Electronic Supplementary Material (ESI) for Chemical Science.

Supplementary Information

1-Azahomocubane

Tyler Fahrenhorst-Jones, David L. Marshall, Jed. M. Burns, Gregory K. Pierens, Robert E. Hormann, Allison M. Fisher, Paul V. Bernhardt, Stephen J. Blanksby, G. Paul Savage, Philip E. Eaton, and Craig M. Williams*

Table of Contents

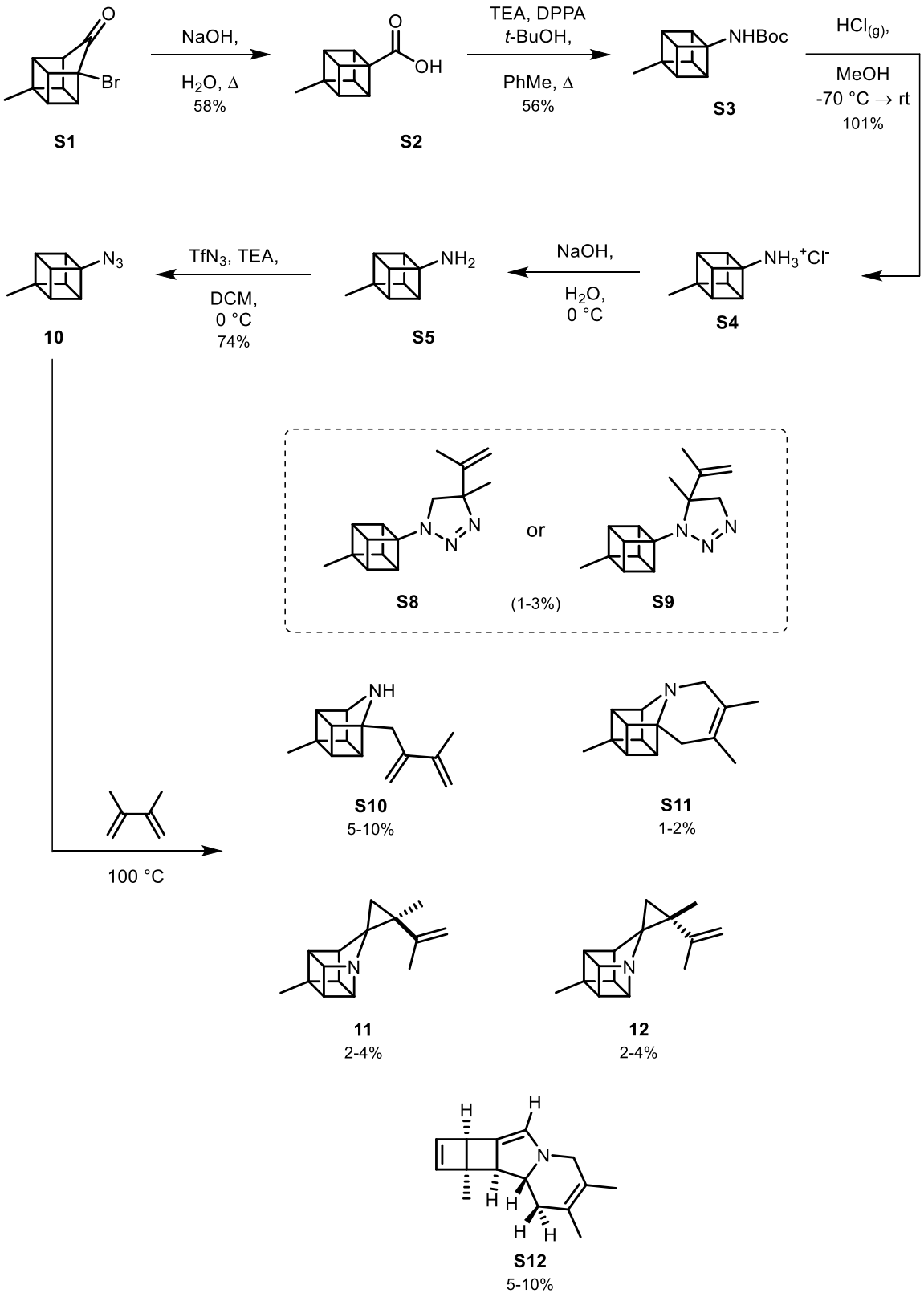
Materials and Methods

Methylazahomocubanes (11 and 12)

