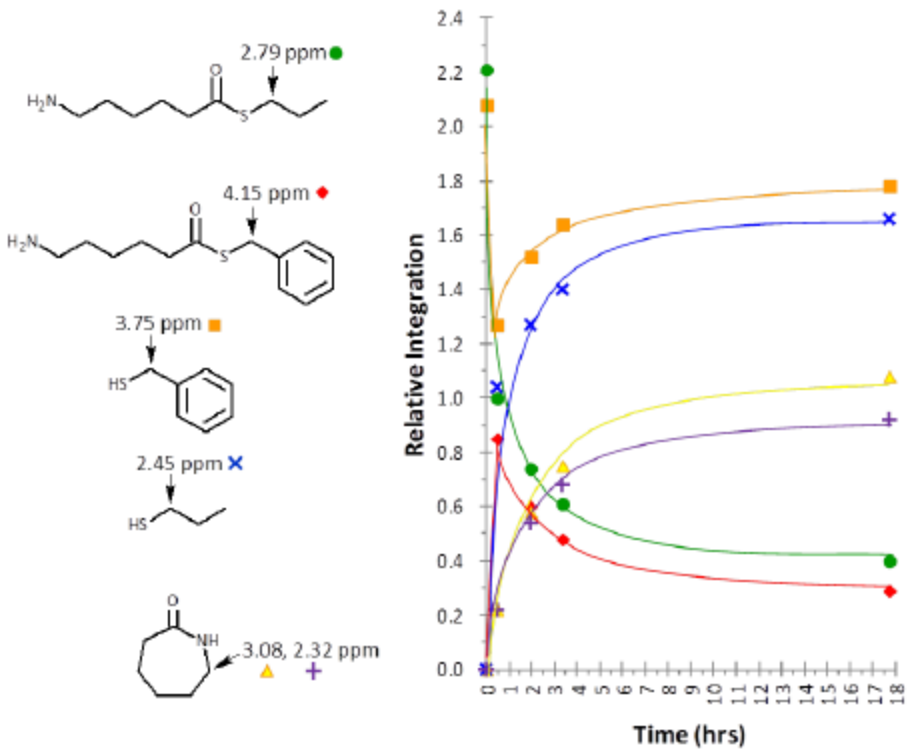


Figure S-3: Relative integrations of the spectra of Figure S2 as a function of time.

HPTS ASSAY

Vesicle preparation: A chloroform solution of 8:1:1 PC:PA:cholesterol (Avanti Polar lipids) was dried in vacuo in a pear-shaped flask and then left on the vacuum line overnight. For compounds that were pre-loaded into the vesicle, a solution of the test compound of interest was added to the initial $CHCl_3$ lipid solution at 0.1 – 1 mol%, and then prepared as described. The 50 mg lipid film was hydrated with 1 mL of internal buffer solution (10 µM HPTS, 10 mM $Na_3PO_4.12H_2O$, 100 mM NaCl in deionized H_2O, pH 6.4, adjusted with conc. H_3PO_4). The suspension was frozen under liquid nitrogen and subsequently thawed at room temperature over ten minutes (3 times). The mixture was then sonicated in an ice bath for 20 seconds with 2 second pulses (at 50% duty cycle and 20% power output) 3 times, with a 30 s rest between cycles. The unilamellar vesicles were then left to anneal overnight. The vesicle solution was then sized 19 times through a 400 nm polycarbonate Nucleopore filter using a LiposoFast membrane extrusion apparatus (Avestin) (0.5 mL x 2) and purified on a PD-10 Sephadex G-25 column (GE Healthsystems) using an external buffer solution (10 mM Na_3PO_4 $.12H_2O$, 100 mM NaCl, pH= 6.4). The first three cloudy drops were discarded but thereafter the cloudy fraction was collected and diluted to 5.00 mL using the external buffer solution. A typical preparation of this vesicle stock solution contained 200 ±20 nm diameter vesicles (determined by dynamic light scattering, Brookhaven Instruments, ZetaPALS particle sizing software) and a lipid concentration of typically 7 mg/mL. The vesicle solution was stored at 50^{o}C and used within 24 hours of preparation.

Typical experiment: in a typical experiment, 100 µL of the vesicle suspension was added to the fluorescence cuvette. 2.00 mL of external buffer (10 mM Na_3PO_4 .$12H_2O$, 100 mM NaCl, pH= 6.4) and 25 µL of a solution of the compound being tested, generally in MeOH, was then added. The solution was placed in the fluorimeter and left to equilibrate, generally 10 minutes. An excitation ratio was started (λEx1= 403 nm, λEx2= 460 nm, λEm= 510 nm, excitation and emission monochromator bandwiths = 3 nm, Integration 1s, duration 600 s). At t= 60 s, 50 µL of a 0.5 M aqueous NaOH solution was added through the injection port (continuous monitoring, no pause). At t= 540 s, the experiment was paused and 50 µL of a 0.5% aqueous solution of Triton X-100 was added. The experiment was then restarted after 30 s of stirring time. The data was analysed as reported previously[3].

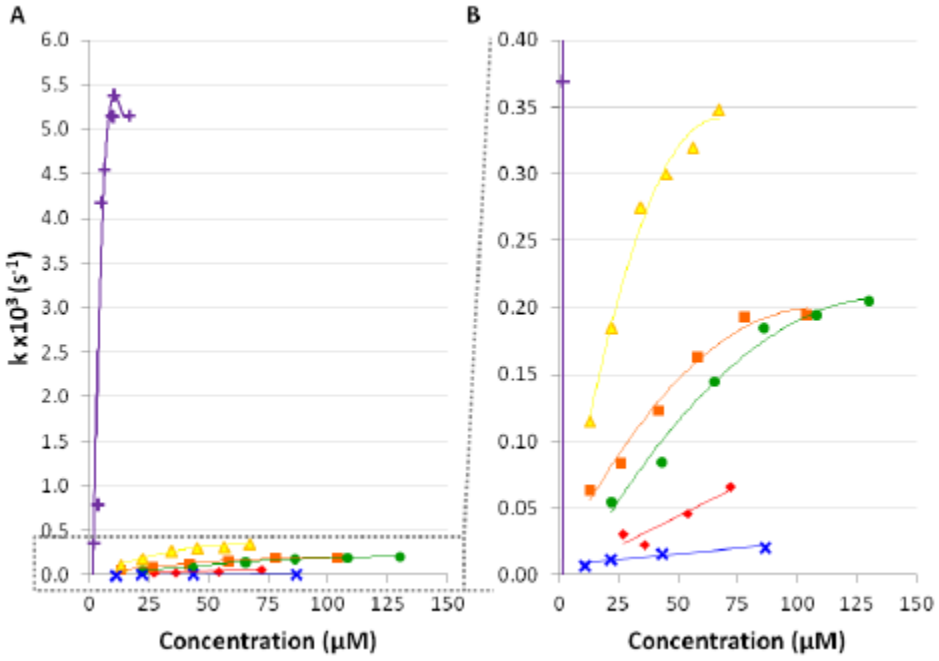


Figure S-4: HPTS transport rate as a function of concentration for compound **1** (blue +), **18a** (red diamond), **18b** (orange square), **18c** (yellow triangle), **18d** (green circle), and **19f** (blue x).

FLUORESCENCE DETREMINATION OF COMPOUND PARTITION

The methods used were previously described in detail[1, 3].

Fig S-5: Fluorescence excitation and emission spectra of **18c** in acetonitrile (A) and in aqueous solution (B). Panel B also illustrates the relative fluorescence quenching in aqueous solution.

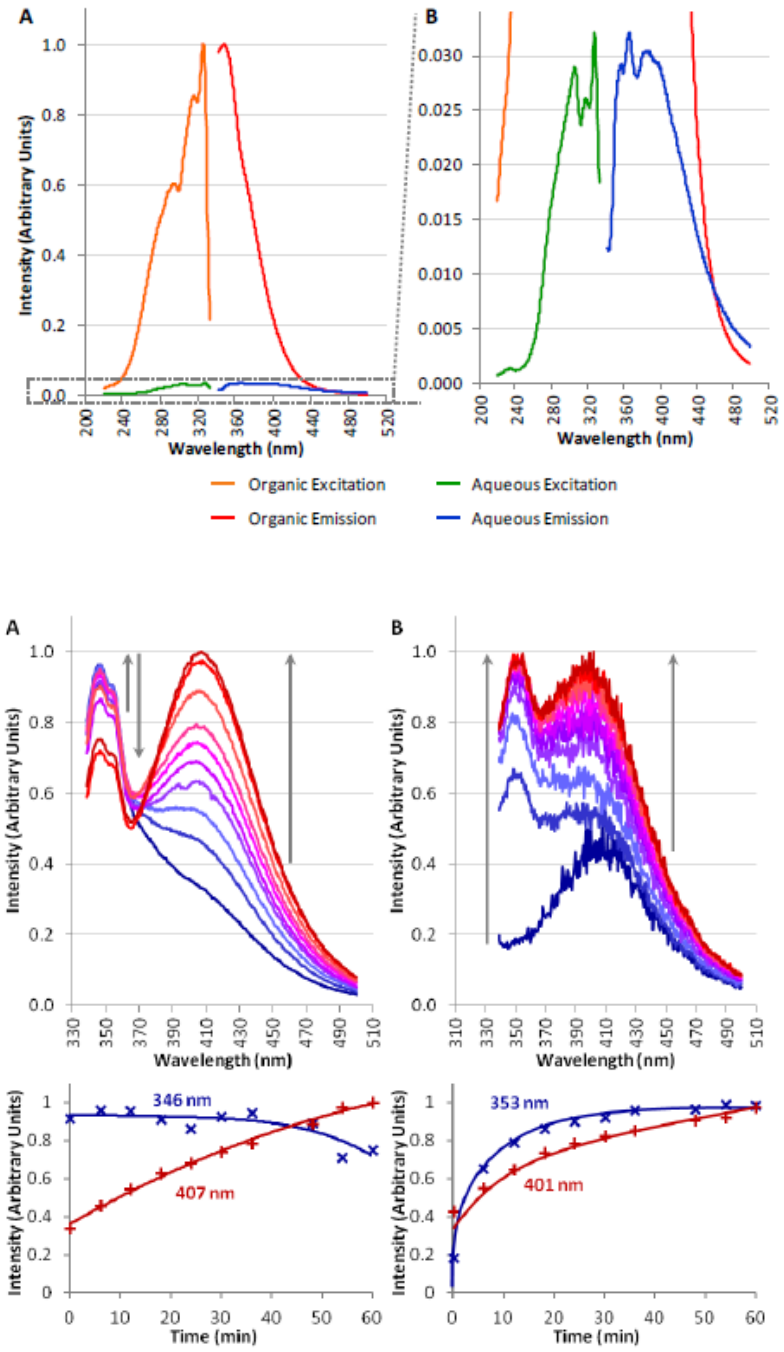


Fig S-6: Top panels: time lapsed emission spectra spanning a one hour period after introduction of vesicles of 16 µM solutions in aqueous buffer of A) **18a** and B) **18d** excited at 324 nm. Spectra are coloured from dark blue (time = 0 min) through intermediate shades to dark red (time = 60 min). Bottom panels: corresponding graphs of the changes in key emission wavelengths for the data presented in the top panels.

BILAYER CLAMP ASSAY

A model BC-525A bilayer clamp (Warner Instrument Corp.) was used for planar bilayer experiments, ClampEx 8 and ClampFit 10 (Axon Instruments) were the software used for acquisition and analysis, respectively. Cups used were made of polystyrene and had 250 μm diameter apertures (Warner Instrument Corp). The lipid used in all cases was diphytanoyl phosphatidylcholine (diPhyPC) (Avanti Polar lipids). A stock solution of 25 mg/mL lipid in $CHCl_3$ was dried under N_2 and then re-suspended in 200 μL decane. For experiments involving pre-loading into the lipid, 0.1 – 1 mol% compound in $CHCl_3$ was added to the lipid mix and then dried down. The electrolytes used were 1 M CsCl in 10 mM HEPES, 10 mM TRIS, pH 7 or 10mM Tris/TrisHCl, pH 8.25. The aperture was primed with 0.5-1 μL of decane/lipid, excess solvent was removed by blowing N_2 over the aperture. The cup was then placed into the electrolyte-filled holding cell, consisting of 5 mL and 3 mL chambers, and salt bridges (KNO_3 or KCl/Agar) and electrodes (Ag/AgCl) were attached. Experiments done under Ar atmosphere had the cell, the electrodes, and the preamplifier inside a box continually flushed with Ar. Bilayers were formed by brushing on 1- 1.5 μL of the decane/lipid mix over the aperture, and were monitored for stability, capacitance and resistance for at least 20 minutes before channel-forming compound was added. Once formed, 'activity' from pristine bilayers was never observed. Bilayers were tested repeatedly for capacitance and resistance.

Compounds were usually added by injection from acetonitrile or THF solution (typically no more than 10 μL of solution). In some cases to ensure physical mixing, a formed lipid-only bilayer was broken by brushing on the compound- lipid mix followed by reforming the bilayer.

All data were hardware filtered (8- pole Bessel filter, 1 kHz) and digitized. Most data were collected in a survey mode using the Gap-free protocol, although some experiments utilized an Episodic protocol to collect data on a fixed cycle of potential changes (see below). Concurrent current and applied potential data were recorded. In some cases a derived conductance was recorded (current divided by applied potential). Average conductance over an interval, typically 5 minutes, was determined by plotting a histogram of the recorded conductance over the interval and fitting the distribution to a Gaussian from which the mean and standard deviation were derived for plotting. In some intervals where an abrupt change in conductance occurred, the histogram required fitting to a sum of two Gaussians; in these cases two points of the same interval are plotted. Reported activity grids were prepared as described previously[4, 5].

The activity of compound **18c** is voltage-dependent. Preliminary indication came from an experiment using an episodic protocol alternating positive and negative potentials with a brief resting period at 30 mV between the episodes. Fig S-7 gives the conductance-time record and the derived conductance-potential profile. A more detailed analysis is given in Fig S-8 based on a series of potentials set manually for durations of 5-10 seconds each within a single long period of erratic activity. Mean conductance within each period was assessed by fitting the current histogram to a Gaussian, and dividing the fitted center value by the applied potential,

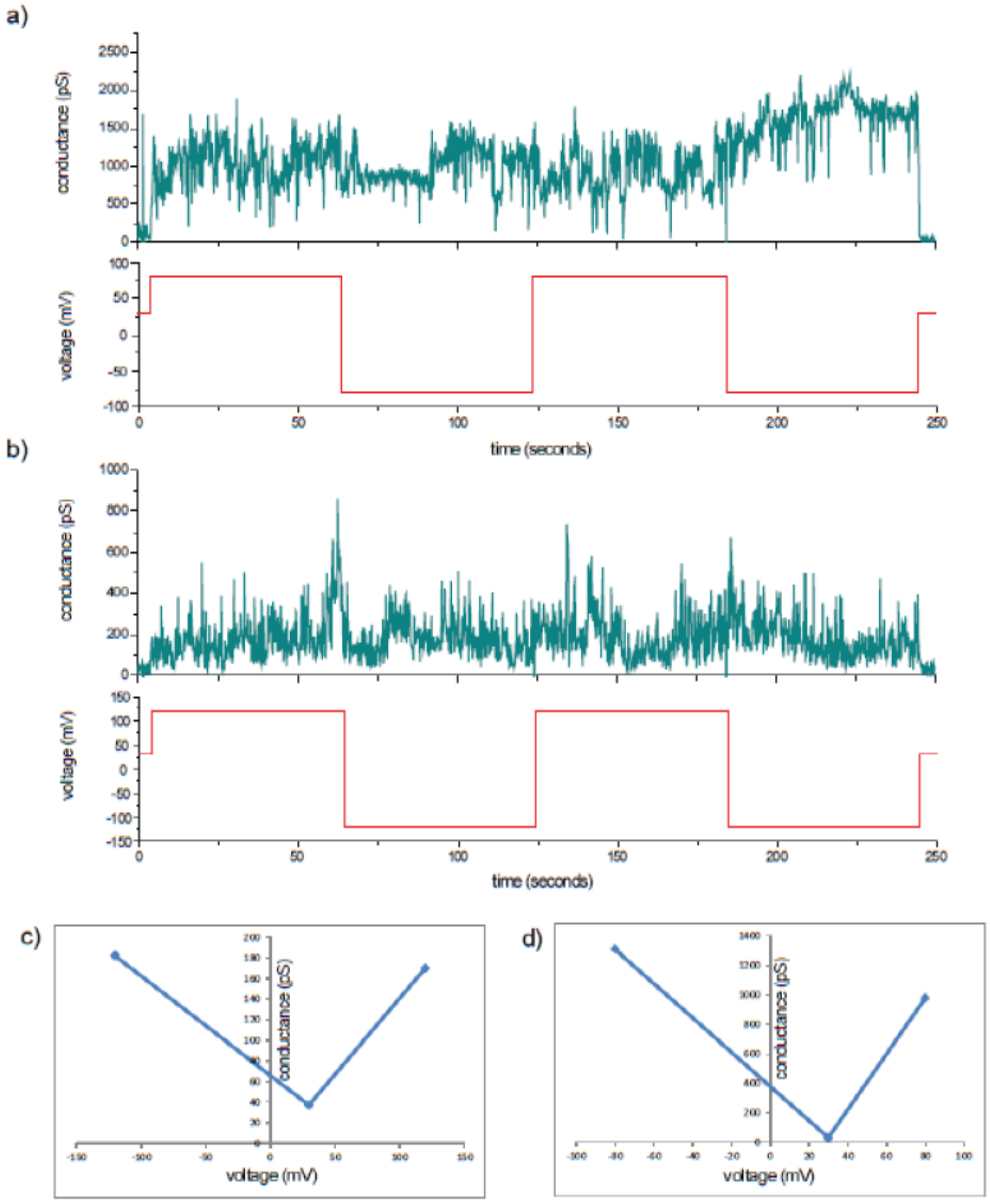


Figure S-7. Voltage-dependent activity of **18c** (diPhayPC, 1M CsCl). a) and b): a single cycle of an episodic protocol showing conductance as a function of time and the applied potential changes (note the brief periods at 30 mV at the start and end of the cycle). c) and d): averaged conductance as a function of applied potential; c) is the data from panel a) while b) is the data from panel a).

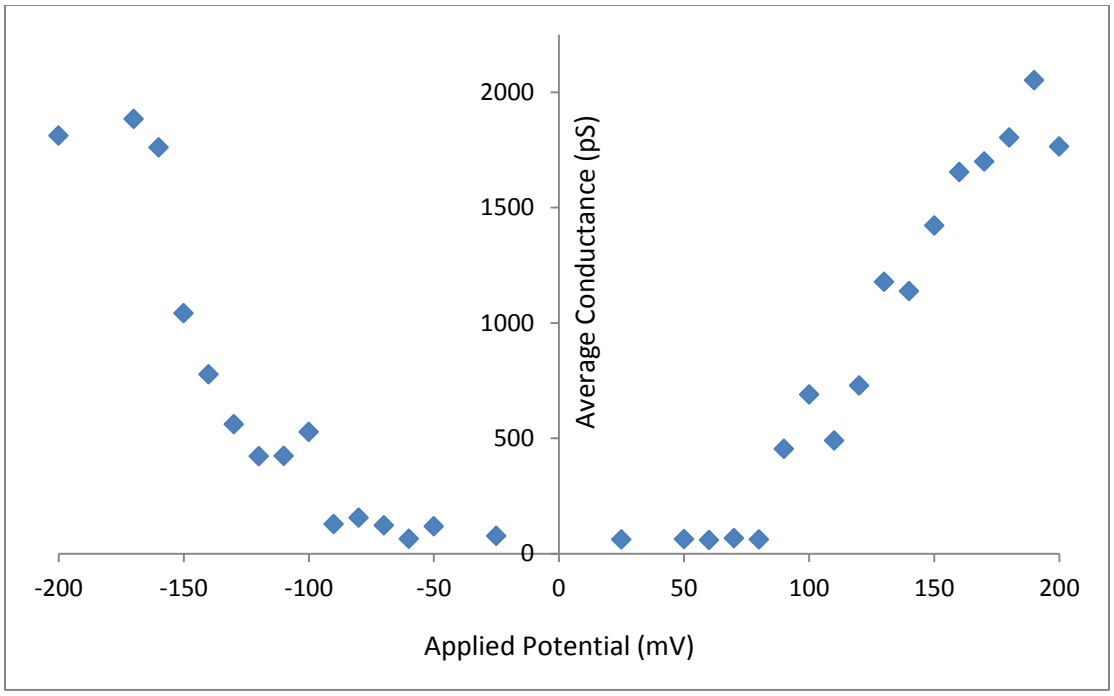
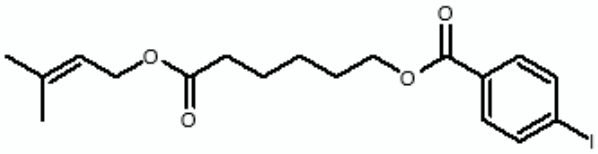


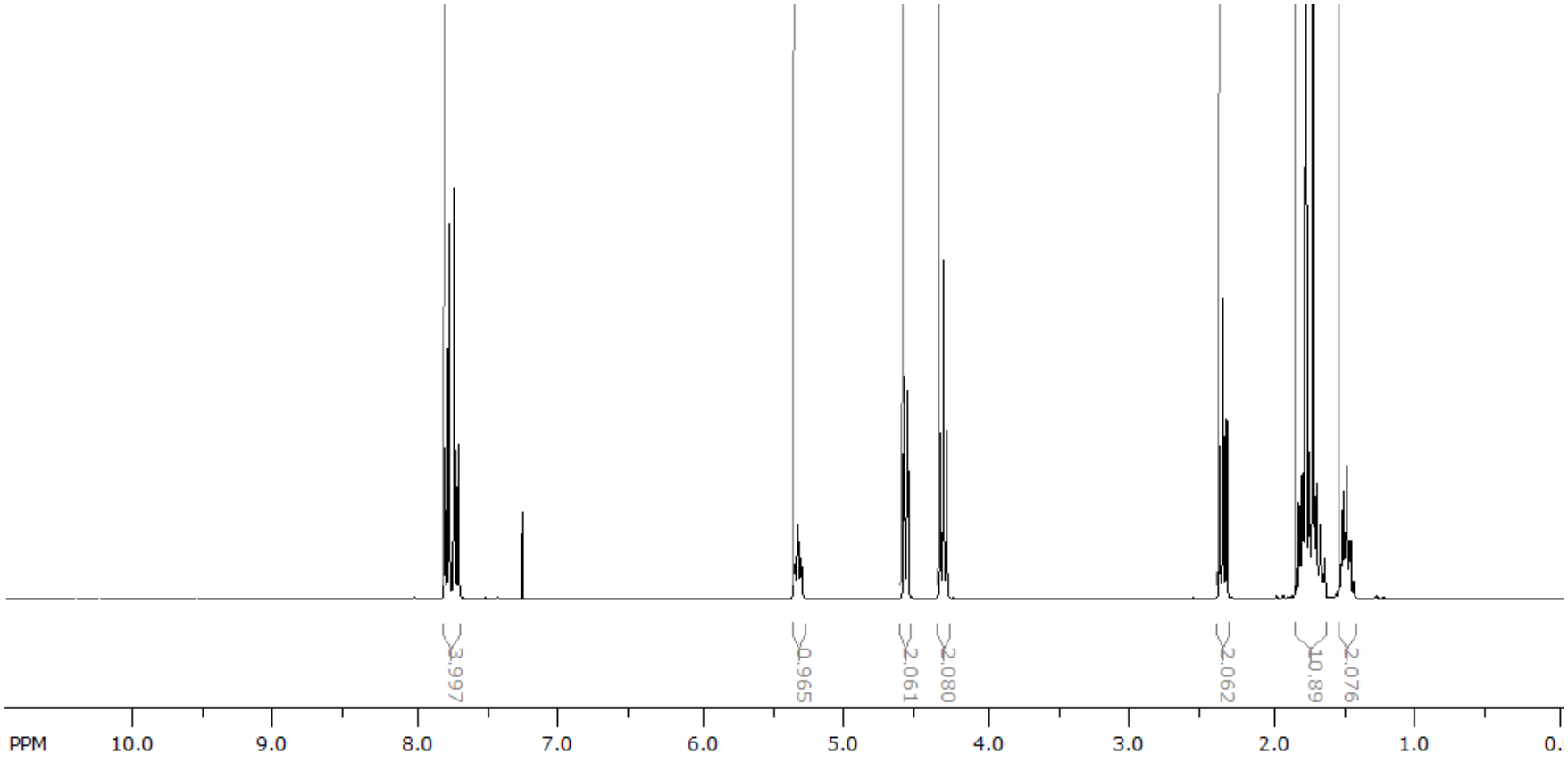
Figure S-8: Average conductance as a function of applied potential for **18c** (diPhyPC, 1M CsCl) Each point is 5-10 seconds of data; the entire curve was accumulated within a single long erratic event.

REFERENCES

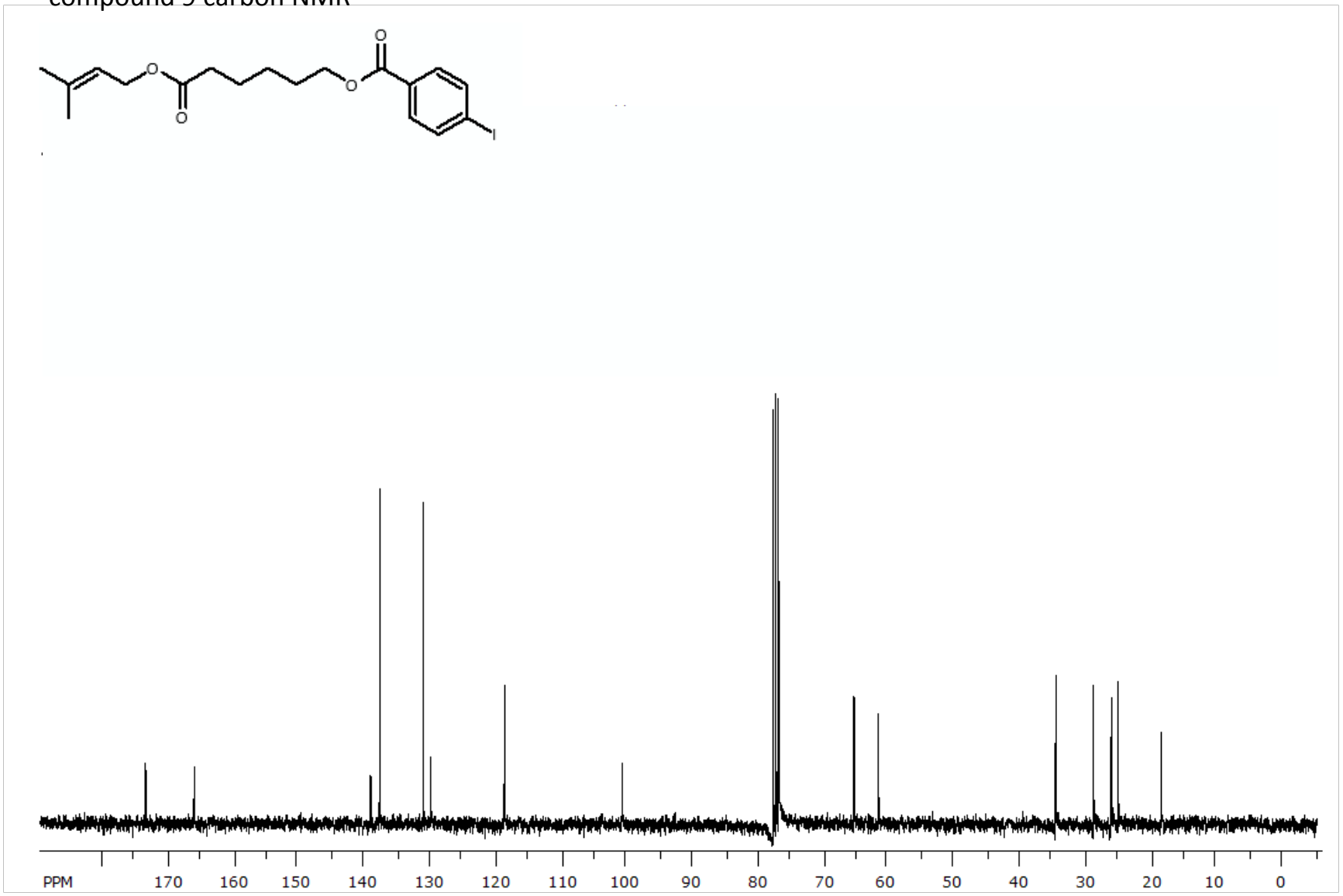
1. J. M. Moszynski and T. M. Fyles, *Org. Biomol. Chem.*, 2010, **8**, 5139-5149.
2. T. M. Fasina, J. C. Collings, J. M. Burke, A. S. Batsanov, R. M. Ward, D. Albesa-Jove, L. Porres, A. Beeby, J. A. K. Howard, A. J. Scott, W. Clegg, S. W. Watt, C. Viney and T. B. Marder, *Journal of Materials Chemistry*, 2005, **15**, 690-697.
3. J. Moszynski and T. M. Fyles *J. Am. Chem. Soc.*, 2012, **134**, 15937−15945.
4. J. K. W. Chui and T. M. Fyles, *Chem. Soc. Rev.*, 2012, **41**, 148-175.
5. J. K. W. Chui, T. M. Fyles and H. Luong, *Beilstein J. Org. Chem.*, 2011, **7**, 1562-1569.

compound 9 proton NMR





compound 9 carbon NMR



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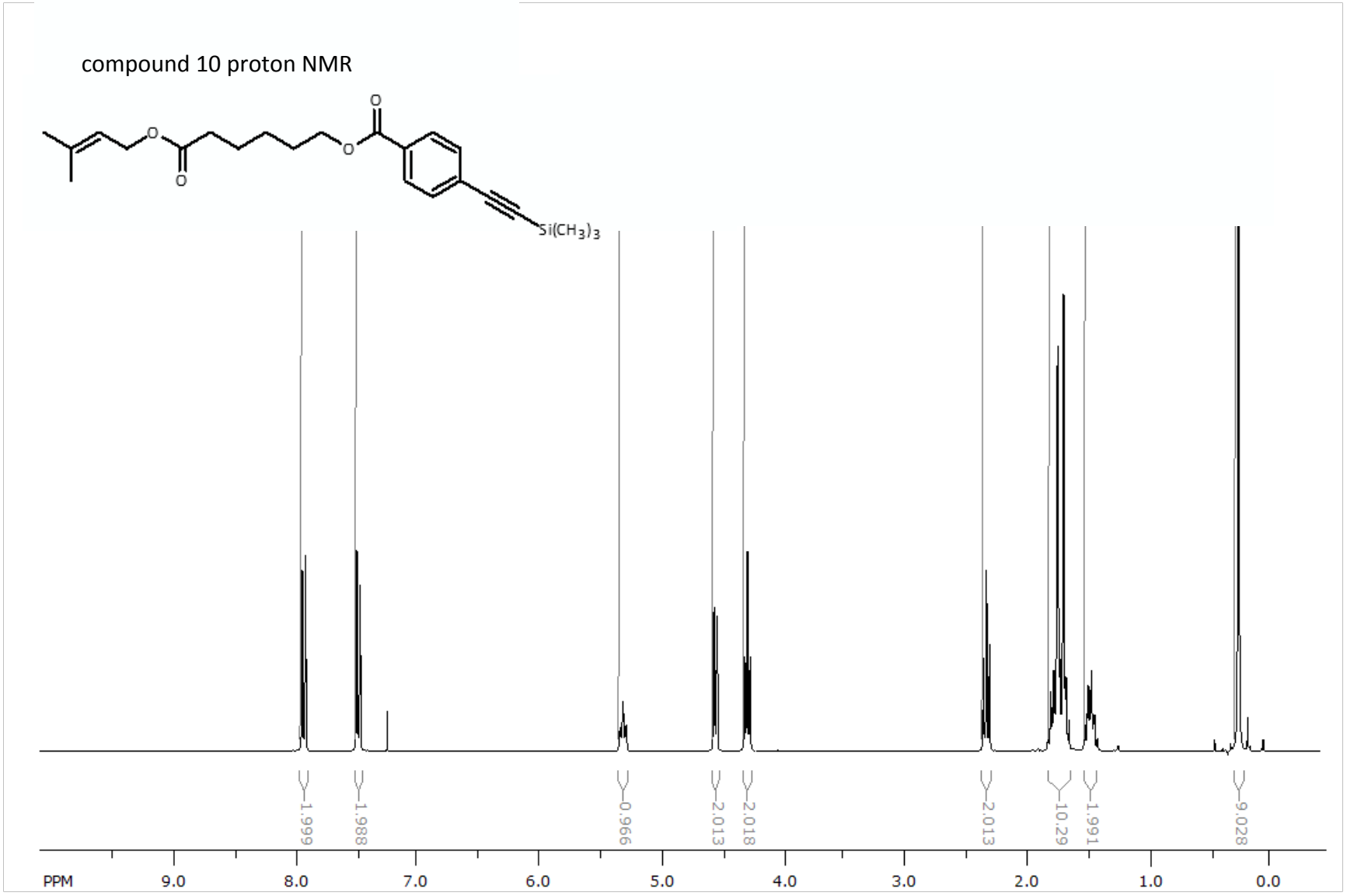

