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Anion Binding Properties of a Cyclic Pseudohexapeptide Containing 1,5-Disubstituted 1,2,3-Triazole Subunits

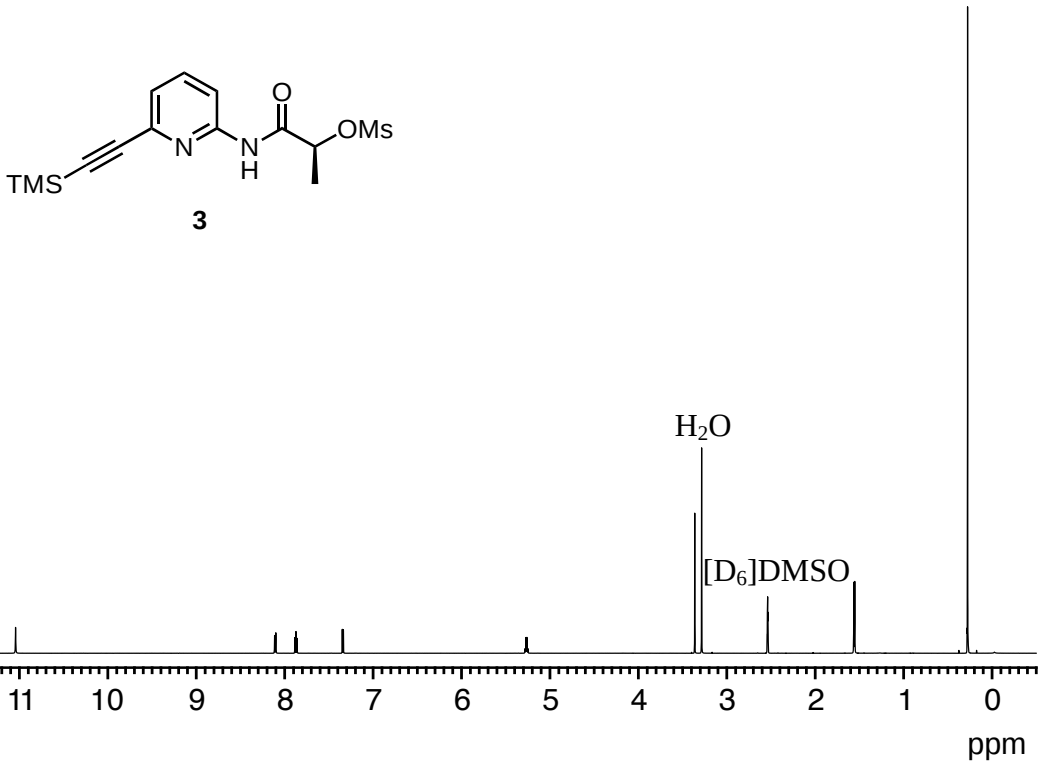
Martin R. Krause,[†] Richard Goddard,[§] Stefan Kubik[*,†]

† Fachbereich Chemie - Organische Chemie, Technische Universität Kaiserlautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany, Fax: +49-631-205-3921, Email: kubik@chemie.uni-kl.de

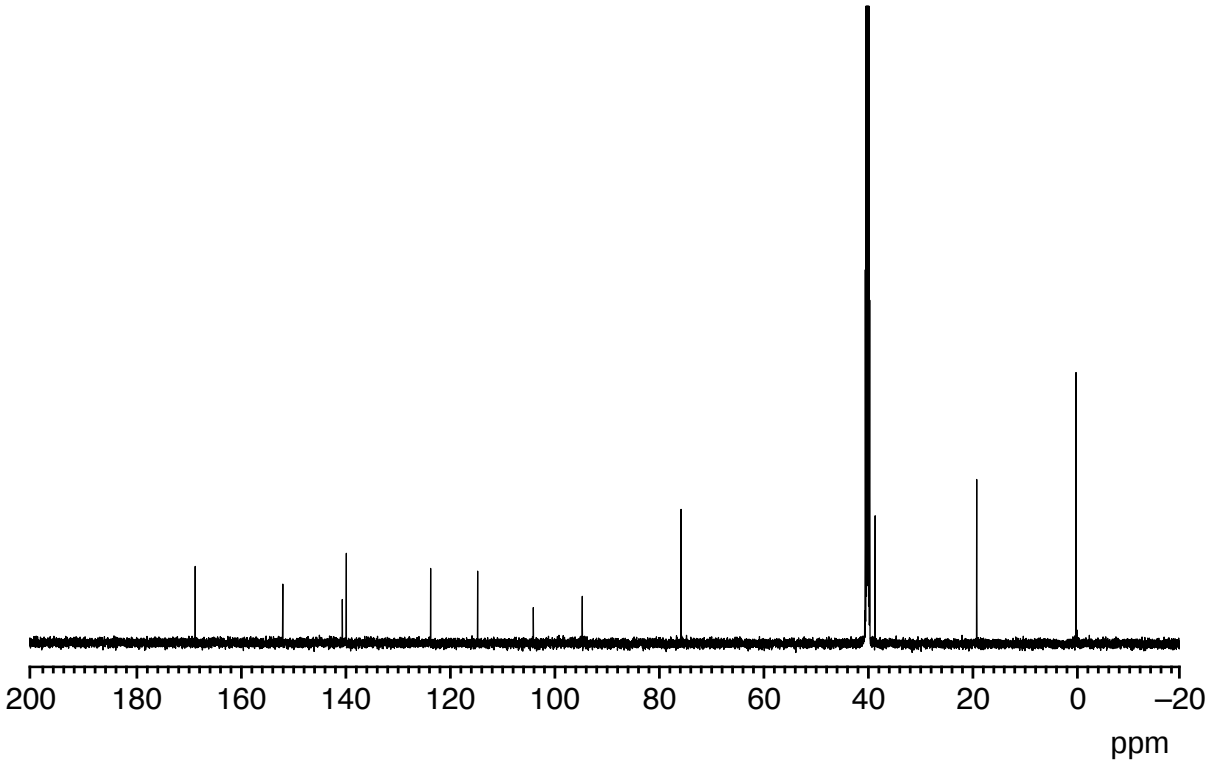
§ Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany

CONTENT

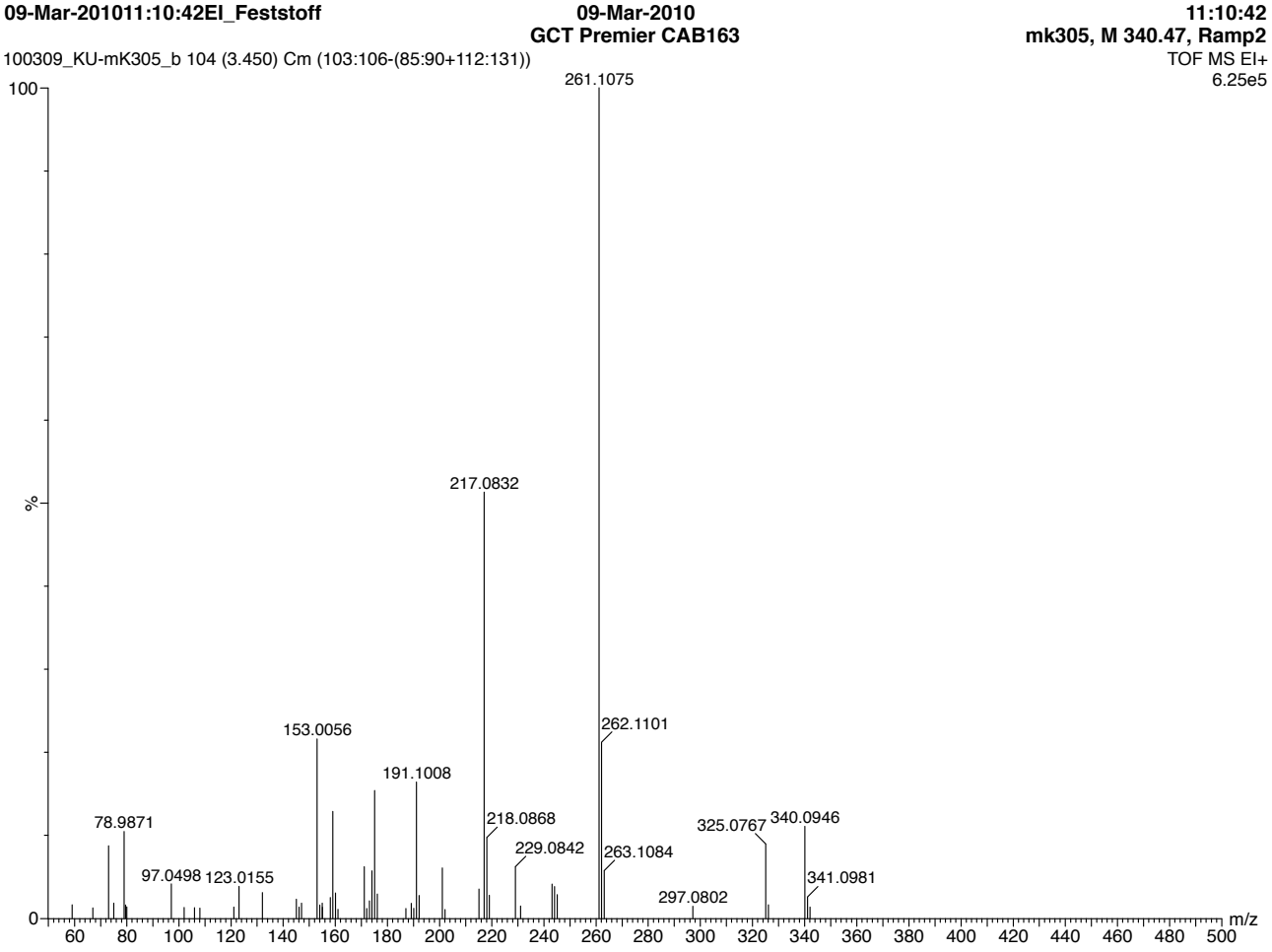
^{1}H NMR Spectrum: **3** in [D_6]DMSO (600 MHz, 25°C).



^{13}C NMR Spectrum: **3** in [D_6]DMSO (151 MHz, 25°C).

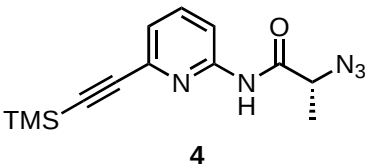


EI MS Spectrum: **3** (positive mode)



		m/z calcd.	*m/z exp.*
$\mathbf{3}^+$–$CH(CH_3)OSO_2CH_3$	$C_{14}H_{20}N_2O_4SSi^+$–$CH(CH_3)OSO_2CH_3$	217.0797	217.0832
$\mathbf{3}^+$–SO_2CH_3	$C_{14}H_{20}N_2O_4SSi^+$–SO_2CH_3	261.1059	261.1075
$\mathbf{3}^+$	$C_{14}H_{20}N_2O_4SSi^+$	340.0913	340.0946

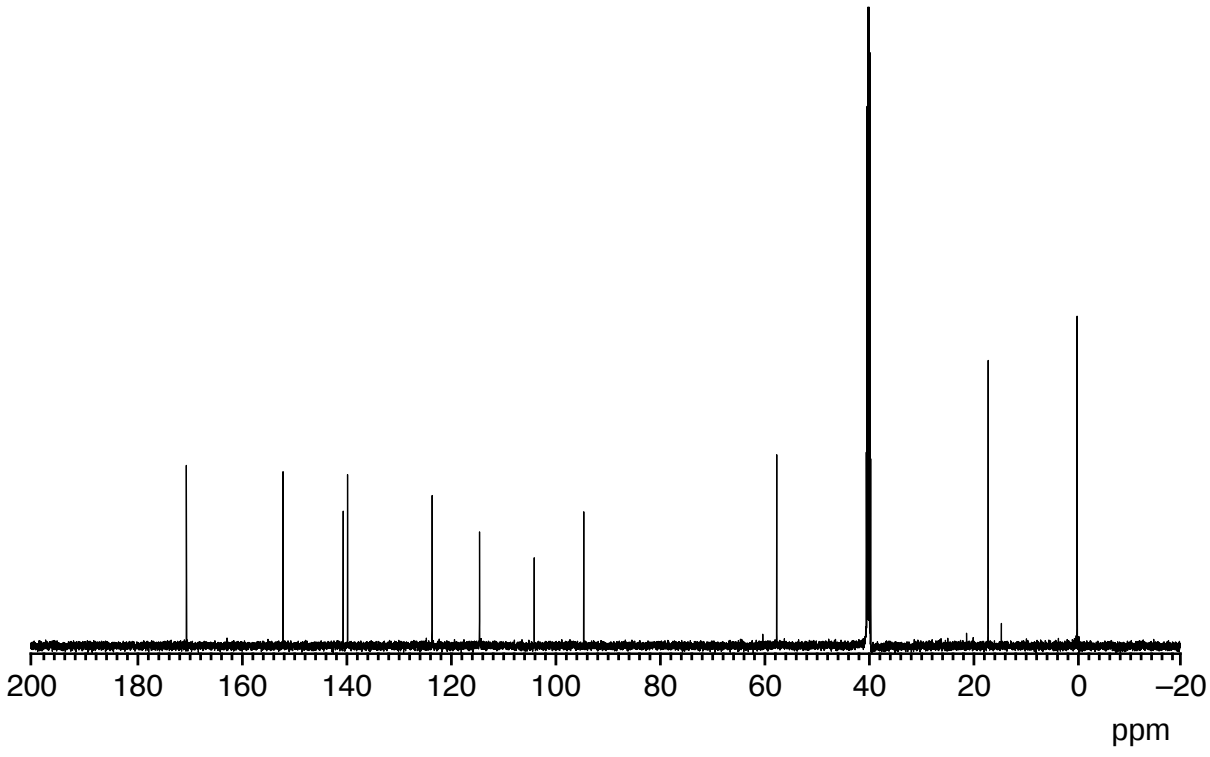
^{1}H NMR Spectrum: **4** in [D_6]DMSO (600 MHz, 25°C).



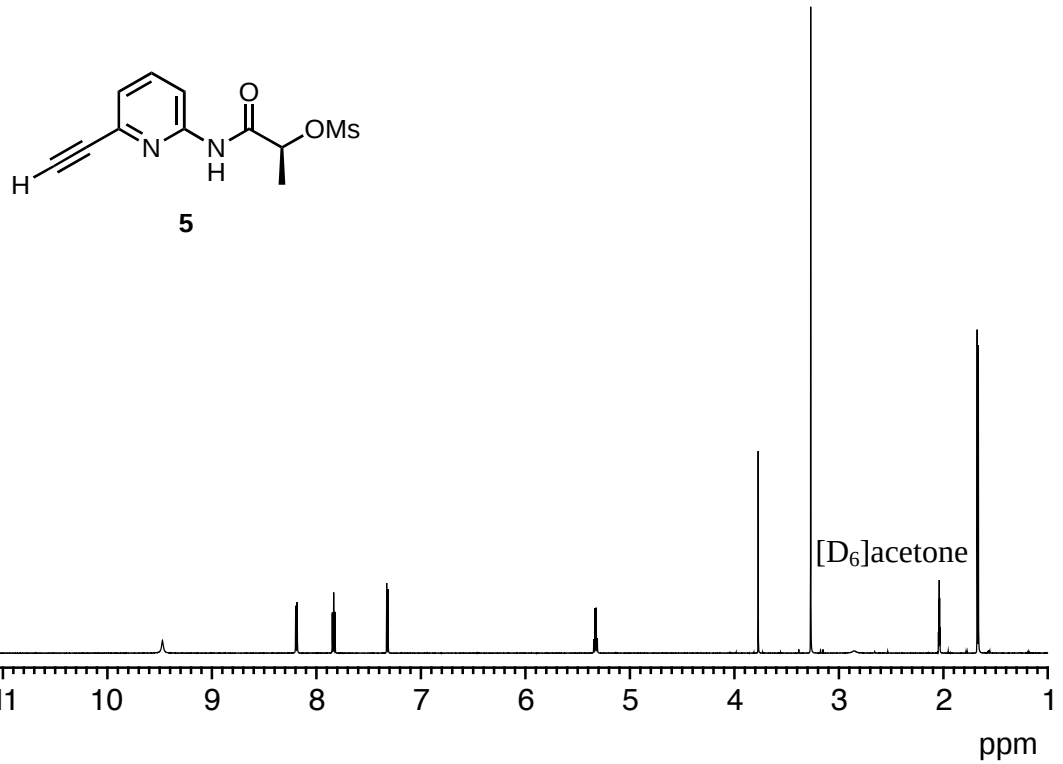
4

This compound is very prone to oligomerization. The spectra were thus recorded of freshly prepared samples.

^{13}C NMR Spectrum: **4** in [D_6]DMSO (151 MHz, 25°C).

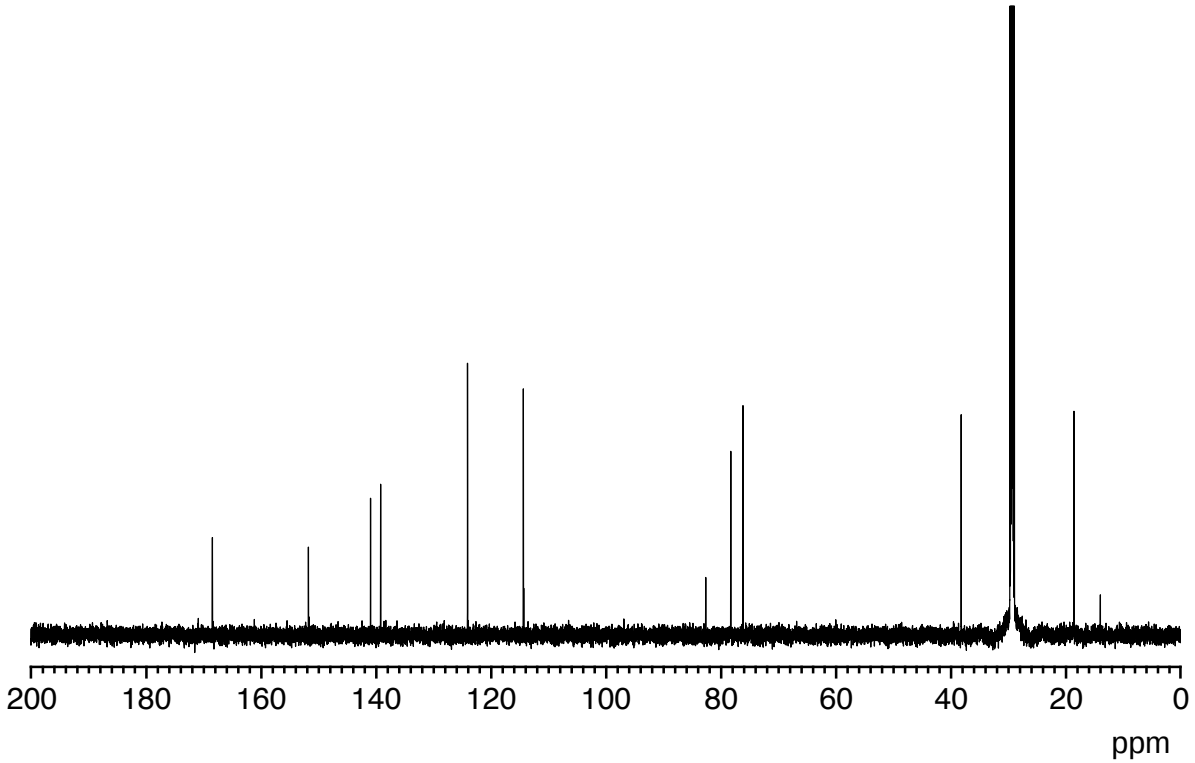


^{1}H NMR Spectrum: **5** in [D_6]acetone (600 MHz, 25°C).