General Experimental

^{1}H-NMR spectra were obtained at 500 MHz using the University of Chicago DS 1000 spectrometer interfaced with a Nicolet 1280 data acquisition system. Spectra were acquired in the pulse-Fourier mode. The digital resolution was at least 8 K of real points over a 10 ppm spectra window. Some routine spectra were obtained at 270 MHz using a Bruker HS-270 spectrometer interfaced with a Nicolet 1180 data acquisition system. Except where noted, spectra were taken of solutions in $CDCl_3$ referenced to tetramethylsilane (δ = 0.00 ppm) as internal standard. Chemical shifts are reported to a precision of ± 0.02 ppm and coupling constants to ± 1 Hz. Proton position and coupling assignments are indicated only when implied from a homonuclear decoupling experiment. ^{13}C-NMR spectra were taken at 100 MHz on a Varian, 5 mm, XL-400 spectrometer. Spectra were referenced internally according to $CDCl_3$ (^{13}C δ: 77.0 ppm) used as solvent. Chemical shifts are reported to a precision of ± 0.1 ppm and coupling constants to ± 3 Hz, except where noted. Each reported signal counts for one carbon except where indicated otherwise. Proton decoupled spectra were obtained with a continuous high power broadband modulation. Proton coupled spectra were obtained with broadband decoupling applied between acquisitions. Single frequency proton decoupled spectra were obtained with the decoupler on continuously. Assignment of carbon position is reported only when implied from a carbon-hydrogen decoupling experiment. Ultraviolet spectra were taken on a Perkin-Elmer λ5 UV/Vis spectrophotometer with quartz cells of 1 cm path length. Routine gas chromatography was performed using a Hewlett-Packard 5880A gas chromatography equipped with a flame ionization detector and column A, 12 M × 0.2 mm dia. Fused silica dimethylsilicone. Preparative gas chromatography was performed with a Varian Areography 1700 gas chromatograph equipped with a thermal conductivity detector. A section of borosilicate glass tubing (4 mm O.D. × 110 mm) was used as a liner for the stainless steel injection port. Three columns were used: column B, 6' × ¼" s.s. 3% SE-30 on a Gas Chrom Q / 100-200 mesh; column C, 6' × ¼" 100-200 mesh s.s. 10% Apiezon L + 2% KOH on Chrom WAW, 100-200 mesh; and column D, 6' × ¼" s.s. 2% OV-17 on 2% WHP, 100-200 mesh. For work with methylcubyl azide **10**, the injection ports and oven temperatures were kept at 130 °C or below; otherwise **10** degraded rapidly. Mass spectra were recorded on a VG analytical 7070E system in the EI^+ or CI^+ (isobutane) mode. Most samples were introduced through a Hewlett-Packard 5790A gas chromatograph using column A or column E, 25 M × 0.25 mm dia. Bonded FSOT RSL-300 (Alltech Assoc.), 0.2 μm thickness. Carbamate **S3** and amine **S5** were introduced by direct insertion probe. Routine IR spectra were obtained using a Nicolet SX-20 system equipped with a TGS detector or a 60X FT-IR system equipped with an MCT-B detector. A digital resolution of at least 4 cm^{-1} was used. GC-IR spectroscopy was