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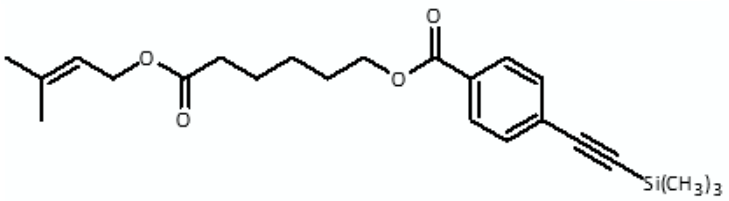
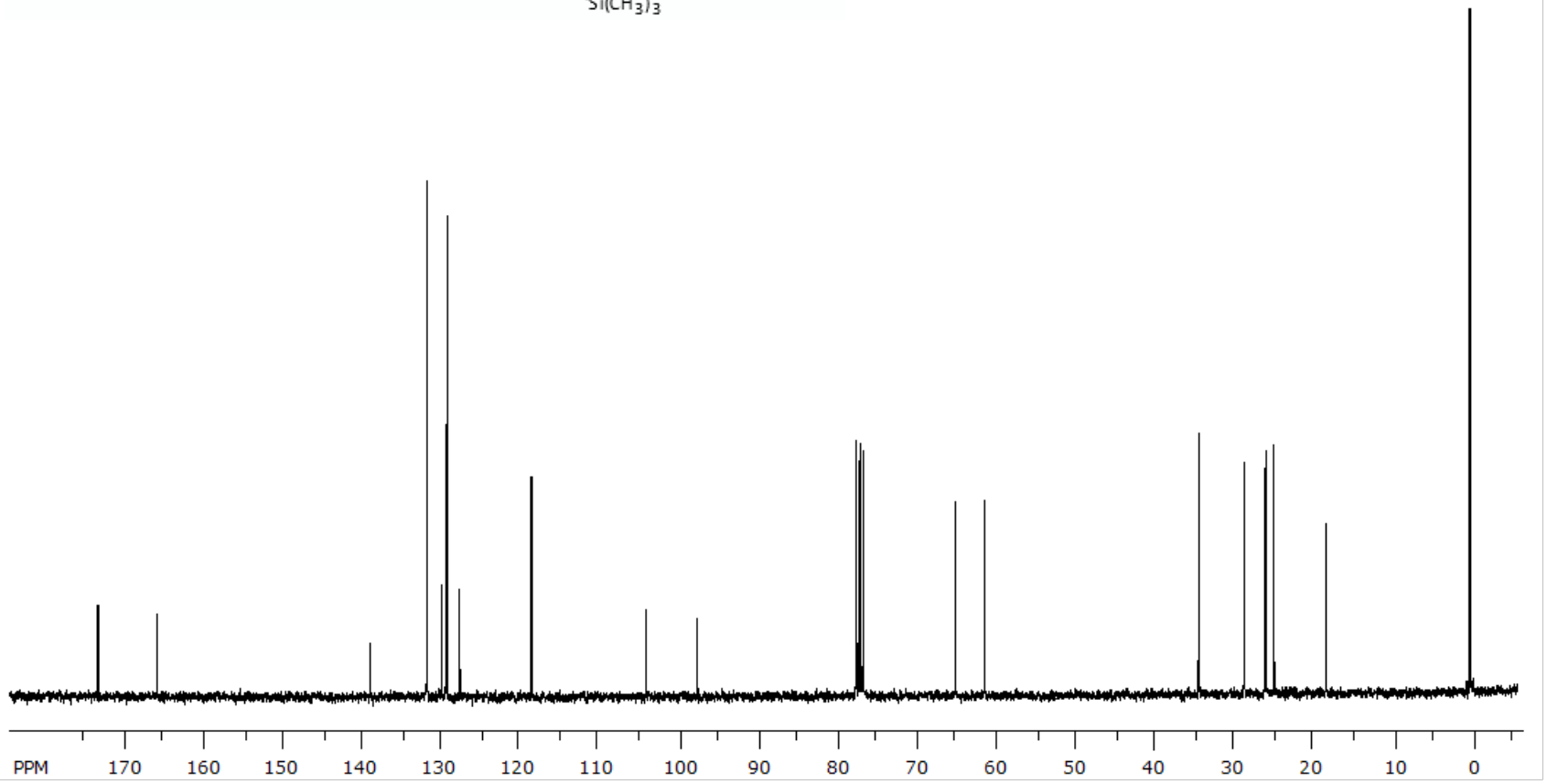
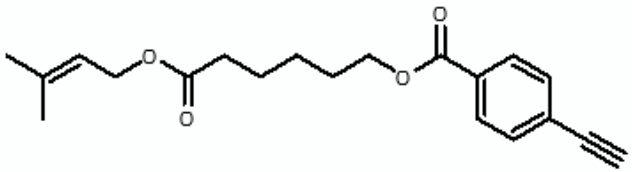
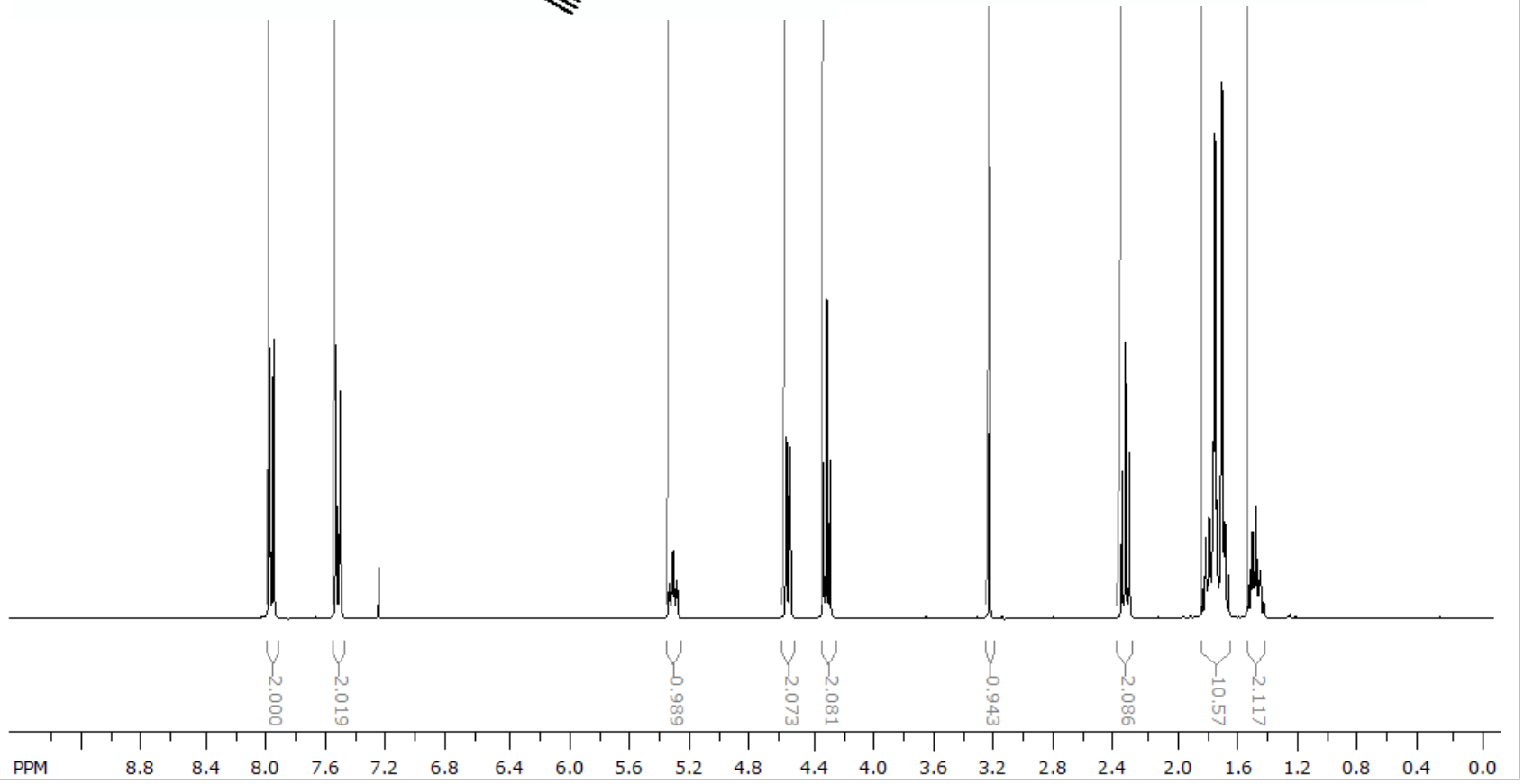