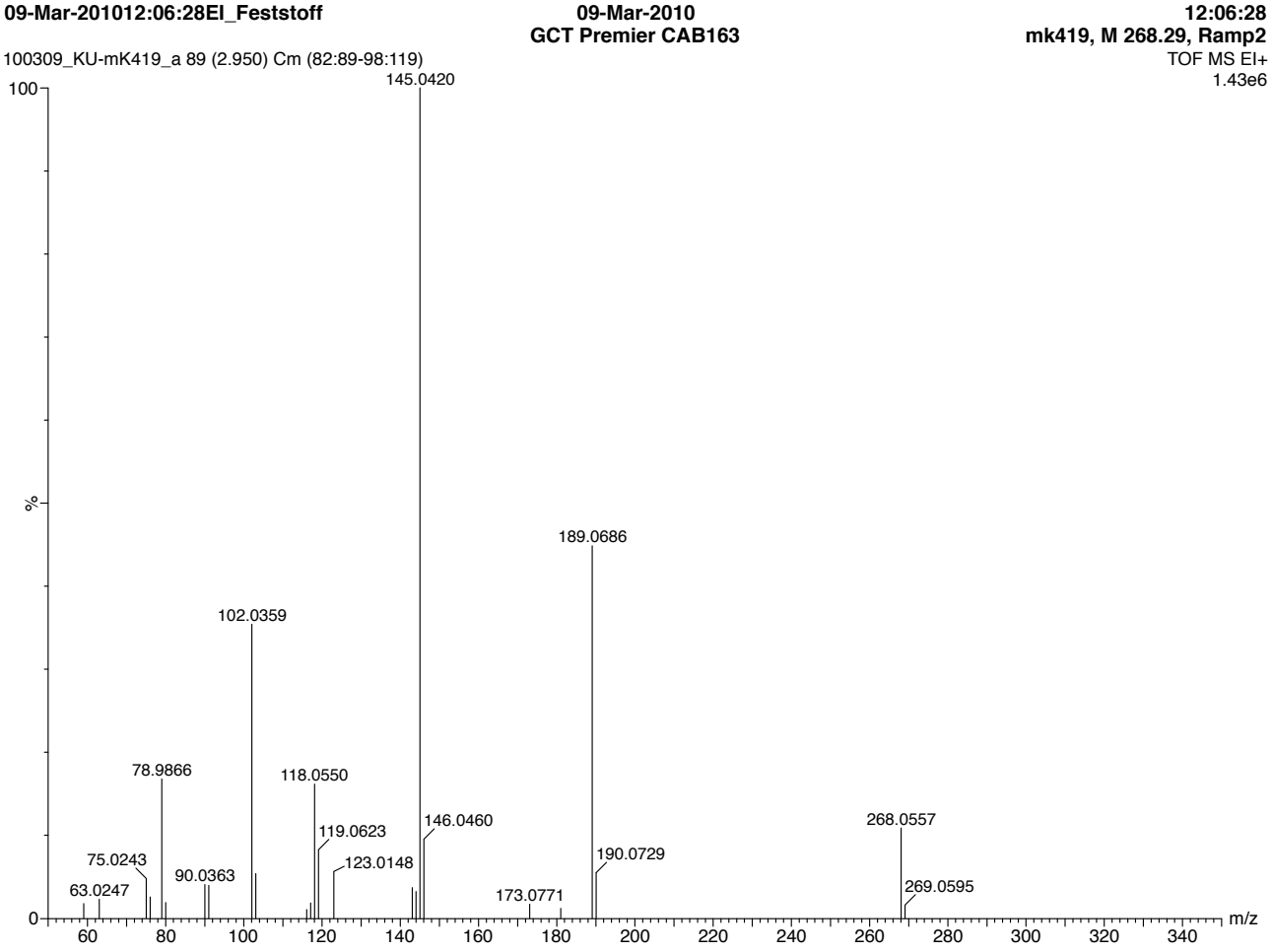


5

^{13}C NMR Spectrum: **5** in [D_6]acetone (151 MHz, 25°C).

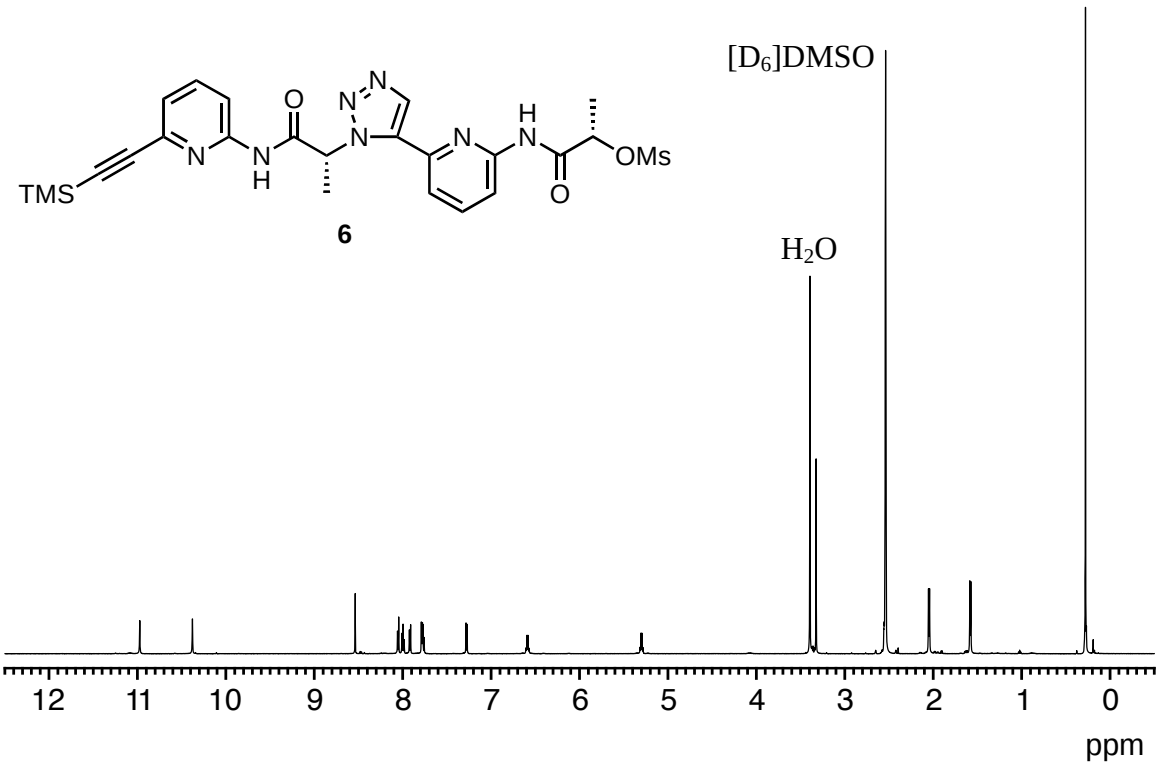


EI MS Spectrum: **5** (positive mode).

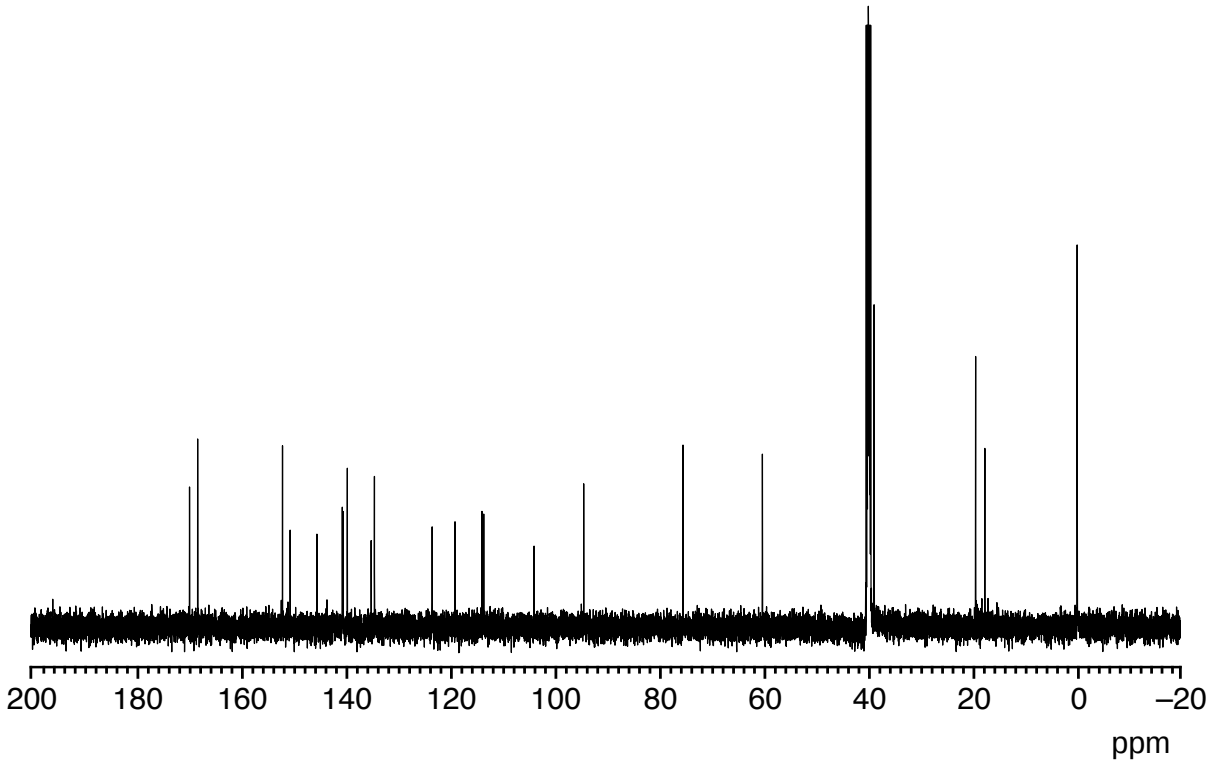


		m/z calcd.	*m/z exp.*
$\mathbf{5}^+$–$CH(CH_3)OSO_2CH_3$	$C_{11}H_{12}N_2O_4S^+$–$CH(CH_3)OSO_2CH_3$	145.0402	145.0420
$\mathbf{5}^+$–SO_2CH_3	$C_{11}H_{12}N_2O_4S^+$–SO_2CH_3	189.0664	189.0686
$\mathbf{5}^+$	$C_{11}H_{12}N_2O_4S^+$	268.0518	268.0557

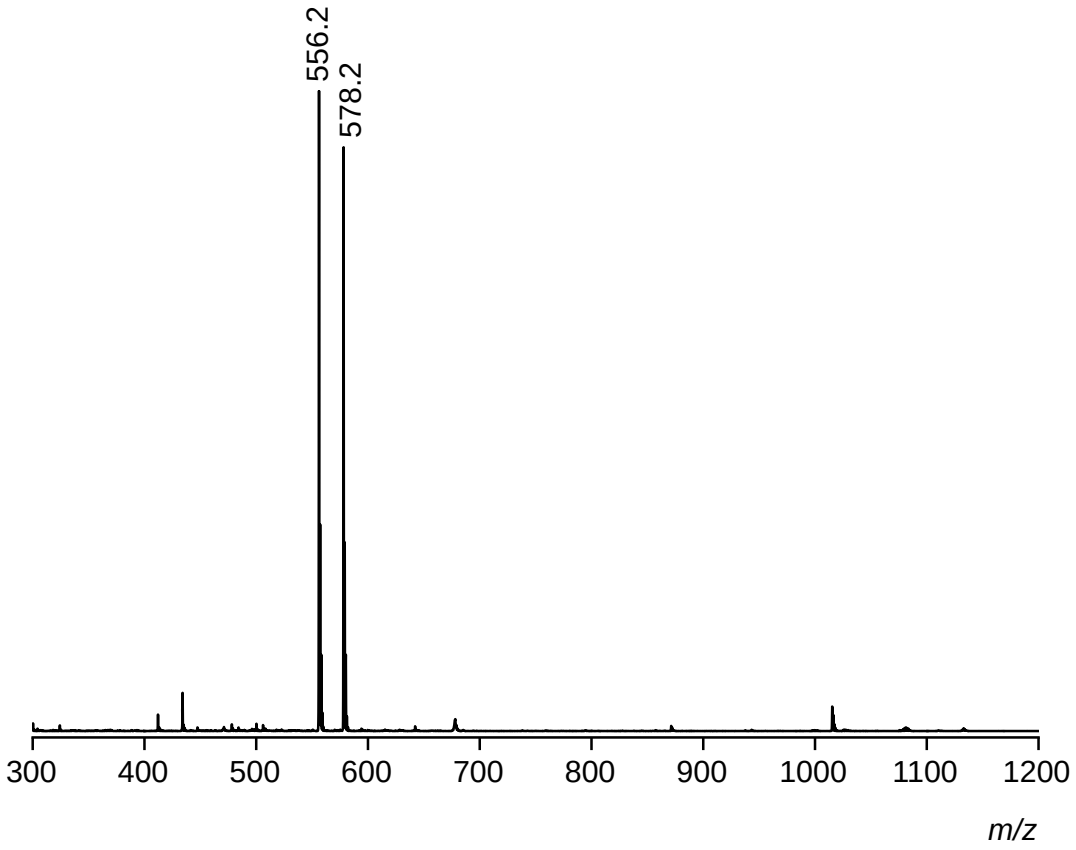
^{1}H NMR Spectrum: **6** in [D_6]DMSO (600 MHz, 25°C).



^{13}C NMR Spectrum: **6** in [D_6]DMSO (151 MHz, 25°C).

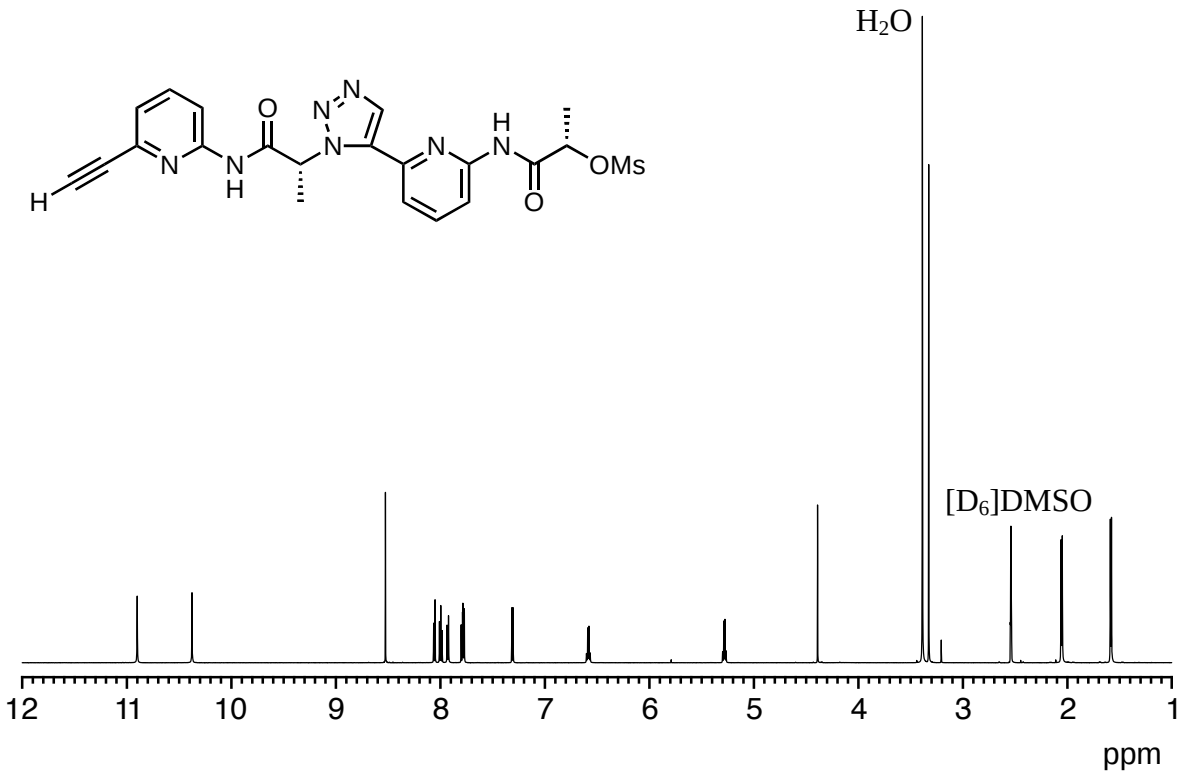


ESI-TOF MS Spectrum: **6** (positive mode).