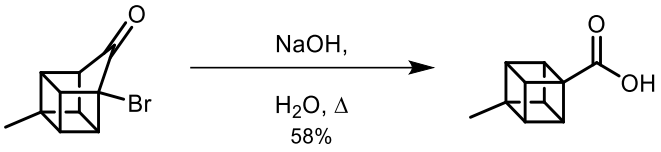
performed with the Nicolet 60SX system equipped with an MCT-A detector and interfaced with a Hewlett-Packard 5890A gas chromatography. Two columns were used: column F, 10 M × 0.53 mm dia. bonded FSOT OV-1701, 1.0 μm thickness; and column G, 10 M 0.53 dia. bonded FSOT RSL-150 (Alltech Assoc.), 1.2 μm thickness. The light pipe and transfer line were maintained at 150-190 °C. A temperature of 150 °C or less was required for GC-IR work with methylcubyl azide **10** and triazoline **S8** (or **S9**) because of their thermal instability. Melting points were determined on a Hoover Unimelt apparatus and are uncorrected. Column chromatography was carried out using Machery Nagel, 200 mesh silica gel. Analytical TLC was performed on 4 × 8 cm polygram sil G/U_{254} plastic plates with a 0.25 mm silica gel layer. The plates were developed by treatment with phosphomolybdic acid stain. Vacuum manipulations were performed on a Pyrex manifold equipped with a mercury diffusion pump. Unless otherwise noted, solutions of methylcubyl azide **10** were prepared for thermolysis and degassed by approximately four freeze-evacuate-thaw cycles and the tubes were flame sealed. Bulk reagent grade solvents were purified in the following manner. Pentane was stirred over sulfuric acid and distilled. Dichloromethane was passed through neutral alumina or distilled from calcium hydride. Benzene was distilled from sodium / benzophenone and kept over 3 Å molecular sieves.



Scheme S1: Synthesis of 1-azahomocubane alkyl derivatives (**11** and **12**).

Experimental Procedures

4-Methylcubyl carboxylic acid (**S2**)

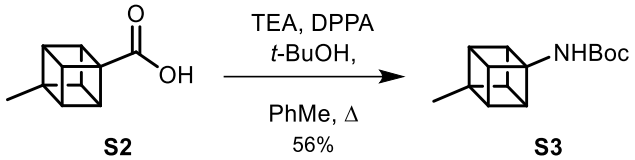


S1 **S2**

Adapted from the procedure of Langford et al.:[1] solid sodium hydroxide (140 g, 3.5 mol) was dissolved in water (420 mL) and heated to near-boiling. Finely ground 1-bromo-4-methyl homocubanone (**S1**, 22.1 g, 98.2 mmol) was sprinkled over a period of 30 minutes into the well-stirred mixture. The suspension was refluxed for 3.5 hours. Gradually, all of the solid material dissolved. The solution turned dark brown but remained transparent. As the mixture was allowed to cool to room temperature over several hours, a voluminous microcrystalline precipitate appeared. This sodium cubyl carboxylate was filtered from the solution using a glass frit and was air-dried. On a steam bath, the light brown material was dissolved in a 4:1 water:methanol solution (400 mL). Colored impurities were removed by washing the solution one time with chloroform. After acidification to pH 1-2 with 10% hydrochloric acid, the free acid itself was extracted in chloroform. Drying over sodium sulfate and removal of solvent *in vacuo* afforded 10.5 g of a bright yellow solid. This was crystallized from benzene by slow evaporation and then sublimed (120 °C, 0.5 torr) to give **S2** (9.15 g, 58%) as white crystals.

m.p. 138.5-139.5 °C (lit.[1] 142.5-143.5 °C); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 6.97 (br, 1H), 4.12 (m, 3H), 3.65 (m, 3H), 1.28 (s, 3H); **IR** (CCl_4, cm^{-1}): υ_{O-H} 3532 (w), 2990 (br), υ_{C-H} 2991, $\upsilon_{C=O}$ 1689 (s).