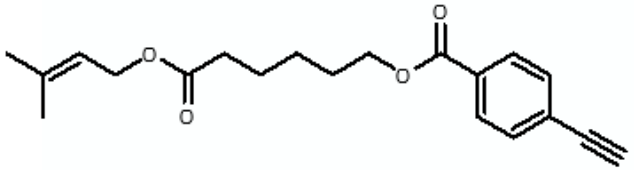


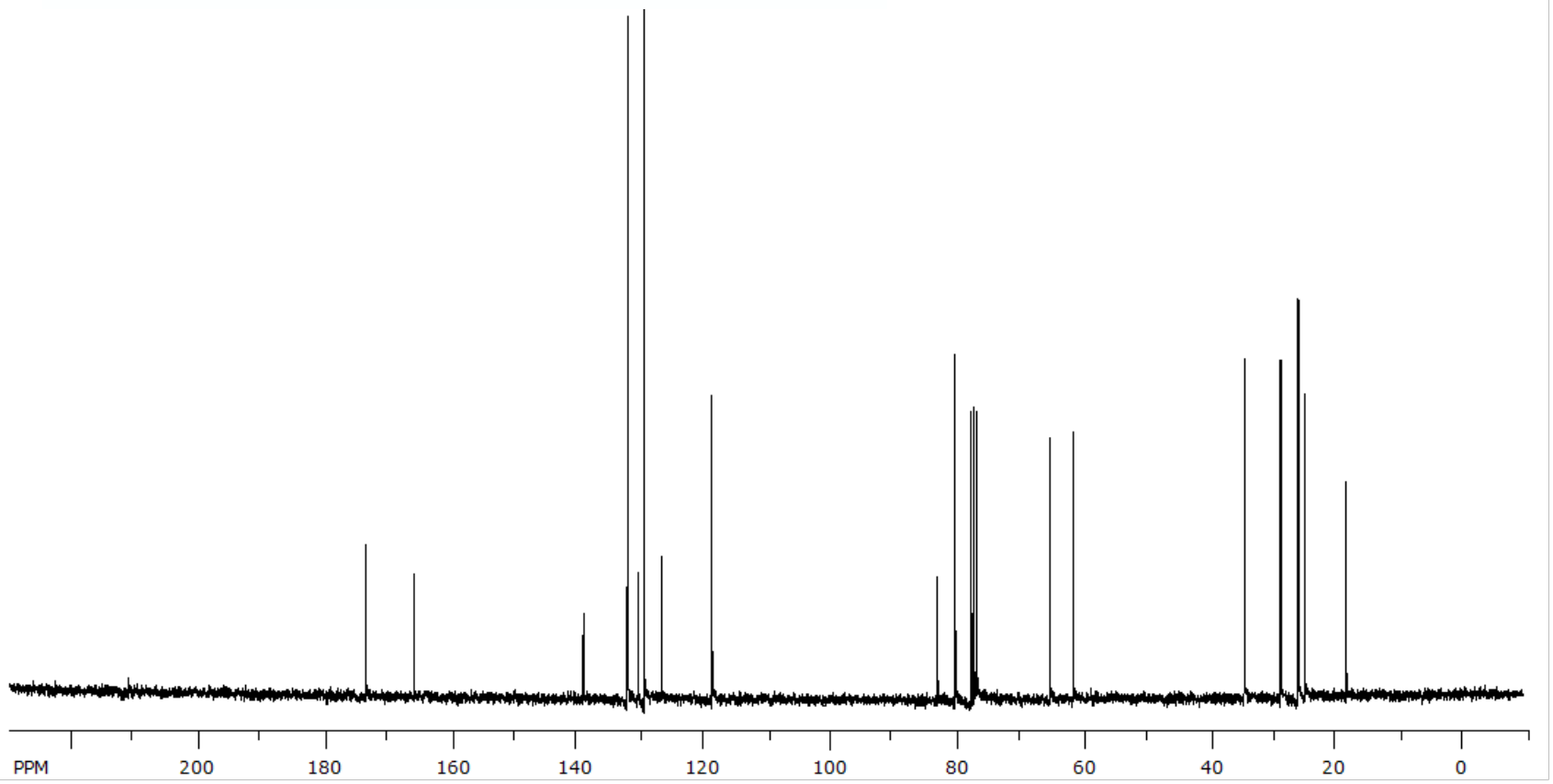
Compound 11 proton NMR

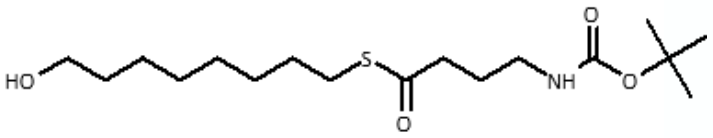




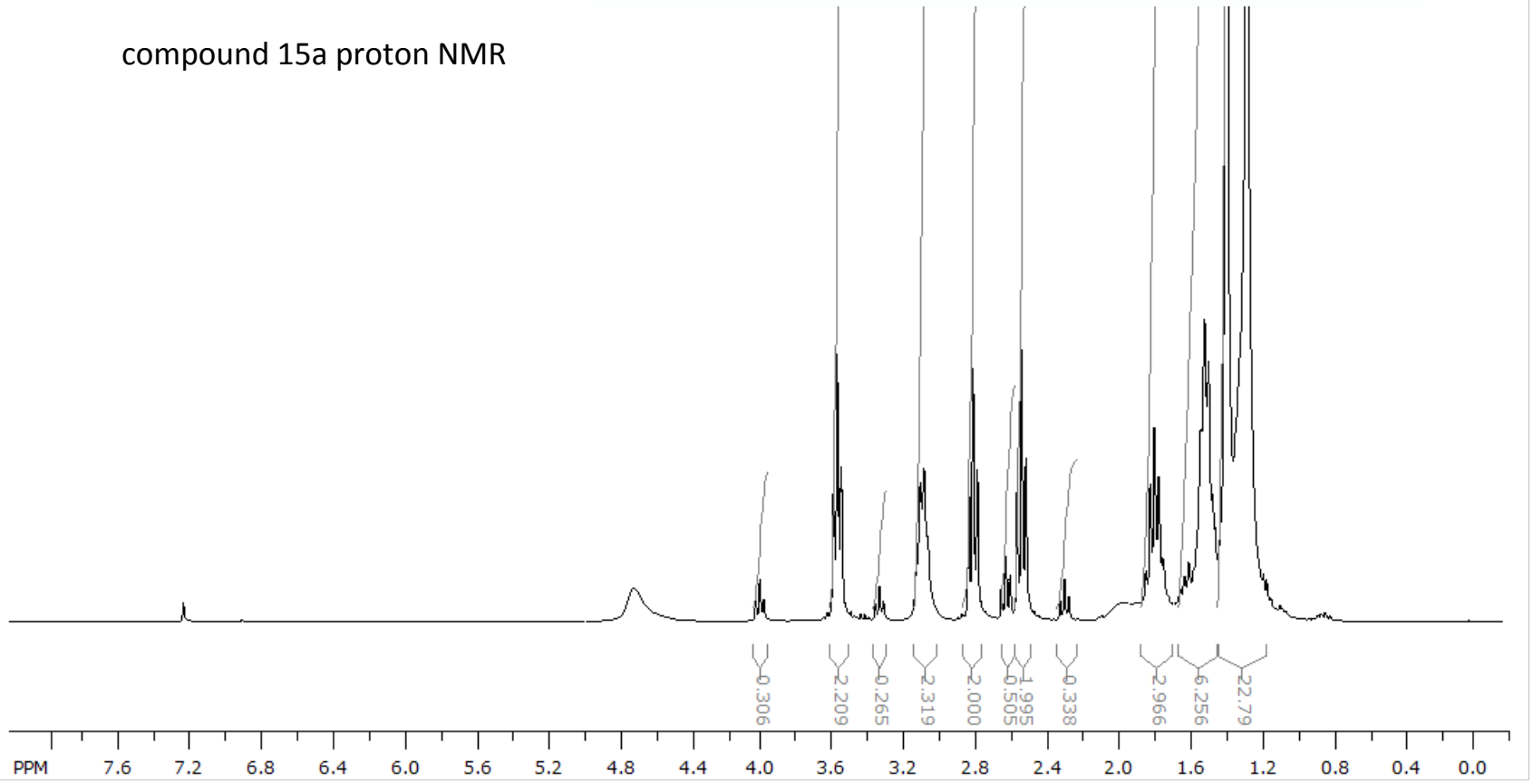
Compound 11 carbon NMR

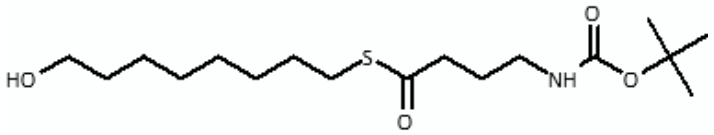




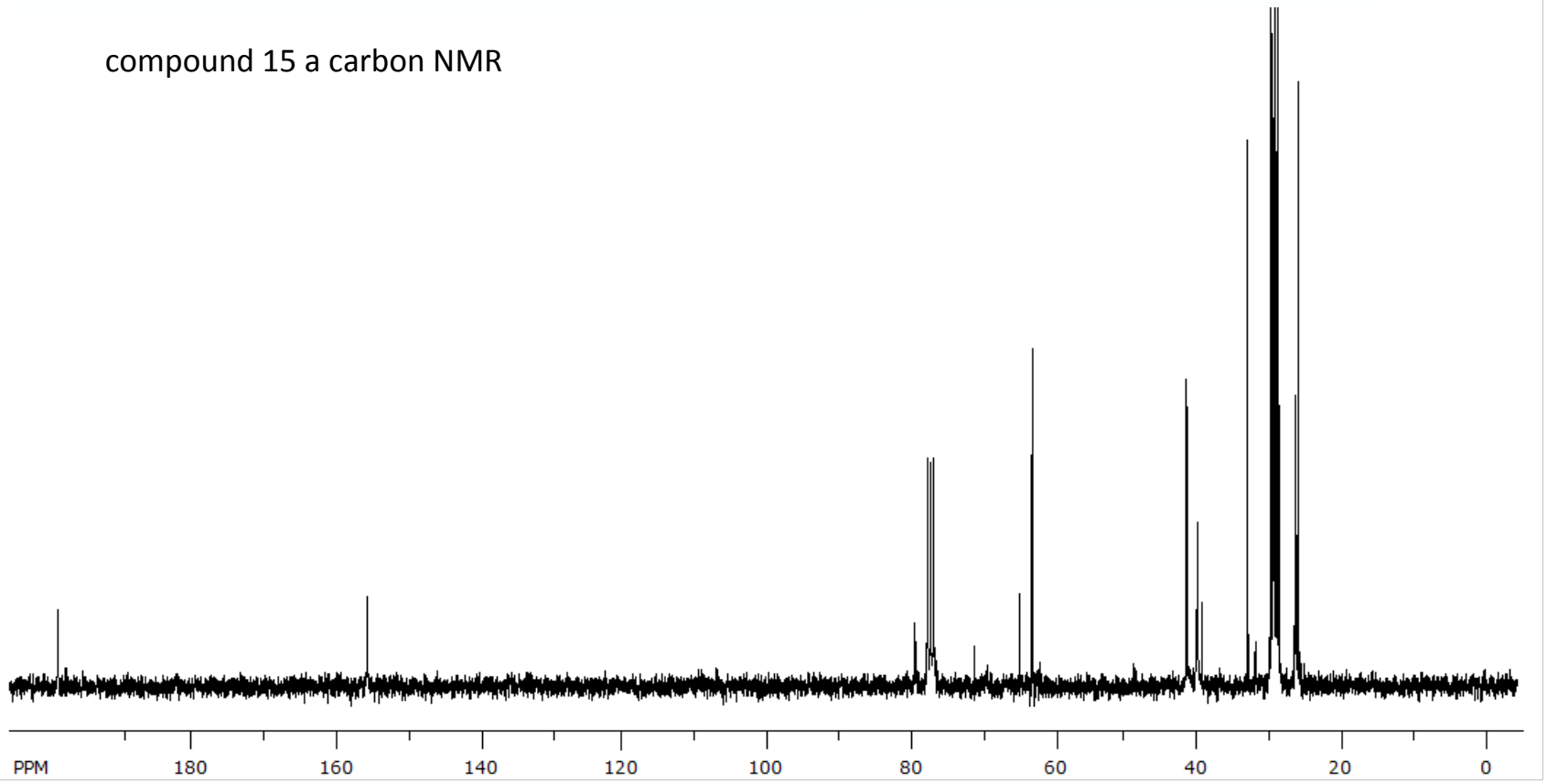


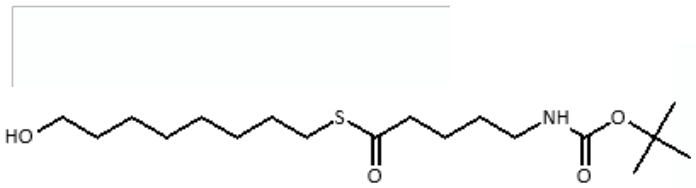
compound 15a proton NMR



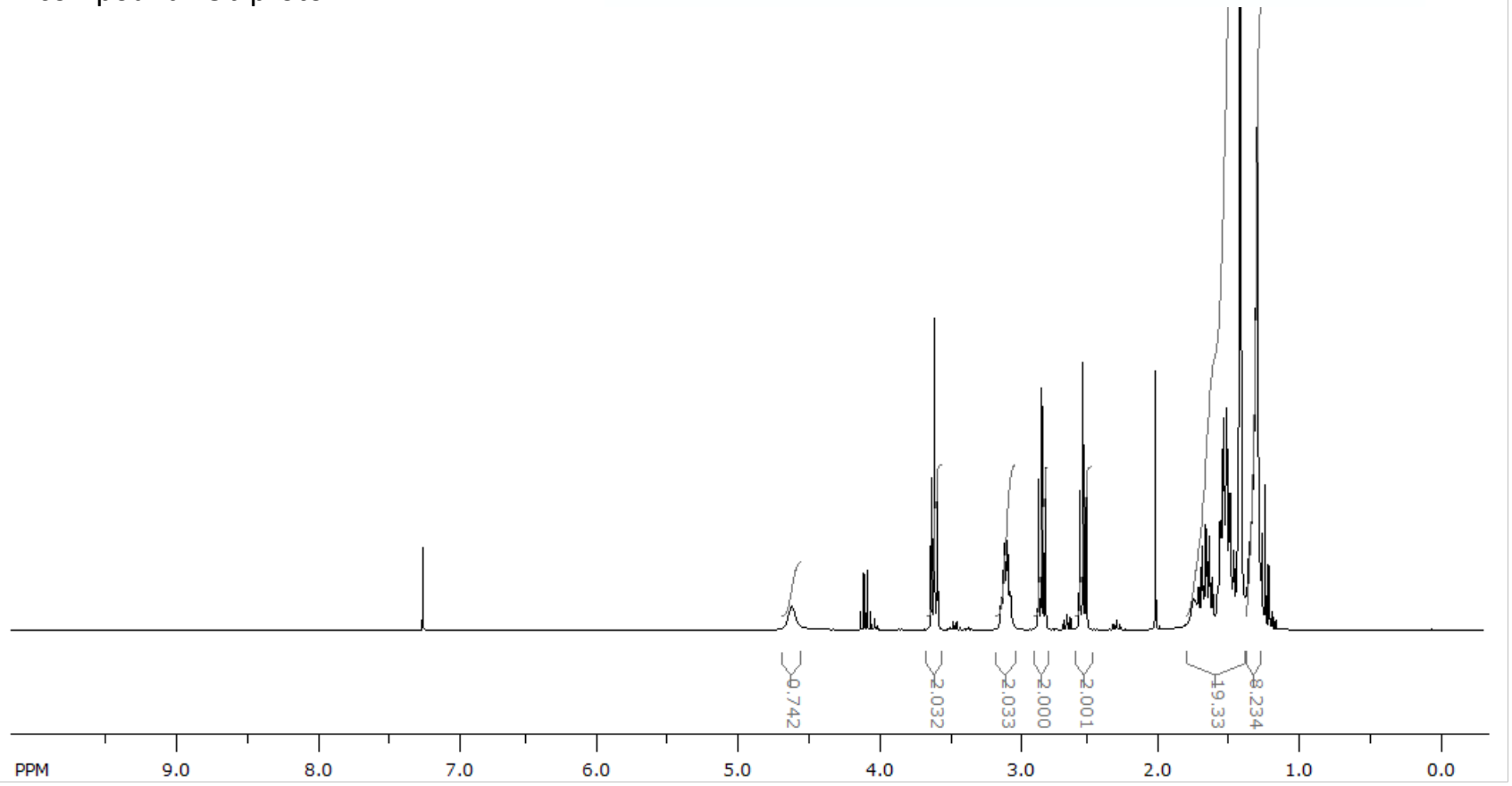


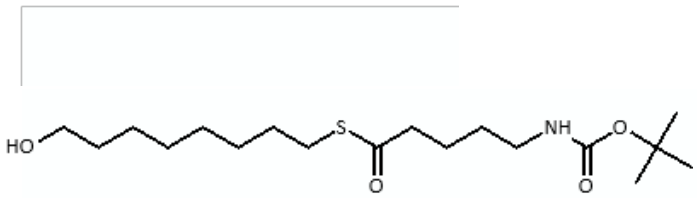
compound 15 a carbon NMR



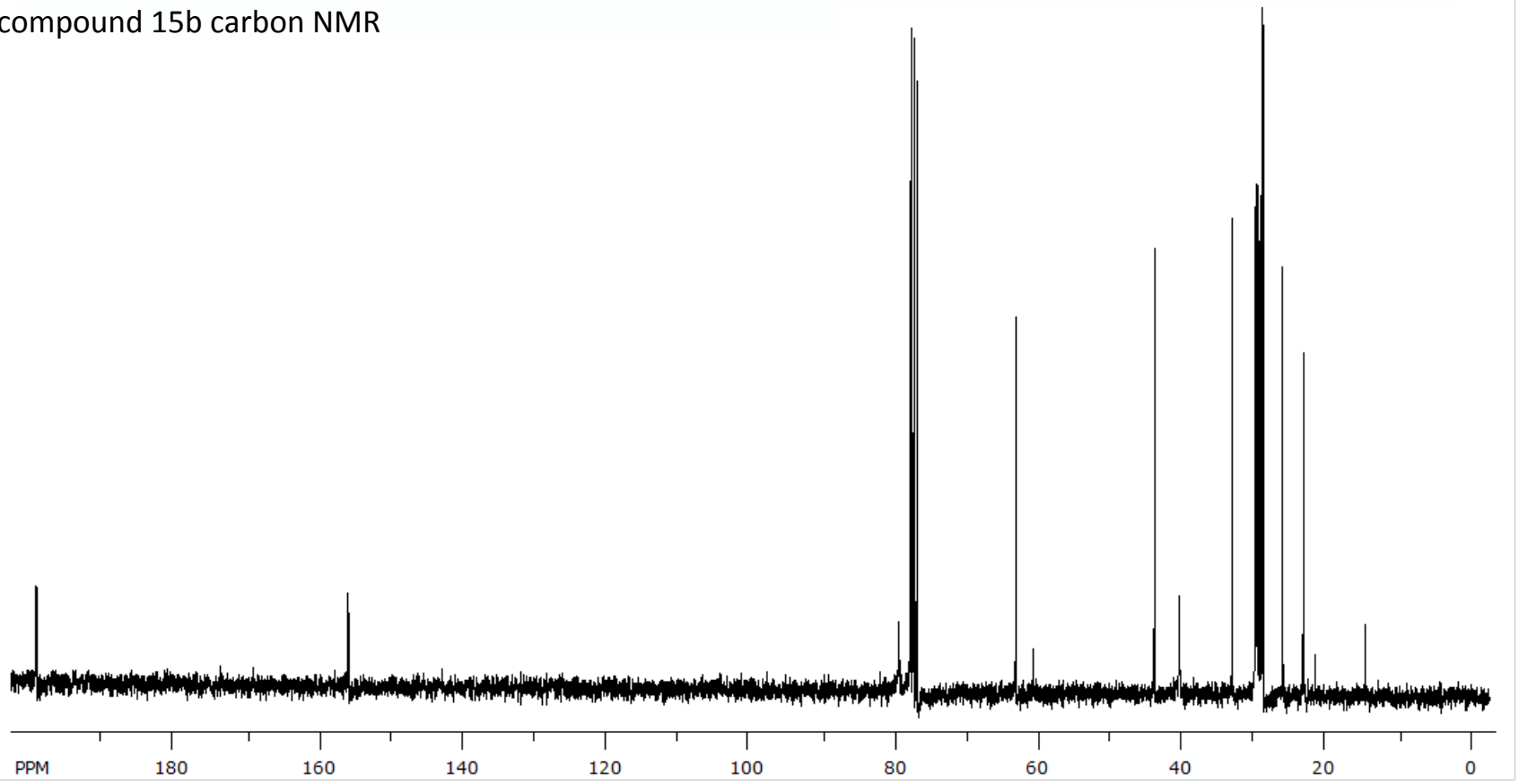


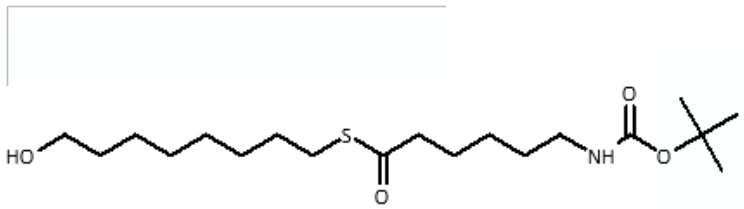
compound 15b proton NMR



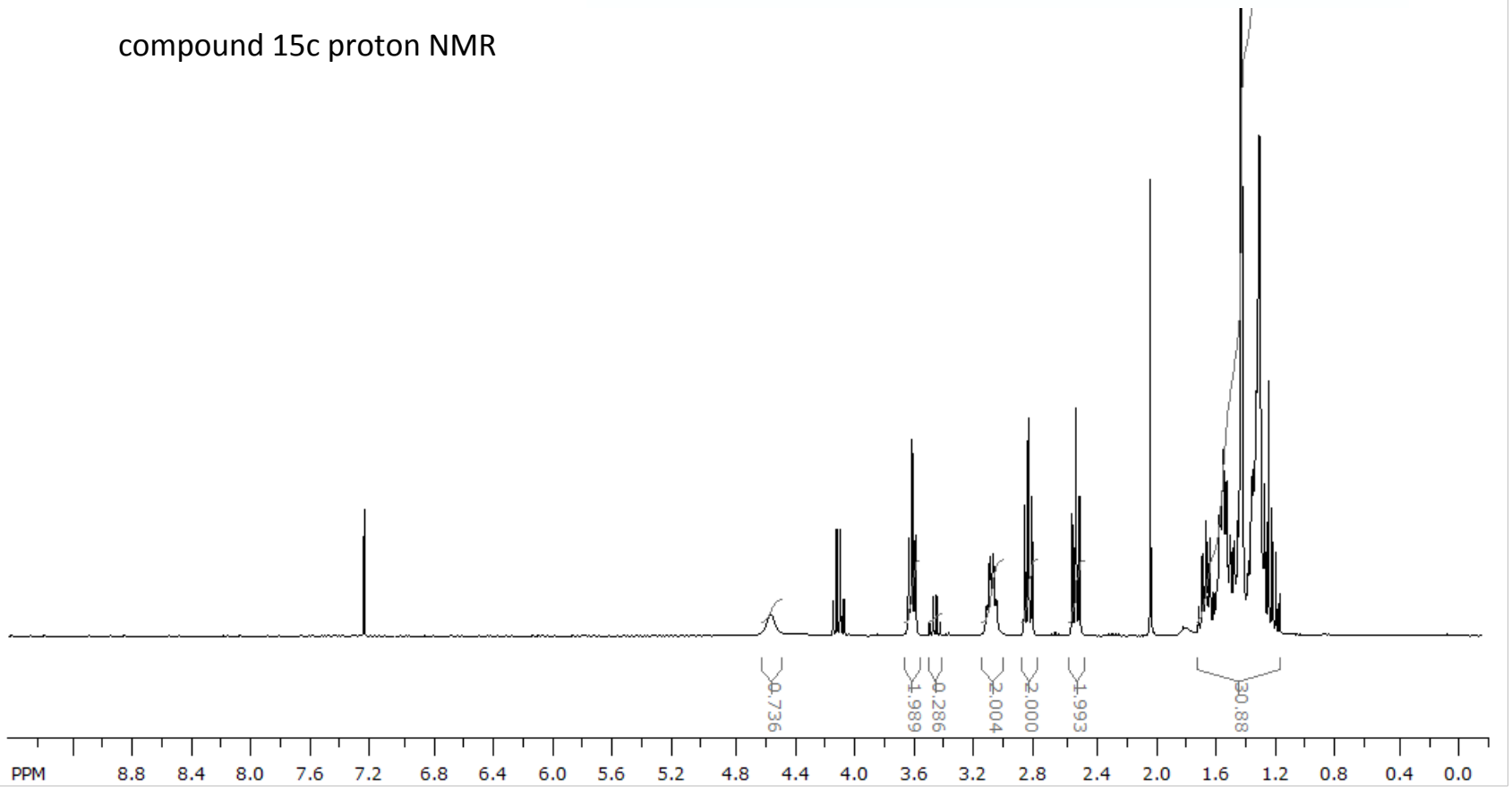


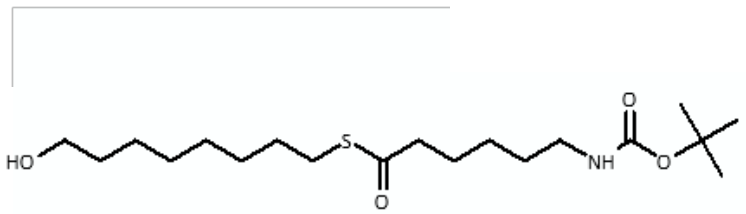
compound 15b carbon NMR



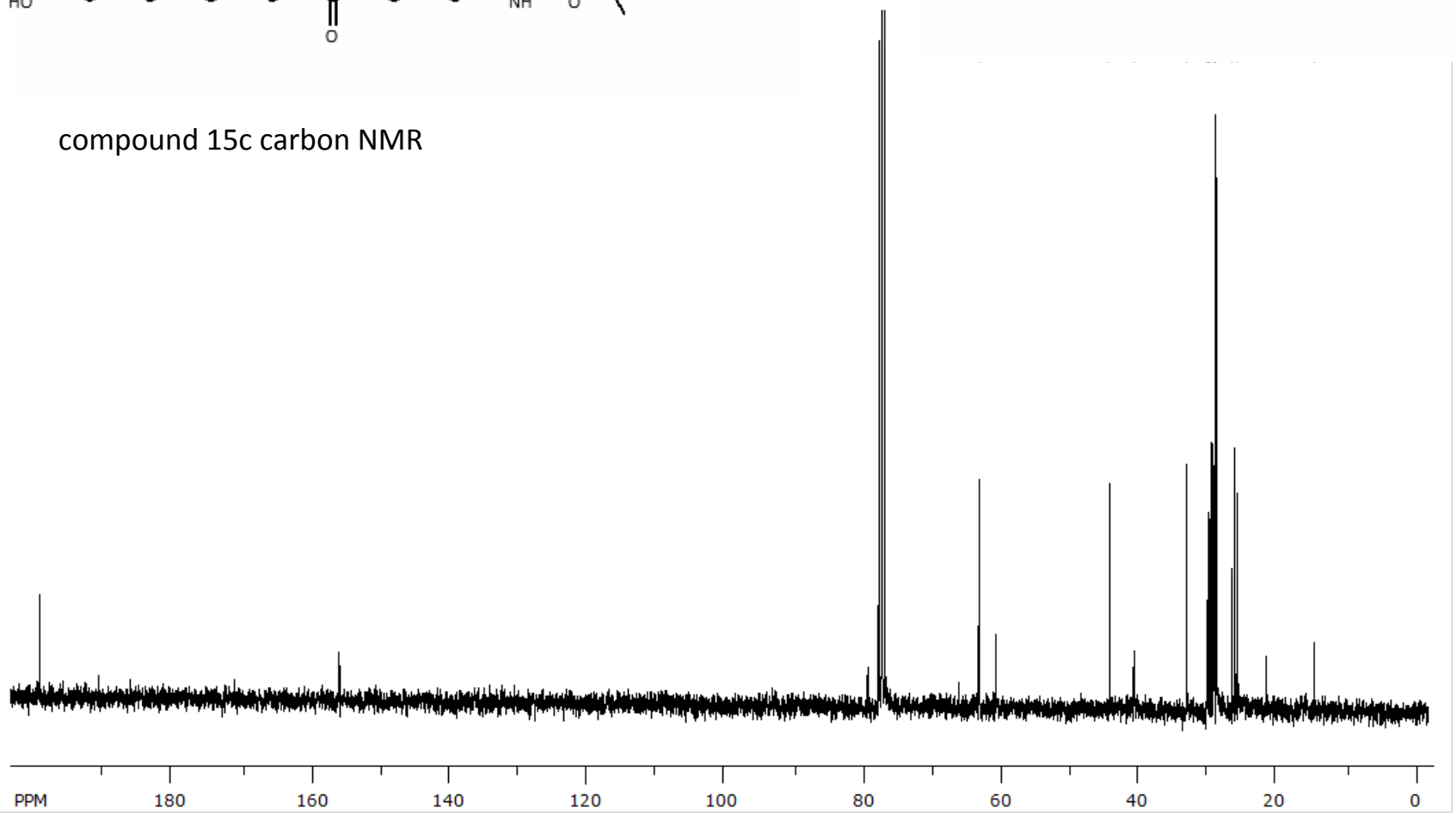


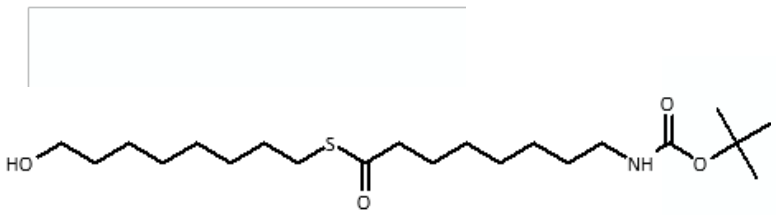
compound 15c proton NMR



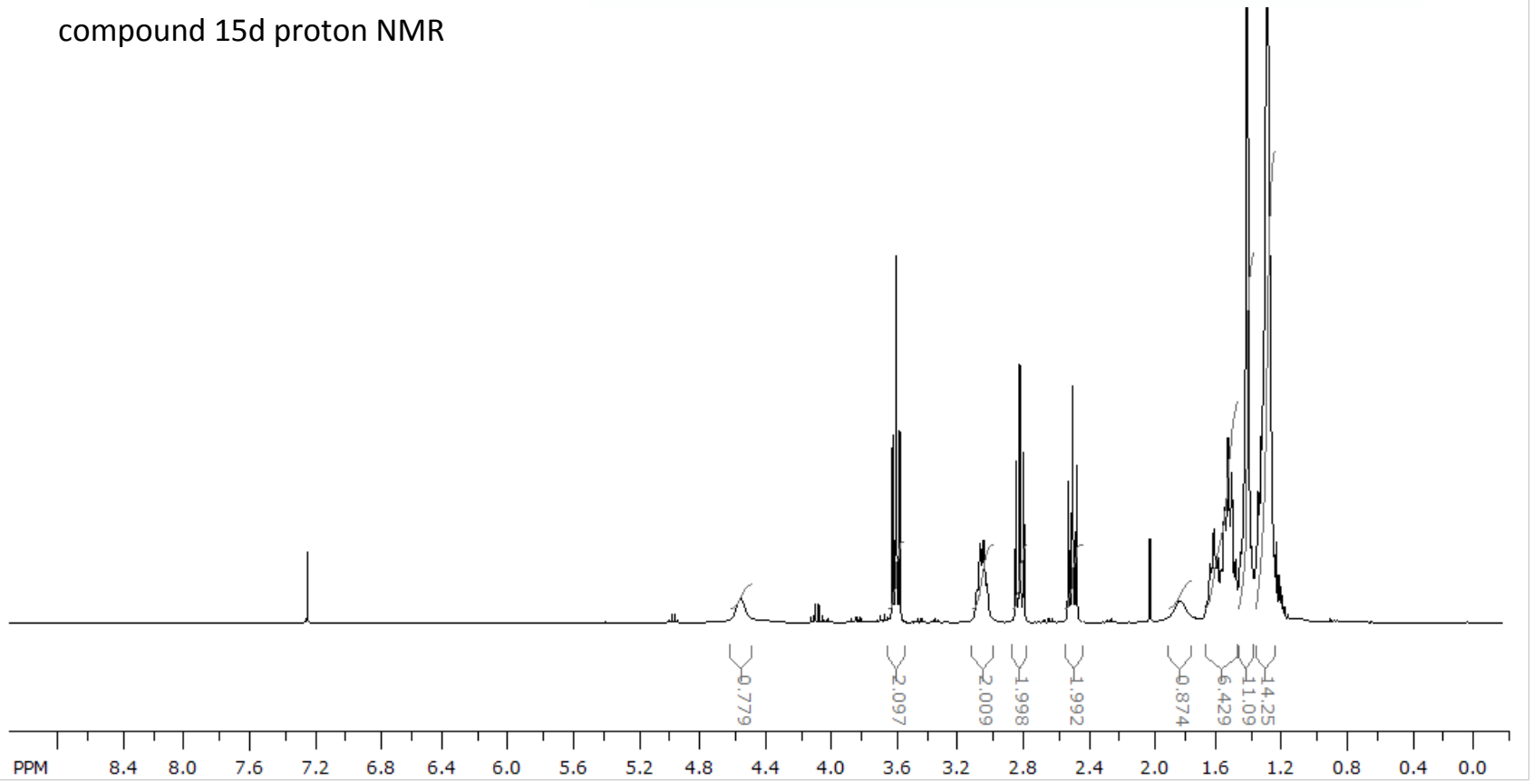


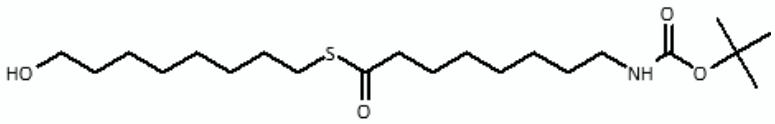
compound 15c carbon NMR



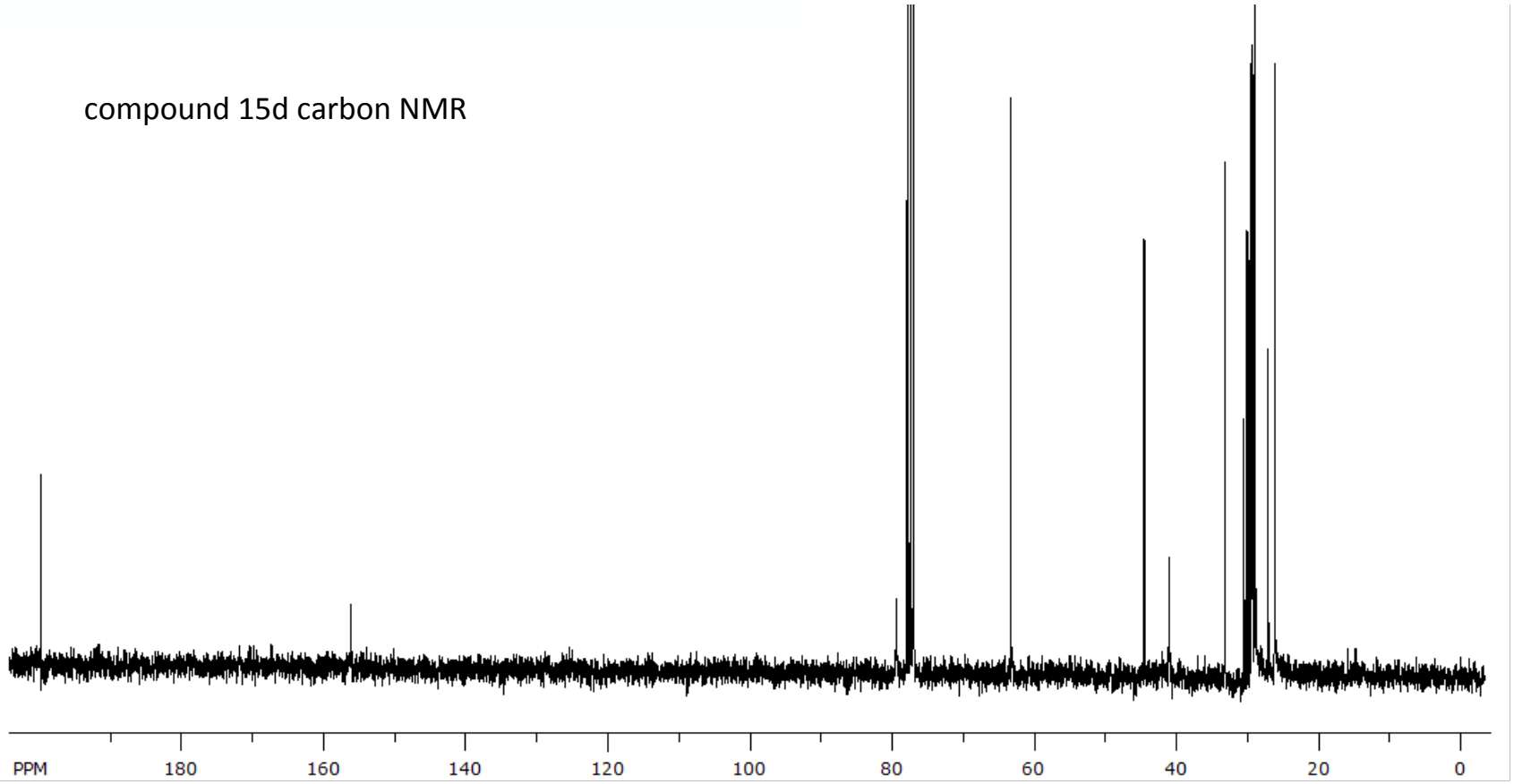


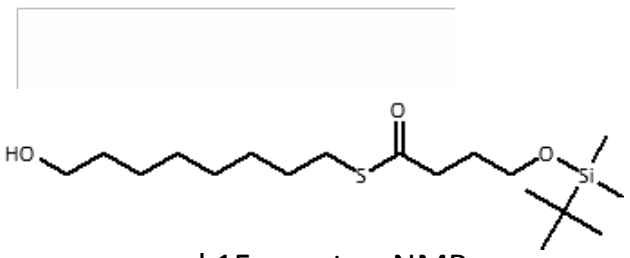
compound 15d proton NMR



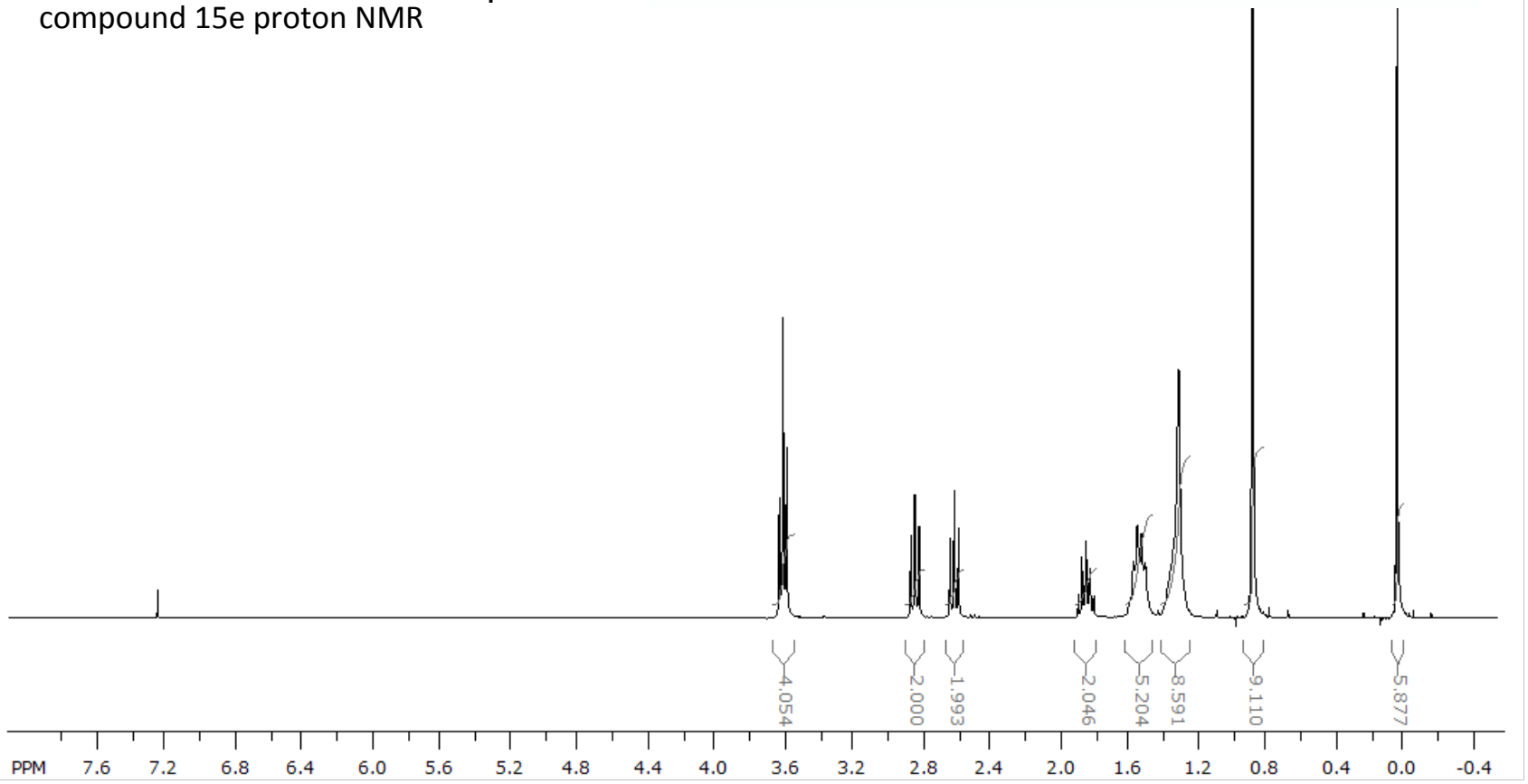


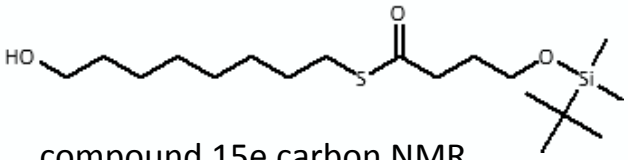
compound 15d carbon NMR