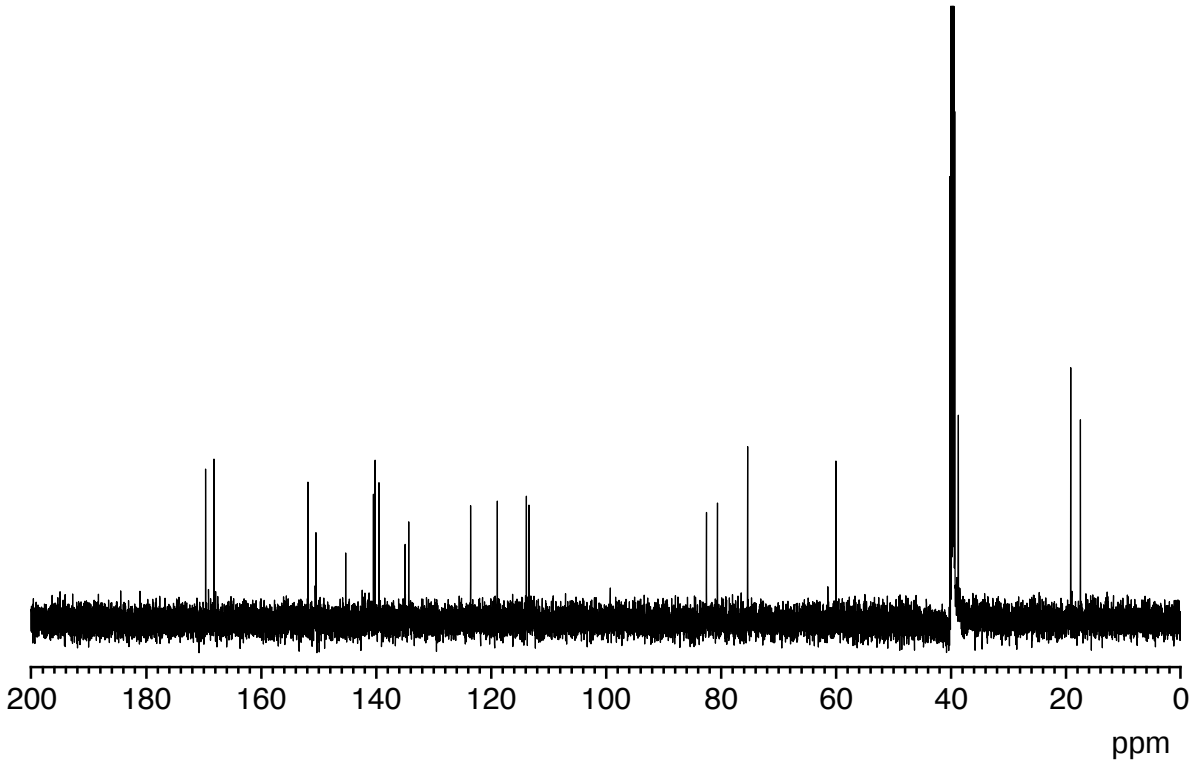


		m/z calcd.	*m/z exp.*
6 + H^+	$C_{24}H_{29}N_7O_5SSi + H^+$	556.18	556.2
6 + Na^+	$C_{24}H_{29}N_7O_5SSi + Na^+$	578.16	578.2

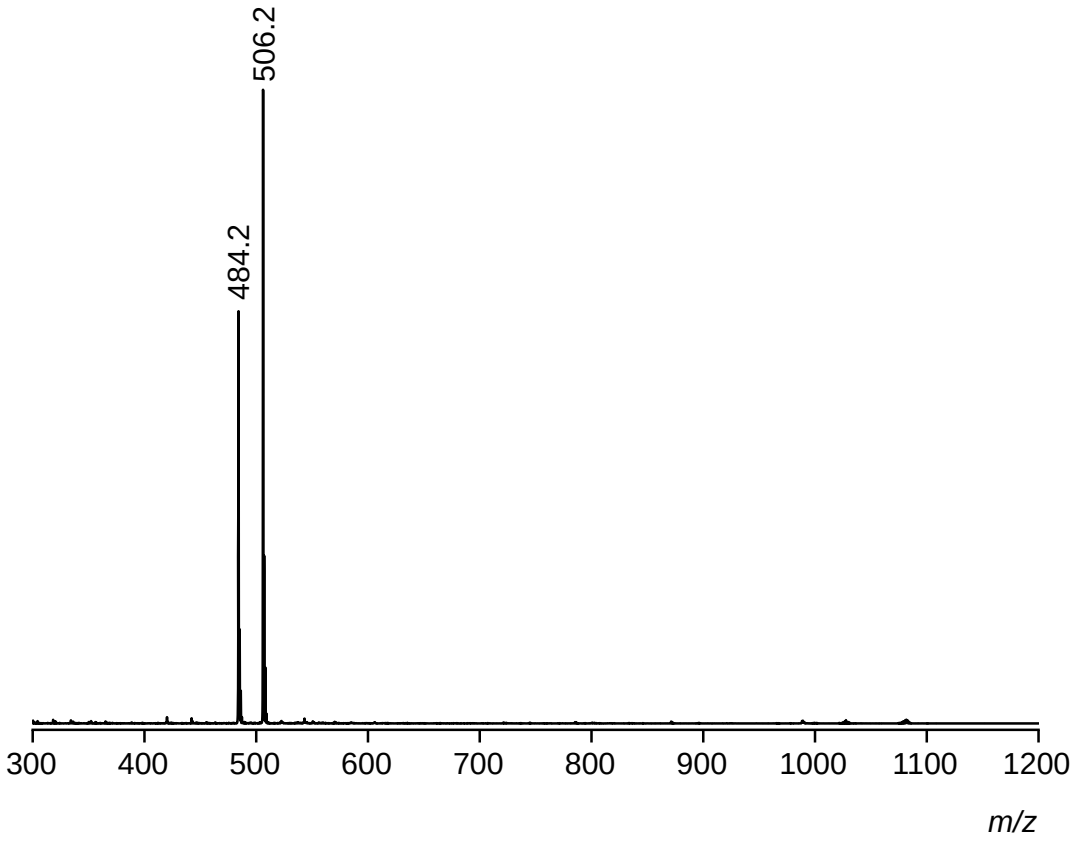
^{1}H NMR Spectrum: TMS-deprotected **6** in [D_6]DMSO (600 MHz, 25°C).



^{13}C NMR Spectrum: TMS-deprotected **6** in [D_6]DMSO (151 MHz, 25°C).

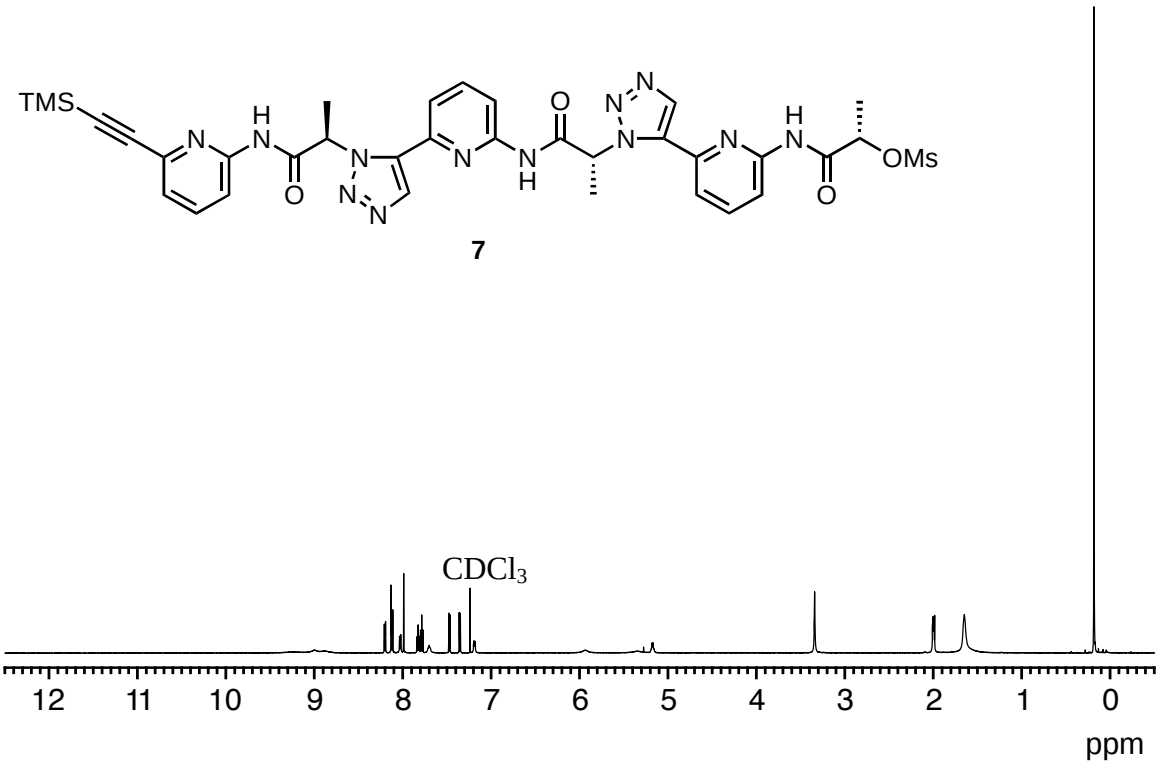


ESI-TOF MS Spectrum: TMS-deprotected **6** (positive mode).



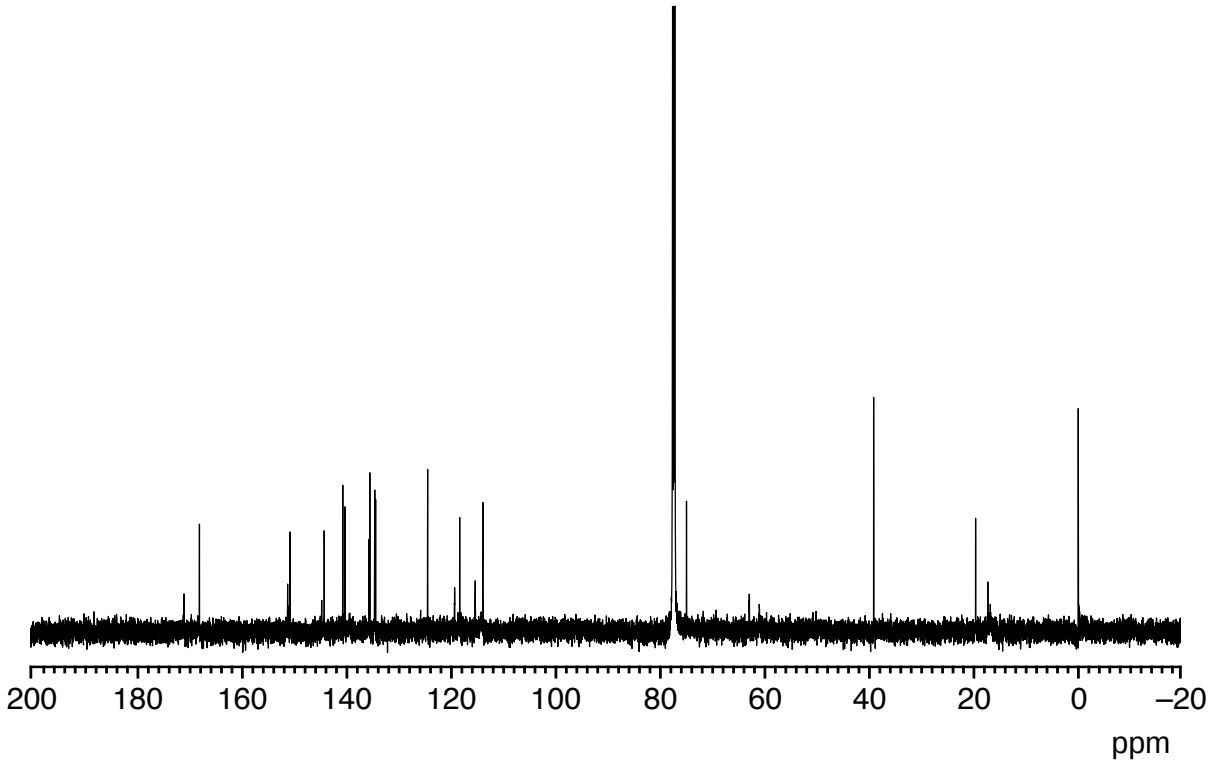
		m/z calcd.	*m/z exp.*
6-TMS + H^+	$C_{21}H_{21}N_7O_5S + H^+$	484.14	484.2
6-TMS + Na^+	$C_{21}H_{21}N_7O_5S + Na^+$	506.12	506.2

^{1}H NMR Spectrum: **7** in $CDCl_3$ (600 MHz, 25°C).

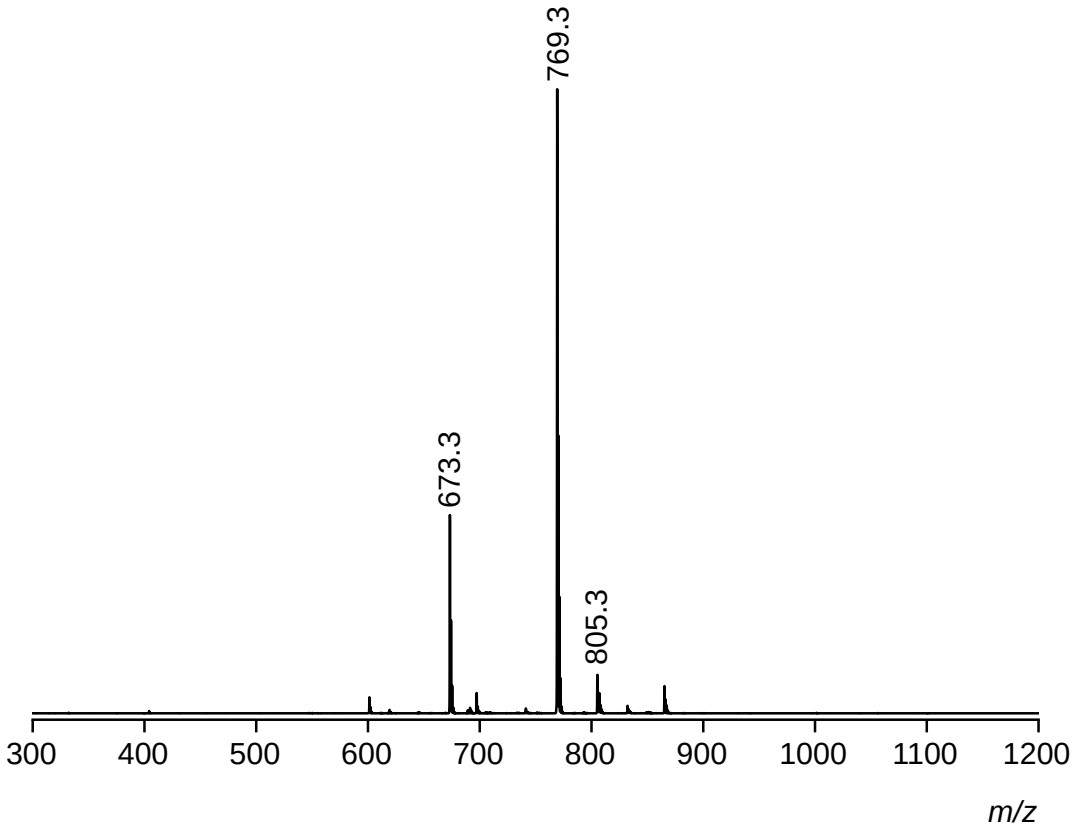


7

^{13}C NMR Spectrum: **7** in $CDCl_3$ (151 MHz, 25°C).

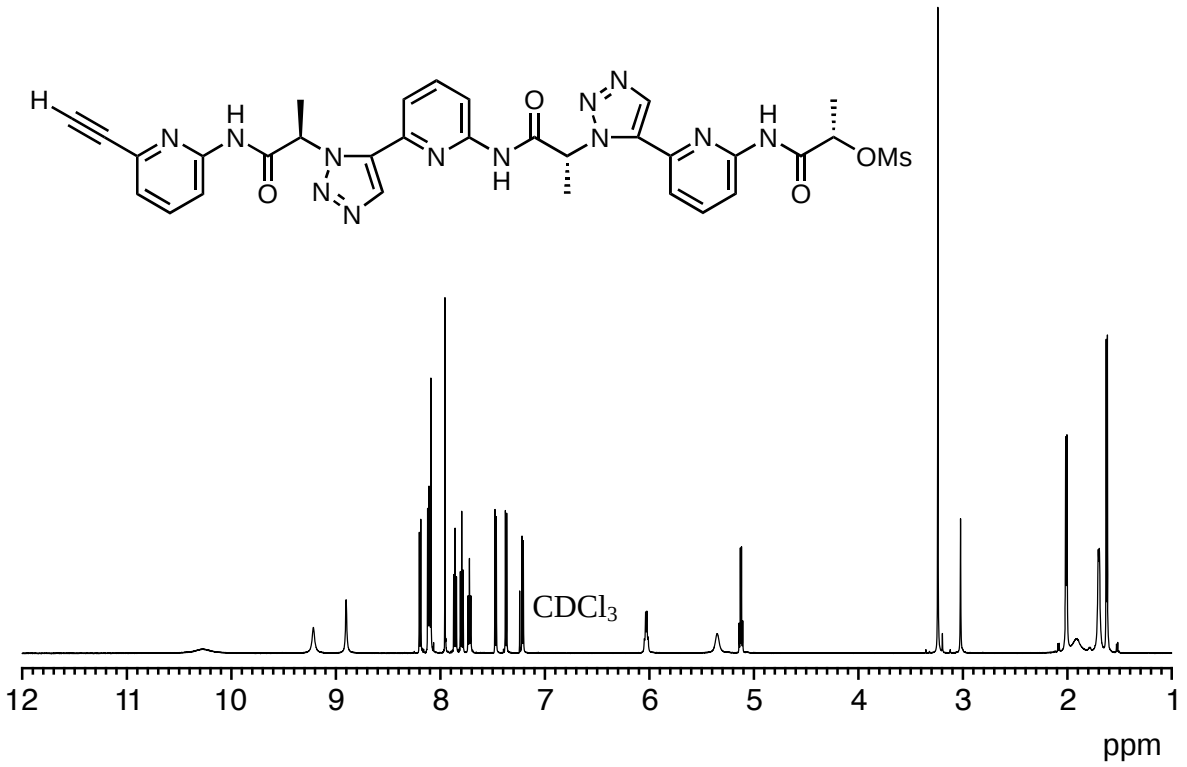


ESI-TOF MS Spectrum: **7** (negative mode).