4-Methylcubane-*t*-butyl carbamate (**S3**)



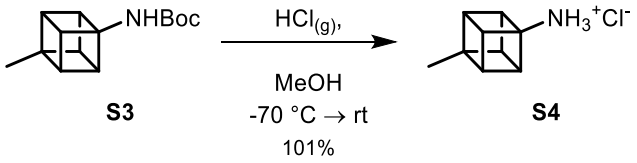
S2 **S3**

4-Methylcubane carboxylic acid (**S2**, 2.00 g, 12.3 mmol) and anhydrous toluene (40 mL) were placed into a flame-dried flask under a nitrogen atmosphere. Diphenyl phosphoryl azide (2.8 mL, 13.0 mmol) and triethylamine (2.2 mL, 15.8 mmol) were added to the solution. The reaction was heated at 50 °C for two hours and then refluxed for one hour. During reflux, evolution of nitrogen was quite noticeable. Dry *t*-butyl alcohol was

added (4.0 mL, 42 mmol) to the clear brown solution. The reaction mixture was then heated under reflux for about nine hours, and then allowed to cool. Saturated aqueous sodium bicarbonate (20 mL) was added, and the biphasic mixture was stirred for several hours during which time a precipitate formed in the aqueous layer. The organic phase was drawn off, filtered and dried over sodium sulfate. The solvent was removed *in vacuo* leaving 2.68 g. of a brown, semi-crystalline solid. The product was extracted into hexanes (40 mL), leaving behind a thick, dark oil which was discarded. The hexane soluble material was sublimed under vacuum (110 °C, 30 mTorr) to give 1.71 g of a white solid. Filtration and chromatography on silica gel or crystallization from hexanes (recommended) gave carbamate **S3** as white needles (1.61 g, 56% yield).

m.p. 151-152 °C (sealed tube); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 4.95 (br, 1H), 3.87 (m, 3H), 3.47 (m, 3H), 1.44 (s, 9H,), 1.26 (s, 3H); **IR** (GC, column F, cm^{-1}): υ_{O-H} 3456, υ_{C-H} 2984, $\upsilon_{C=O}$ 1748 (s), 1479; **MS** (EI^+) *m/z* (rel intensity): 233 (0.3, M^+), 177 (1.4), 162 (1.1), 132 (10), 118 (13), 116 (12), 93 (22), 57 (100).

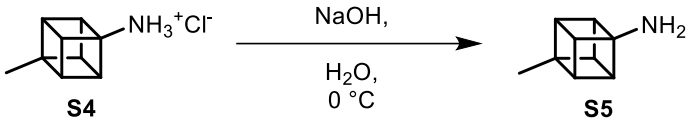
4-Methylcubyl amine hydrochloride (**S4**)



Adapted from the procedure of Eaton et al.:[2] 4-methylcubane-*t*-butyl carbamate (**S3**, l.64 g, 7.03 mmol) was partially dissolved in methanol (25 mL). The suspension was cooled to -70° C under a positive pressure of nitrogen and saturated with hydrogen chloride. After it was stirred for 15 minutes at -70°, the light yellow suspension was allowed to warm to 0 °C over one hour, by which time no undissolved material remained. Nitrogen was then bubbled through the solution to expedite removal of hydrogen chloride. The solvent was removed *in vacuo* without warming, first on a rotary evaporator (NaOH trap) and then overnight at high vacuum (6 mTorr). 4-Methylcubyl amine hydrochloride (**S4**) remained as an ivory-colored powder (1.2 g, 101%) containing traces of water. This material can be crystallized from hot benzene/methanol or by slow evaporation from methanol alone. However, neither method was completely satisfactory, the amine hydrochloride tends to decompose under these conditions. If good quality methylcubane carbamate is used to start in this procedure, the crude product is sufficiently pure for cubyl azide preparation.

m.p. 163-165 °C (dec.); **^{1}H-NMR** (500 MHz, DMSO) δ: 8.7 (br, 3H), 3.95 (m, 3H), 3.56 (m, 3H), 1.26 (s, 3H); **IR** (KBr, cm^{-1}): υ_{N-H} 3320, υ_{C-H} 2980, υ_{N-H} 1630, 1550 (s).