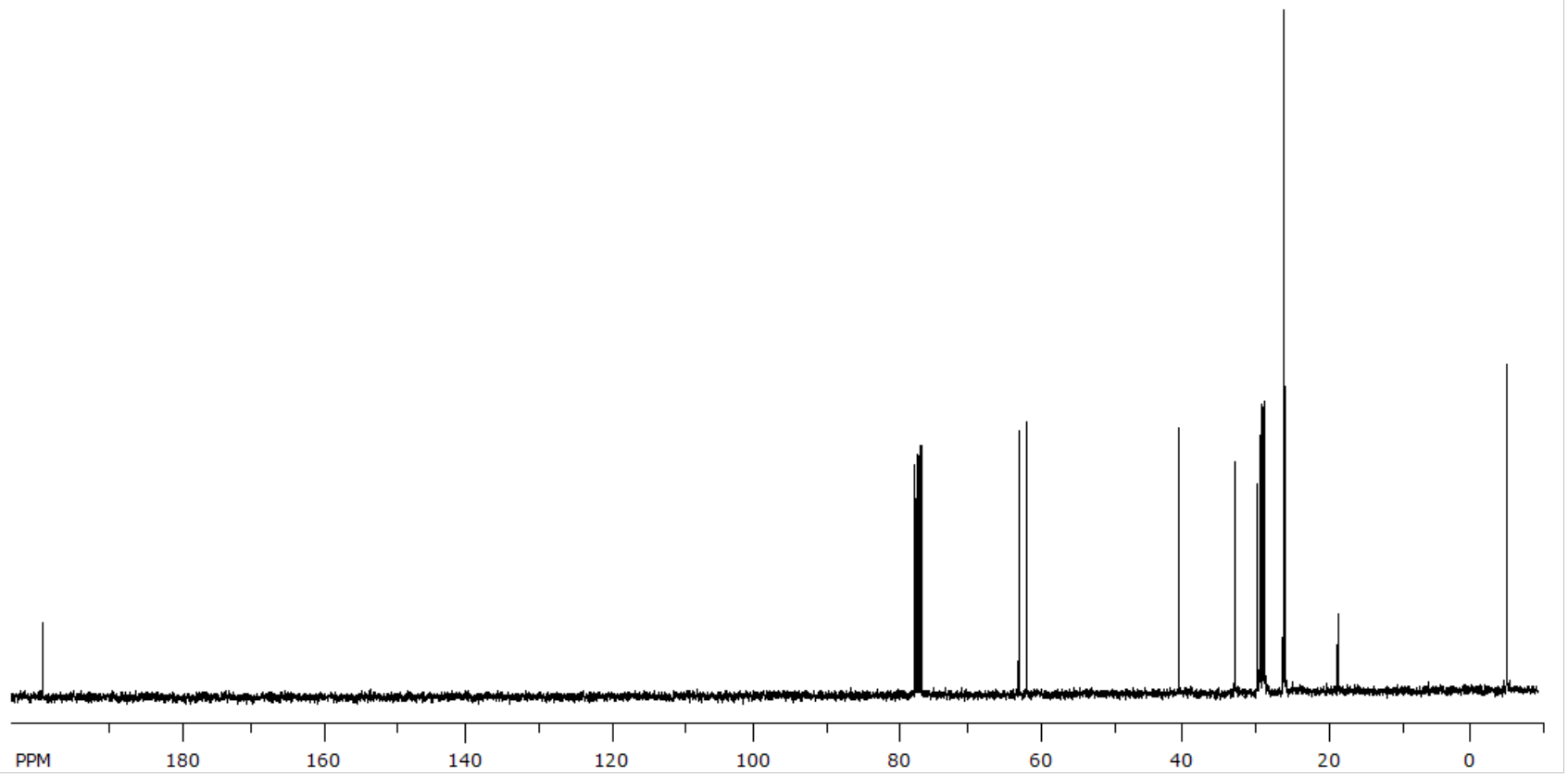


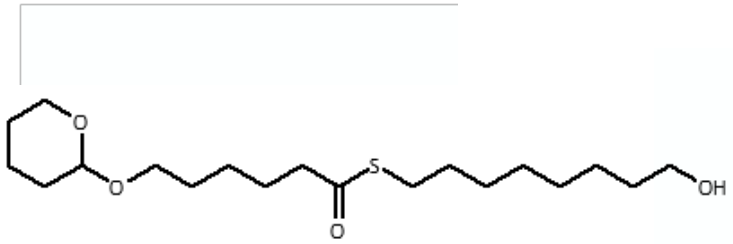
compound 15e proton NMR



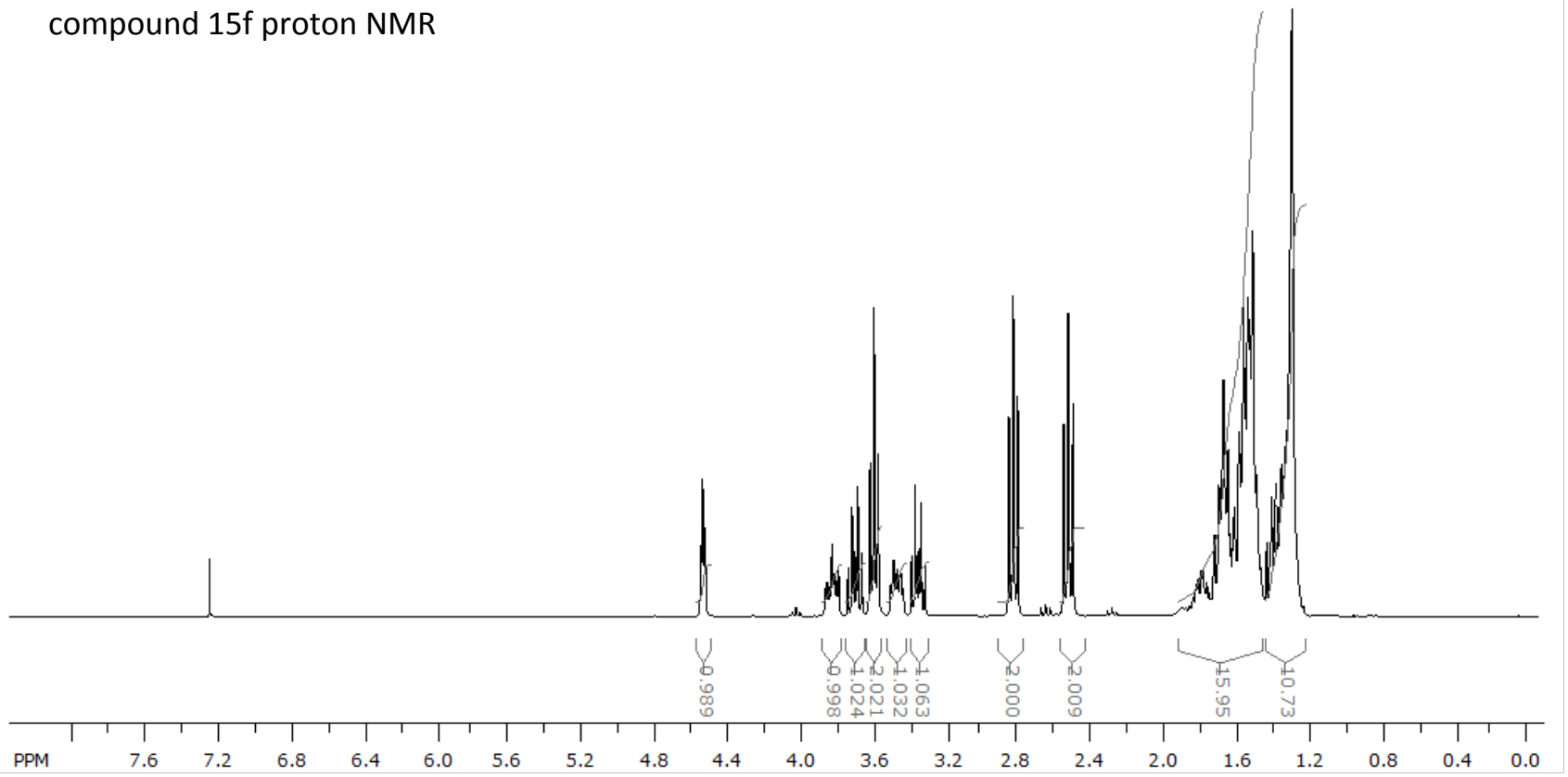


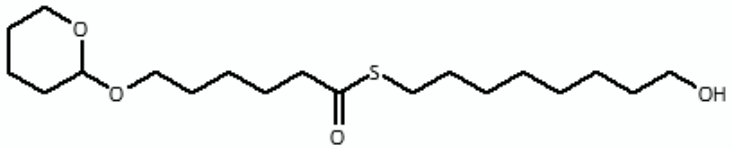
compound 15e carbon NMR



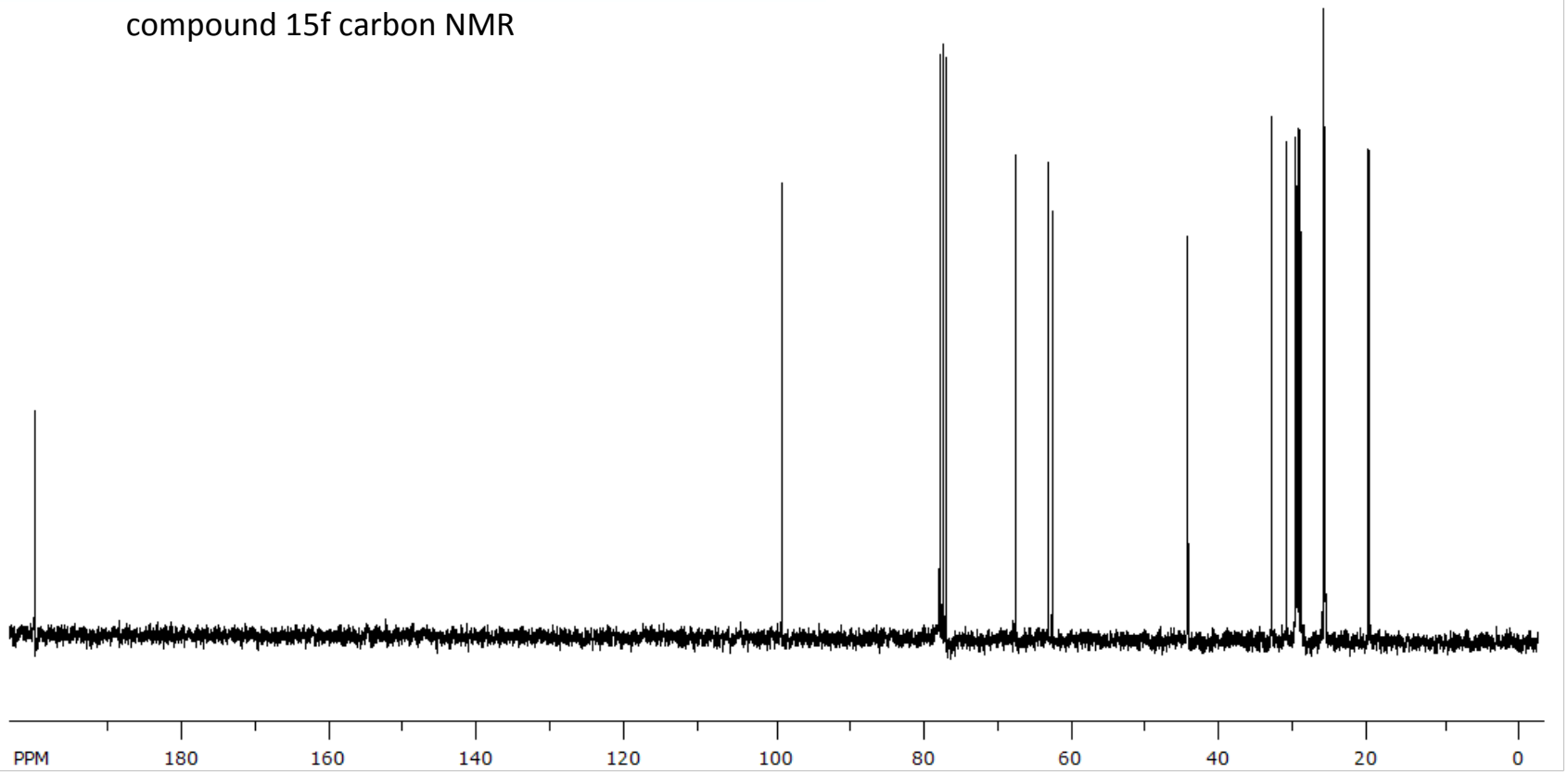


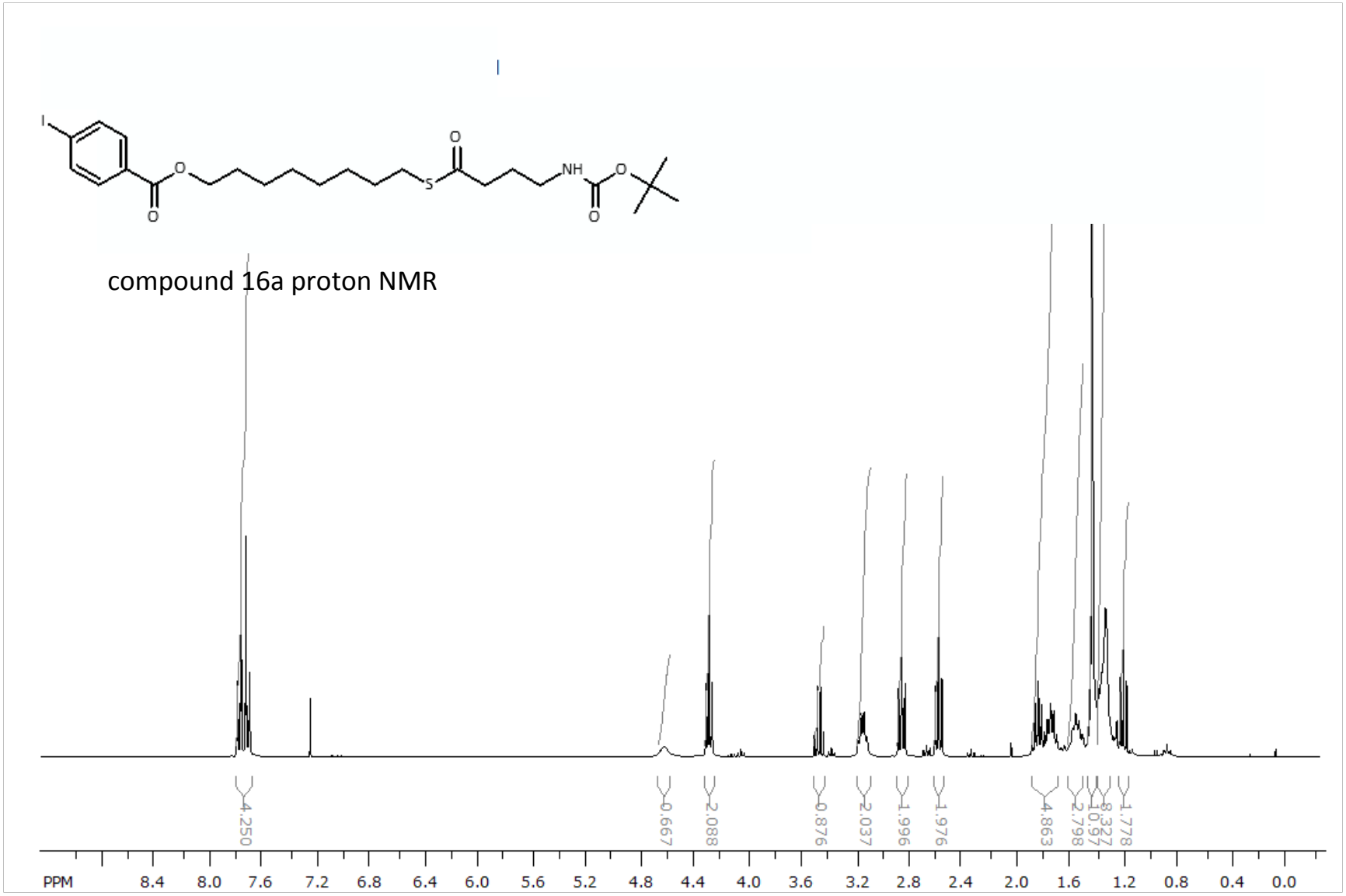
compound 15f proton NMR

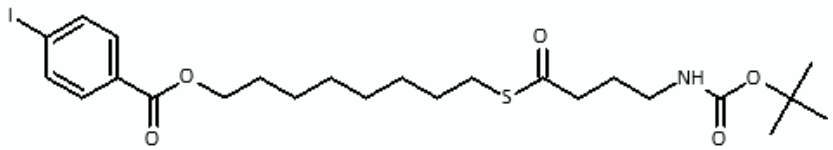




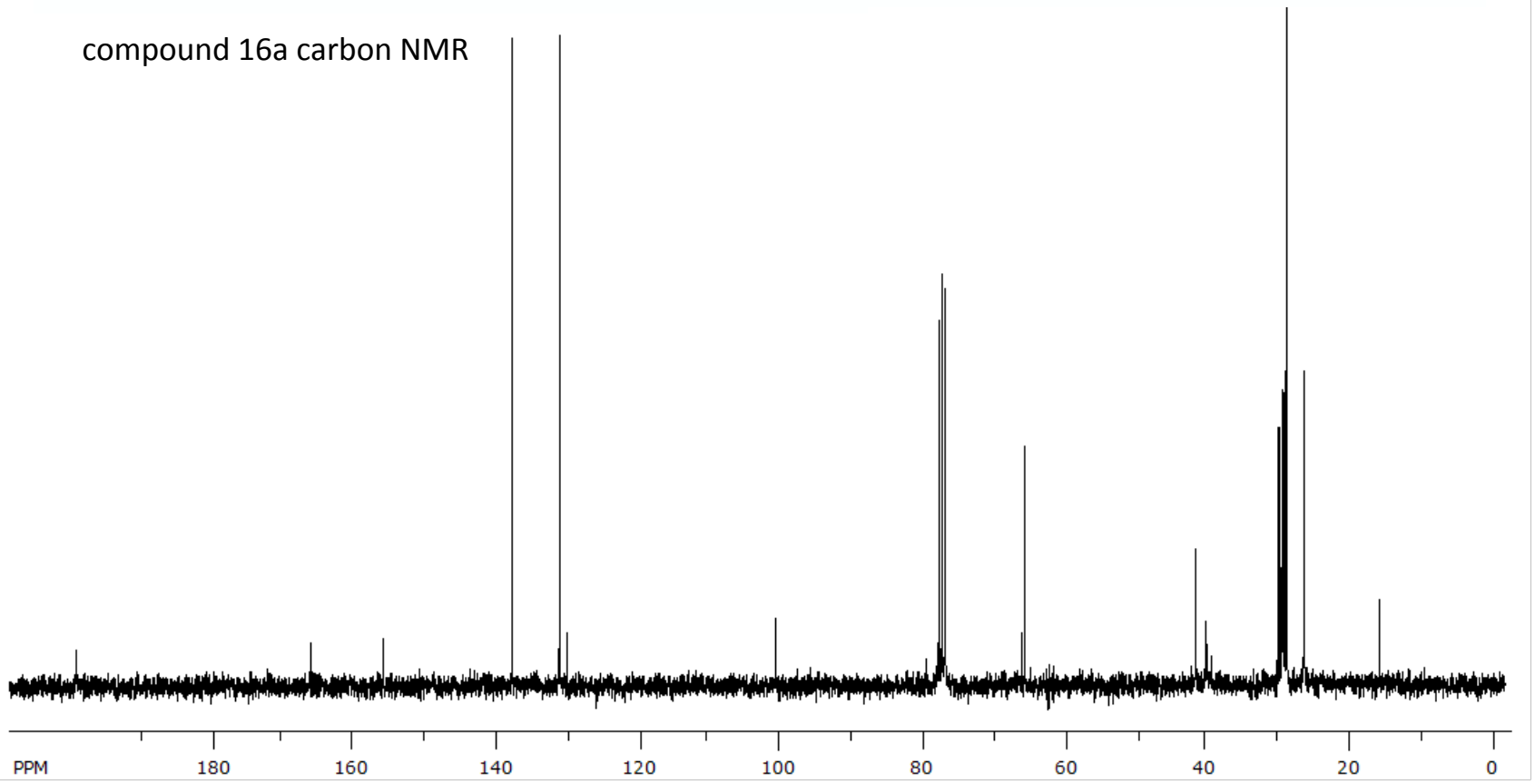
compound 15f carbon NMR

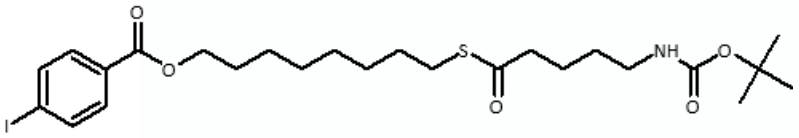



I
O
O
S
O
NH
O
O
compound 16a proton NMR
4.250
0.667
2.088
0.876
2.037
1.996
1.976
4.863
2.798
10.97
8.327
1.778
PPM
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0

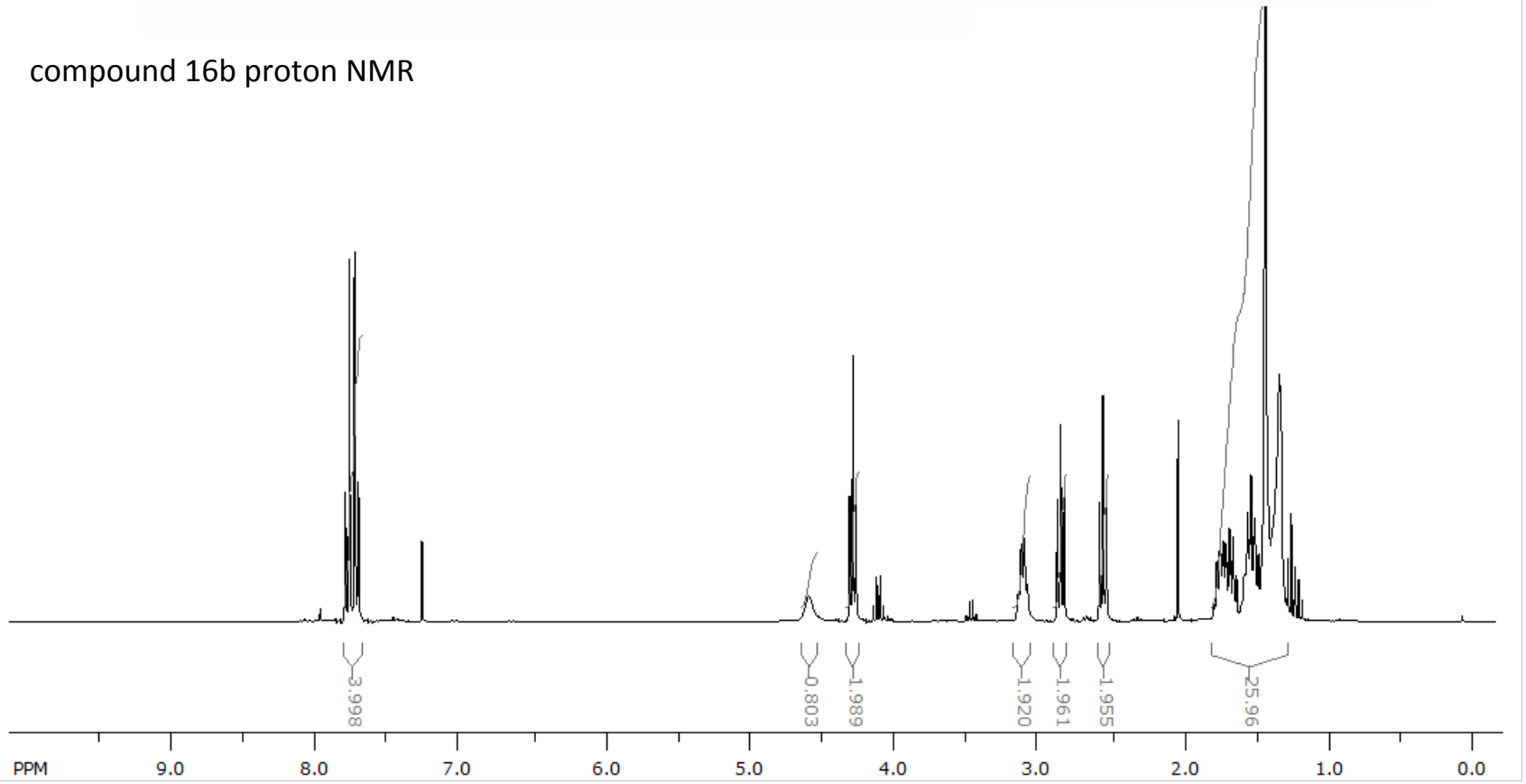


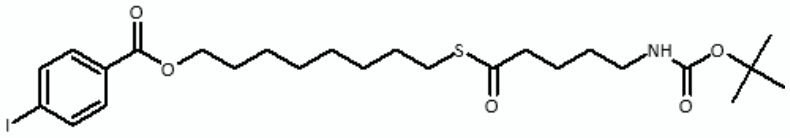
compound 16a carbon NMR



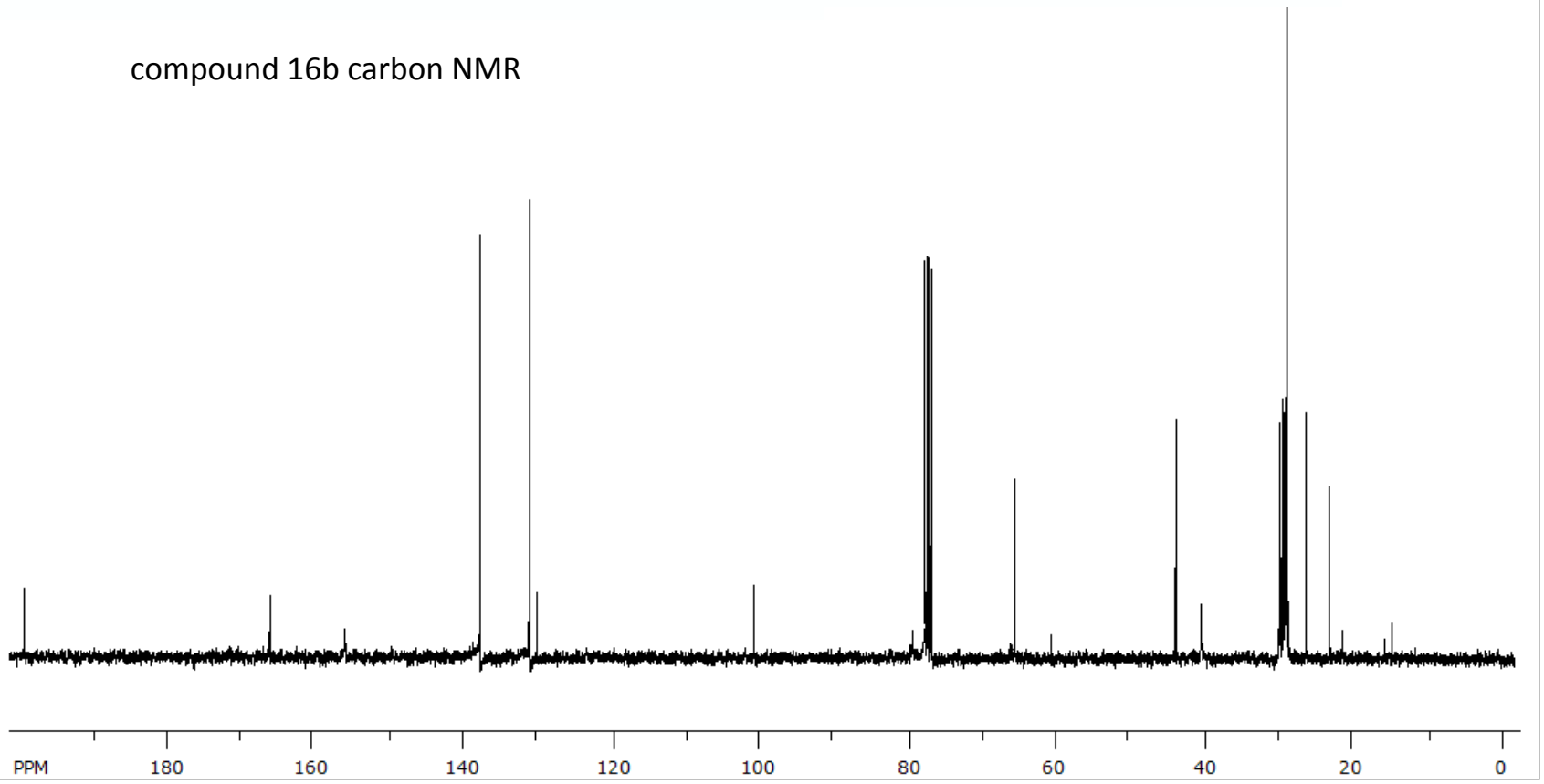


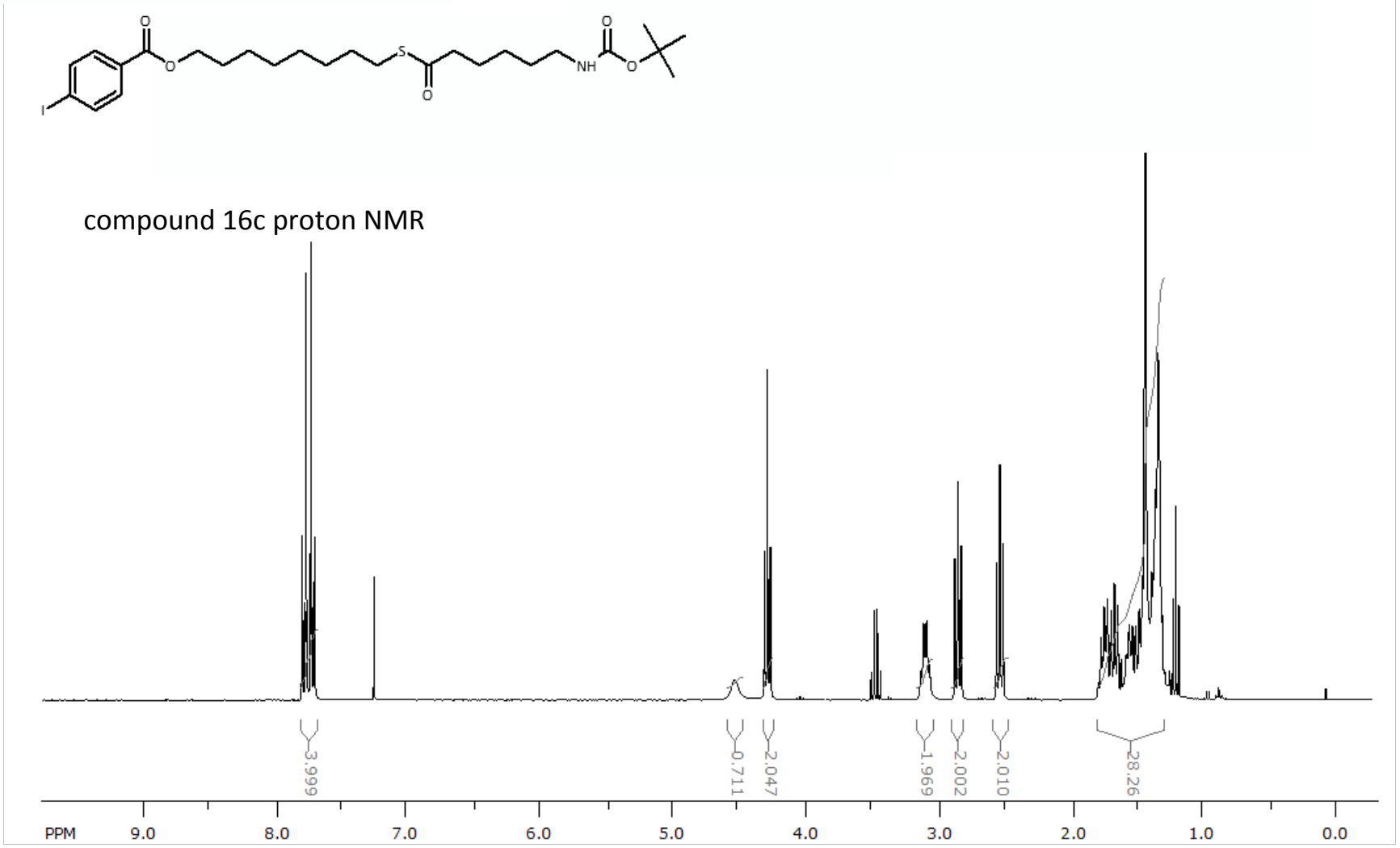
compound 16b proton NMR

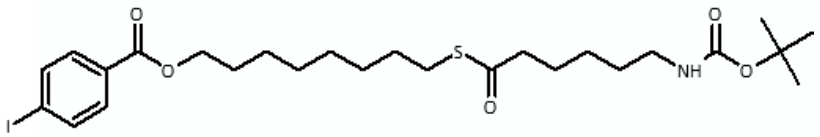




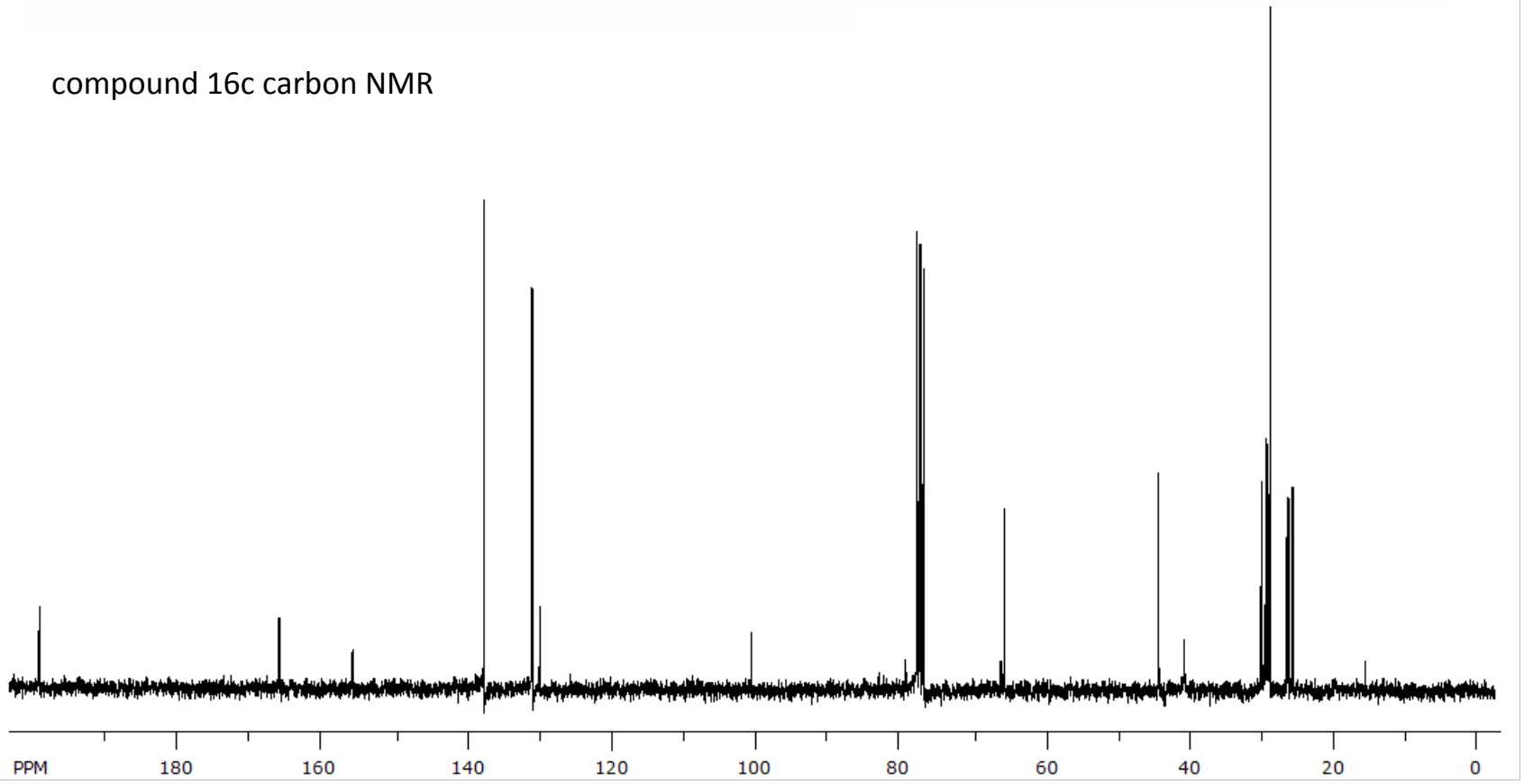
compound 16b carbon NMR

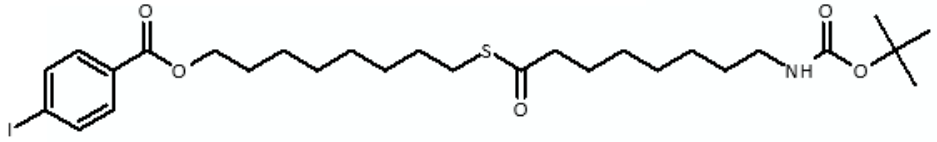



compound 16c proton NMR
3.999
0.711
2.047
1.969
2.002
2.010
28.26
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