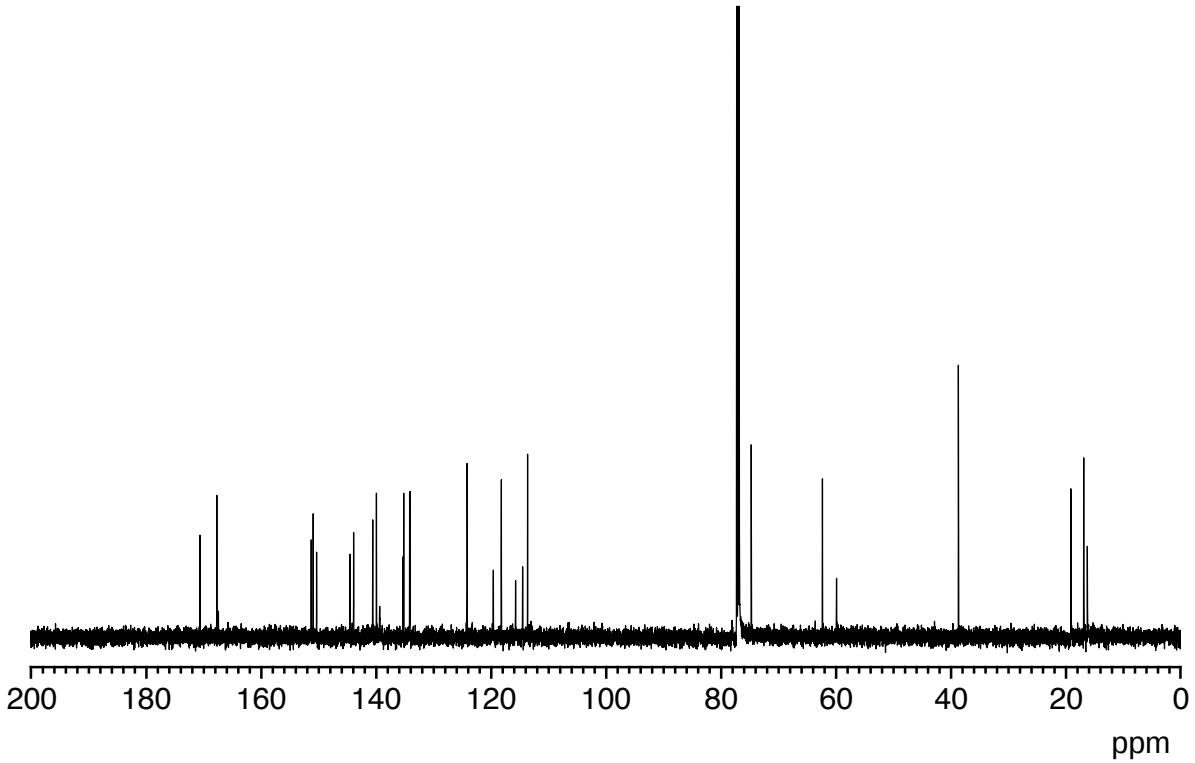


		m/z calcd.	*m/z exp.*
7 – CH_3SO_3H – H^+	$C_{34}H_{38}N_{12}O_6SSi$ – CH_3SO_3H – H^+	673.26	673.3
7 – H^+	$C_{34}H_{38}N_{12}O_6SSi$ – H^+	769.24	769.3
7 + Cl^-	$C_{34}H_{38}N_{12}O_6SSi$ + Cl^-	805.22	805.3

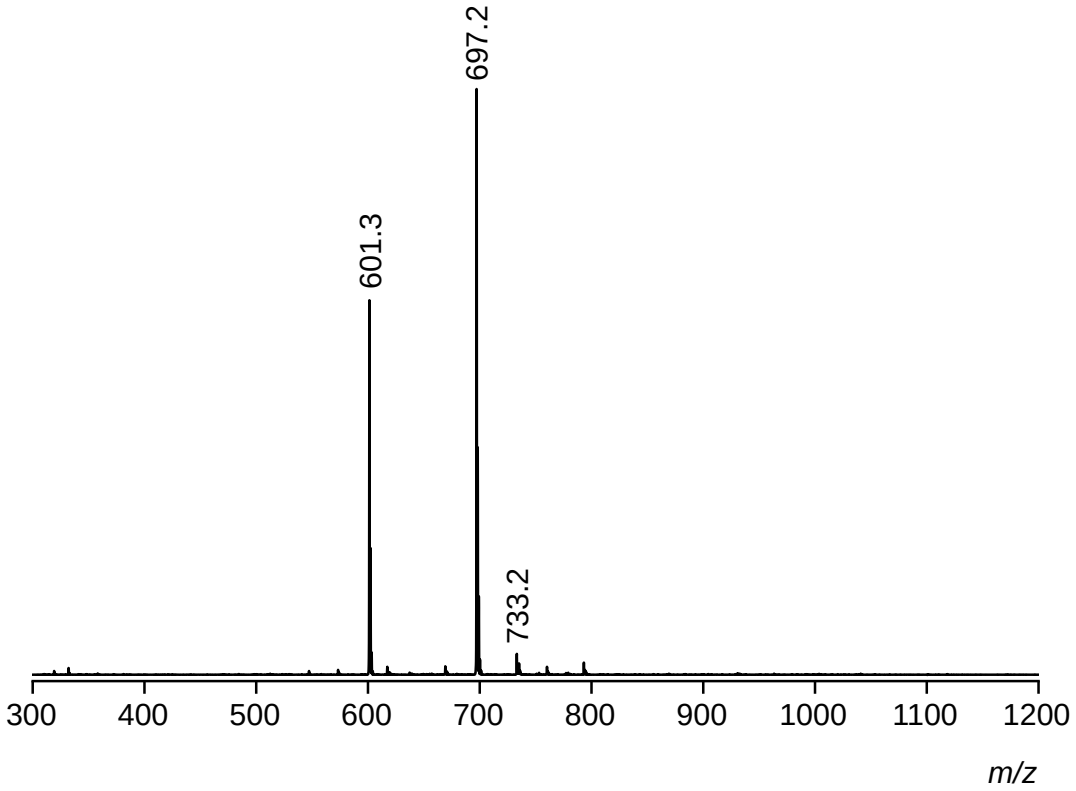
^{1}H NMR Spectrum: TMS-deprotected **7** in $CDCl_3$ (600 MHz, 25°C).



^{13}C NMR Spectrum: TMS-deprotected **7** in $CDCl_3$ (151 MHz, 25°C).

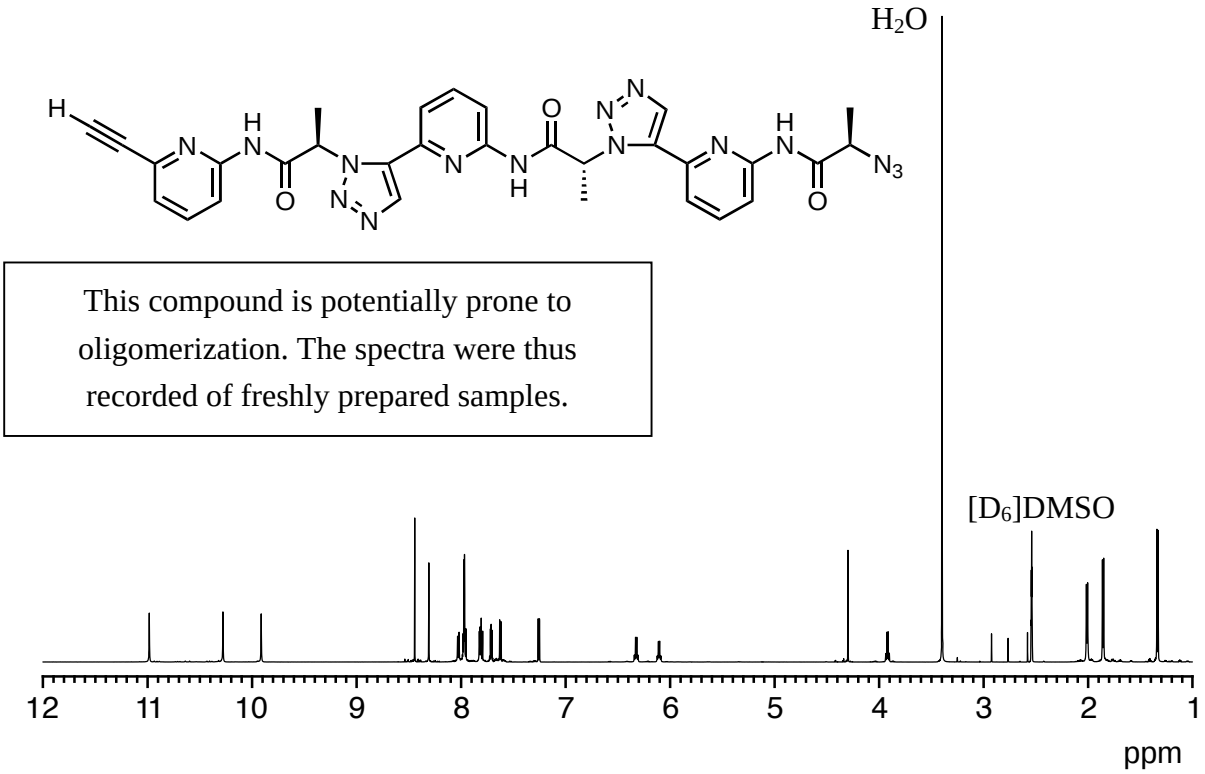


ESI-TOF MS Spectrum: TMS-deprotected **7** (negative mode).



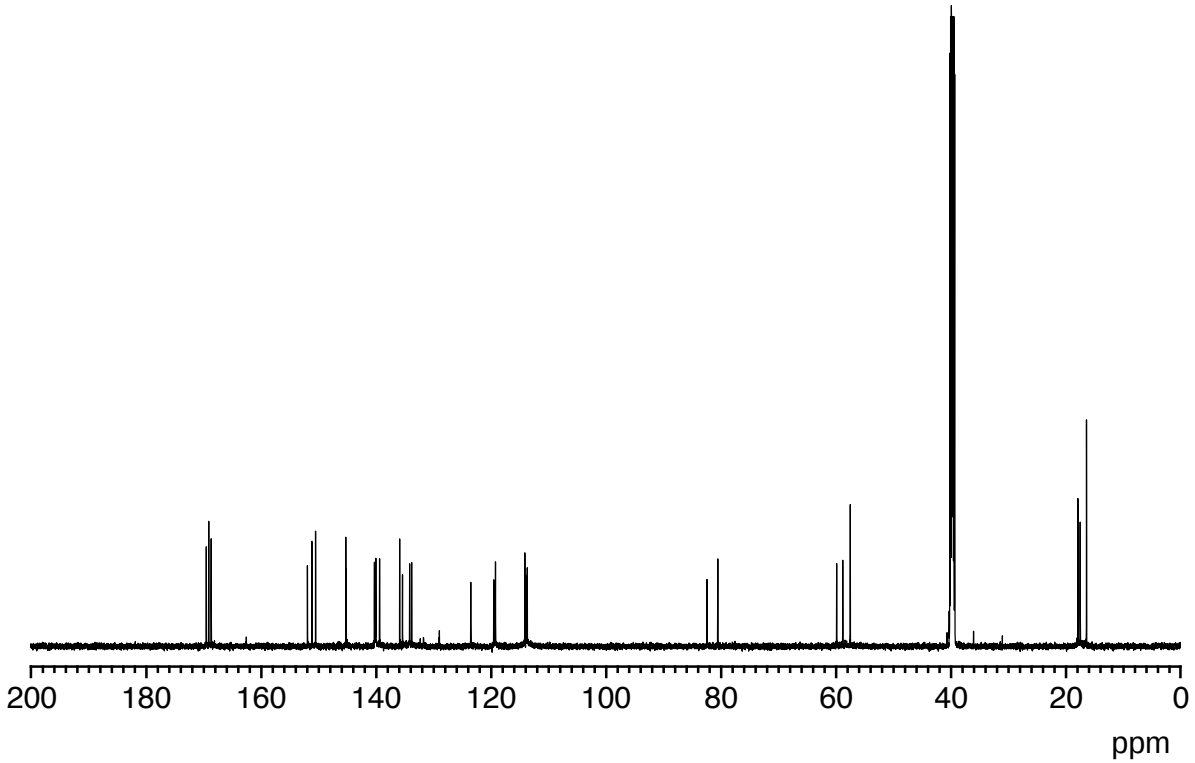
		m/z calcd.	*m/z exp.*
7-TMS – CH_3SO_3H – H^+	$C_{31}H_{30}N_{12}O_6S$ – CH_3SO_3H – H^+	601.22	601.3
7-TMS – H^+	$C_{31}H_{30}N_{12}O_6S$ – H^+	697.21	697.2
7-TMS + Cl^-	$C_{31}H_{30}N_{12}O_6S$ + Cl^-	733.18	733.2

^{1}H NMR Spectrum: Linear precursor of **8** in [D_6]DMSO (600 MHz, 25°C).

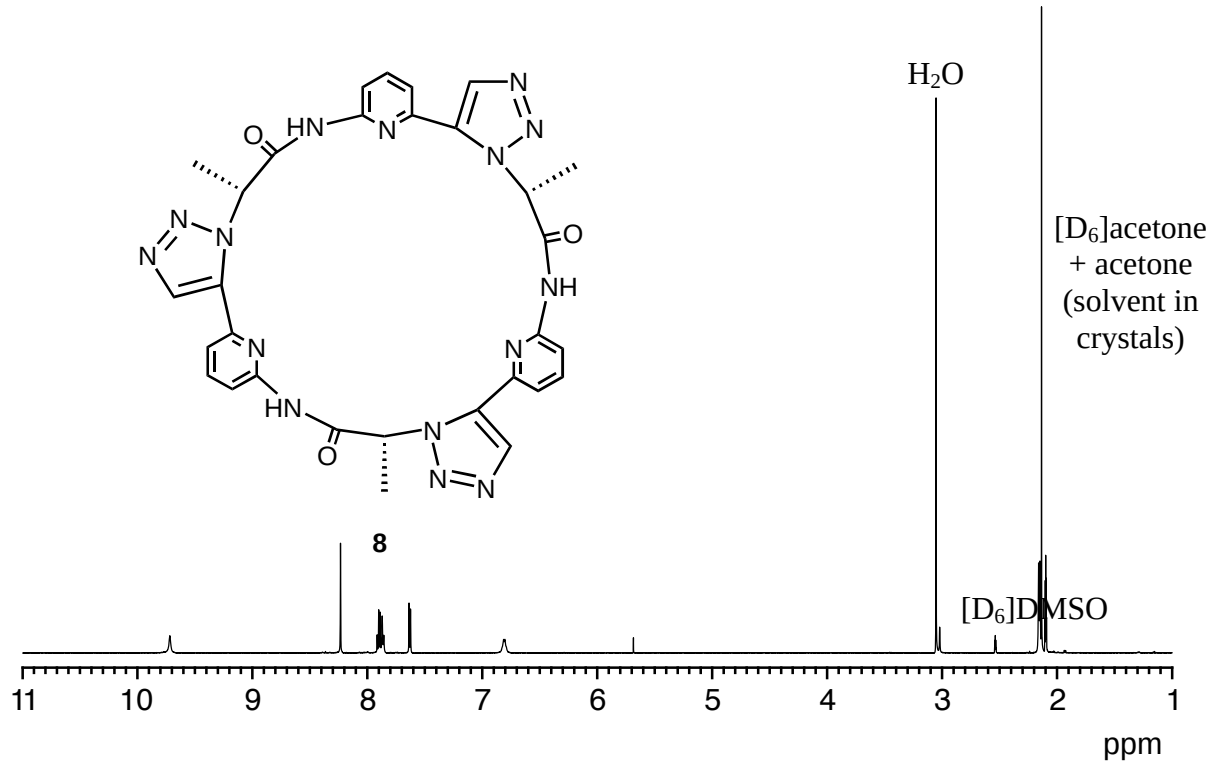


This compound is potentially prone to oligomerization. The spectra were thus recorded of freshly prepared samples.

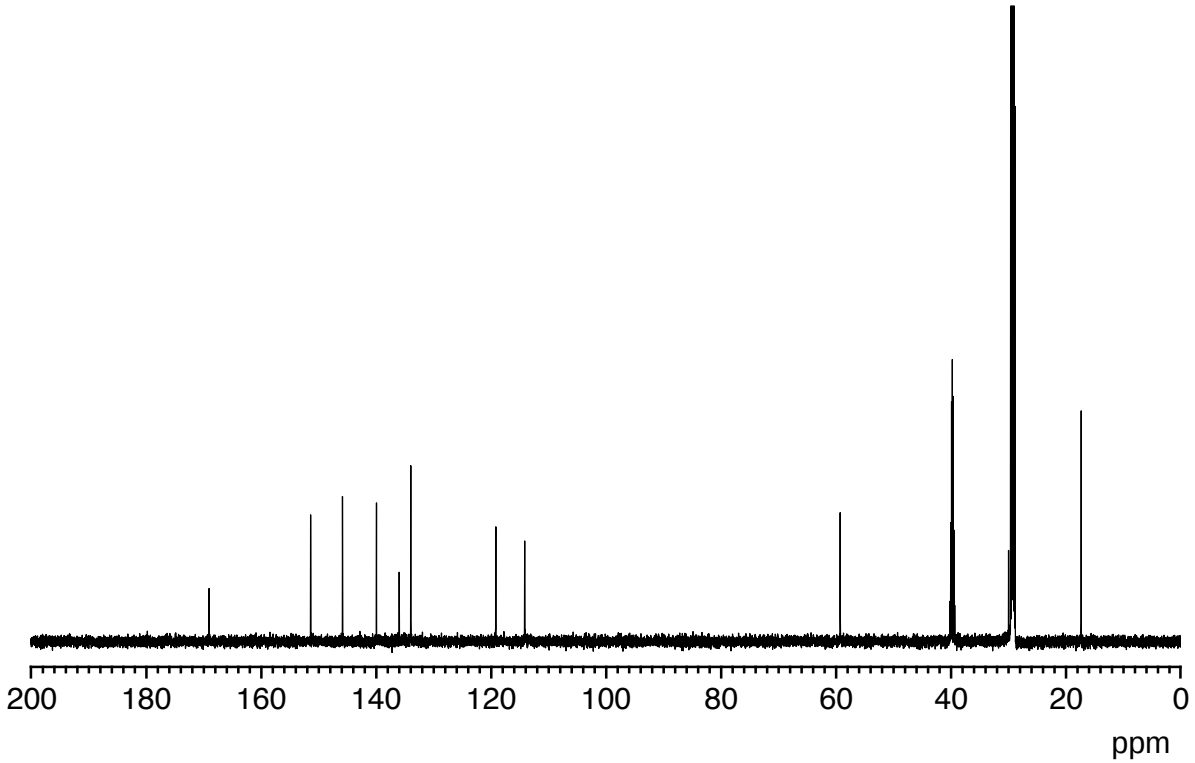
^{13}C NMR Spectrum: Linear precursor of **8** in [D_6]DMSO (151 MHz, 25°C).