4-Methylcubyl amine (**S5**)

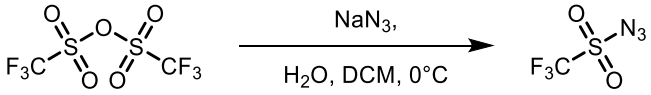


S4 **S5**

4-Methylcubyl amine hydrochloride (**S4**, 256 mg, 1.51 mmol) was partially dissolved in 0.5 mL water in a 10 mL test tube cooled on ice. Ice-cold aqueous sodium hydroxide (1 M, 3 mL) was added slowly. Free 4-methylcubyl amine **S5** precipitated as a voluminous white solid. The product was extracted into ice-cold dichloromethane (2 mL total). Emulsions were clarified by brief centrifugation; and the combined extract was dried over sodium sulfate. 4-Methylcubyl amine (**S5**) can be stored in dichloromethane for hours at -15 °C without decomposition.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.60 (m, 3H), 3.37 (m, 3H), 1.75 (br, 2H), 1.26 (s, 3H); **IR** (CCl_4, cm^{-1}): $\upsilon_{N\text{-}H}$ 3383 (w), $\upsilon_{C\text{-}H}$ 2972, $\upsilon_{N\text{-}H}$ 1607 (w), υ 1339 (sh, m); **MS** (EI^+) *m*/*z* (rel intensity): 133 (38), 132 (67), 118 (48), 91 (100).

Triflyl azide (**S7**)

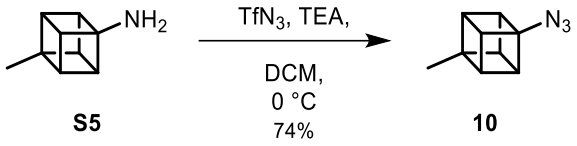


S6 **S7**

[**Note**: Triflyl azide (**S7**) can be explosive as a neat oil and should only be handled as a solution with glassware that contain smooth glass joints or fire polished edges.]

Adapted from the procedure of Cavender and Shiner:[3] triflic anhydride (**S6**, 0.62 mL,1.04 g, 3.7 mmol) was added dropwise to an ice-cold mixture of 3.7 mL saturated aqueous sodium azide (*ca*. 6 M) and 3 mL dichloromethane. The biphasic mixture was stirred briskly for two hours at 0 °C after which time the colorless organic layer was removed and washed with water. The reaction was shown to be complete by **IR** ($CHCl_3$, 2151 cm^{-1}). The solution was stored at 0 °C (1-3 hours) until use.

4-Methylcubyl azide (**10**)



Adapted from the procedure of Cavender and Shiner:[3] a dichloromethane solution of good quality methylcubylamine (**S5**, 2 mL, 1.5 mmol) was stirred at 0 °C in a 25 mL flask bearing a non-frosted joint. Triethylamine (0.62 mL, 4.45 mmol) was added followed by dropwise addition of the triflyl azide solution **S7** (3 mL) described above. The azide was added at a rate sufficiently slow to avoid gas evolution. After stirring at 0 °C for two hours, *t*-butylamine (0.22 mL, 2.1 mmol) was added to destroy remaining triflyl azide. The mixture was stirred again for 15 minutes, and then washed twice with ice-cold aqueous 10% sodium hydroxide and then twice with 10% hydrochloric acid. Trace hydrochloric acid was neutralized with saturated aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate to give an amber dichloromethane solution of crude methylcubyl azide **10**.