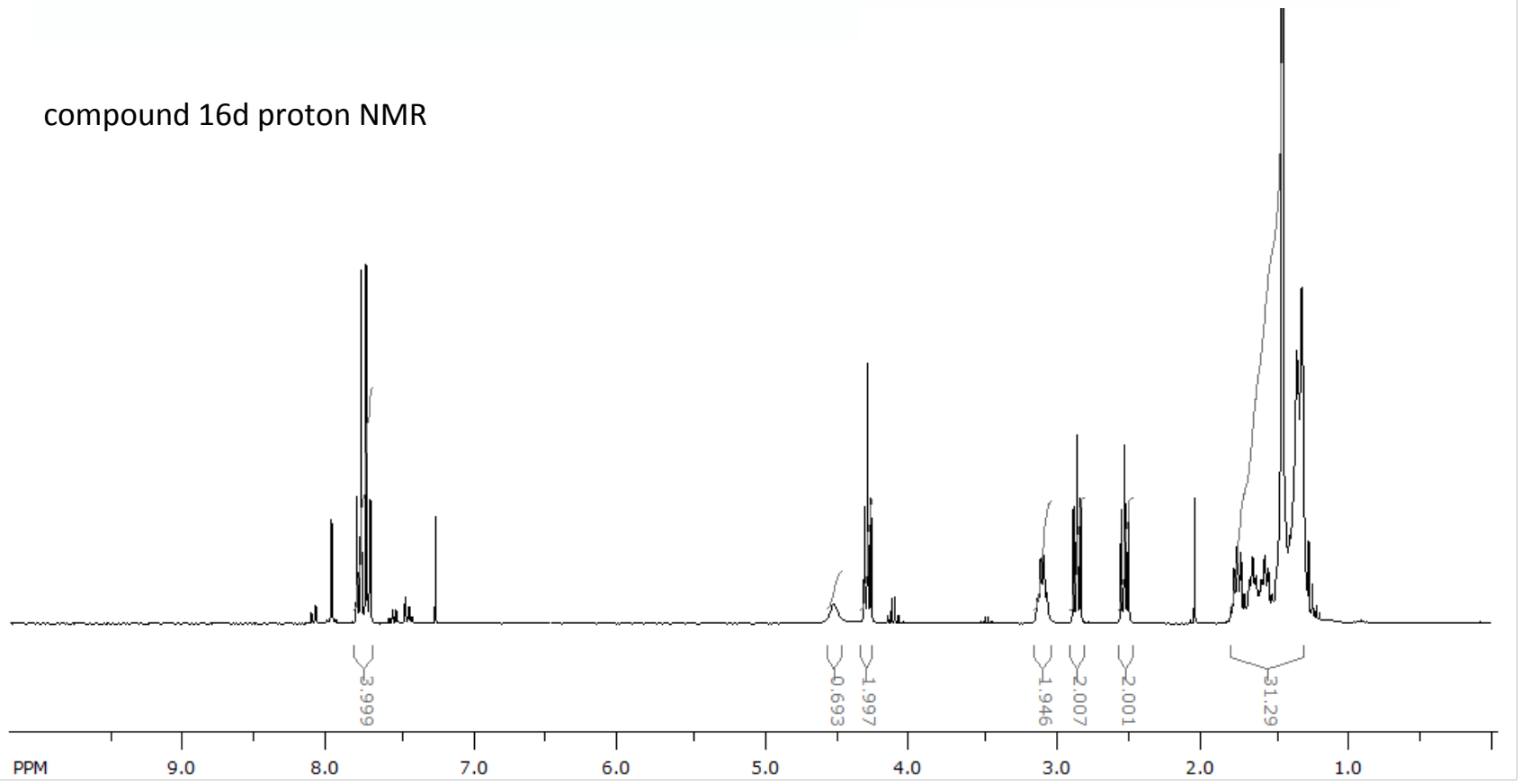


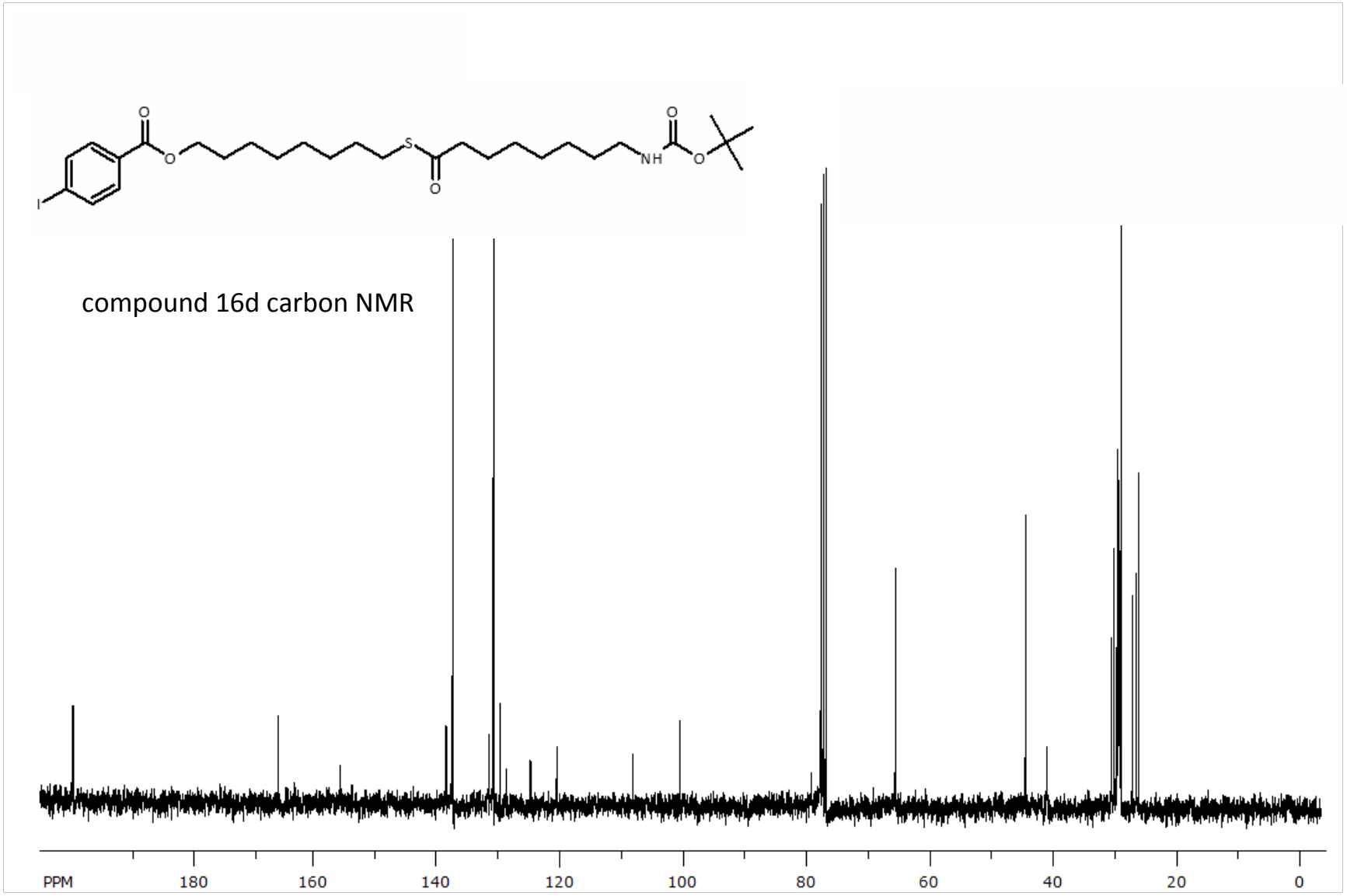
compound 16c carbon NMR

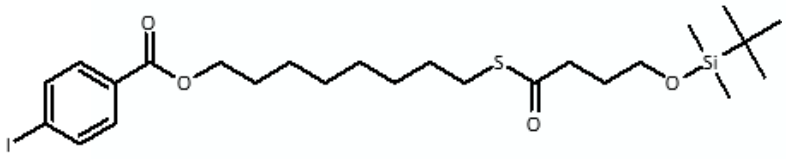




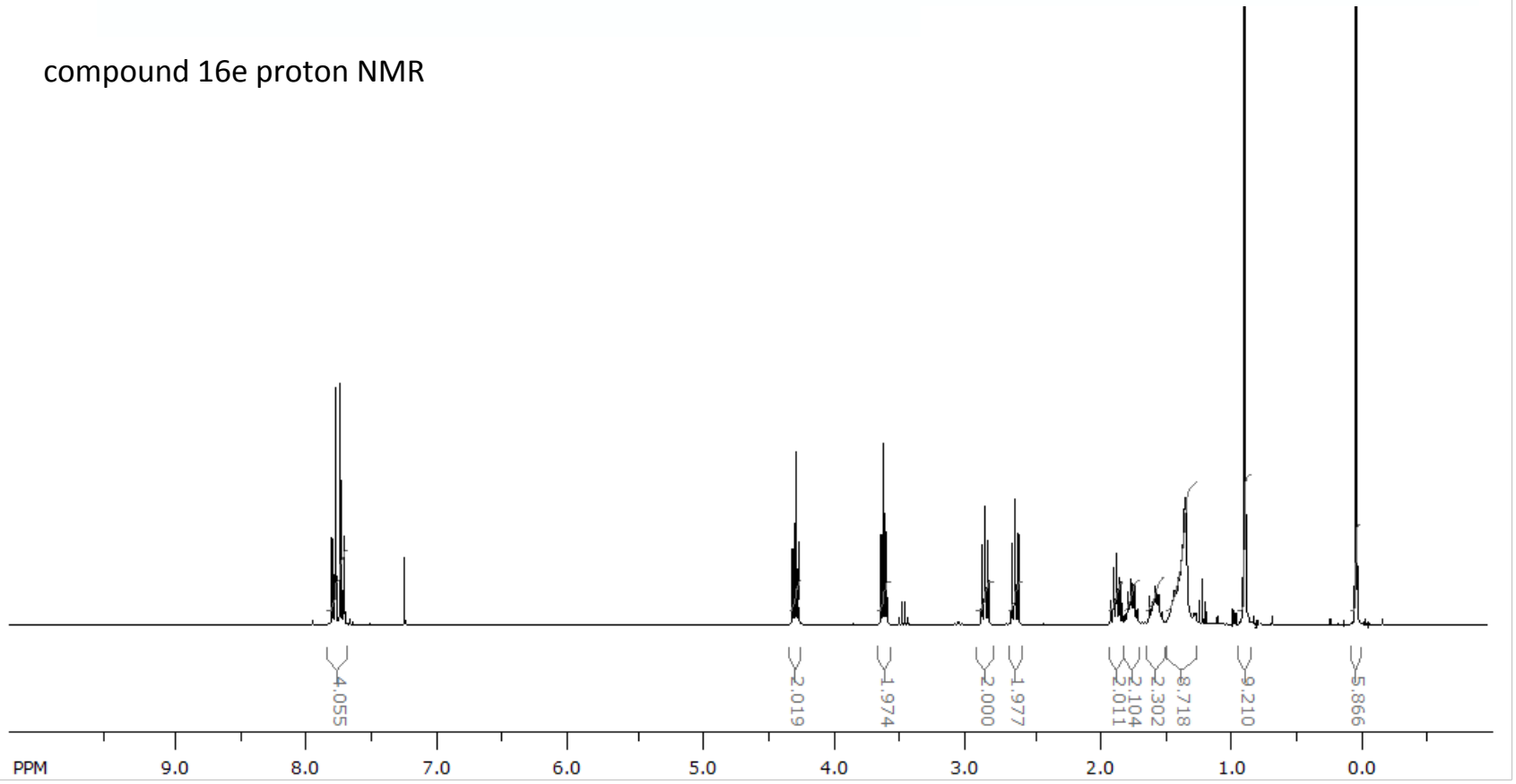
compound 16d proton NMR

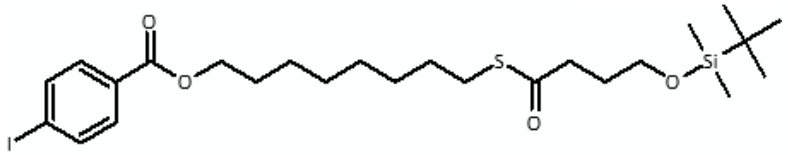



compound 16d carbon NMR
PPM
180
160
140
120
100
80
60
40
20
0

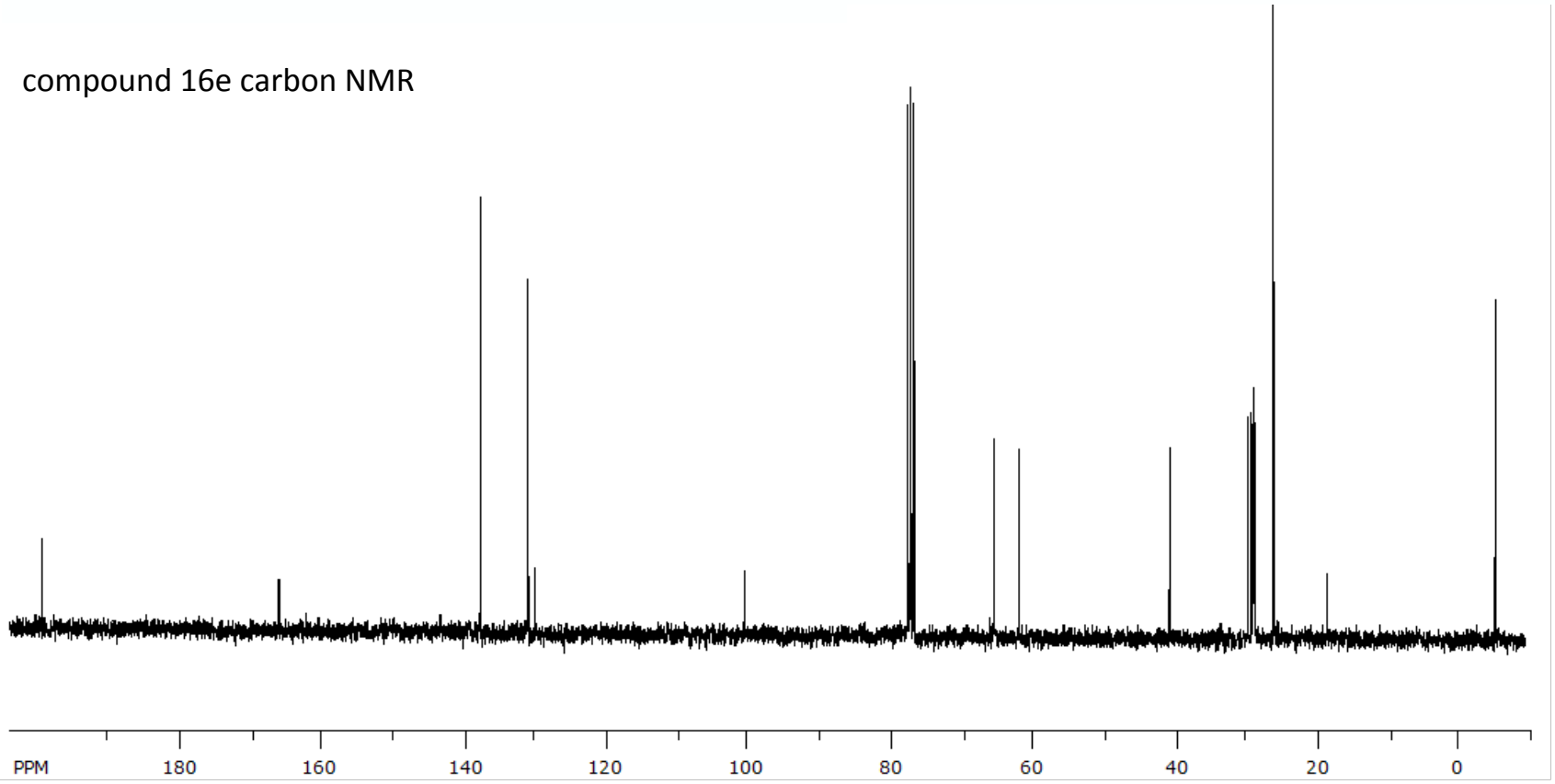


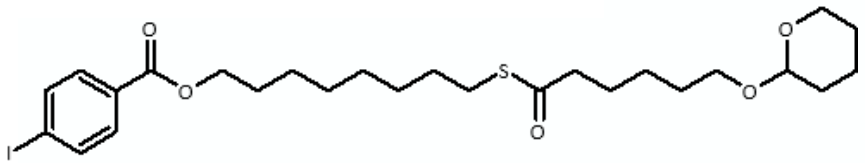
compound 16e proton NMR



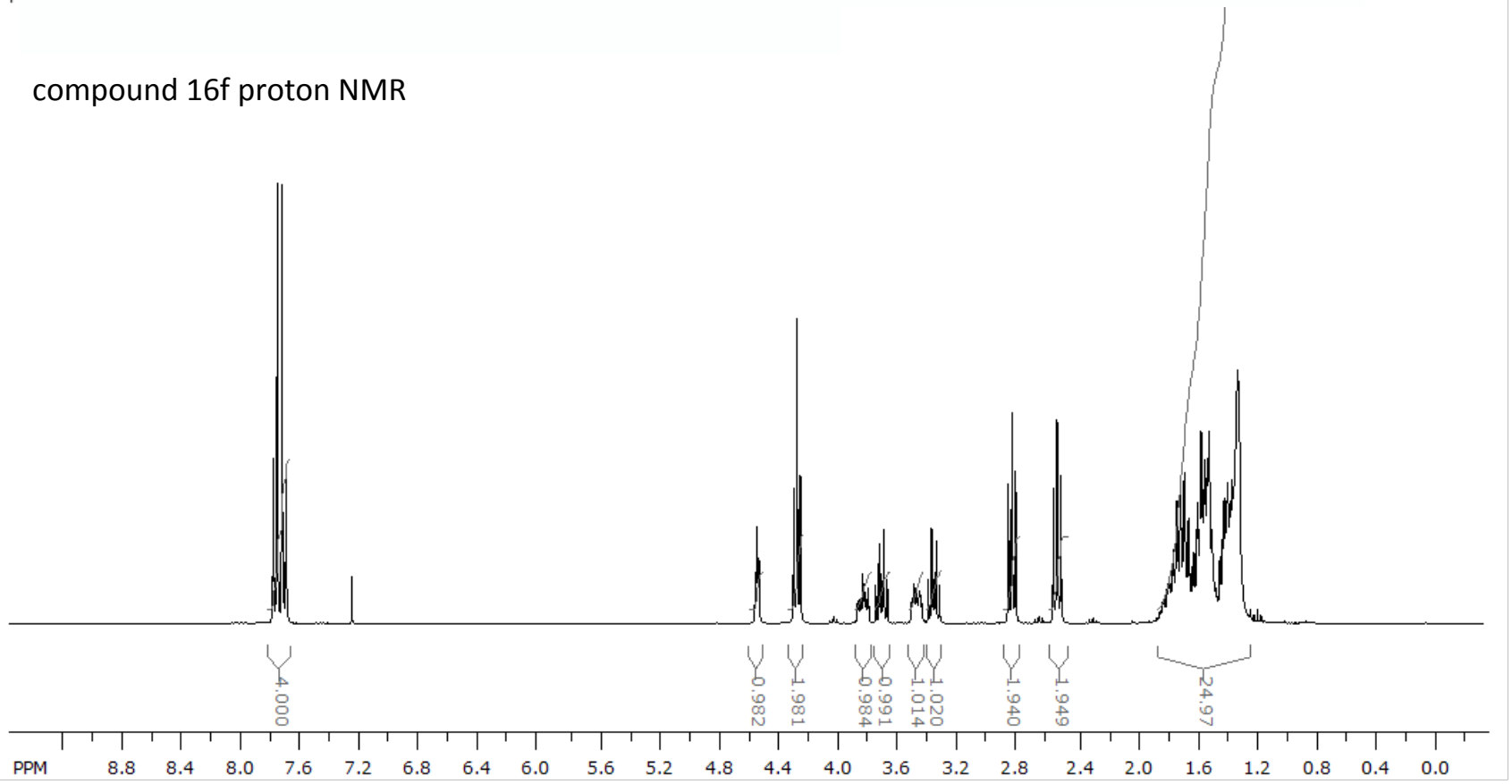


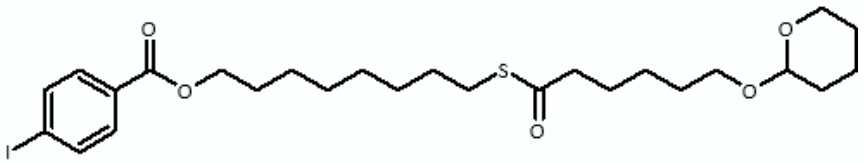
compound 16e carbon NMR



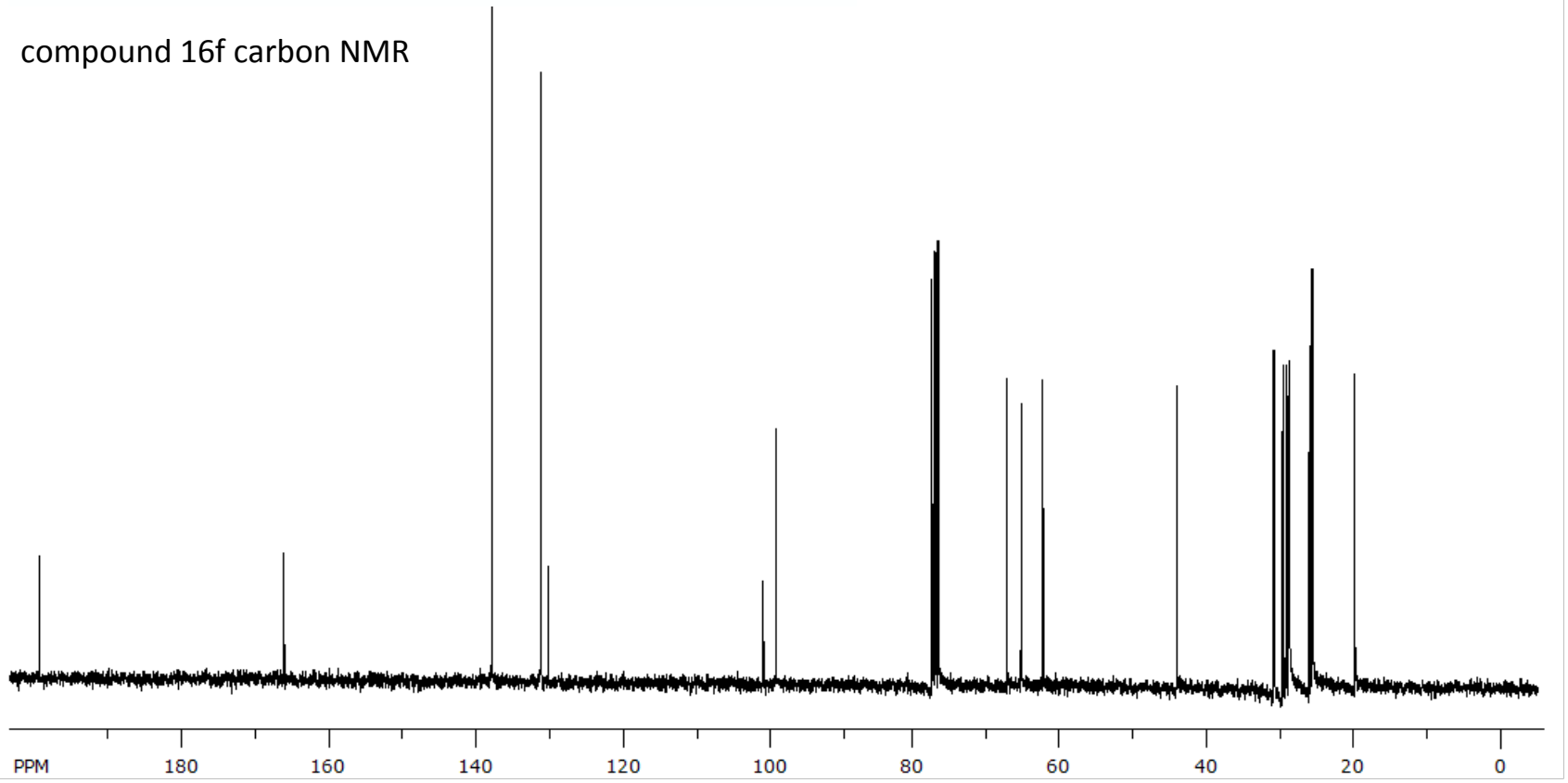


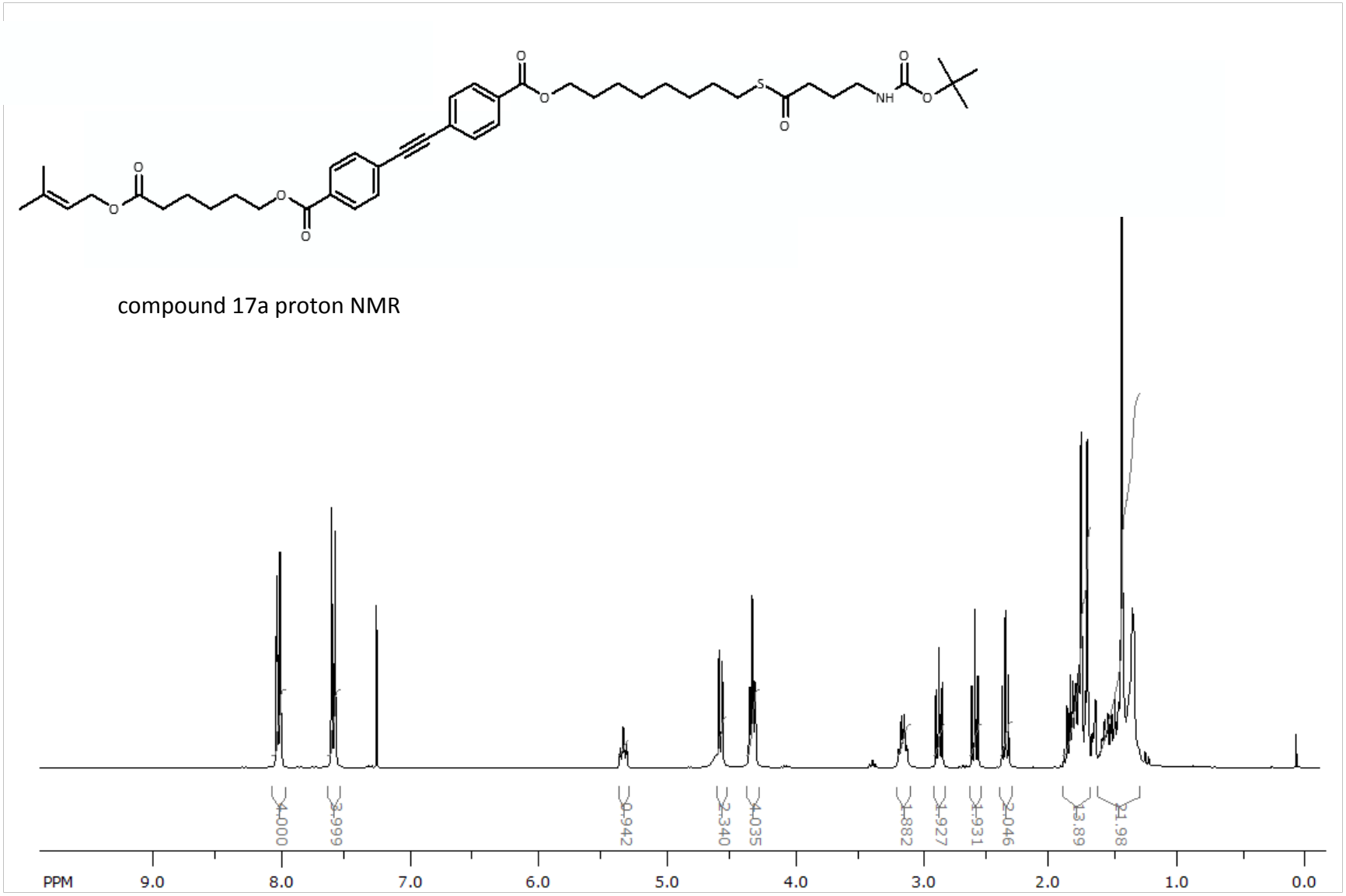
compound 16f proton NMR

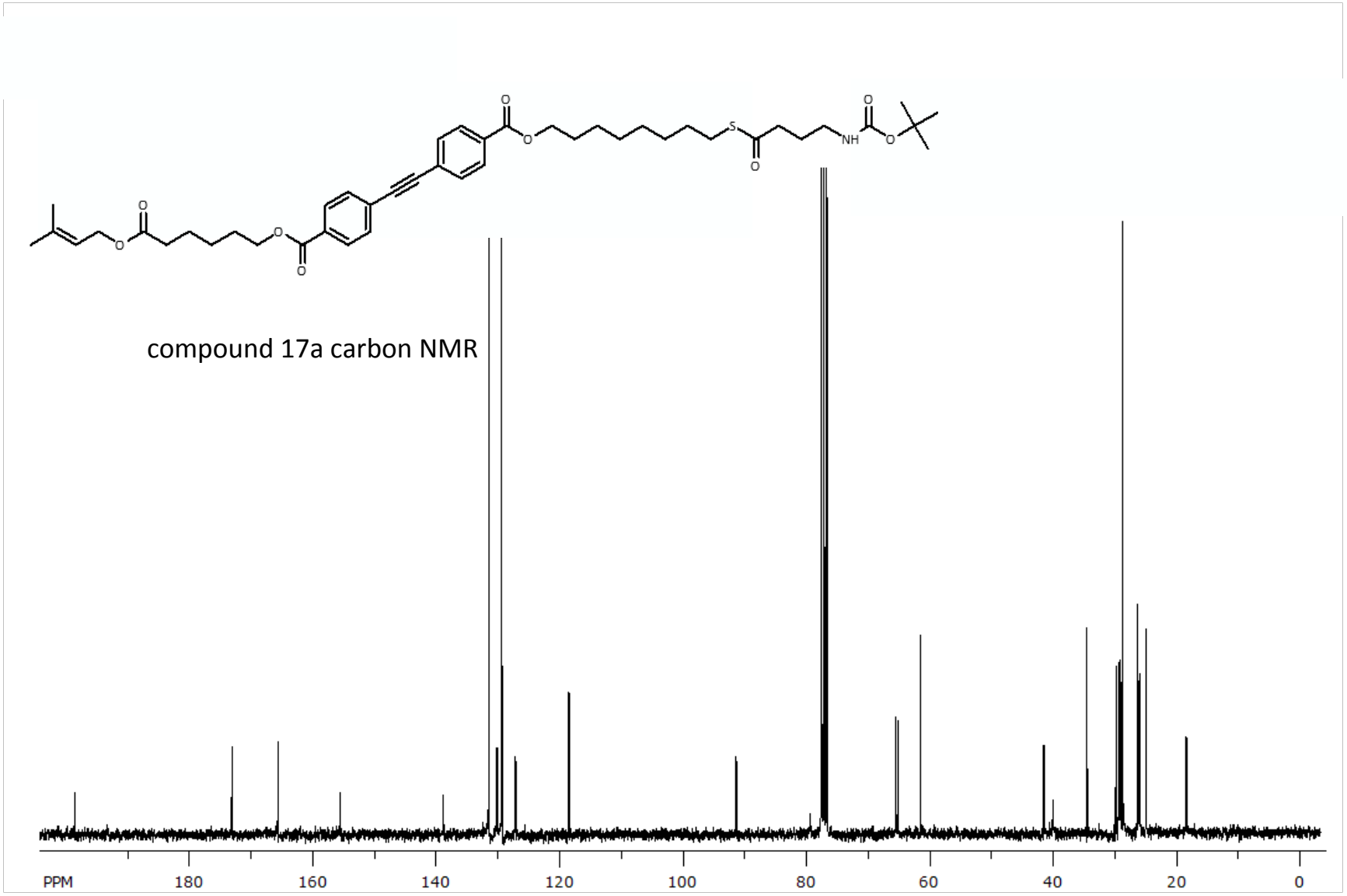


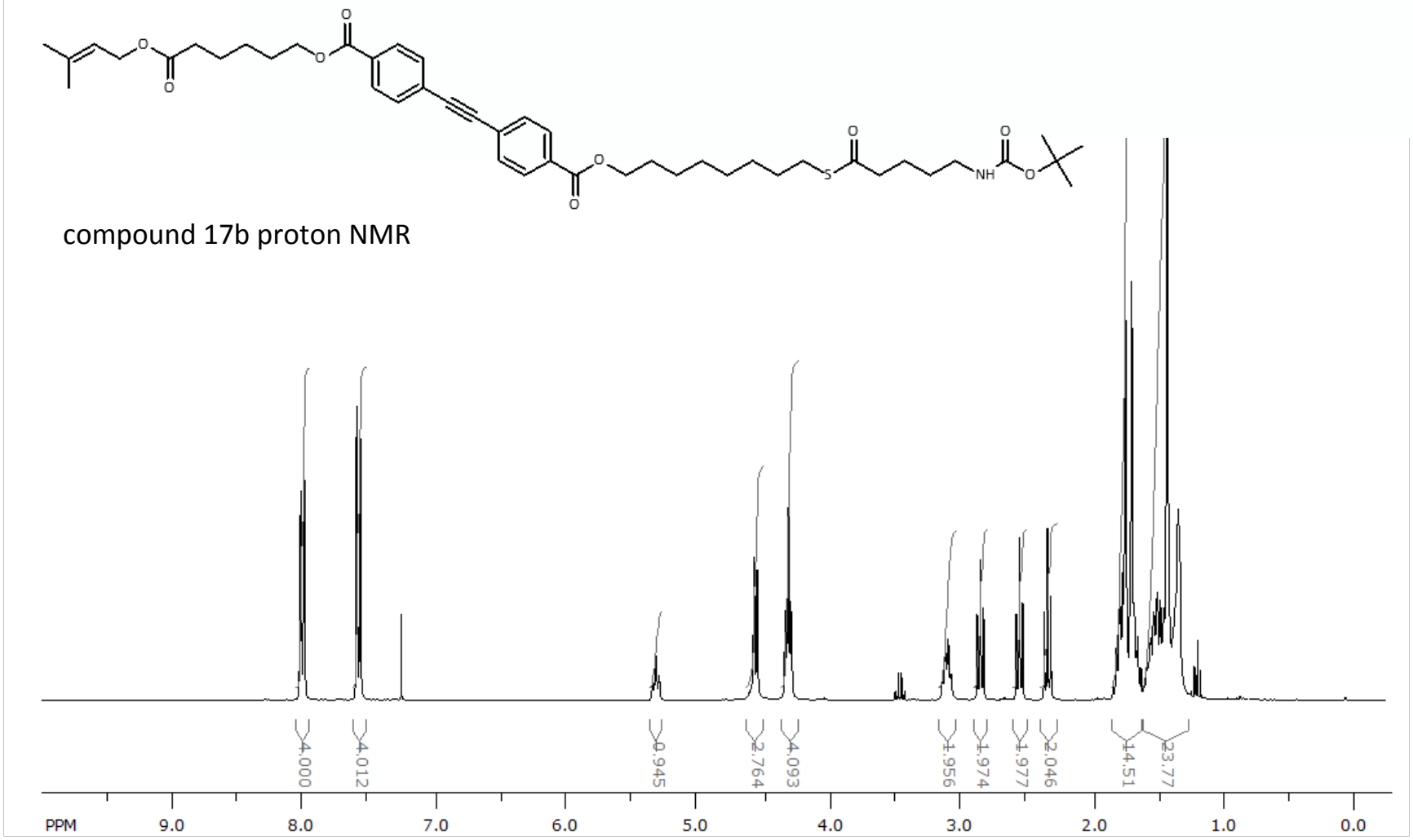


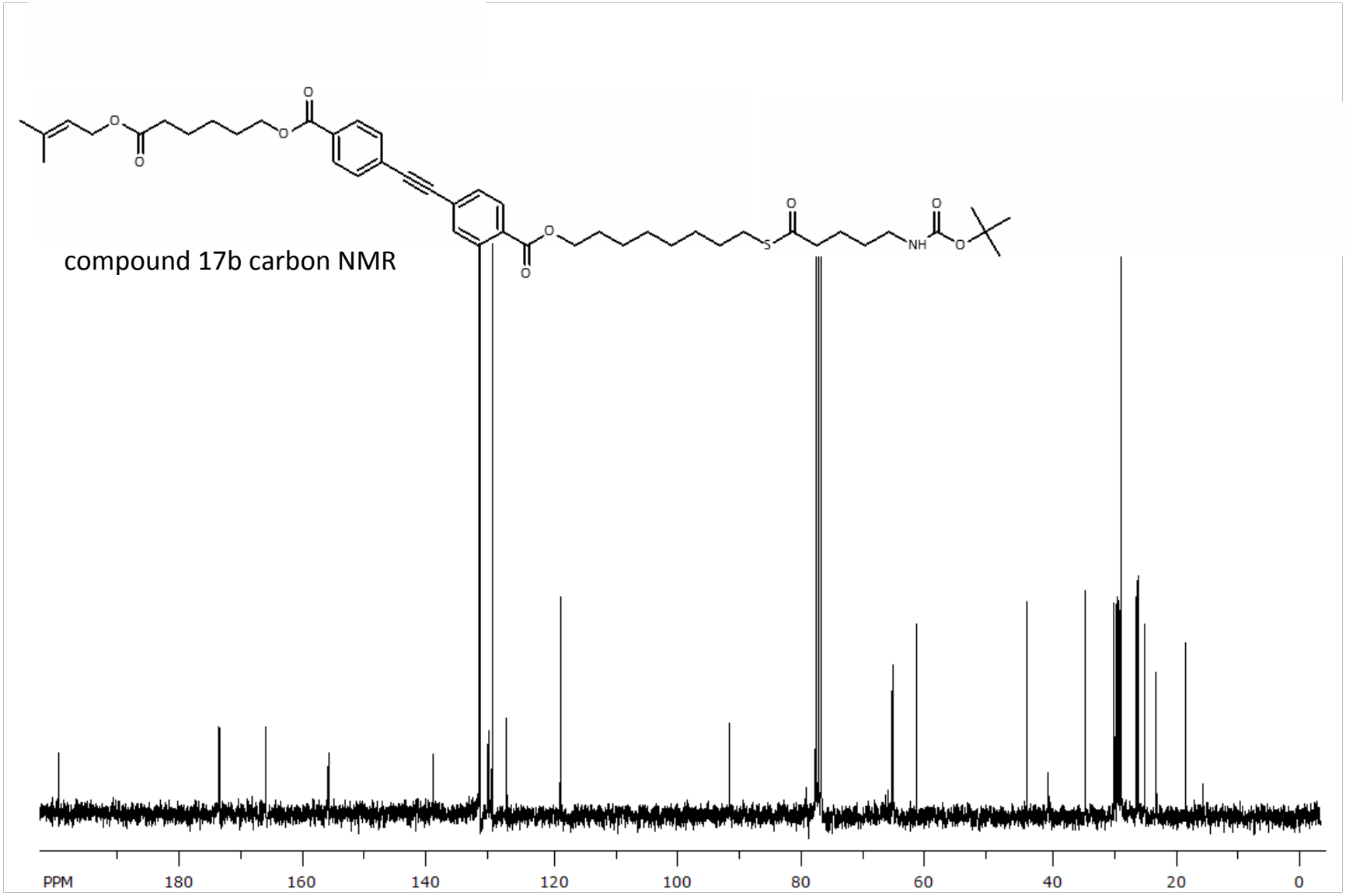
compound 16f carbon NMR

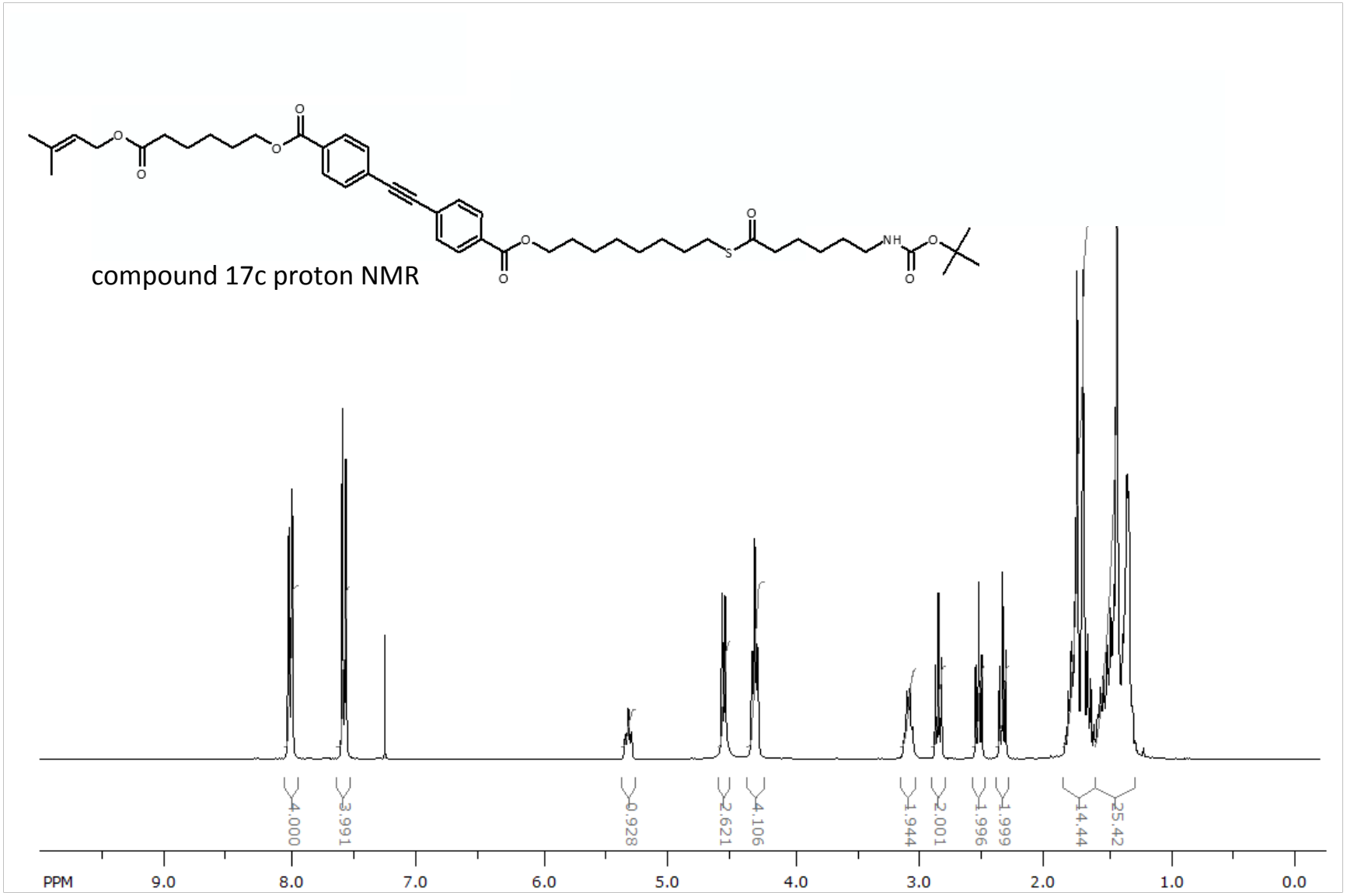


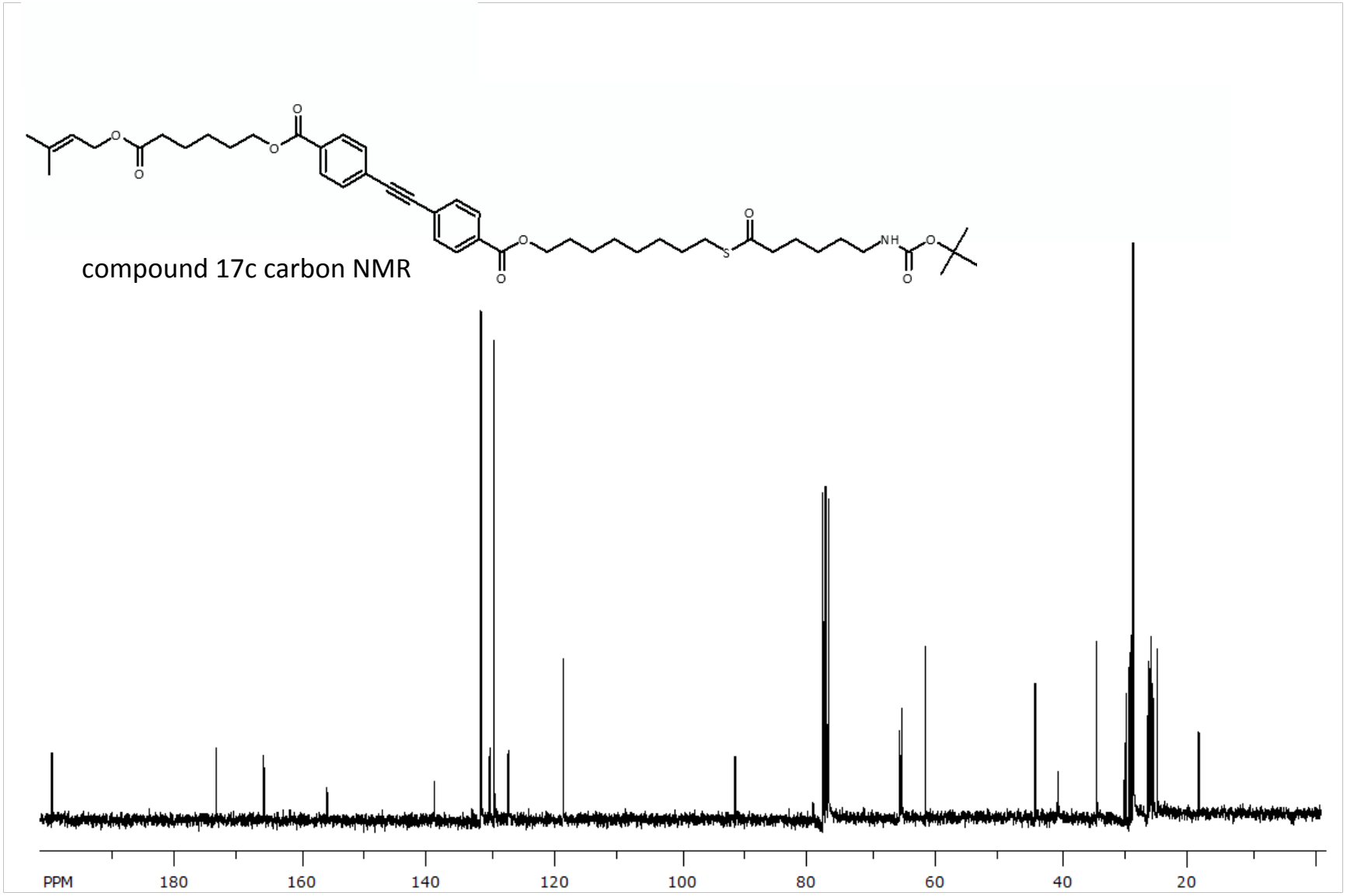

compound 17a proton NMR
4.000
3.999
0.942
2.340
4.035
1.882
1.927
1.931
2.046
3.89
11.98
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