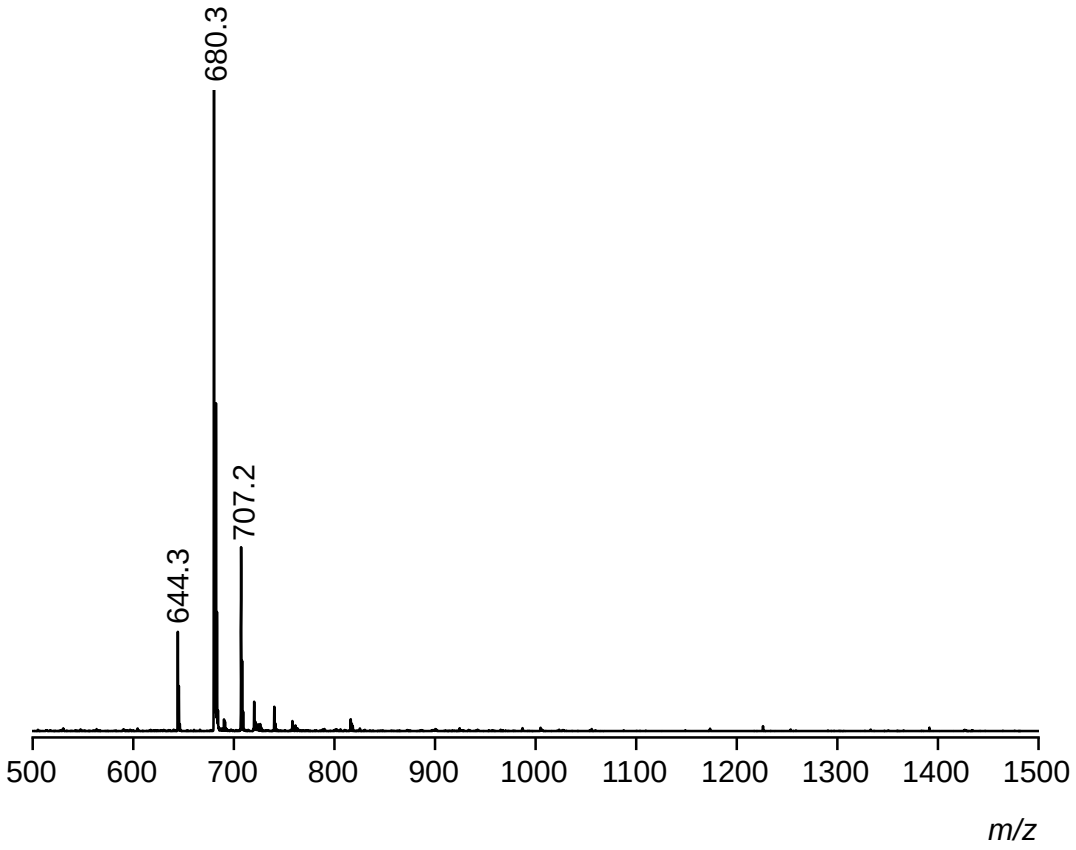
^{1}H NMR Spectrum: **8** in [D_6]DMSO/[D_6]acetone 1:9 (*v/v*) (600 MHz, 25°C).



^{13}C NMR Spectrum: **8** in [D_6]DMSO/[D_6]acetone 1:9 (*v/v*) (151 MHz, 25°C).

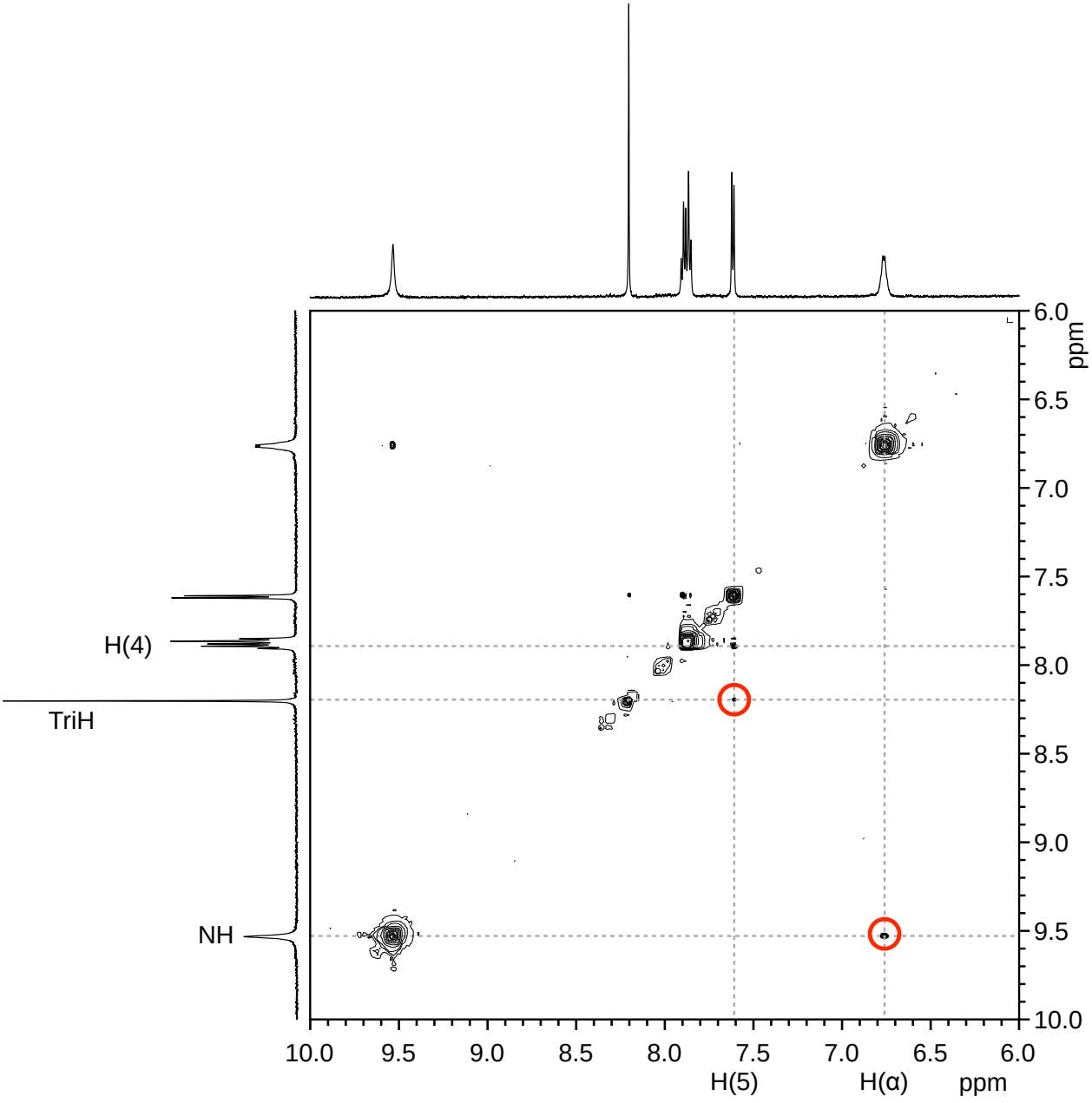


ESI-TOF MS Spectrum: **8** (negative mode).

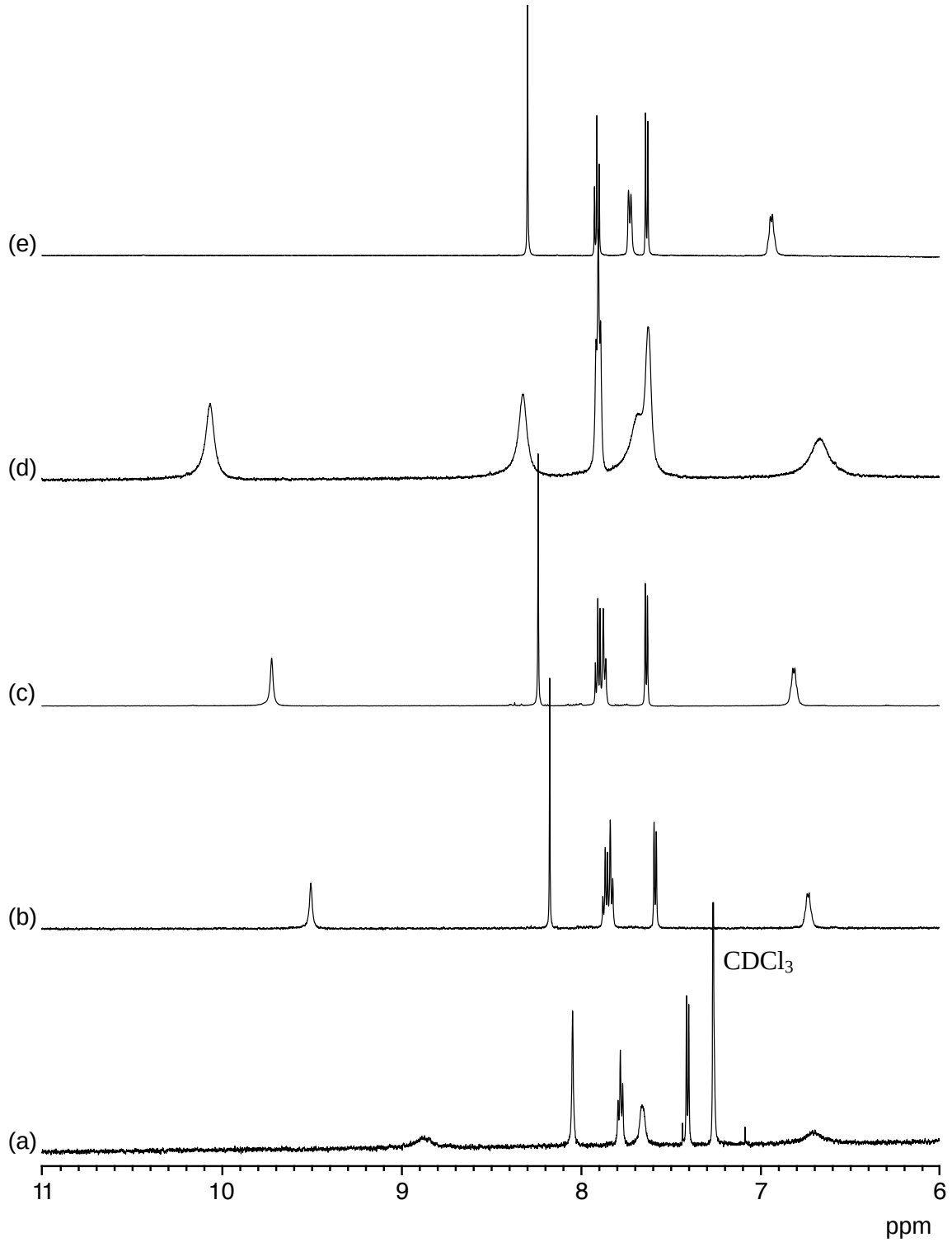


		m/z calcd.	*m/z exp.*
8 – H^+	$(C_{30}H_{27}N_{15}O_3) - H^+$	644.23	644.3
8 + Cl^-	$(C_{30}H_{27}N_{15}O_3) + Cl^-$	680.21	680.3
8 + NO_3^-	$(C_{30}H_{27}N_{15}O_3) + NO_3^-$	707.23	707.2

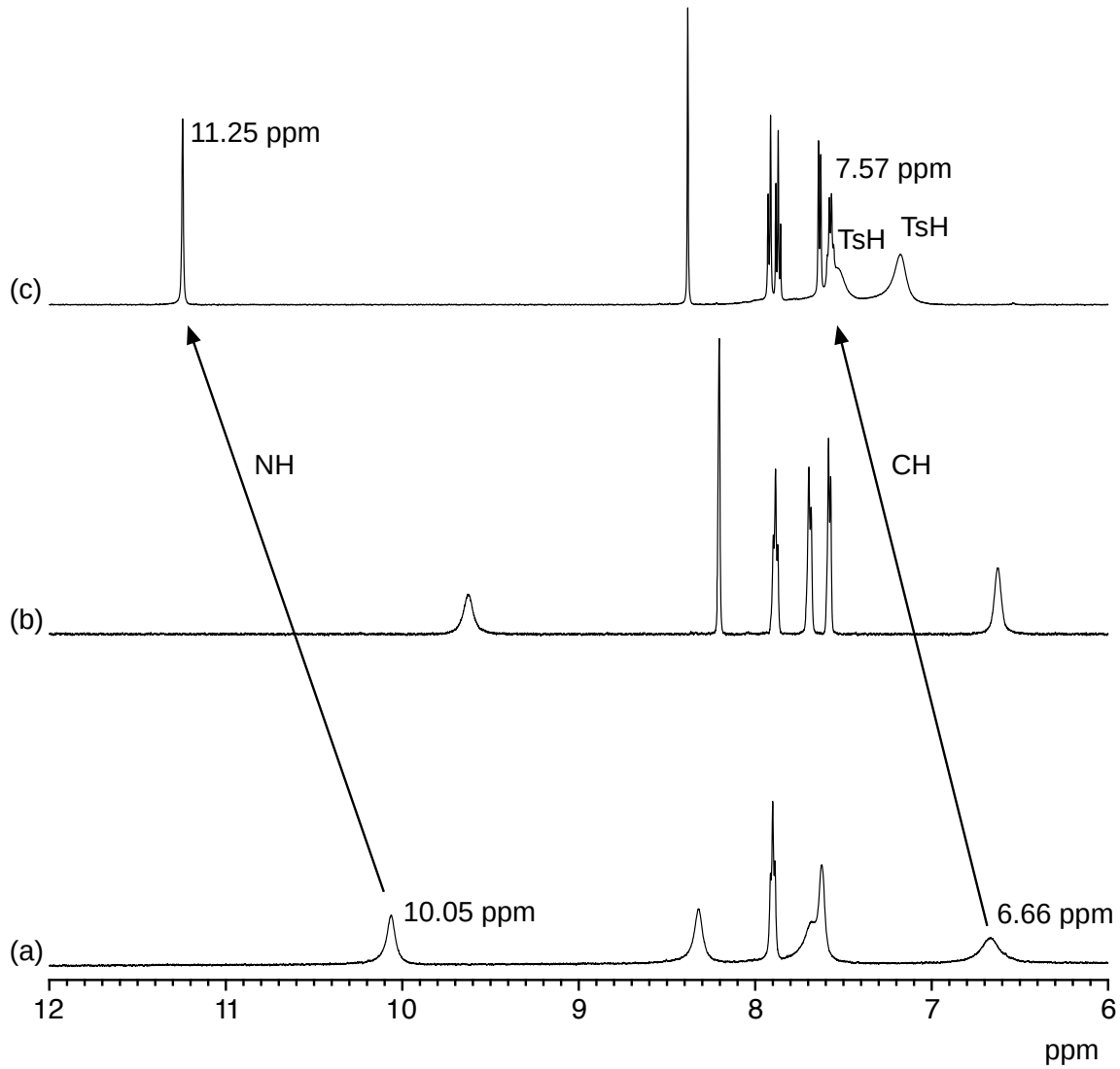
NOESY NMR Spectrum: **8** (2 mM) in [D_6]acetone (mixing time 150 ms) (600 MHz, 25 °C).



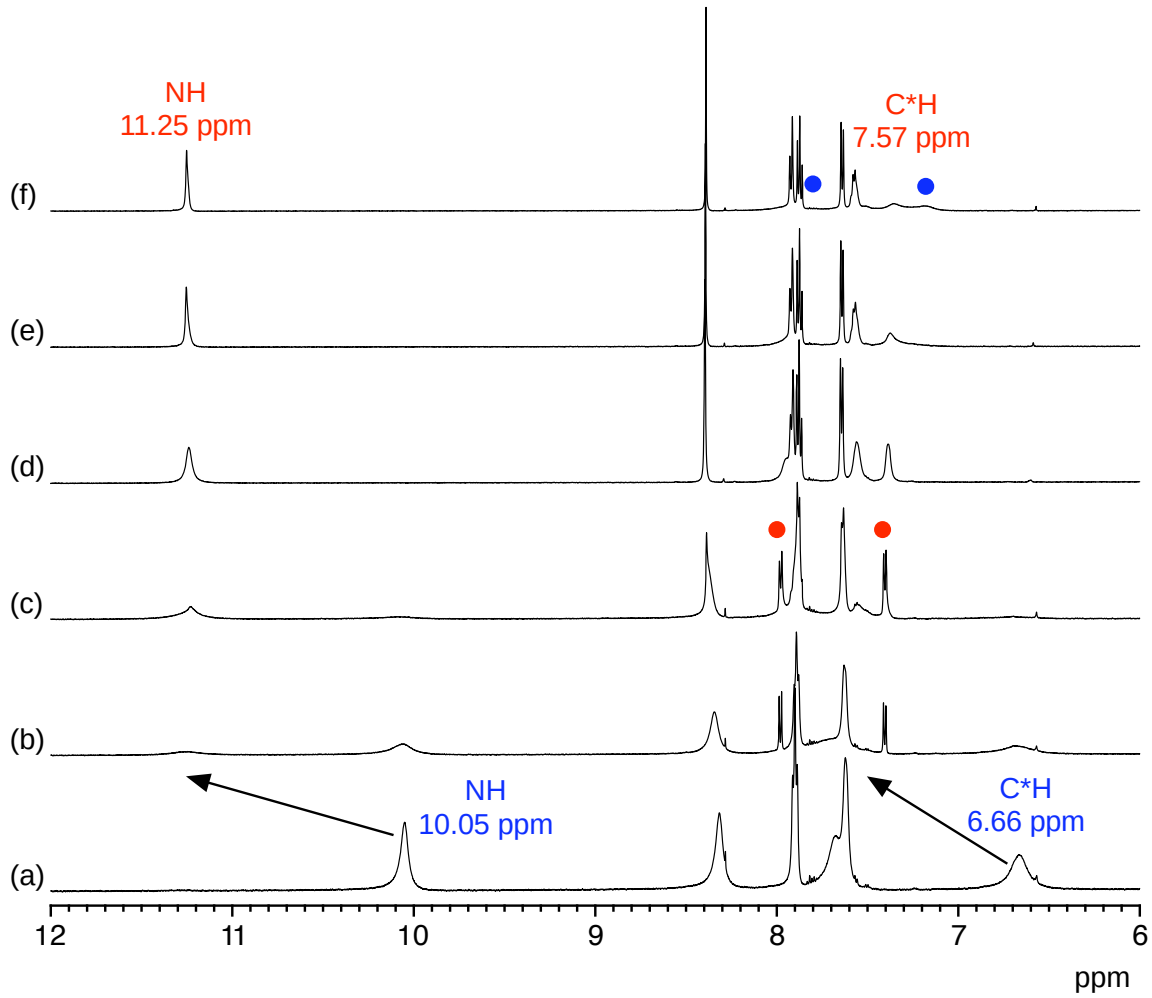
^{1}H NMR Spectrum: **8** in $CDCl_3$ (a), in [D_6]acetone (b), in 10% [D_6]DMSO/[D_6]acetone (c), in [D_6]DMSO (d), and in D_2O/CD_3OD 1:1 (*v/v*) (e) (600 MHz, 25°C).