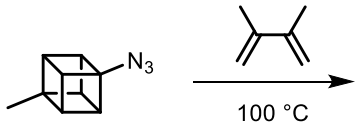
CAUTION: Methylcubyl azide **10** explodes upon mechanical shock. On one occasion, a 5 mg sample of the neat oil detonated when touched with the tip of an as-received glass pipette. All solutions should be handled in glassware with smooth joints or fire-polished surfaces. Manipulations of concentrated solutions should be carried out behind a shield, wearing gloves and face protection. The neat oil can be transferred from vessel to vessel by vacuum line techniques performed behind a shield. For the quantitative work described herein, the mass of small quantities (10 mg) of neat methylcubyl azide **10** was determined by evaporation of the solvent from a tared vial positioned in a gravimetric balance. After constant weight was achieved and measured, new solvent was gently added to the oil. Hand and face protection were worn at all times. In this manner the neat oil need not be jostled or carried about. The mass of larger quantities of methylcubyl azide could be determined by extrapolation from the mass of an aliquot.

The azide solution of **10** (*ca*. 5 mL) in a 100 mL flask was cooled in a toluene/liquid nitrogen bath at -70 to -60 °C. Dichloromethane was removed under high vacuum (6 mTorr, two hours) and the azide itself was transferred by evaporation to a vial containing 2-3 mL pentane. A thick orange oil remained behind. On occasion, 10-15 mg quantities of methylcubyl azide **10** could be retrieved from this oil by extraction with pentane. The combined solution, light yellow in color, was passed through a silica plug (20 × 4 mm) of

silica gel to give methylcubyl azide **10** (174 mg, 74% yield) as a colorless solution in pentane.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.98 (m, 3H), 3.52 (m, 3H), 1.28 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 73.3 (s), 57.0 (s), 49.0 (d, 156 Hz, 2C), 44.6 (d, 154 Hz, 2C), 19.4 (q, 125 Hz); **IR** (gas, cm^{-1}): υ_{C-H} 2988 (m), $\upsilon_{N=N=N}$ 2105 (s), $\upsilon_{N=N=N}$ 1283 (s); **UV** (CH_3CN) λ_{max} (approximate ε): 288 (40), 235 (900, shoulder), 196 (5000) nm; **MS** (EI^+, HRES, column A) *m*/*z* (rel intensity): 131.0703 (2.8, M^+-N_2), 130.0667 (3.8), 116.0456 (2.6), 103.0535 (2.7), calcd for C_9H_9N 131.0734.

Thermolysis of 4-methylcubyl azide (**10**) in 2,3-dimethylbutadiene

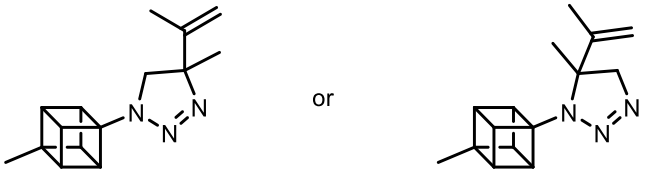


10

[**Note**: 4-methylcubyl azide (**10**) is a volatile impact sensitive oil. Detonation of 4-methylcubyl azide has been observed when a 5 mg sample was touched with the tip of sharp-edged glass pipette. Cubyl azides are best handled as a solution and only in glassware with smooth glass joints or fire polished edges.[4,5]]

Methylcubyl azide (**10**, 110 mg, 0.69 mmol) was vacuum transferred to a heavy-walled glass tube (15 × 150 mm) containing 2,3-dimethylbutadiene with 100 ppm hydroquinone as a radical inhibitor (6 mL, 4.4 g) and 2-3 mg hexadecane as a GC standard. The solution was freeze-thaw-degassed and the tube was flame-sealed and heated for two hours at 100 °C. The tube was cracked open and the contents removed. Most of the solvent was evaporated from the transparent brown reaction mixture at 6 mTorr while cooling at -15 °C. Approximately 2 mL benzene was added to the resulting brown oil. The products were separated by preparative gas chromatography on column B. A section of borosilicate glass tubing (4 mm O.D. × *ca.* 110 mm) was used as a liner for the stainless steel injection port. Frequent cleaning or replacement of this insert was essential for good resolution and recovery. Further purification was accomplished by chromatography on column C. Six compounds were isolated as follows.