compound 17a carbon NMR
PPM
180
160
140
120
100
80
60
40
20
0

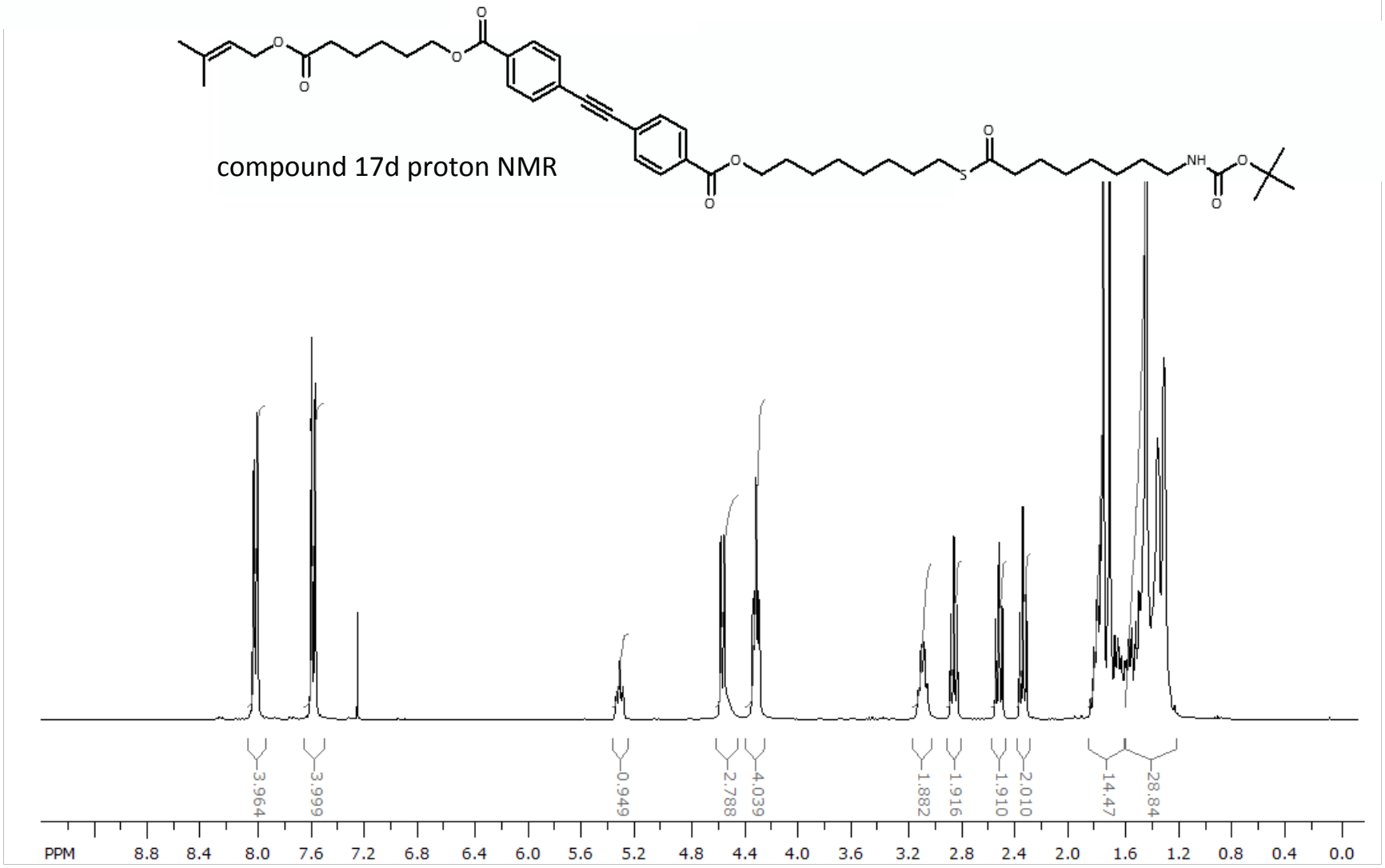

compound 17b proton NMR
4.000
4.012
0.945
2.764
4.093
1.956
1.974
1.977
2.046
14.51
23.77
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

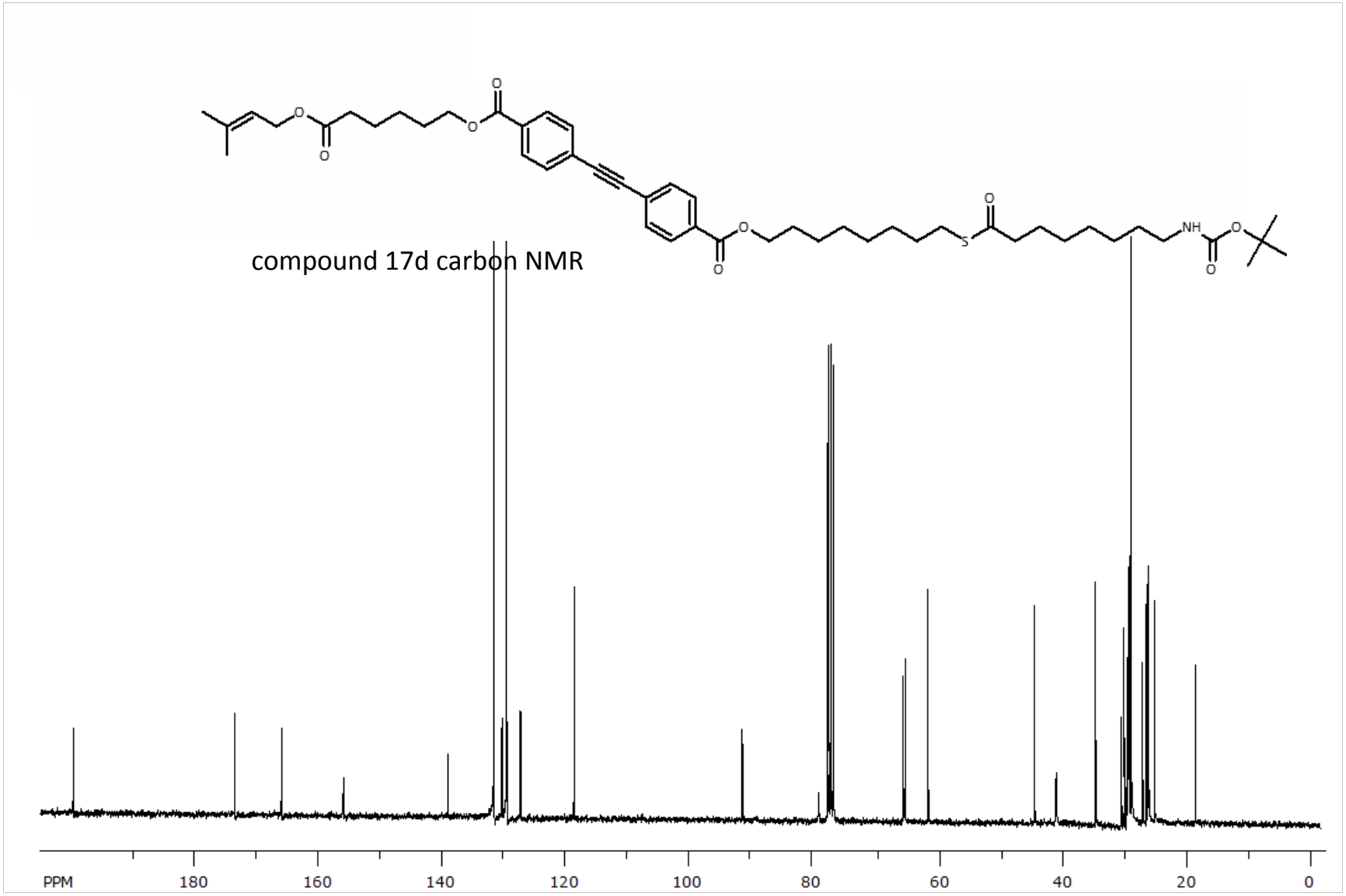

compound 17b carbon NMR
PPM
180
160
140
120
100
80
60
40
20
0

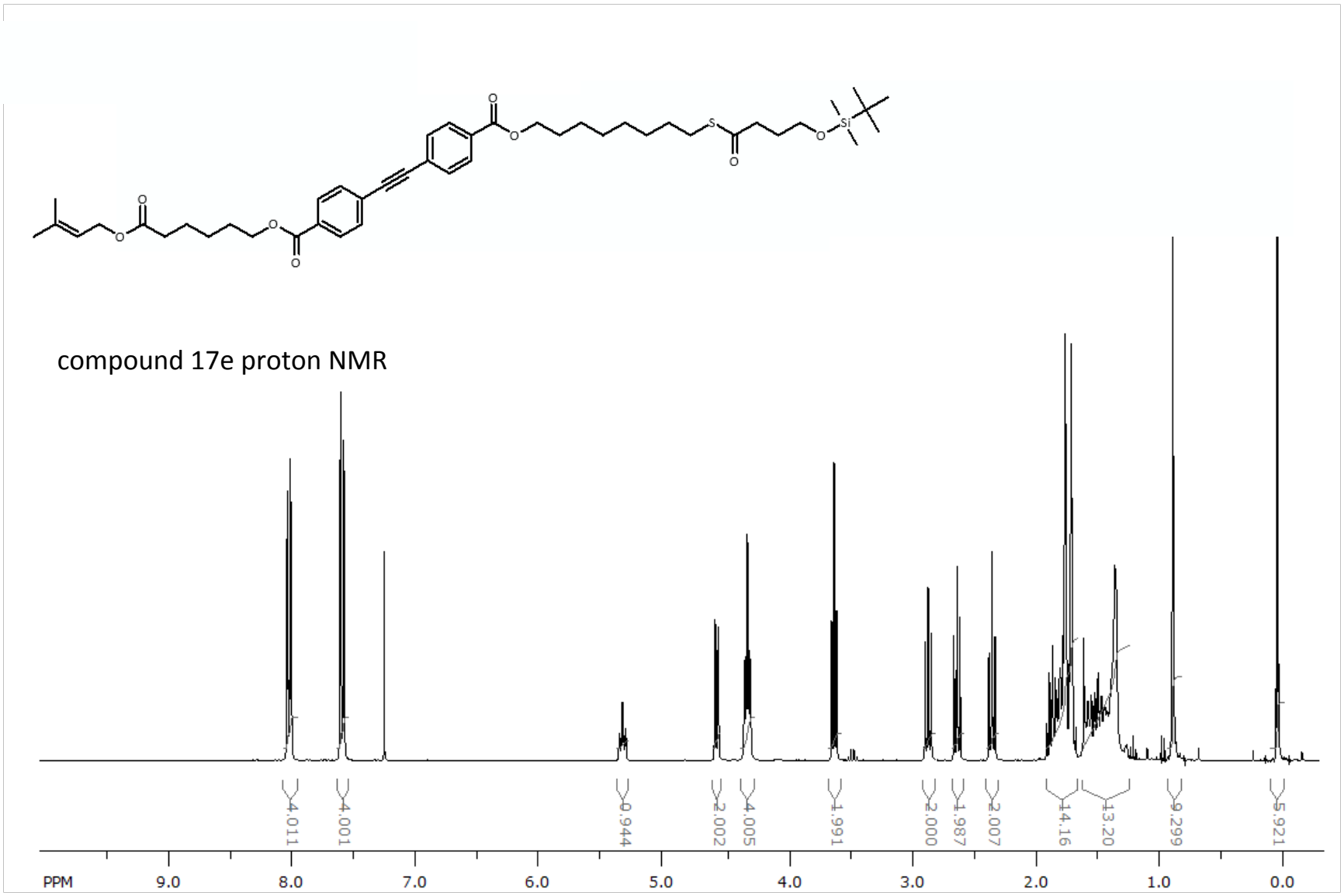

compound 17c proton NMR
4.000
3.991
0.928
2.621
4.106
1.944
2.001
1.996
1.999
14.44
25.42
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

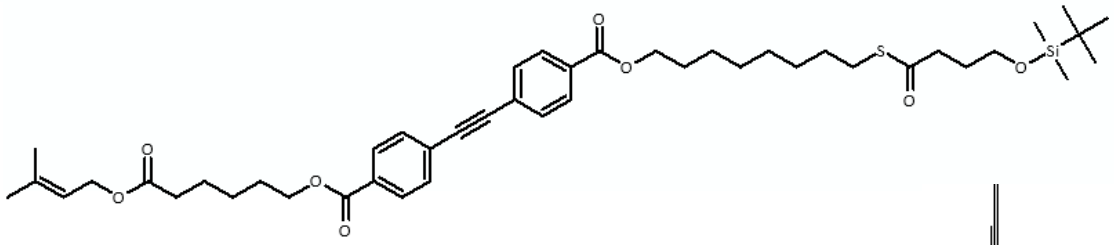

compound 17c carbon NMR
PPM
180
160
140
120
100
80
60
40
20

compound 17d proton NMR

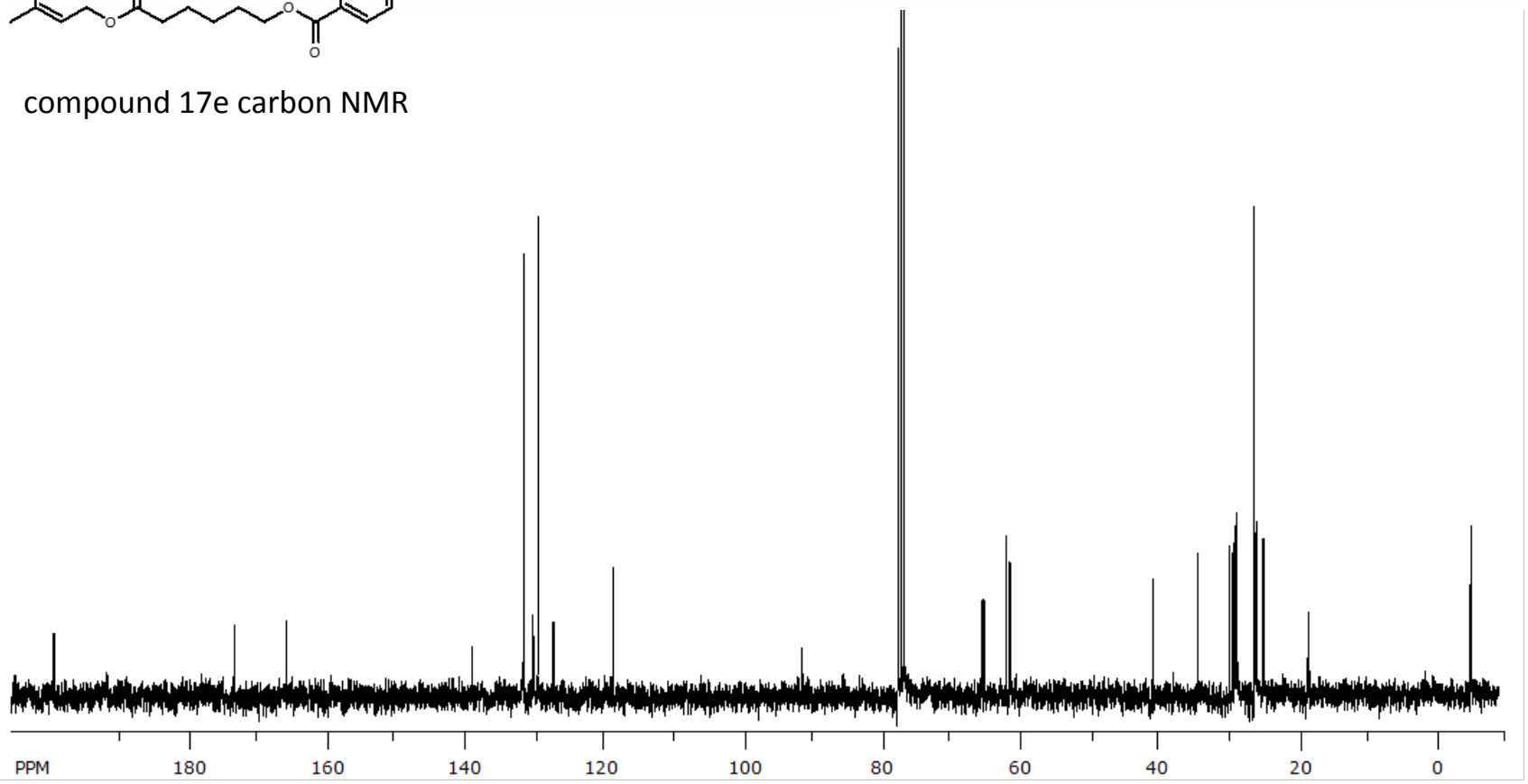


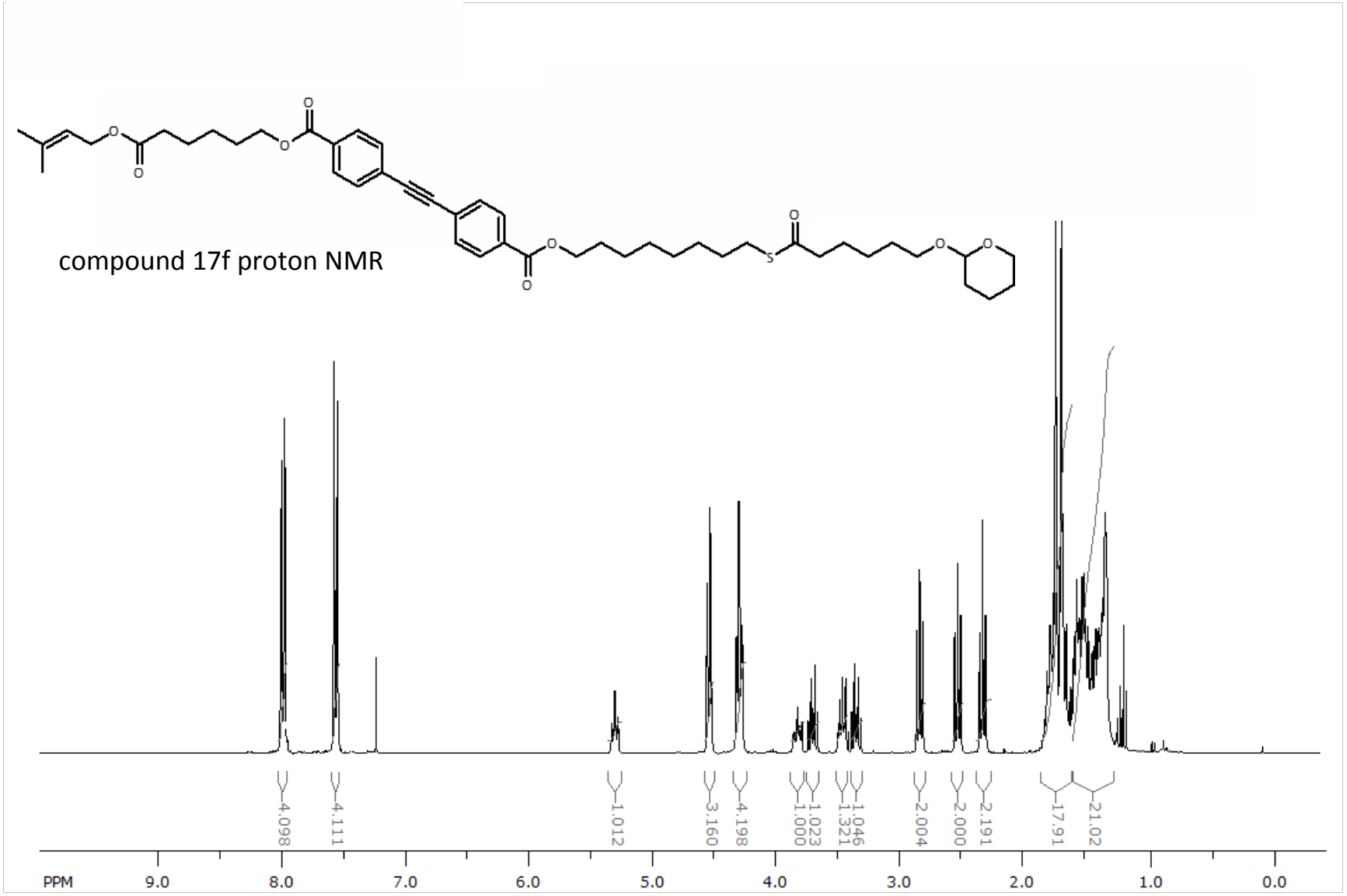

compound 17d carbon NMR
PPM
180
160
140
120
100
80
60
40
20
0

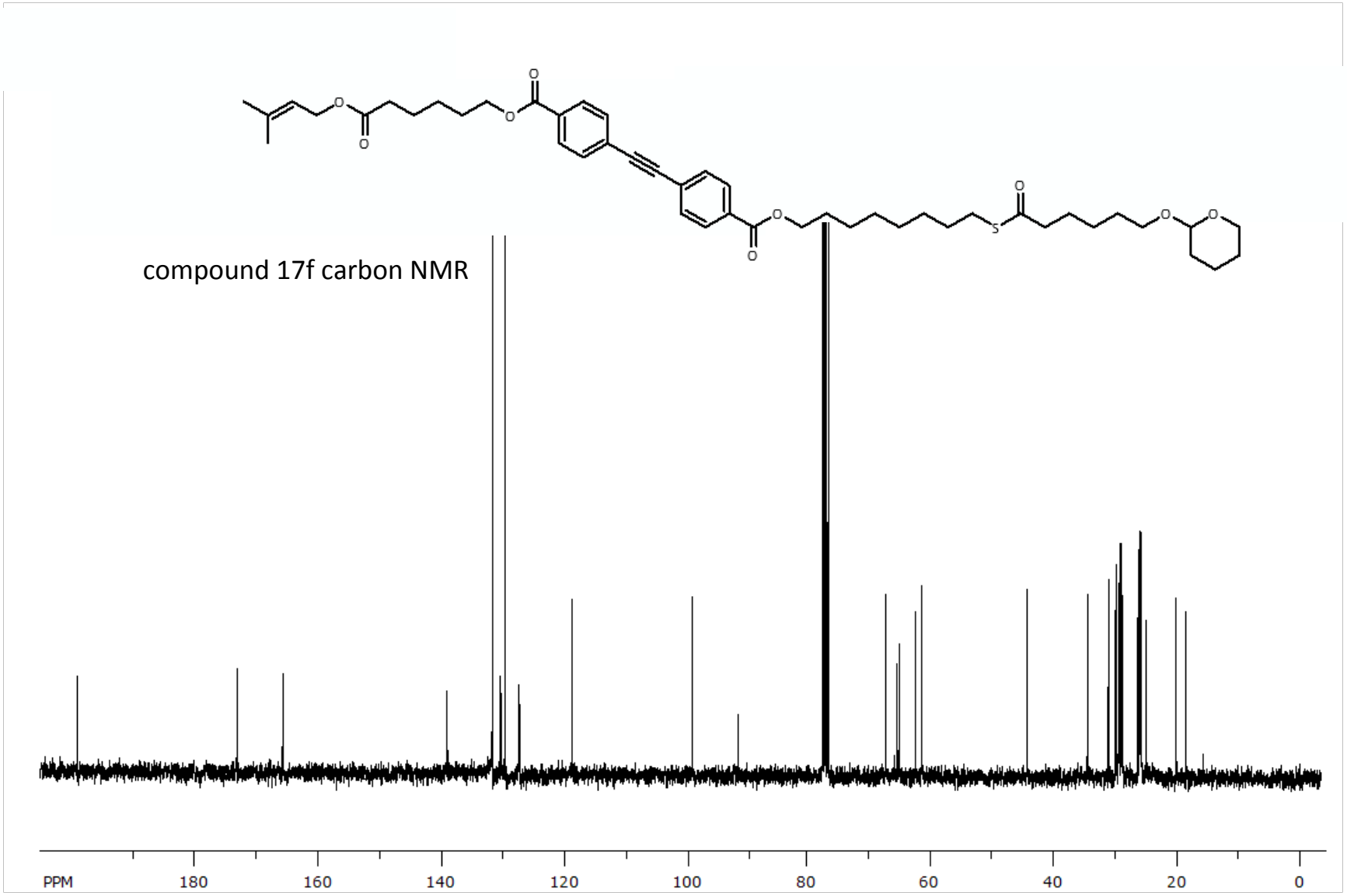

compound 17e proton NMR
4.011
4.001
0.944
2.002
4.005
1.991
2.000
1.987
2.007
14.16
13.20
9.299
5.921
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

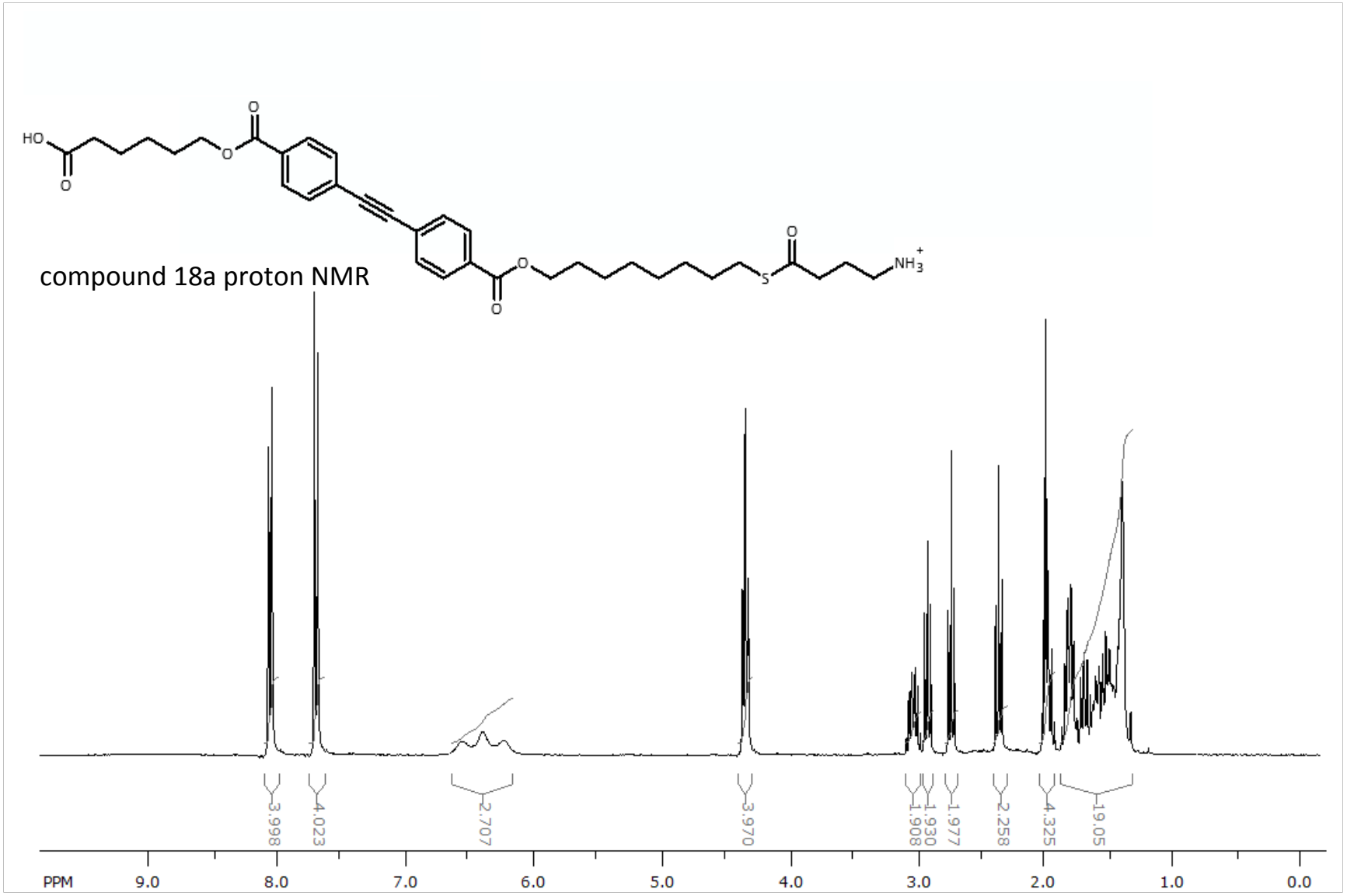


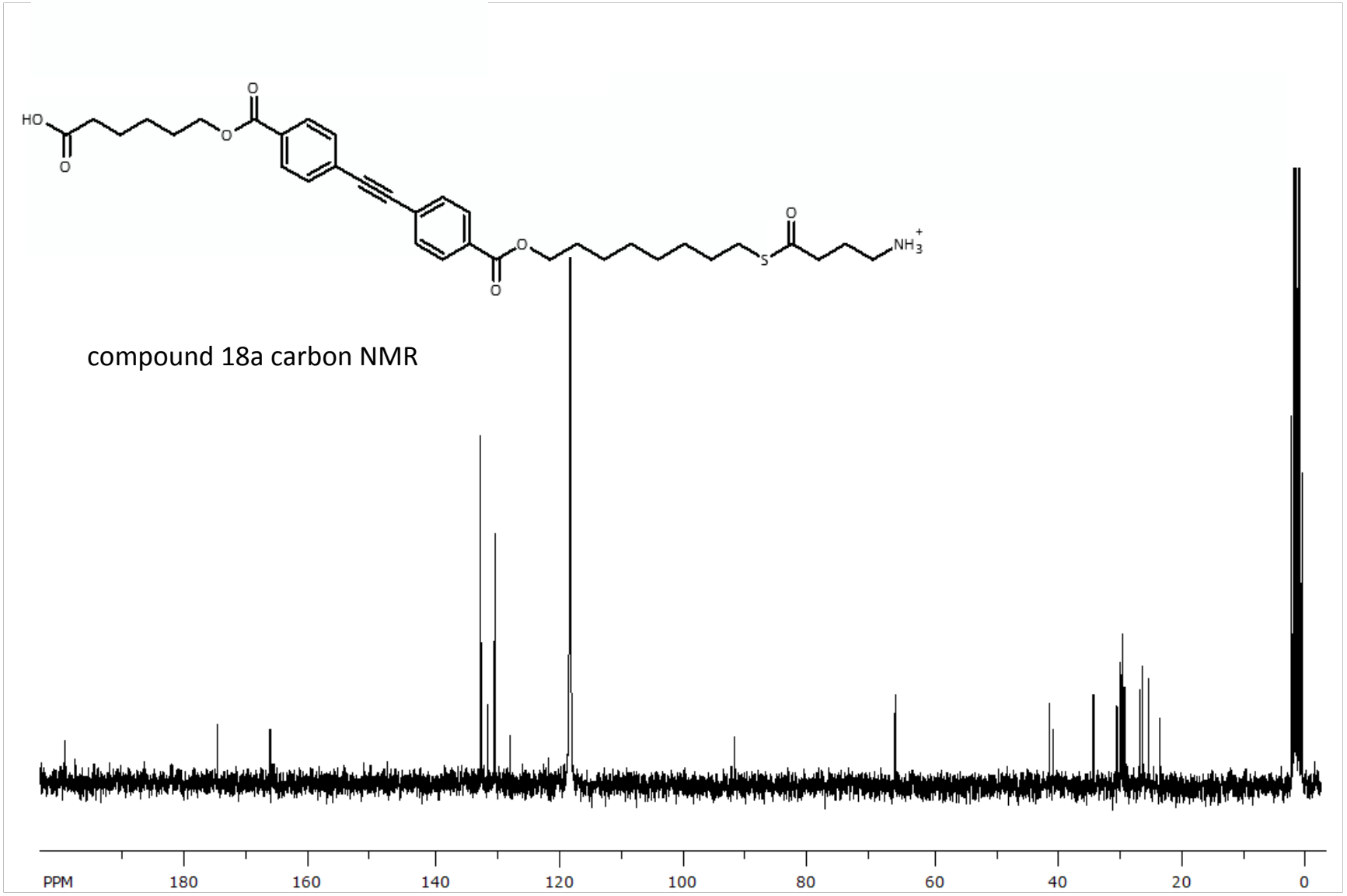
compound 17e carbon NMR

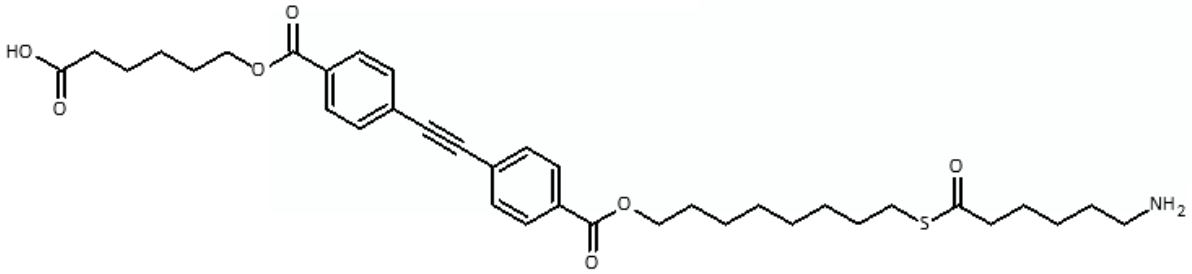



compound 17f proton NMR
4.098
4.111
1.012
3.160
4.198
1.000
1.023
1.321
1.046
2.004
2.000
2.191
17.91
21.02
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