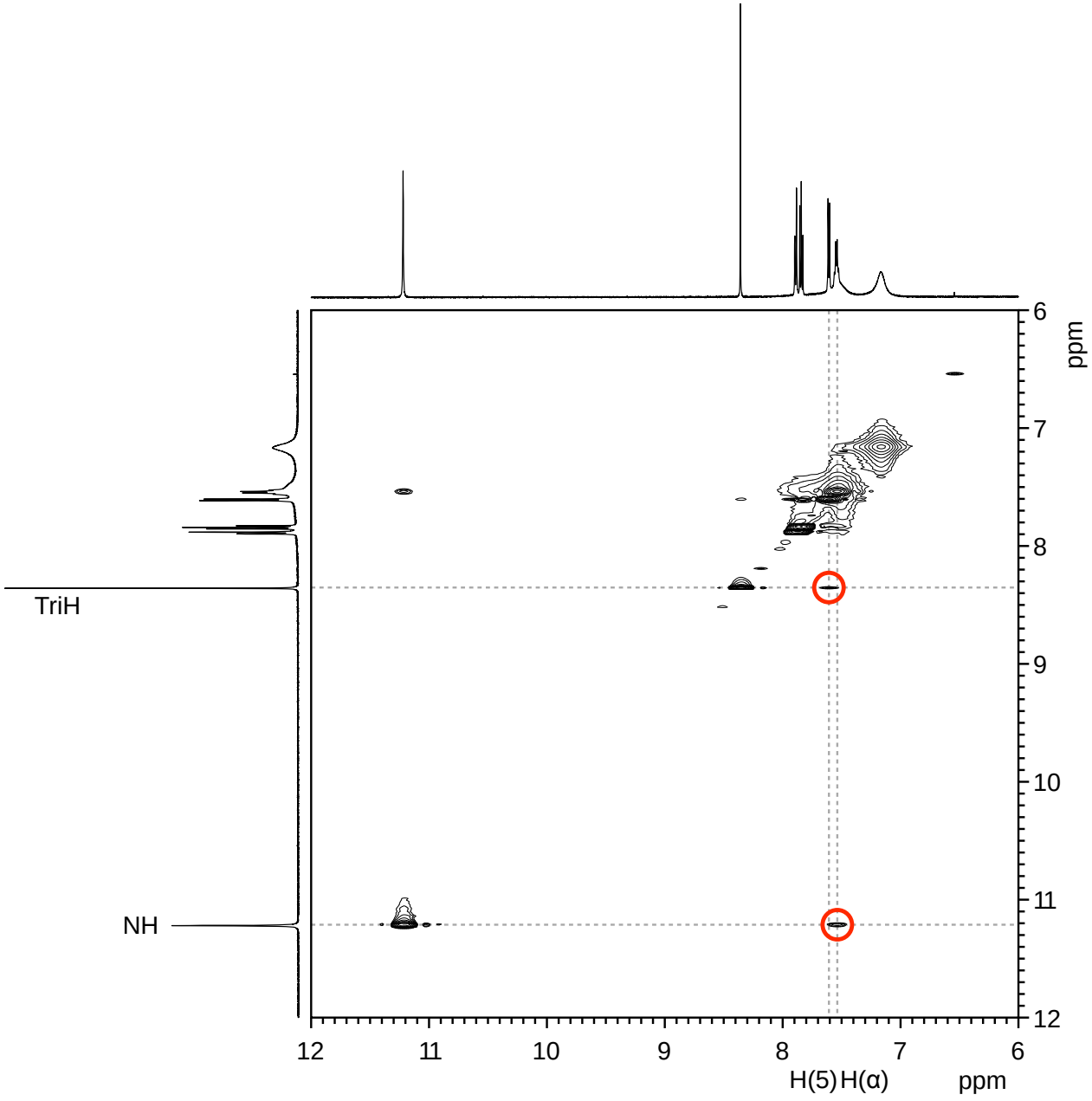
^{1}H NMR Spectrum: **8** (2 mM) in [D_6]DMSO at 25 °C (a), at 100 °C (b), and at 25 °C in the presence of 3.5 equivalents of *n*-butyltrimethylammonium tosylate (c) (600 MHz).



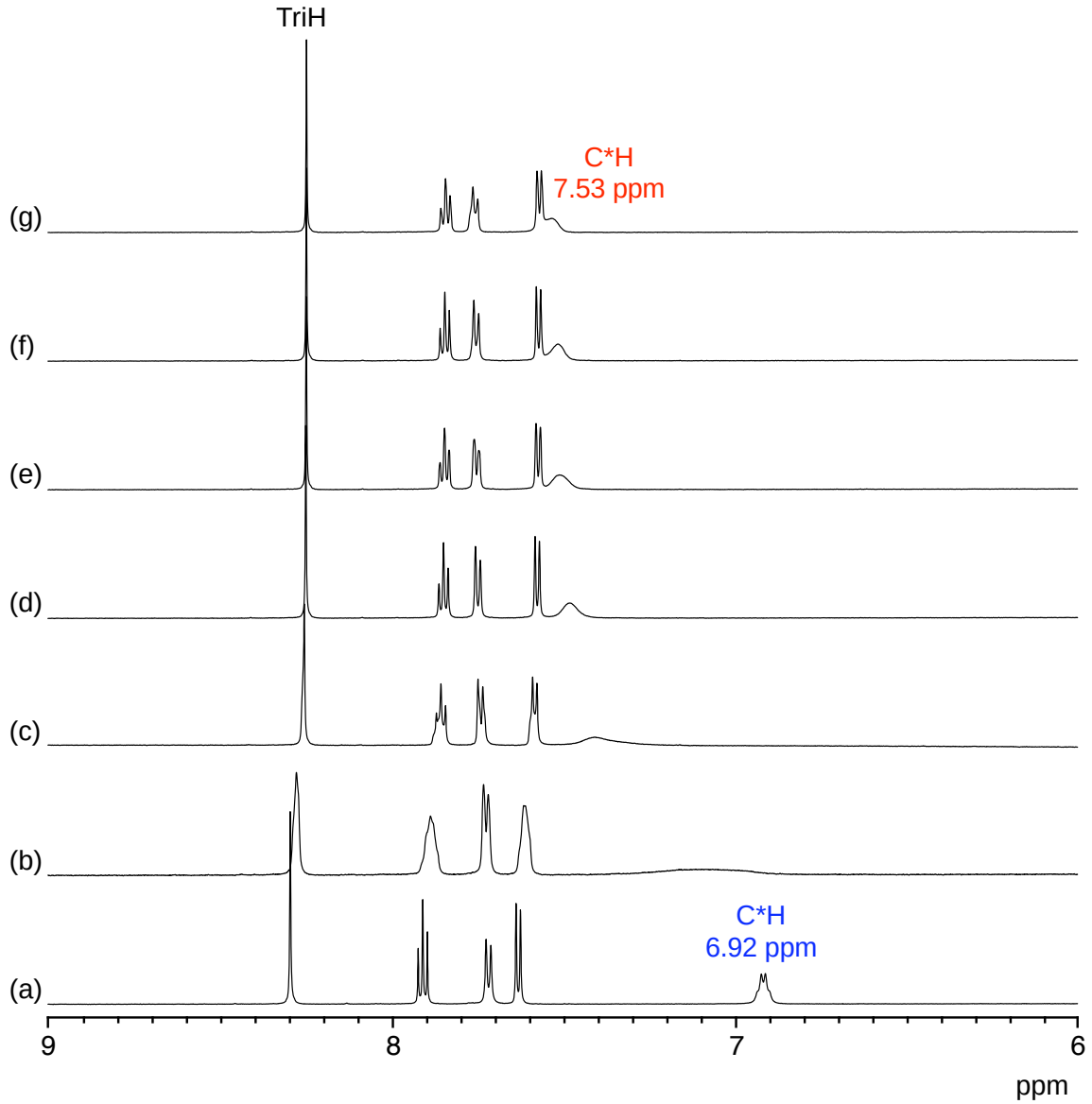
^{1}H NMR Spectrum: **8** (2 mM) in [D_6]DMSO in the presence of 0 equiv (a), 0.4 equiv (b), 0.8 equiv (c), 1.0 equiv (d), 1.4 equiv (e), and 1.8 equiv (f) of *n*-butyltrimethylammonium tosylate at 25 °C. The blue assignments correspond to the signals of the free receptor and the red ones to those of the complex. The dots mark the aromatic tosylate signals with red indicating complexed and blue indicating free anion (600 MHz, 25°C).



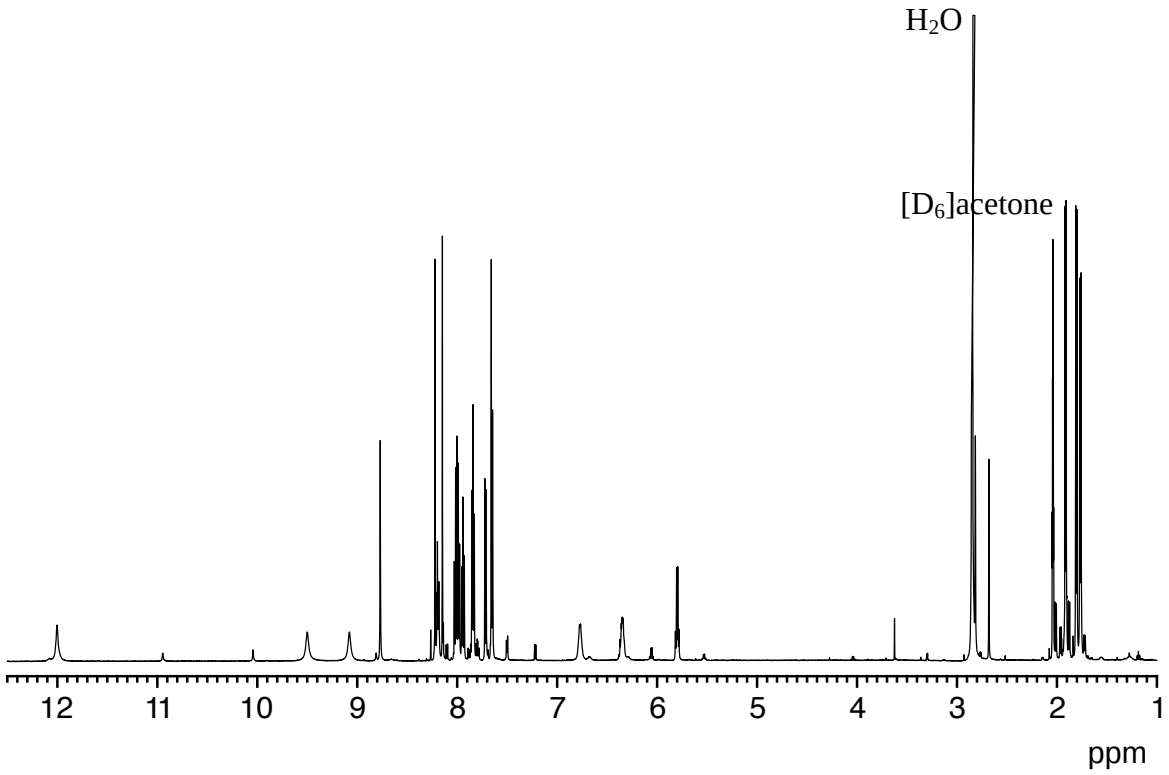
NOESY NMR Spectrum: **8** (2 mM) in [D_6]DMSO in the presence of 3.5 equivalents of *n*-butyltrimethylammonium tosylate (mixing time 150 ms) (600 MHz, 25 °C).



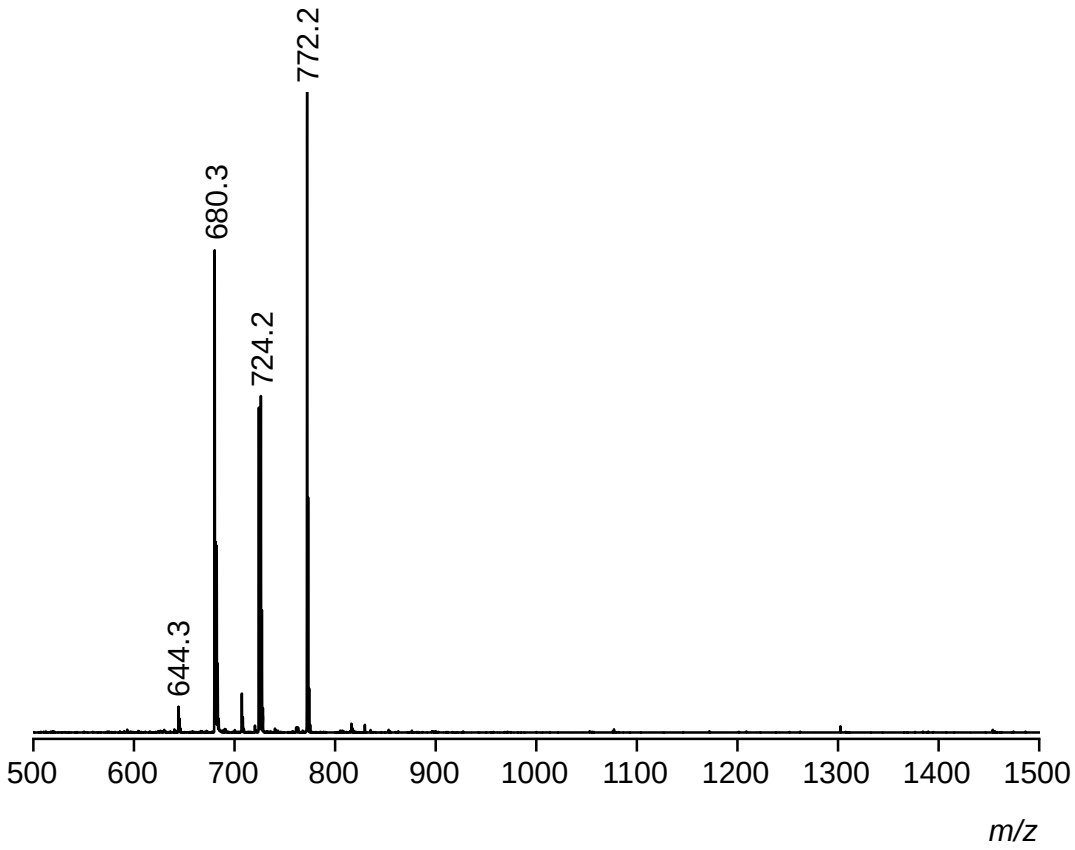
^{1}H NMR Spectrum: **8** (1 mM) in CD_3OD/D_2O 2:1 (*v/v*) in the presence of 0 equiv (a), 0.25 equiv (b), 0.5 equiv (c), 0.75 equiv (d), 1.0 equiv (e), 1.25 equiv (f), and 1.50 equiv of Na_2SO_4. The blue assignments correspond to the signals of the free receptor and the red ones to those of the complex (600 MHz, 25°C).



^{1}H NMR Spectrum: Side product formed besides **8** during the cyclization in [D_6]acetone (600 MHz, 25°C).

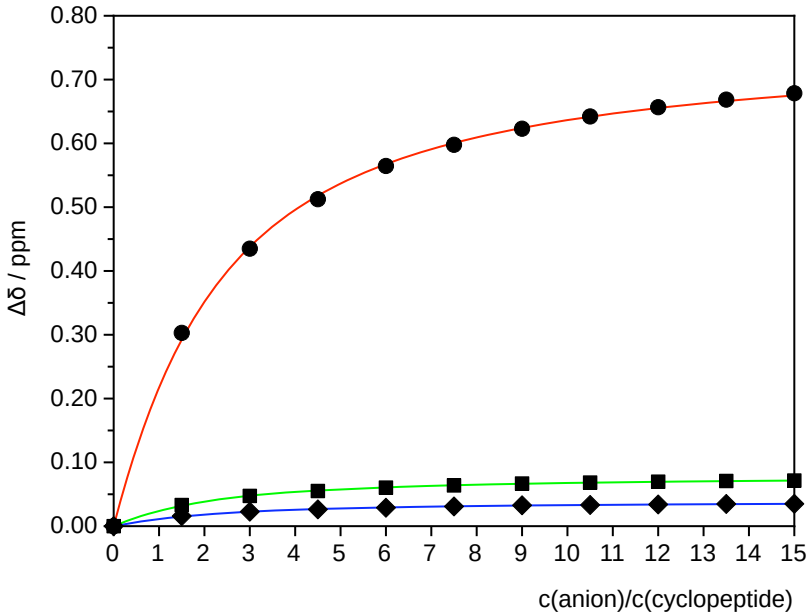


ESI-TOF MS Spectrum: **8** (10 μM) in the presence of 0.33 equivalents of each NaCl, NaBr, NaI in 1:1 (*v/v*) H_2O/CH_3OH (negative mode).