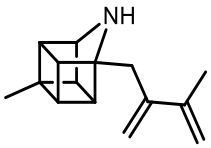
4- (or 5-) Isopropenyl-4- (or 5-) methyl-1-(4-methylcubyl)-Δ^2 triazoline (**S8** or **S9**)



S8 **S9**

1.8 mg (1-3% GC yield) thermally labile yellow oil. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 4.96 (s, 1H), 4.92 (s, 1H), 4.13 (m, 3H), 4.02 (s, 2H), 3.54 (m, 3H), 1.70 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H); **IR** (GC, 150 °C, column G, cm^{-1}): υ_{C-H} 2979 (m), $\upsilon_{C=C}$ 1643 (w), $\upsilon_{N=N}$ 1503 (m), υ_{CH3} 1452 (w) and 1356 (m), $\upsilon_{C=C-H}$ 974 (m).

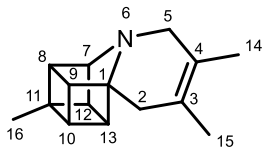
4-Methyl-1-(3-methyl-2-methylene-3-butenyl)-9-azapentacyclo[4.3.0.0.^{2,5}.0^{3,8}.0^{4,7}]nonane (**S10**)



S10

Clear oil, 1.8 mg (5-10% GC yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 5.22 (s, 1H) 5.20 (br, 1H), 5.03 (br, 1H), 5.00 (br, 1H), 4.23 (t, *J* = 2.6 Hz, 1H), 2.94 (*t* = 3.1 Hz, 4H), 2.93 (s, 2H), 2.64 (t, *J* = 3.1 Hz, 1H) 1.92 (s, 3H), 1.11 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 145.1, 143.4, 114.8 (t, *J* = 156 Hz), 113.8 (t, *J* = 157 Hz), 71.2, 58.2 (d, *J* = 153 Hz), 48.6 (d, *J* = 156 Hz, 2C), 44.2, 43.8 (d, *J* = 154 Hz, 2C), 38.7 (d, *J* = 158 Hz), 33.5 (t, *J* = 122 Hz), 21.3 (q, *J* = 126 Hz), 18.2 (q, *J* = 126 Hz); **IR** (GC, cm^{-1}): υ_{N-H} 3306 (w), $\upsilon_{C=C-H}$ 3097 (w), υ_{C-H} 2986 (s), $d_{C=CH2}$ 895 (m); **MS** (EI$^+$) *m*/*z* (rel intensity): 213 (11, M^+), 212 (41), 198 (34, M^+-CH_3), 146 (85), 132 (100).

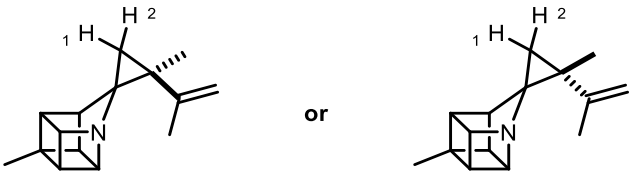
3,4,11-Trimethyl-6-azahexacyclo[7.4.0.0^{1,9}.0^{7,12}.0^{8,11}.0^{10,13}]tridec-3-ene (**S11**)