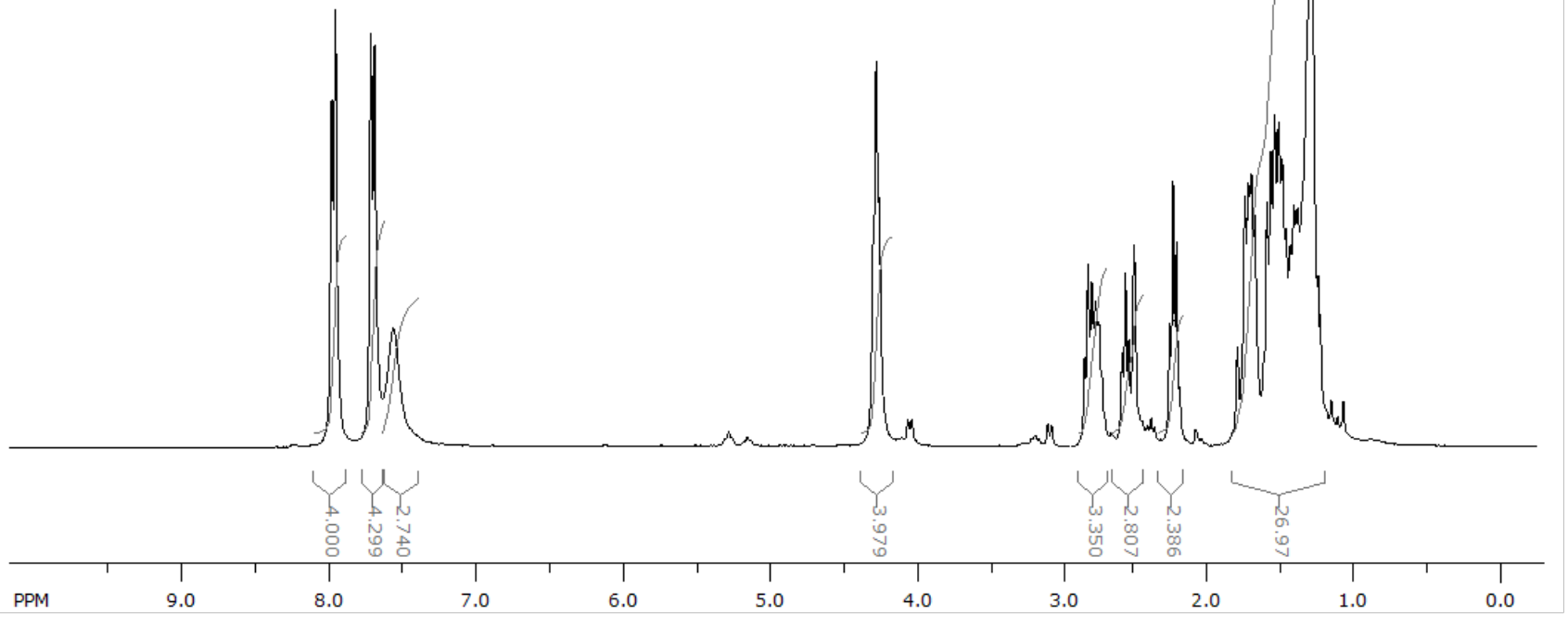

compound 17f carbon NMR
PPM
180
160
140
120
100
80
60
40
20
0

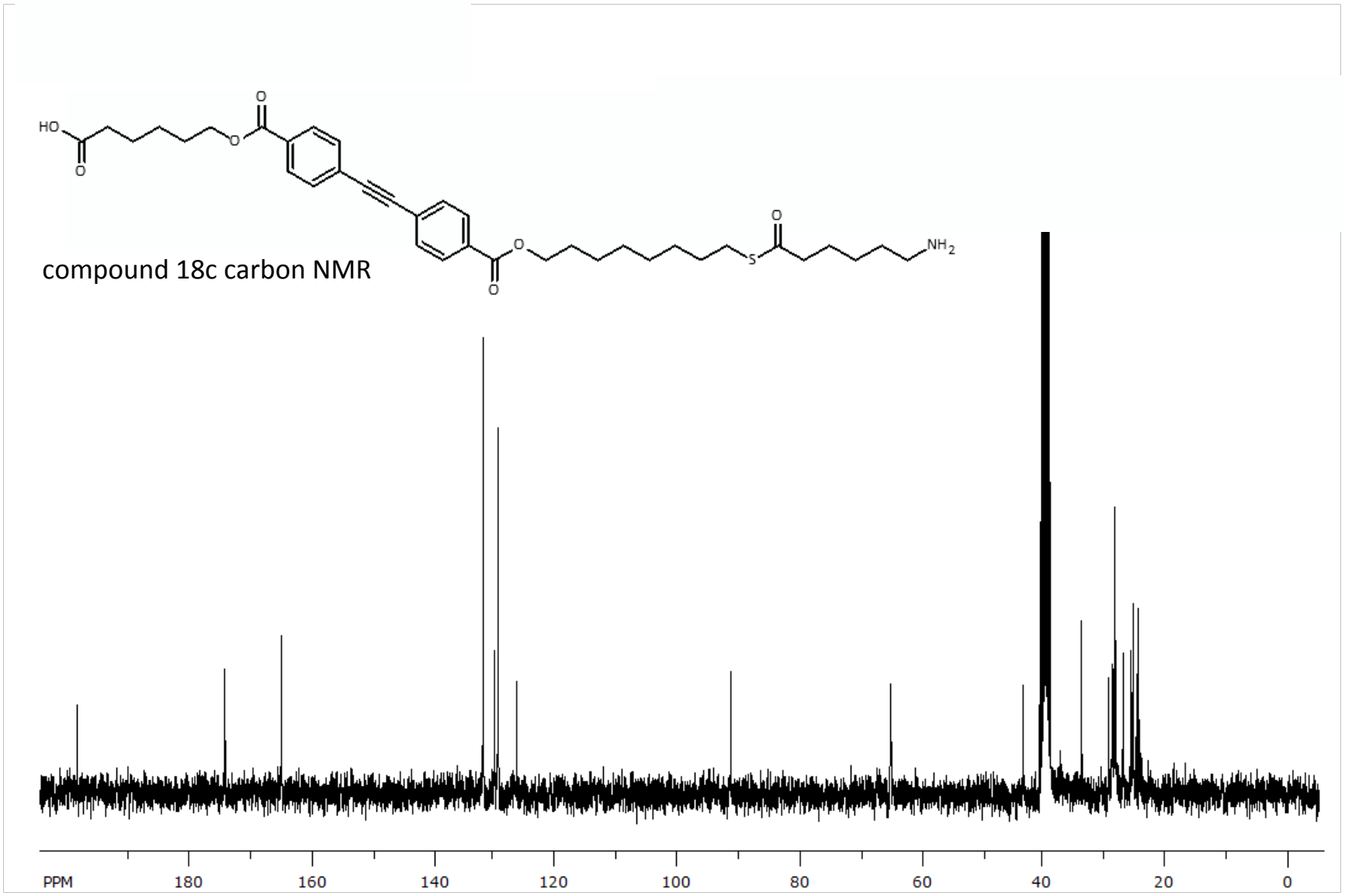

compound 18a proton NMR
HO
O
O
O
O
O
O
O
S
NH3+
3.998
4.023
2.707
3.970
1.908
1.930
1.977
2.258
4.325
19.05
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

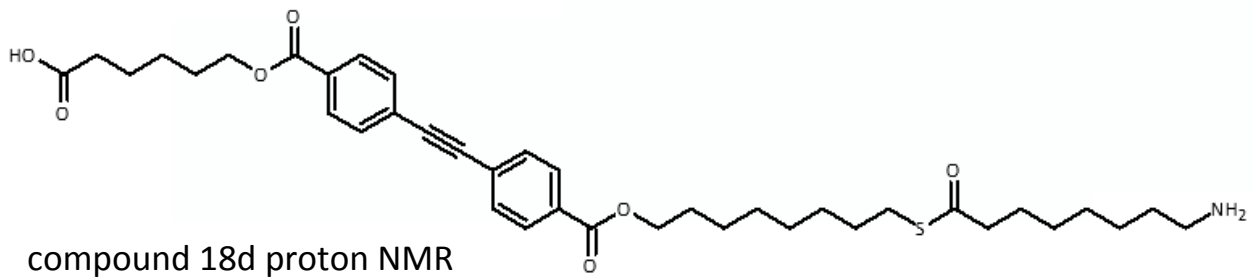

HO
O
O
O
O
O
O
O
S
NH3+
compound 18a carbon NMR
PPM
180
160
140
120
100
80
60
40
20
0



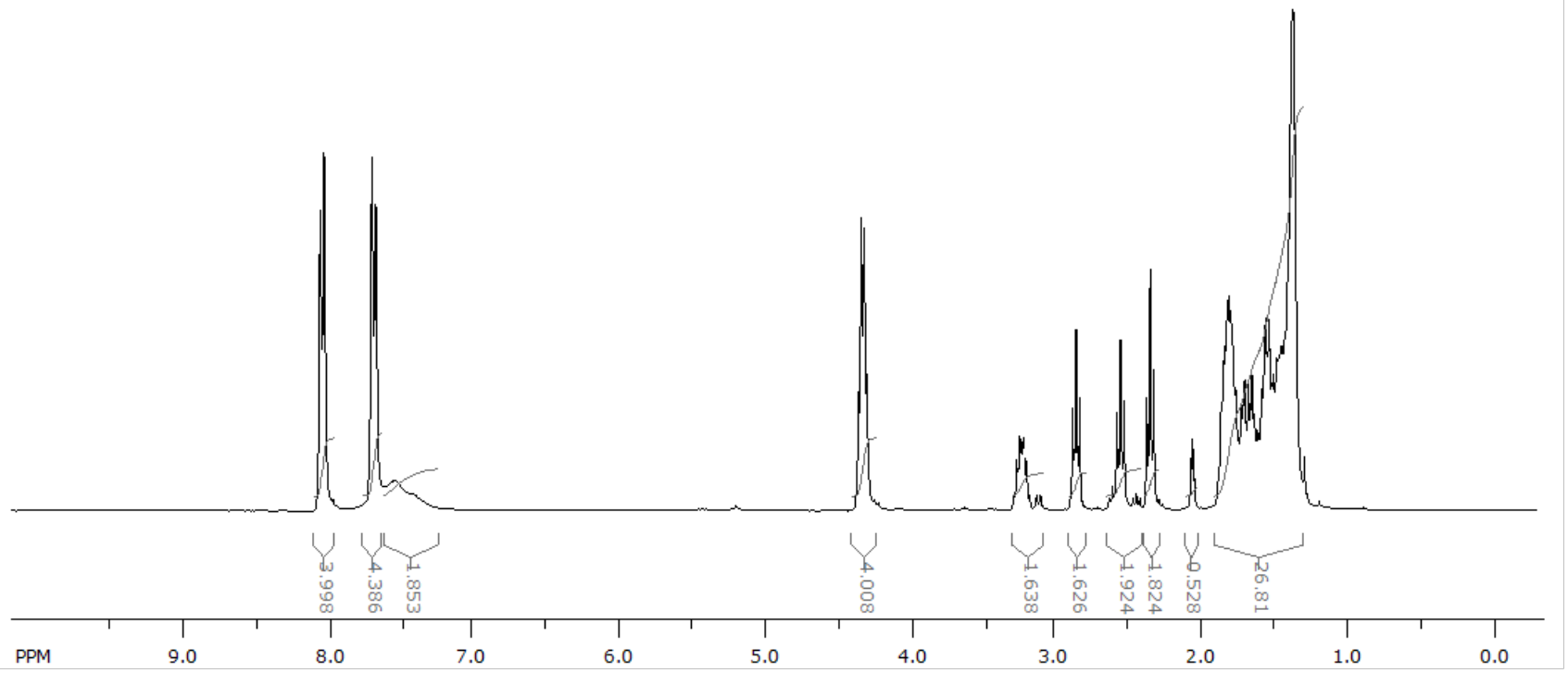
compound 18c proton NMR

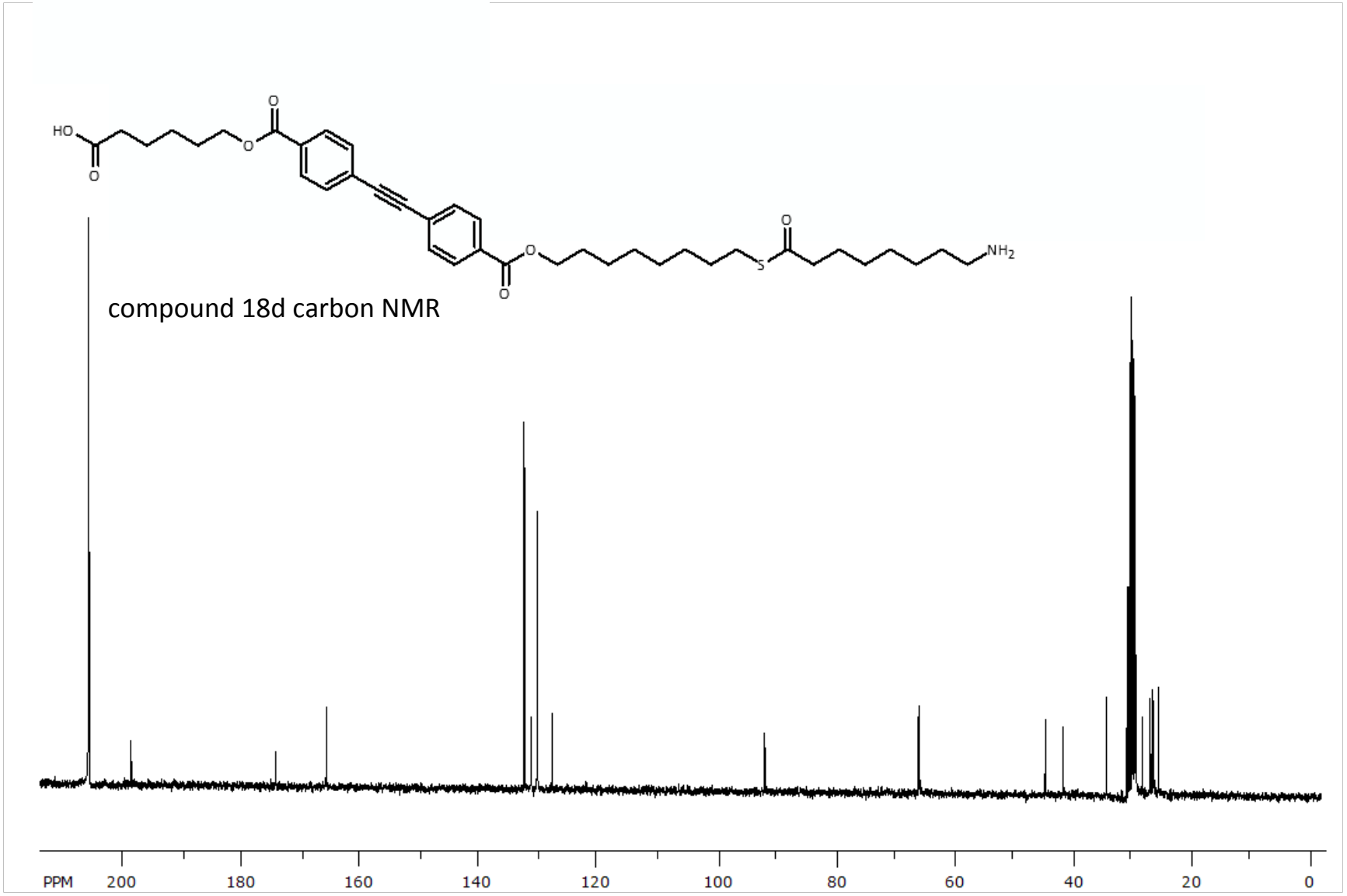


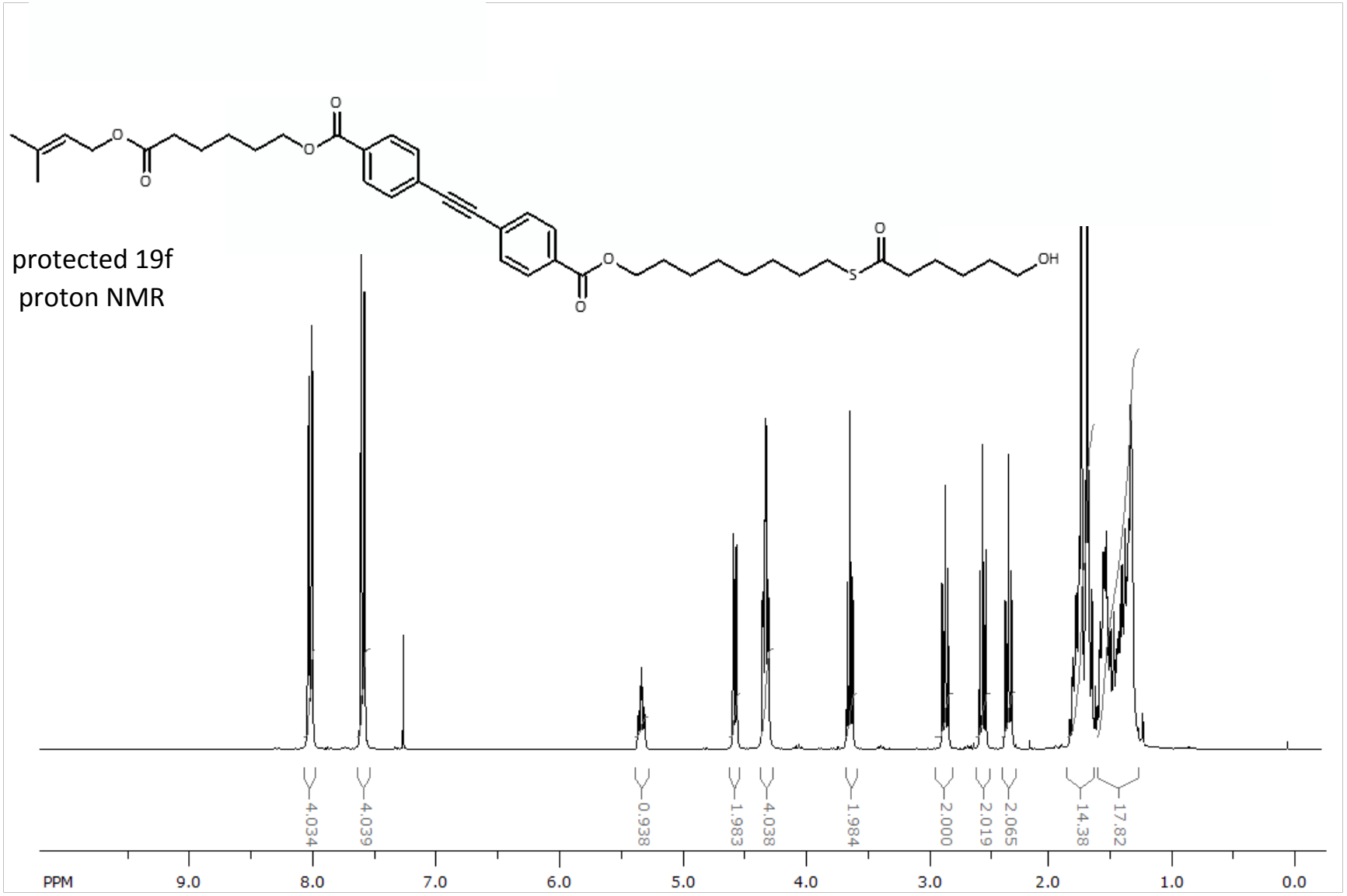

HO
O
O
O
O
O
O
O
S
NH2
compound 18c carbon NMR
PPM
180
160
140
120
100
80
60
40
20
0



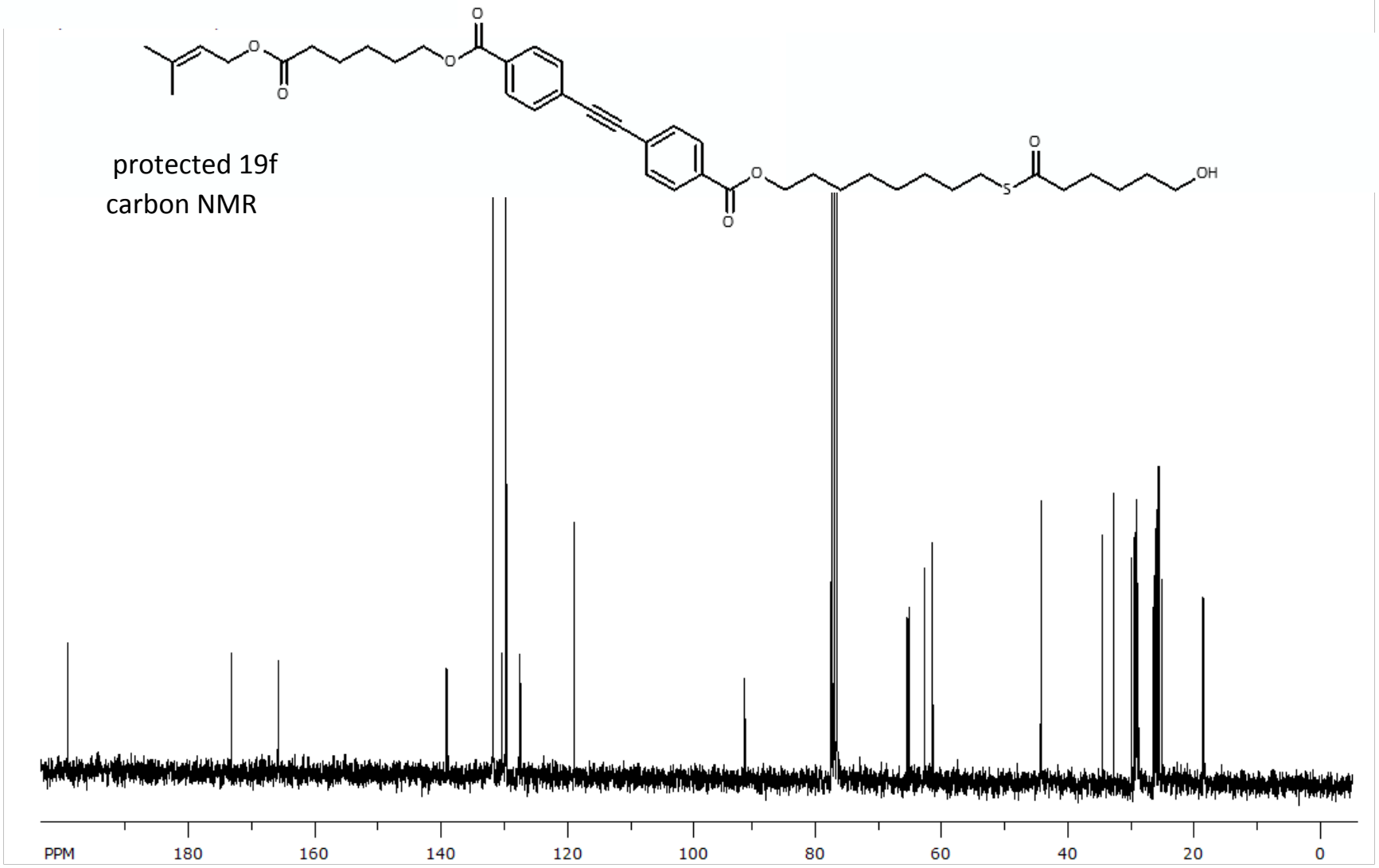
compound 18d proton NMR

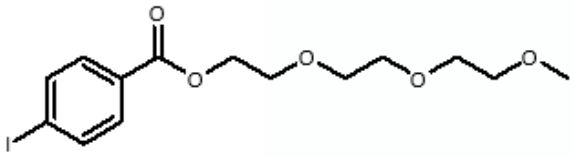



HO
O
O
O
O
O
O
S
O
NH2
compound 18d carbon NMR
PPM
200
180
160
140
120
100
80
60
40
20
0

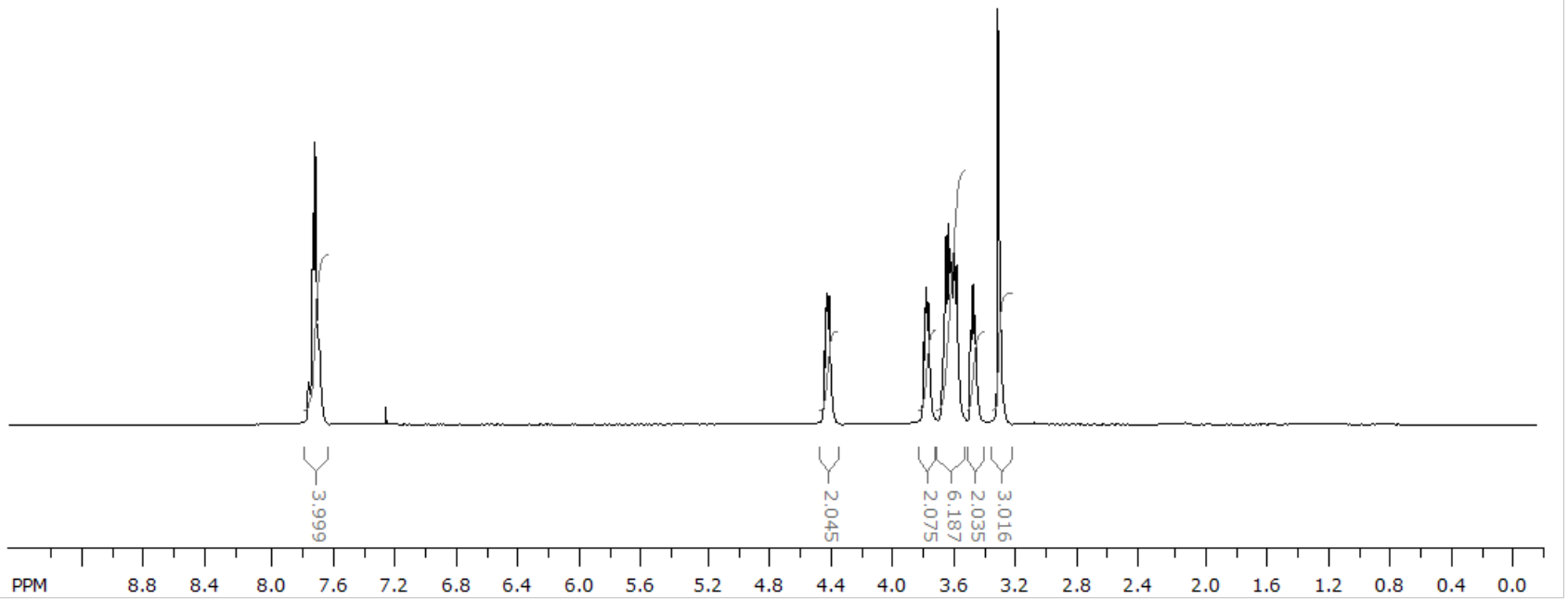

protected 19f
proton NMR
O
O
O
O
O
O
O
S
OH
4.034
4.039
0.938
1.983
4.038
1.984
2.000
2.019
2.065
14.38
17.82
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

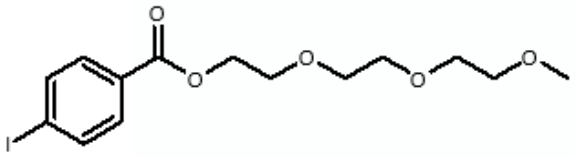
protected 19f
carbon NMR



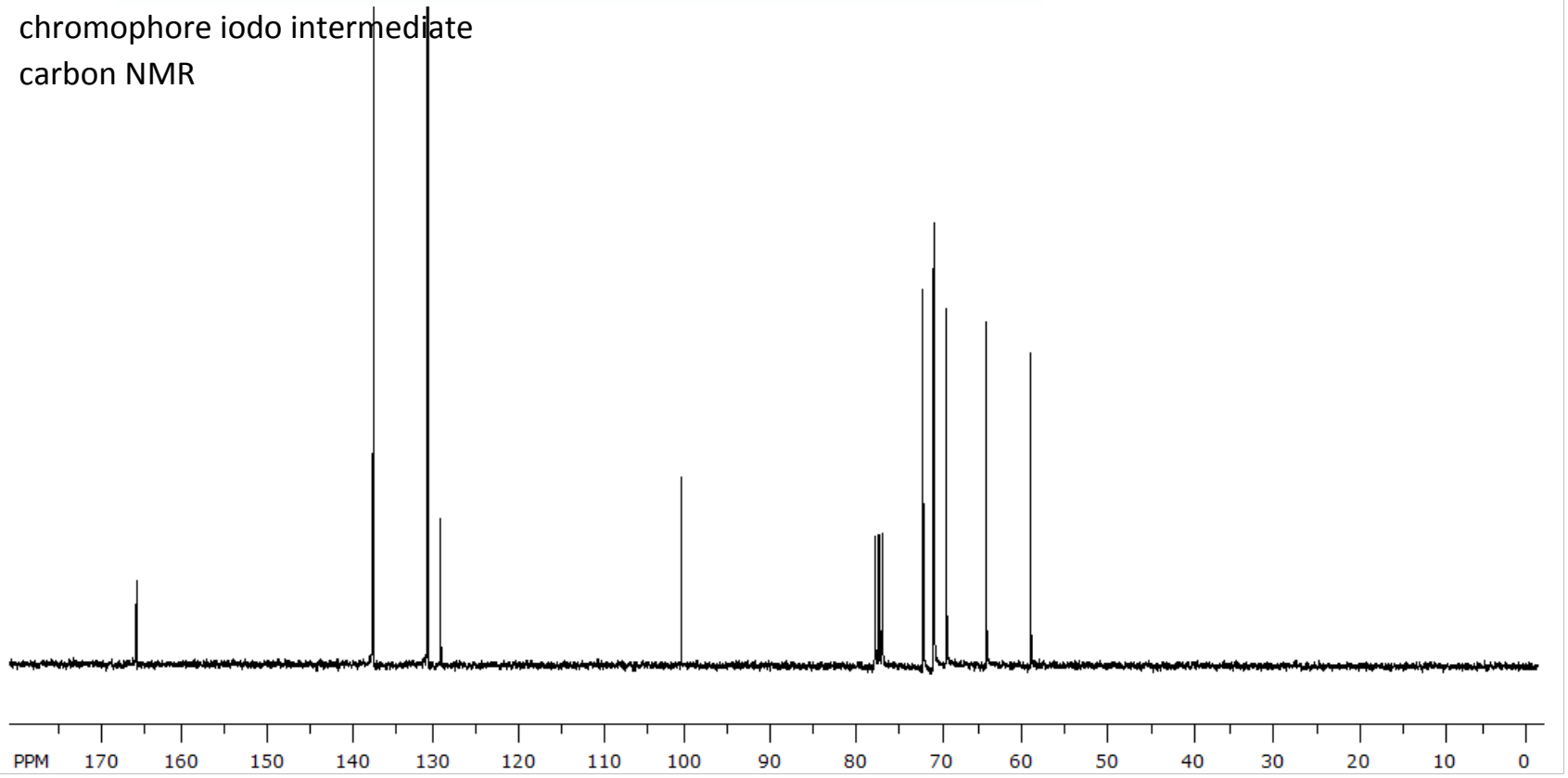


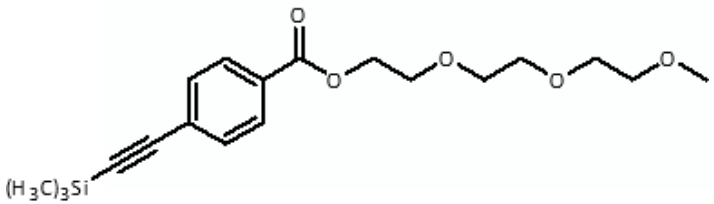
chromophore iodo intermediate
proton NMR