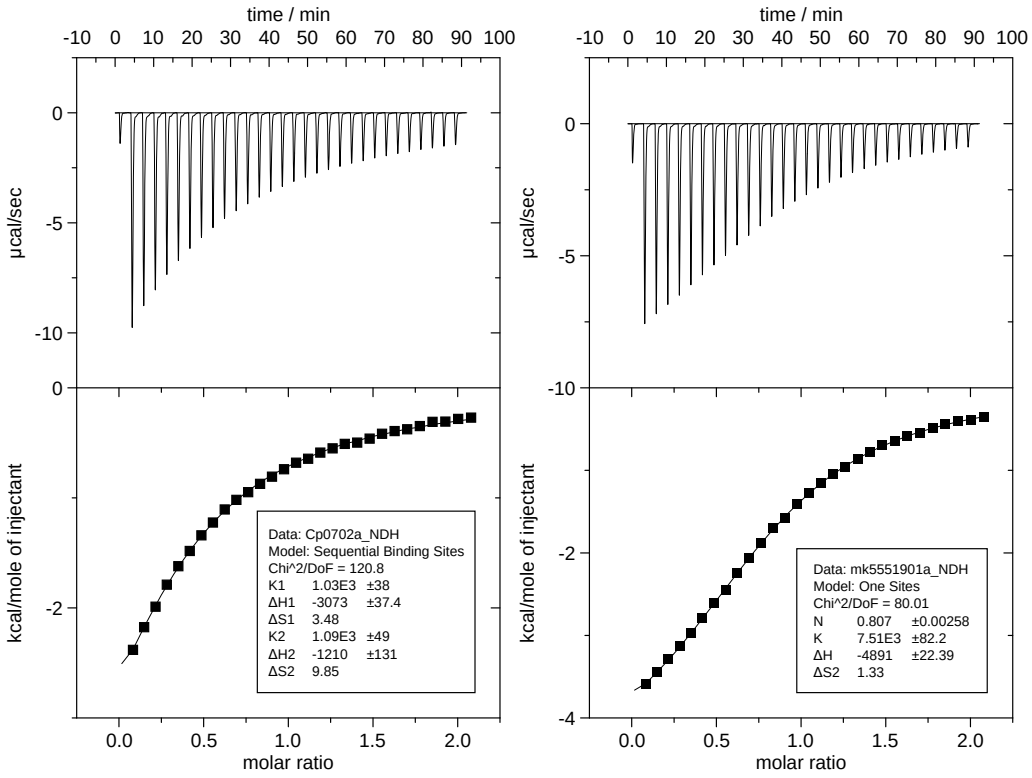
		m/z calcd.	*m/z exp.*
8 – H^+	$(C_{30}H_{27}N_{15}O_3) - H^+$	644.23	644.3
8 + Cl^-	$(C_{30}H_{27}N_{15}O_3) + Cl^-$	680.21	680.3
8 + Br^-	$(C_{30}H_{27}N_{15}O_3) + Br^-$	724.16	724.2
8 + I^-	$(C_{30}H_{27}N_{15}O_3) + I^-$	772.15	772.2

NMR Titration: **1b** with tetramethylammonium bromide in CD_3OD (T = 298 K)

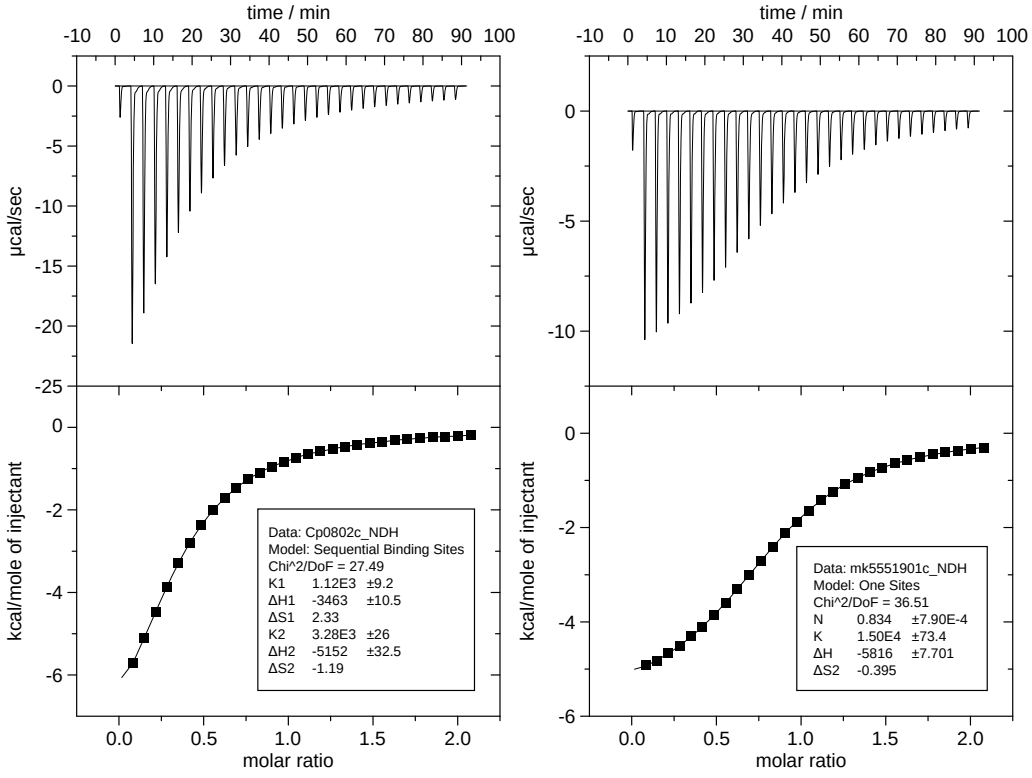


H(α)	**Parameters:**		**Standard deviations:**
	K	= 559	ΔK = 16
	$\Delta\delta_{max}$	= 0.7607	$\Delta\Delta\delta_{max}$ = 0.0045
ApaH(5)	**Parameters:**		**Standard deviations:**
	K	= 558	ΔK = 24
	$\Delta\delta_{max}$	= 0.0394	$\Delta\Delta\delta_{max}$ = 0.0004
ApaH(3)	**Parameters:**		**Standard deviations:**
	K	= 616	ΔK = 17
	$\Delta\delta_{max}$	= 0.0797	$\Delta\Delta\delta_{max}$ = 0.0004

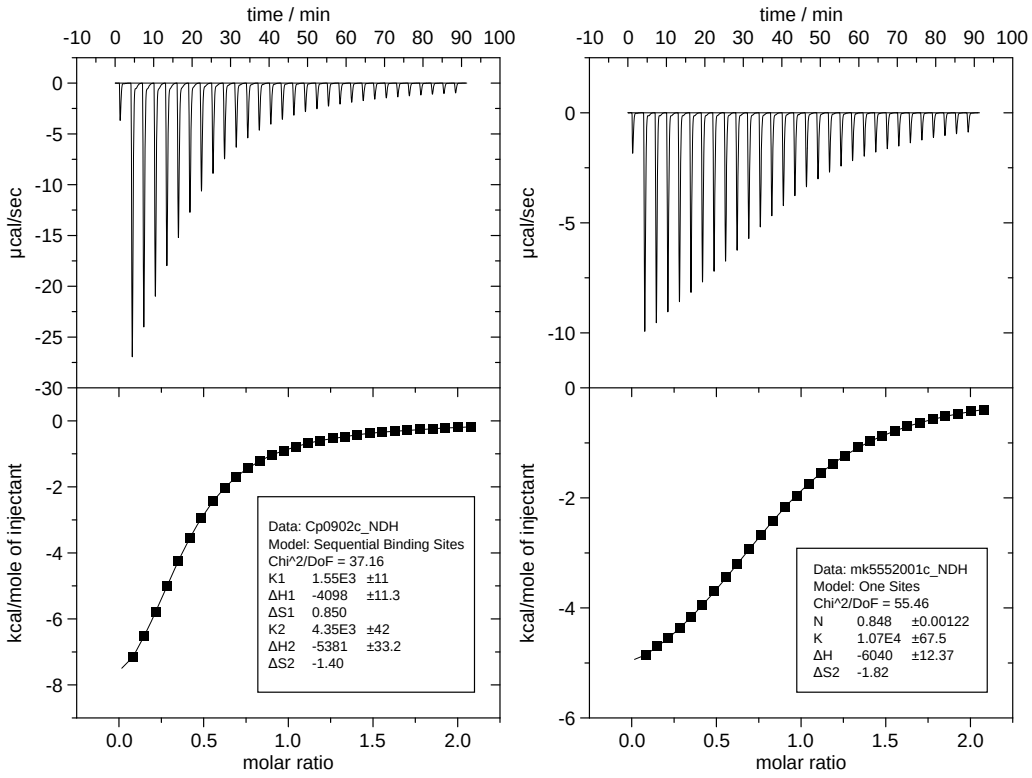
ITC Traces and Binding Isotherms: Titrations of receptors **1a** (left) **8** (right) with $(CH_3)_4NCl$ in CH_3OH at 298 K.



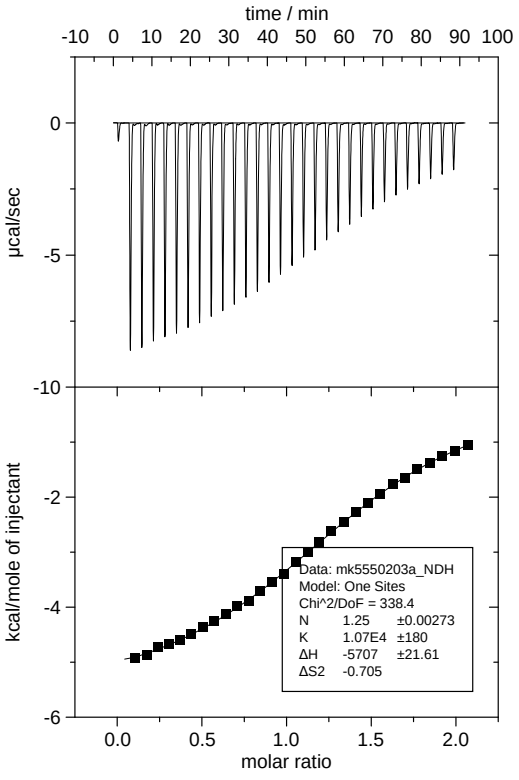
ITC Traces and Binding Isotherms: Titrations of receptors **1a** (left) **8** (right) with $(CH_3)_4NBr$ in CH_3OH at 298 K.



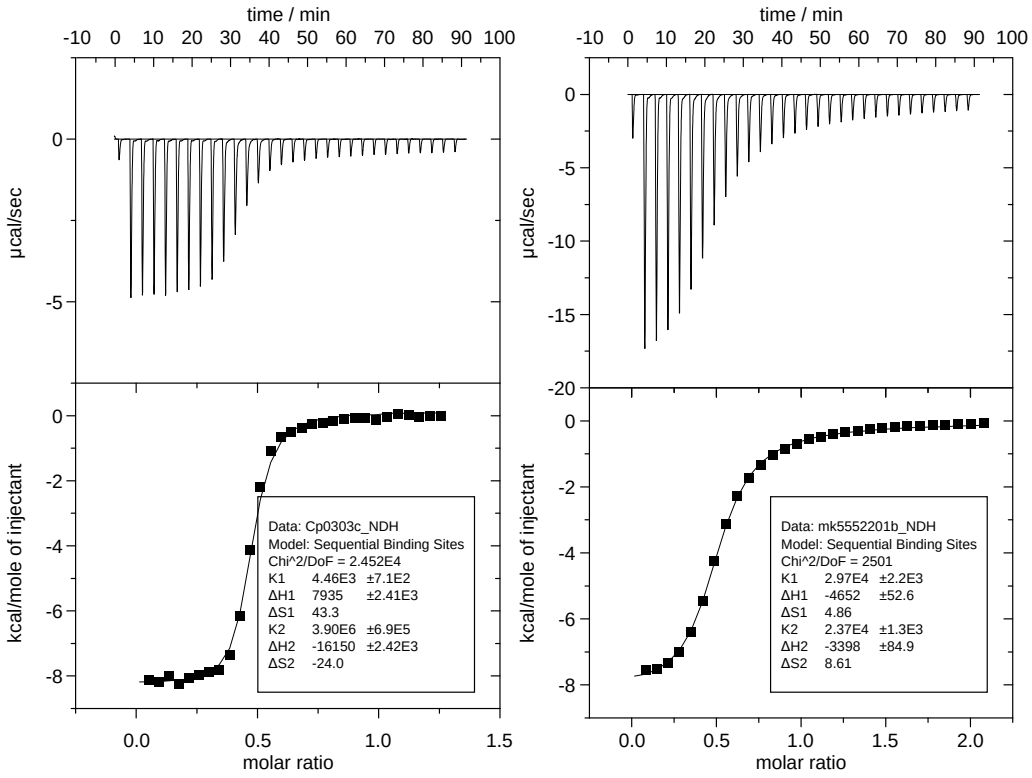
ITC Traces and Binding Isotherms: Titrations of receptors **1a** (left) **8** (right) with $(CH_3)_4NI$ in CH_3OH at 298 K.



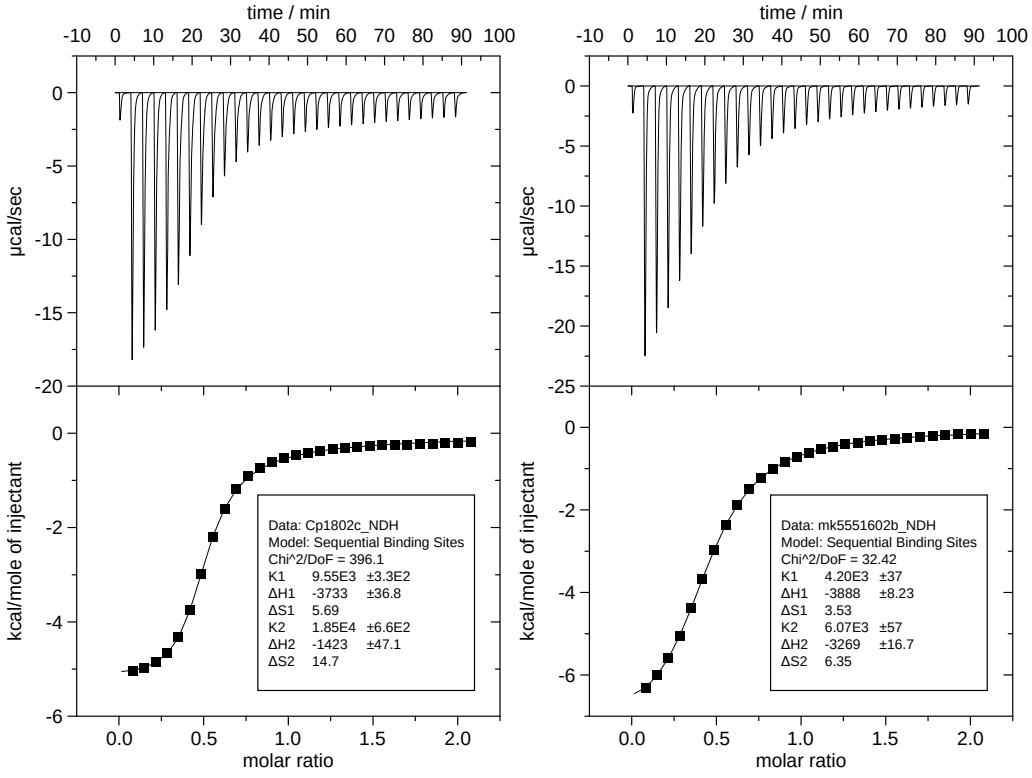
ITC Traces and Binding Isotherms: Titration of $(CH_3)_4NI$ with receptor **8** in CH_3OH at 298 K.



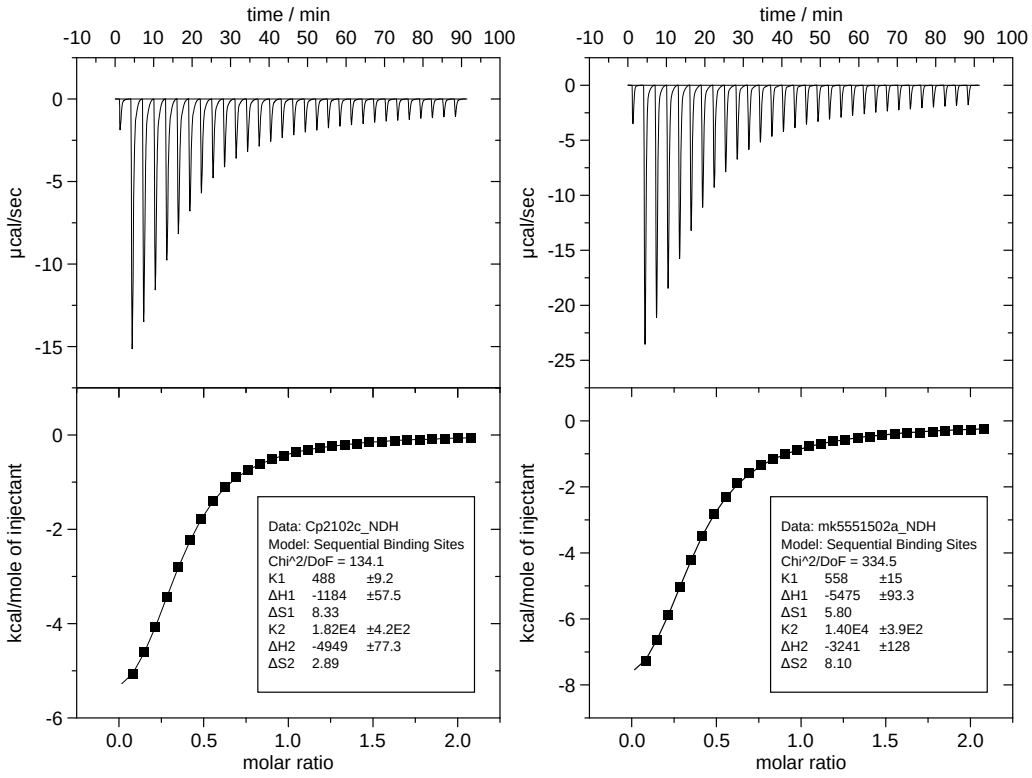
ITC Traces and Binding Isotherms: Titrations of receptors **1a** (left) **8** (right) with $[(CH_3)_4N]_2SO_4$ in CH_3OH at 298 K.



ITC Traces and Binding Isotherms: Titrations of receptors **1a** (left) **8** (right) with $[(CH_3)_4N]_2SO_4$ in CH_3OH/H_2O 4:1 (*v/v*) at 298 K.

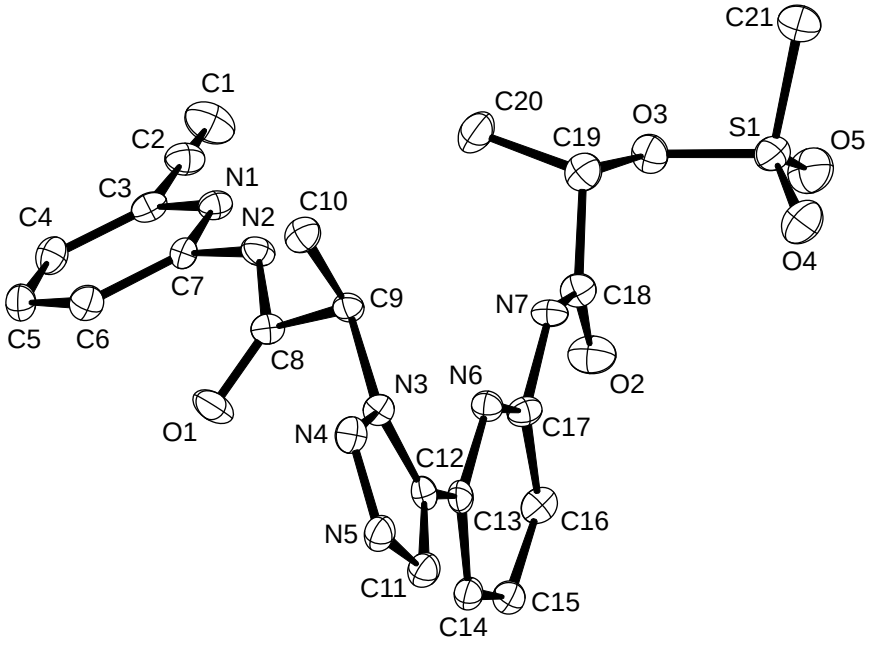


ITC Traces and Binding Isotherms: Titrations of receptors **1a** (left) **8** (right) with $[(CH_3)_4N]_2SO_4$ in CH_3OH/H_2O 2:1 (*v/v*) at 298 K.