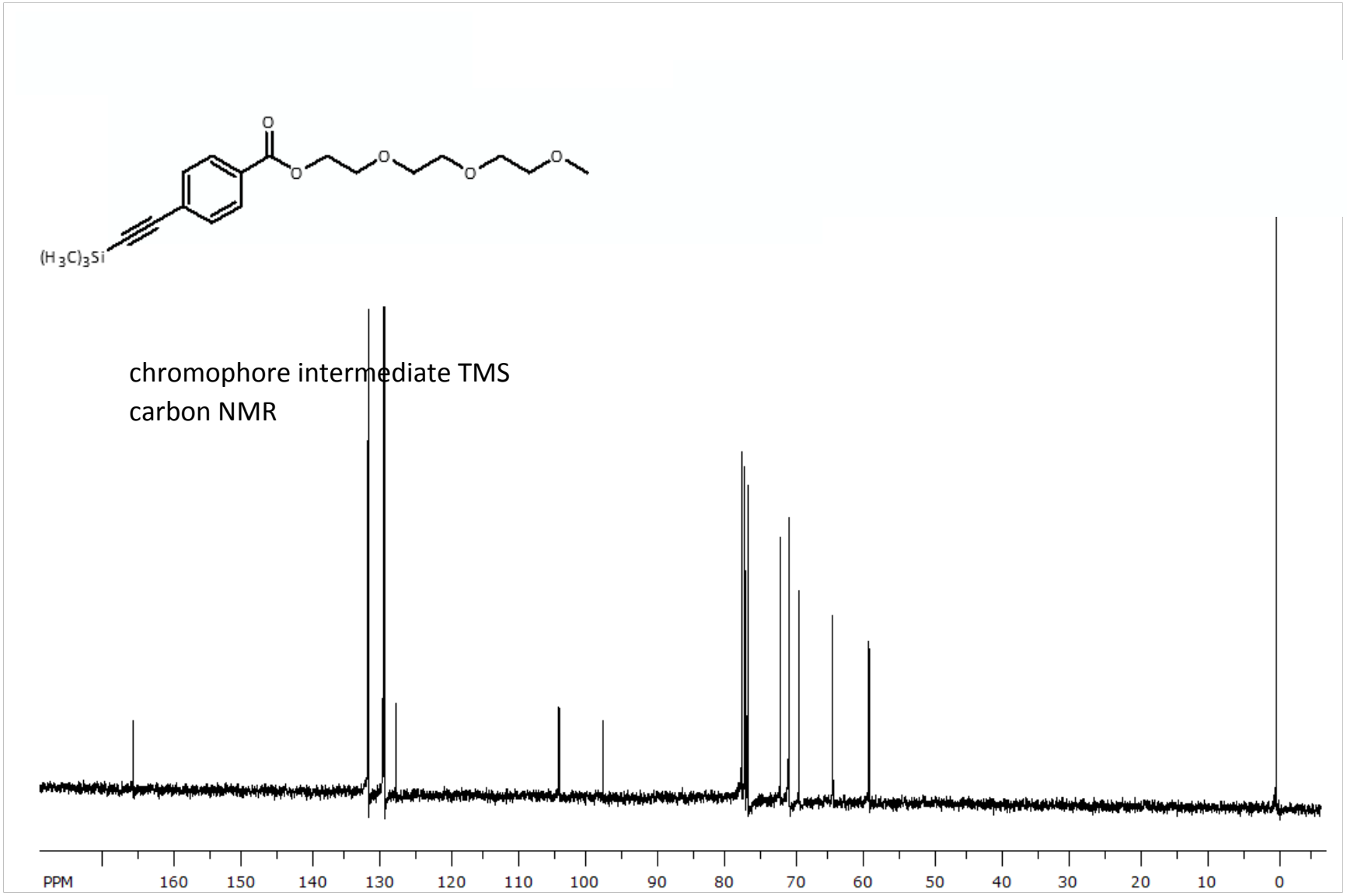


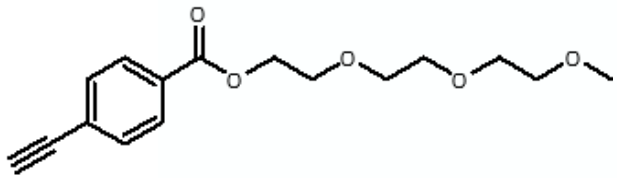
chromophore iodo intermediate
carbon NMR



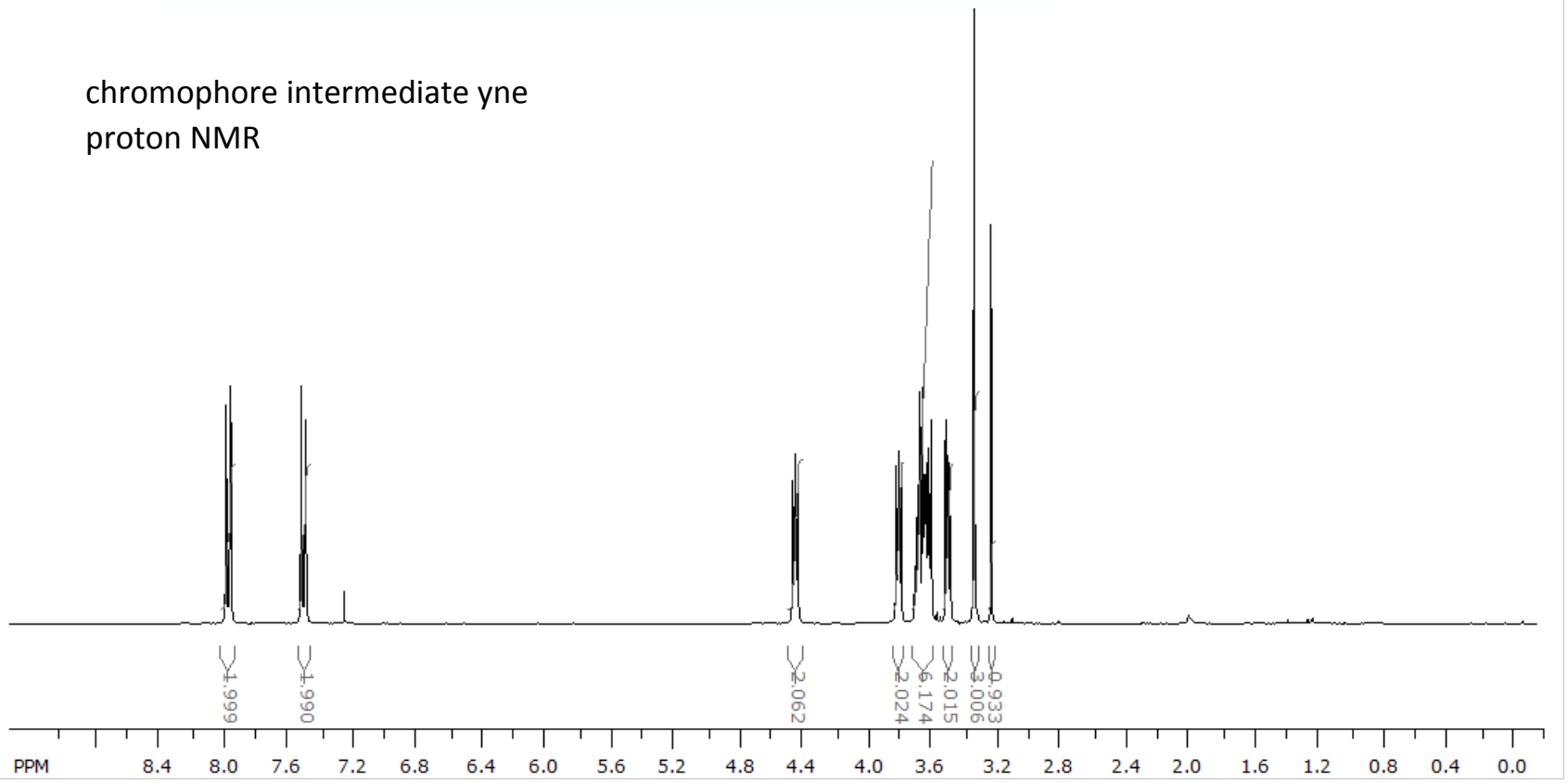


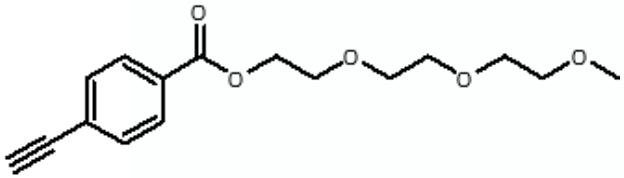
chromophore intermediate TMS
proton NMR


chromophore intermediate TMS
carbon NMR
PPM
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

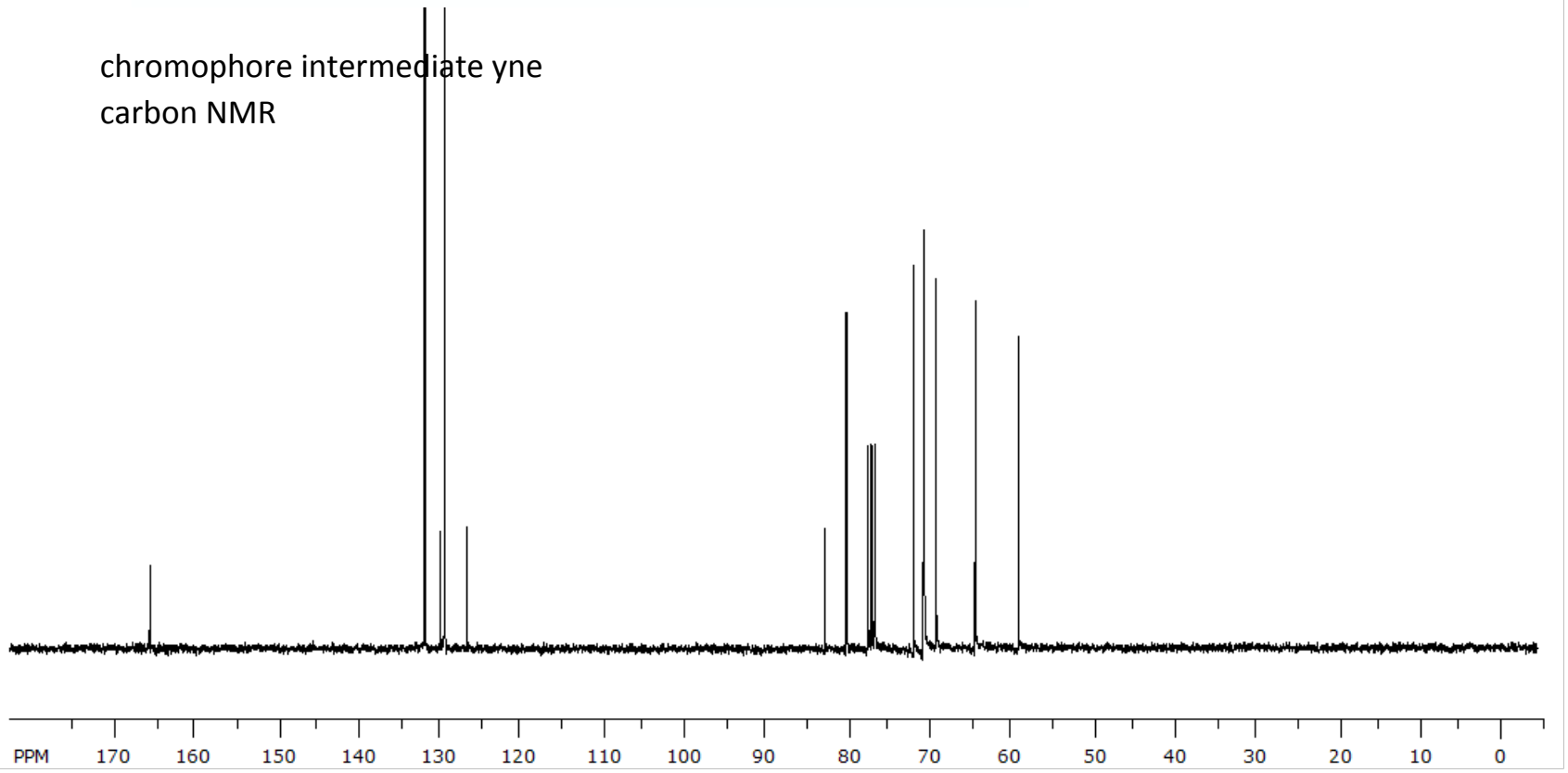


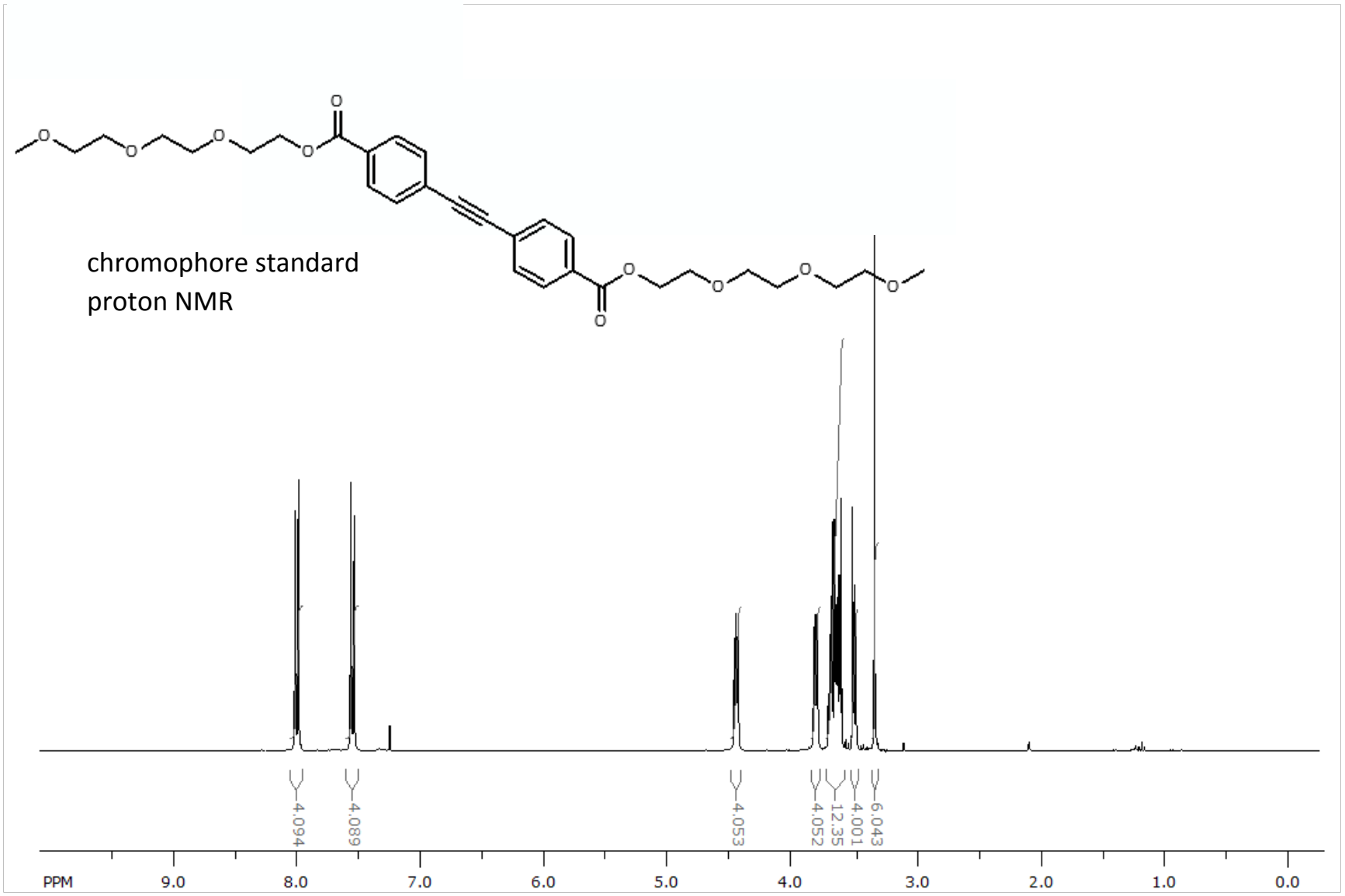
chromophore intermediate yne
proton NMR

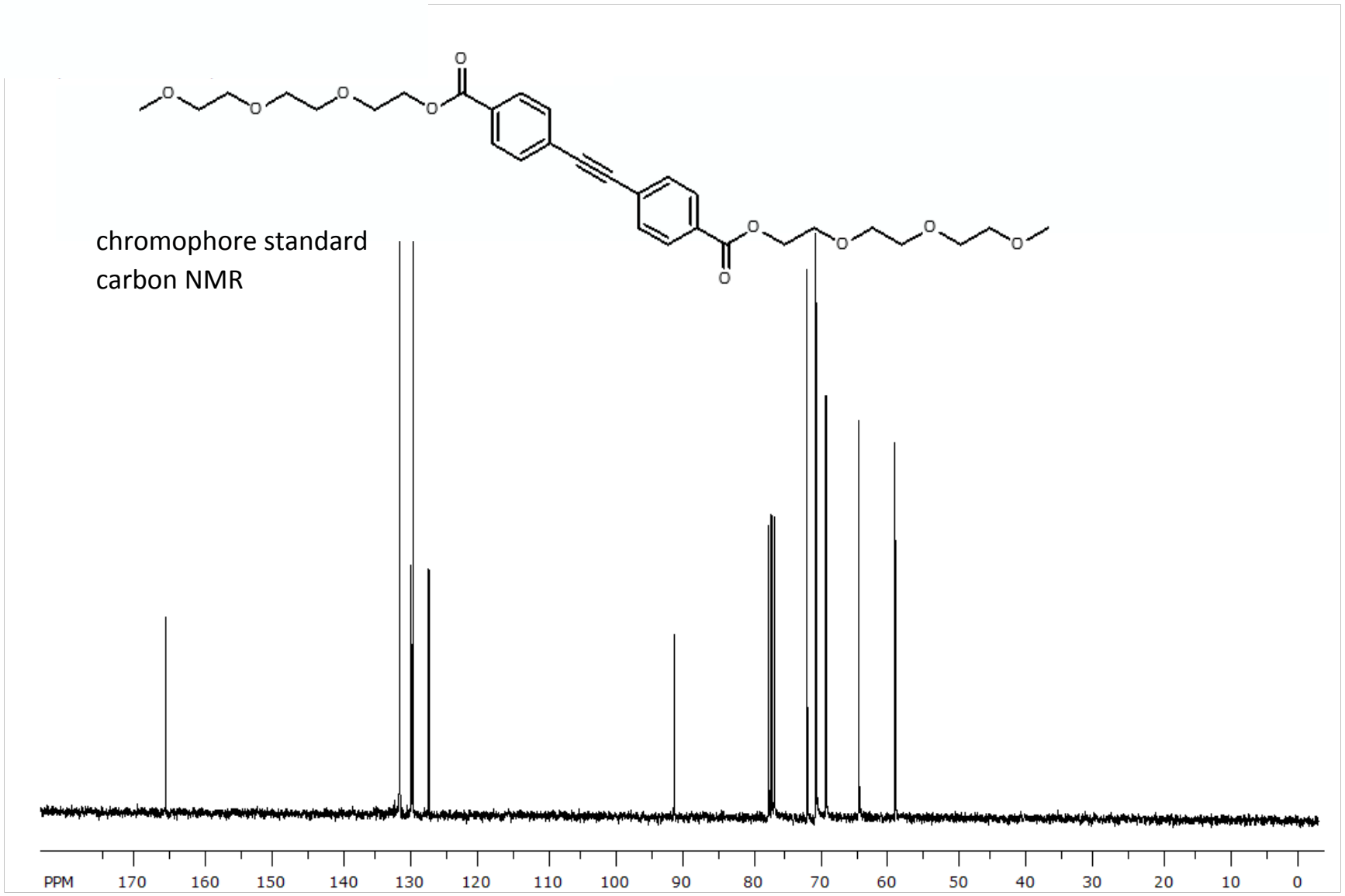


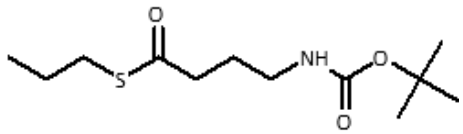


chromophore intermediate yne
carbon NMR

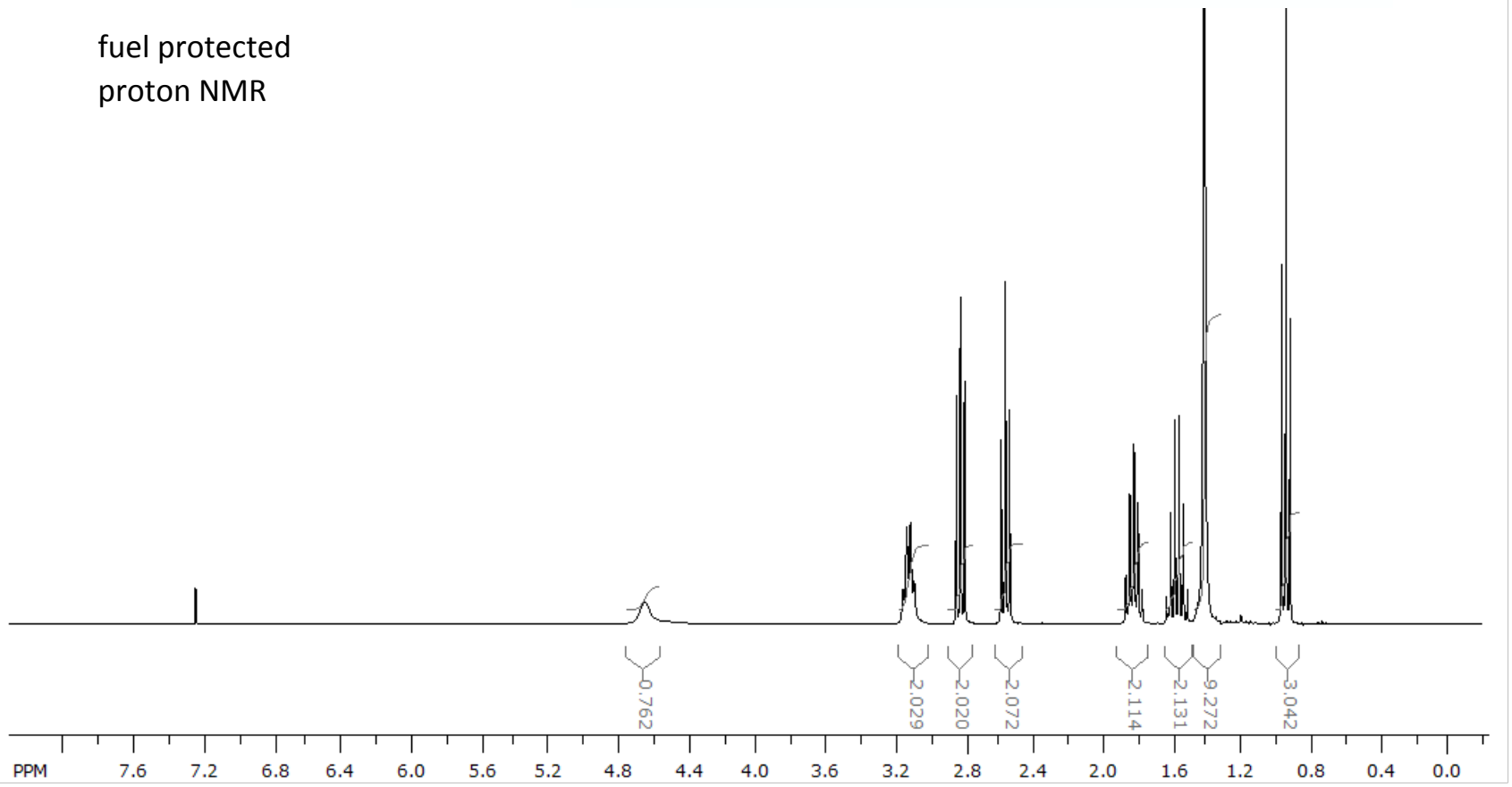


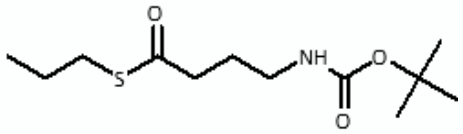

chromophore standard
proton NMR
4.094
4.089
4.053
4.052
12.35
4.001
6.043
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


chromophore standard
carbon NMR
PPM
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

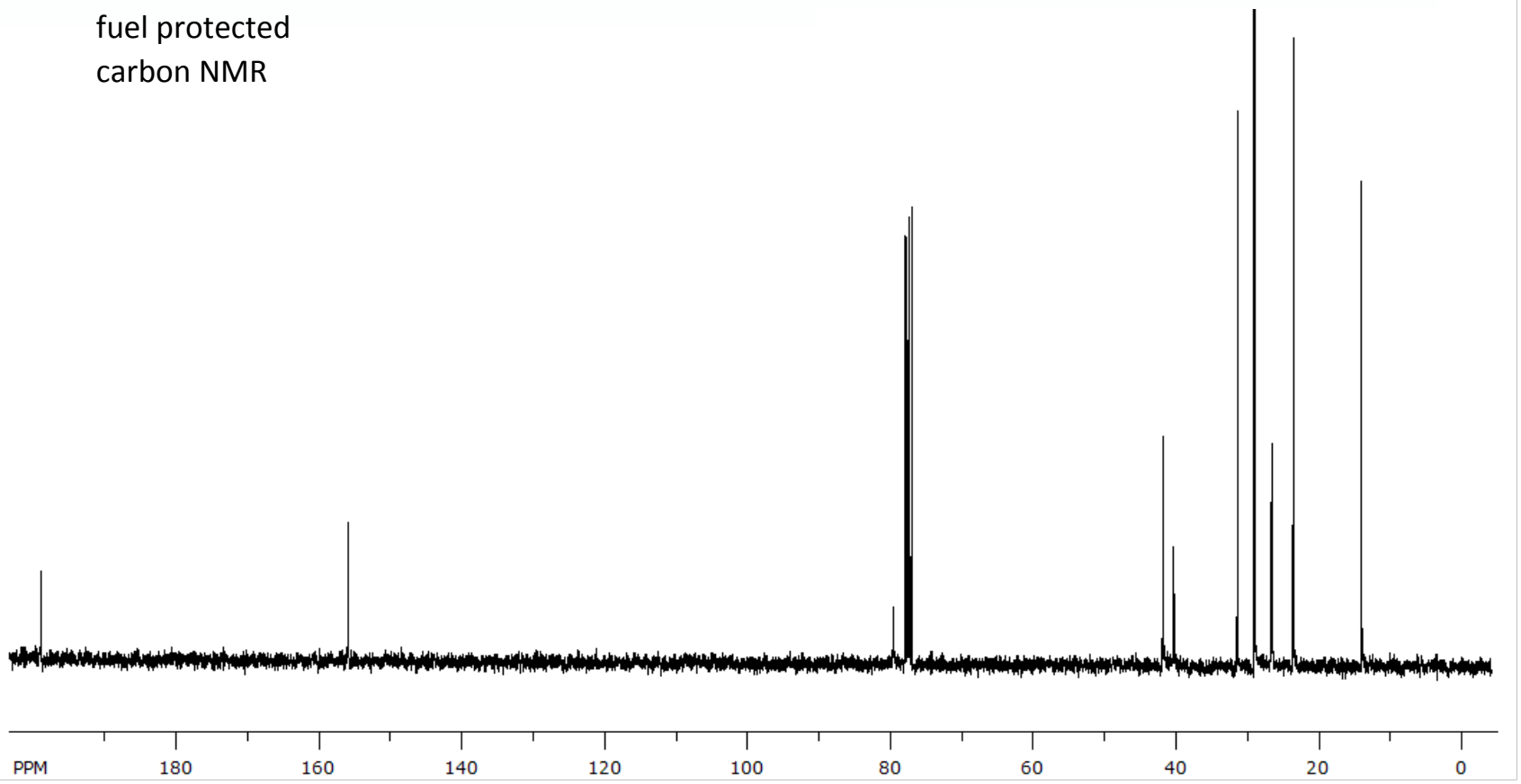


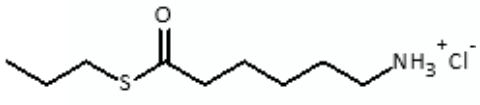
fuel protected
proton NMR



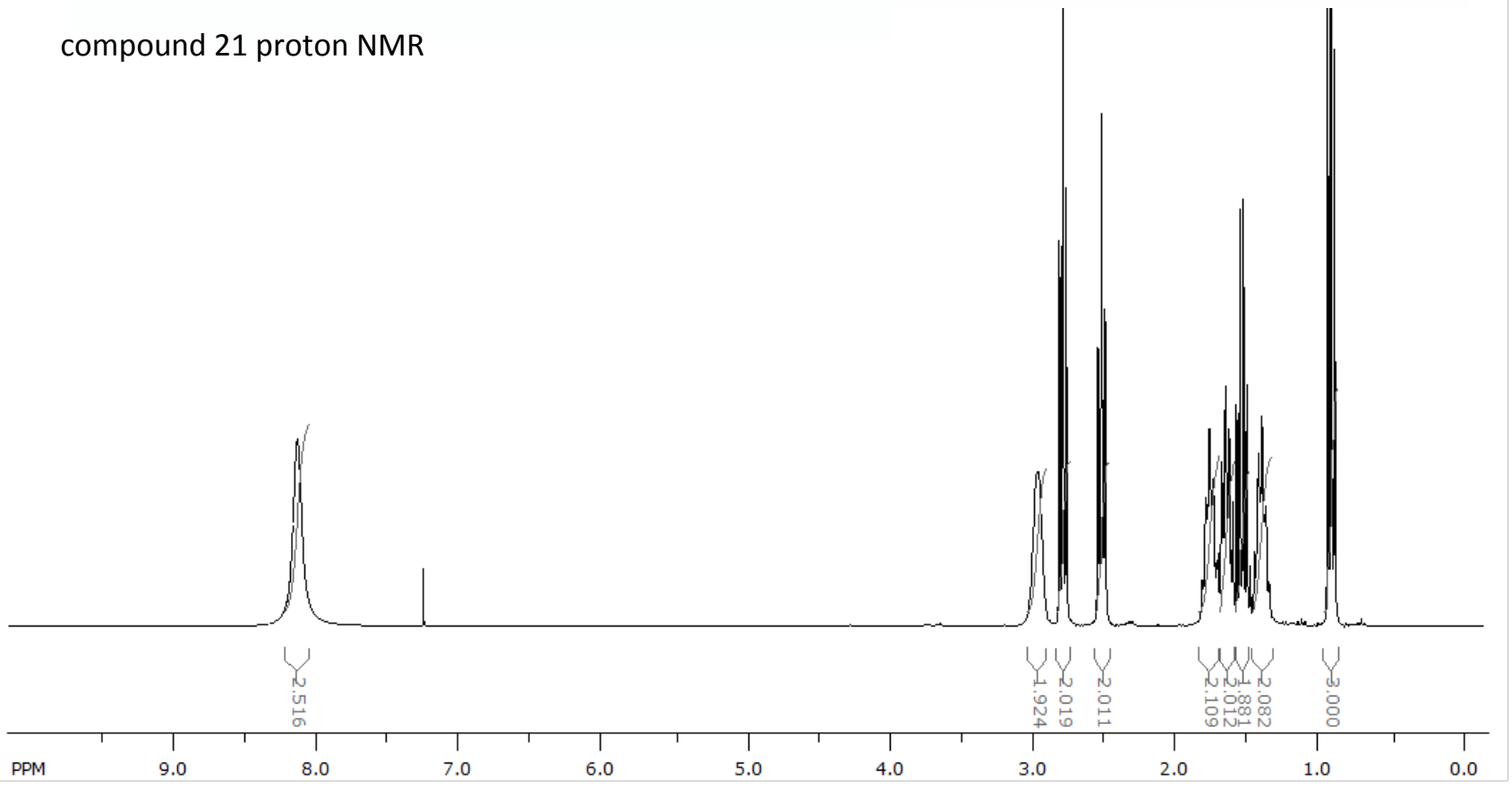


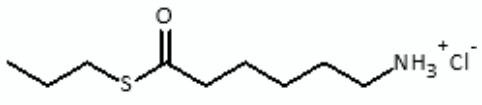
fuel protected
carbon NMR





compound 21 proton NMR





compound 21 carbon NMR