X-ray Crystal Structure Analysis: TMS-Deprotected Derivative of **6**

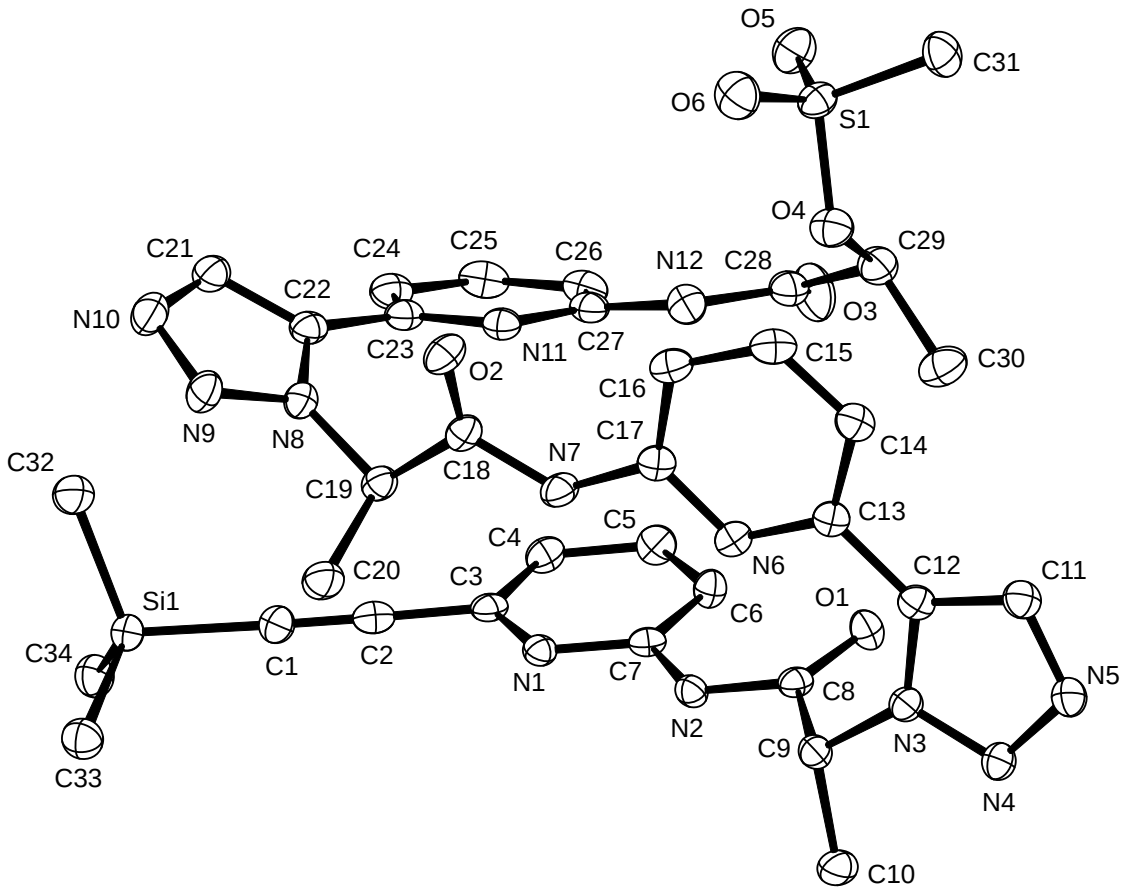
Structure of TMS-deprotected 6 in the crystal. Hydrogen atoms omitted for clarity. Ellipsoids are shown at the 50 % probability level.



Crystal Data for TMS-deprotected 6: $C_{21}H_{21}N_7O_5S$, M_r = 483.51 g·mol^{-1}, colorless needle from methanol/dichloromethane, crystal size 0.47 x 0.09 x 0.04 mm^3, monoclinic, space group C*2* [No. 5], a = 18.534(4) Å, b = 8.8696(17) Å, c = 13.761(3) Å, β = 97.078(8)°, V = 2244.8(7) Å^3, T = 100 K, Z = 4, D_{calc} = 1.431 g·cm^{-3}, λ = 1.54178 Å, μ(*Cu*-K_α) = 1.711 mm^{-1}, Gaussian absorption correction (T_{min} = 0.6510, T_{max} = 0.9353), 3.24 < θ < 66.47°, 24475 measured reflections, 3821 independent reflections (R_{int} = 0.106), 3169 reflections with $I > 2\sigma(I)$. Structure solved by direct methods (SHELXS) and refined by full-matrix least-squares (SHELXL) against F^2 to R_1 = 0.041 [$I > 2\sigma(I)$], wR_2 = 0.092 (all data), 311 parameters, H atoms riding, S = 1.169, residual electron density +0.26/–0.33 e Å^{-3}.

X-ray Crystal Structure Analysis: Compound **7**

Structure of 7 in the crystal. Hydrogen atoms omitted for clarity. Ellipsoids are shown at the 50 % probability level.



Crystal Data for 7: $C_{34}H_{38}N_{12}O_6SSi$, M_r = 770.91 g·mol^{-1}, colorless prism from methanol/ dichloromethane, crystal size 0.061 x 0.042 x 0.030 mm^3, tetragonal, space group P4_3 [No. 78], a = 17.235(2) Å, c = 12.720(3) Å, V = 3778.4(11) Å^3, T = 100 K, Z = 4, D_{calc} = 1.355 g·cm^{-3}, λ = 0.71073 Å, μ(*Mo-K*$_\alpha$) = 0.179 mm^{-1}, Gaussian absorption correction (T_{min} = 0.9922, T_{max} = 0.9961), 1.99 < θ < 26.75°, 81307 measured reflections, 8005 independent reflections (R_{int} = 0.060), 7394 reflections with $I > 2\sigma(I)$. Structure solved by direct methods (SHELXS) and refined by full-matrix least-squares (SHELXL) against F^2 to R_1 = 0.033 [$I > 2\sigma(I)$], wR_2 = 0.082 (all data), 494 parameters, H atoms riding, absolute structure parameter = –0.29(5), S = 1.038, residual electron density +0.39/–0.24 e Å^{-3}. Both the Flack parameter and the Hooft parameter are significantly negative (ca. –0.3) in spite of measuring the data with a high redundancy (Hooft, R.; Straver, L.; Spek, A. *J. Appl. Cryst.* **2008**, *41*, 96-103). We currently have no explanation for this, apart from

the fact that the normal probability plot has a slope of 1.49 (correlation coefficient 0.98) indicating that the standard uncertainties of the reflections may be underestimated due to averaging:

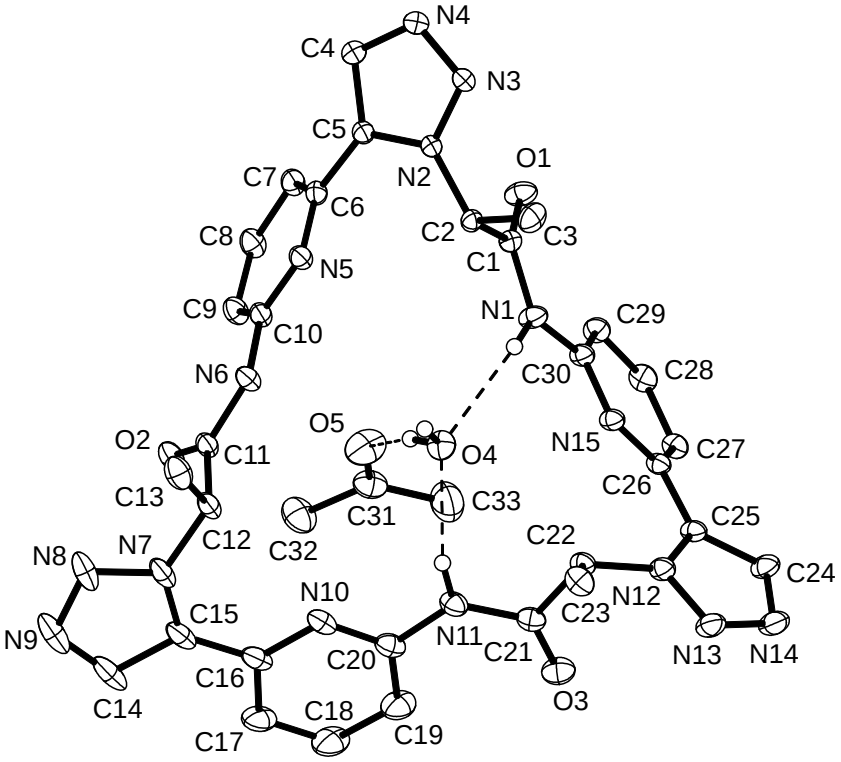
Intensity Statistics for Dataset

Resolution	#Data	#Theory	%Complete	Redundancy	Mean I	Mean I/s	R(int)	Rsigma
Inf - 2.20	211	212	99.5	22.57	85.2	87.17	0.0381	0.0101
2.20 - 1.73	215	215	100.0	23.87	32.7	79.96	0.0423	0.0109
1.73 - 1.50	228	228	100.0	23.61	21.6	69.06	0.0475	0.0122
1.50 - 1.35	223	223	100.0	23.71	14.2	59.04	0.0596	0.0140
1.35 - 1.25	228	228	100.0	23.01	14.6	55.52	0.0602	0.0147
1.25 - 1.17	236	236	100.0	22.07	14.1	51.52	0.0652	0.0159
1.17 - 1.11	233	233	100.0	21.17	10.9	42.51	0.0754	0.0185
1.11 - 1.06	221	221	100.0	20.12	10.4	38.97	0.0819	0.0206
1.06 - 1.01	278	278	100.0	19.54	9.2	36.58	0.0855	0.0224
1.01 - 0.97	258	258	100.0	18.86	6.1	27.68	0.1108	0.0299
0.97 - 0.94	240	240	100.0	18.09	5.9	25.02	0.1146	0.0321
0.94 - 0.91	250	250	100.0	17.70	4.6	21.17	0.1361	0.0396
0.91 - 0.88	297	297	100.0	17.05	4.2	19.14	0.1539	0.0446
0.88 - 0.86	216	216	100.0	16.46	4.3	18.54	0.1586	0.0464
0.86 - 0.84	258	258	100.0	16.18	3.7	16.22	0.1707	0.0525
0.84 - 0.82	259	259	100.0	15.81	3.2	14.04	0.1945	0.0614
0.82 - 0.80	294	294	100.0	15.24	2.9	12.49	0.2173	0.0698
0.80 - 0.79	58	66	87.9	7.82	3.5	10.82	0.1949	0.0953
0.89 - 0.79	1274	1282	99.4	15.63	3.5	15.33	0.1804	0.0573
Inf - 0.79	4203	4212	99.8	19.32	13.4	37.65	0.0633	0.0183

Merged [A], lowest resolution = 12.65 Angstroms, 4149 outliers downweighted

X-ray Crystal Structure Analysis: Compound **8**·C_3H_6O·H_2O

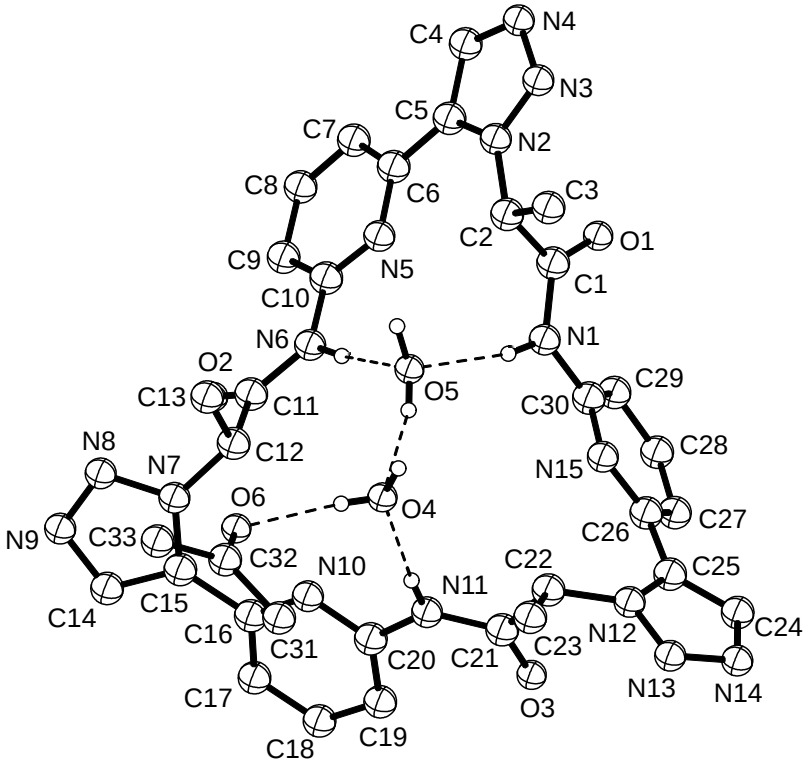
Structure of 8·C_3H_6O·H_2O in the crystal. Except for those involved in hydrogen bonding to water and acetone, hydrogen atoms omitted for clarity. Ellipsoids are shown at the 50 % probability level.



Crystal Data for 8·C_3H_6O·H_2O: $C_{30}H_{27}N_{15}O_3 \cdot C_3H_6O \cdot H_2O$, Mr = 721.76 g·mol^{-1}, colorless prism from acetone/hexane/trace water, crystal size 0.11 x 0.05 x 0.04 mm^3, monoclinic, space group P2_1 [No. 4], a = 9.9601(9) Å, b = 9.3717(9) Å, c = 19.2123(18) Å, β = 101.469(2)°, V = 1757.5(3) Å^3, T = 100 K, Z = 2, D_{calc} = 1.364 g·cm^{-3}, λ = 0.71073 Å, μ(*Mo*-K_α) = 0.098 mm^{-1}, Gaussian absorption correction (T_{min} = 0.9911, T_{max} = 0.9967), 2.43 < θ < 32.89°, 103103 measured reflections, 6846 independent reflections (R_{int} = 0.078), 6524 reflections with $I > 2\sigma(I)$. Structure solved by direct methods (SHELXS) and refined by full-matrix least-squares (SHELXL) against F^2 to R_1 = 0.037 [$I > 2\sigma(I)$], wR_2 = 0.106 (all data), 489 parameters. The positions of the H atoms on the water molecule were located on a difference Fourier synthesis and the atoms were refined with isotrotropic atomic displacement parameters, otherwise H atoms riding, absolute structure was not determined (total number of reflections without merging Friedel pairs (MERG 3) is 12993), S = 0.820, residual electron density +0.40/–0.20 e Å^{-3}.

X-ray Crystal Structure Analysis: Compound **8**·C_3H_6O·$2H_2O$

Structure of 8·C_3H_6O·$2H_2O$ in the crystal. Except for those involved in hydrogen bonding to water and acetone and neighboring triazole N atoms in neighboring molecules (not shown), hydrogen atoms omitted for clarity. Ellipsoids are shown at the 50 % probability level.



Crystal Data for 8·C_3H_6O·$2H_2O$: $C_{30}H_{27}N_{15}O_3$·C_3H_6O·$2H_2O$, M_r = 739.78 g·mol^{-1}, colorless needle from water/acetone (1:1), crystal size 1.024 (see below) x 0.052 x 0.052 mm^3, orthorhombic, space group P$2_12_12_1$ [No. 18], a = 12.4653(5) Å, b = 17.1970(7) Å, c = 17.6158(8) Å, V = 3776.2(3) Å^3, T = 100 K, Z = 4, D_{calc} = 1.301 g·cm^{-3}, λ = 1.54178 Å, μ(*Cu*-K_α) = 0.785 mm^{-1}, Gaussian absorption correction (T_{min} = 0.6789, T_{max} = 0.9666), 3.59 < θ < 54.35°, 63933 measured reflections, 4532 independent reflections (R_{int} = 0.086), 4203 reflections with $I > 2\sigma(I)$. Structure solved by direct methods (SHELXS) and refined by full-matrix least-squares (SHELXL) against F^2 to R_1 = 0.056 [$I > 2\sigma(I)$], wR_2 = 0.146 (all data), 505 parameters. The positions of the four H atoms on the two water molecules were located on a difference Fourier synthesis and the atoms were refined with isotrotropic atomic displacement parameters, otherwise H atoms riding, absolute structure parameter = –0.1(4), S = 1.143, residual electron density +0.37/–0.22 e Å^{-3}. The crystals grew as very fine needles, which were difficult to cut. In order to obtain adequate diffraction

intensity, it was necessary to choose a long crystal, since the longer crystals were thicker. In order to minimize the effects of a needle that was longer than the diameter of the X-ray beam, data were measured at the constant chi angle 54.74°, and the frames were scaled using SADABS. Data were collected with a high redundancy in order to reduce bias in the scaling process. Intensity statistics are shown below.

Intensity Statistics for Dataset

Resolution	#Data	#Theory	%Complete	Redundancy	Mean I	Mean I/s	R(int)	Rsigma
Inf - 3.96	70	70	100.0	6.60	104.9	20.94	0.0410	0.0454
3.96 - 2.62	163	163	100.0	11.26	49.9	27.46	0.0538	0.0392
2.62 - 2.07	223	223	100.0	23.17	24.1	40.19	0.0569	0.0223
2.07 - 1.80	232	232	100.0	23.08	17.5	38.71	0.0567	0.0229
1.80 - 1.63	232	233	99.6	21.00	13.1	33.20	0.0639	0.0256
1.63 - 1.52	220	220	100.0	19.92	8.7	30.42	0.0836	0.0282
1.52 - 1.43	227	227	100.0	19.12	7.2	26.13	0.1018	0.0322
1.43 - 1.35	259	259	100.0	17.91	6.2	22.24	0.1131	0.0355
1.35 - 1.30	192	192	100.0	16.68	5.8	22.73	0.1282	0.0372
1.30 - 1.24	261	261	100.0	16.39	5.8	19.95	0.1394	0.0391
1.24 - 1.20	234	234	100.0	14.81	5.6	19.10	0.1537	0.0441
1.20 - 1.16	242	242	100.0	12.49	5.0	16.53	0.1463	0.0489
1.16 - 1.13	195	196	99.5	11.53	6.1	17.37	0.1391	0.0486
1.13 - 1.10	237	237	100.0	10.86	5.6	15.92	0.1491	0.0518
1.10 - 1.07	253	256	98.8	10.85	4.1	13.94	0.1747	0.0581
1.07 - 1.05	196	197	99.5	9.89	3.1	11.50	0.1977	0.0762
1.05 - 1.02	310	310	100.0	9.82	3.1	11.43	0.1996	0.0742
1.02 - 1.00	234	242	96.7	9.24	2.6	10.55	0.2304	0.0816
1.00 - 0.98	218	222	98.2	8.72	2.5	9.71	0.2408	0.0896
0.98 - 0.97	138	138	100.0	8.43	1.7	7.66	0.2944	0.1169
0.97 - 0.95	219	306	71.6	3.55	1.8	5.75	0.2505	0.1664
1.05 - 0.95	1119	1218	91.9	7.77	2.4	9.33	0.2274	0.0956
Inf - 0.95	4555	4660	97.7	13.75	9.9	20.07	0.0849	0.0403