S11

Approximately 100 µg clear oil (1-2% yield GC yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 4.06 (H_7, t, *J* = 5 Hz), 3.03 ($H_{8 \text{ and } 12}$, br), 2.87 ($H_{9 \text{ and } 13}$, t, *J* = 5-6 Hz), 2.73 (H_{10}, m), 2.7 (H_5, br), 2.44 (H_2, s), 1.68 ($H_{14 \text{ or } 15}$, s), 1.58 ($H_{14 \text{ or } 15}$, s), 1.14 (H_{16}, s), $J_{9,10}$ and $_{10,13}$ = 5 Hz, $J_{8,9}$ and $_{12,13}$ = 5 Hz, $J_{8,10}$ and $_{10,12}$ = ≤1 Hz, $J_{7,8}$ and $_{7,12}$ = 5 Hz; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 123.3, 122.5, 69.3, 64.1 (d, *J* = 155 Hz), 48.5, 47.5 (2C, d), 45.9 (d), 43.8 (t), 39.2 (2C, d, *J* = 155 Hz), 34.2 (t, *J* = 125 Hz), 18.7, 18.5, 17.0; IR (CCl_4, cm^{-1}): 2975 (sh), 1448 (w), 1274 (w), 1171 (w), 1025 (w), 639 (w); **MS** (EI$^+$, column E) *m*/*z* (rel intensity): 213 (3, M$^+$), 212 (3, M$^+$-1), 196 (16), 182 (19), 146 (250), 131 (68, M$^+$-C_6H_{10}), 117 (19).

1α- (or 1β) -Spiro[4-methyl-1-azapentacyclo[4.3.0.0^{2,5}0.^{3,8}.0^{4,7}]nonane-9,2'-1′-methyl-1′-isopropenylcyclopropane] **(11** or **12**) (diastereomer #2)



11 **12**

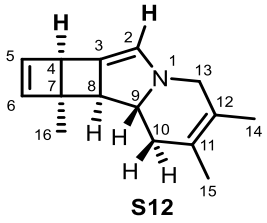
Clear oil, 0.4 mg (2-4% GC yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 4.70 (br, 1H), 4.63 (br, 1H), 4.40 (q, *J* = 4.5 Hz, 1H), 4.34 (q, *J* = 4.5 Hz, 1H), 3.09 (m, 2H), 2.98 (m, 1H), 2.89 (t, *J* = 5 Hz, 1H), 1.66 (s, 3H), 1.30 (s, 3H), 1.12 (s, 3H), 0.90 (d, $J_{1,2}$ = 4.9 Hz, 1H), 0.70 (d, $J_{1,2}$ = 4.9 Hz, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 148.3, 110.2 (t, *J* = 154 Hz), 69.4, 67.3 (d, *J* = 167 Hz), 67.3 (d, *J* = 161 Hz), 48.5 (d, *J* = 154 Hz), 47.9 (d, *J* = 144 Hz), 46.5, 43.0 (d, *J* = 146 Hz), 41.3 (d, *J* = 155 Hz), 30.5, 21.2, 19.9, 18.2, 17.5 (t, *J* = 162 ± 5 Hz); **IR** (GC, column G, cm^{-1}): $\upsilon_{\text{cyclopropyl C-H or C=C-H}}$ 3086 (w), $\upsilon_{\text{C-H}}$ 2978 (s), $\upsilon_{\text{C=C}}$ 1644 (w), υ_{CH3} 1448 (w), 1380 (w), 893 (m); **MS** (EI$^+$, column E) *m*/*z* (rel intensity): 212 (10, M$^+$-1), 211 (56), 197 (100), 180 (50), 129 (91), 104 (71).

1α- (or 1β) -Spiro[4-methyl-1-azapentacyclo[4.3.0.0^{2,5}0.^{3,8}.0^{4,7}]nonane-9,2′-1′-methyl-1′-isopropenylcyclopropane] (**11** or **12**) (diastereomer #1)

11 **12**

Clear oil, 0.4 mg (2-4% GC yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 4.83 (br, 1H), 4.76 (br, 1H), 4.33 (m, 2H), 3.11 (m, 3H), 2.91 (t, 1H), 1.72 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.09 (d, *J* = 5 Hz, 1H), 0.49 (d, *J* = 5 Hz, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 147.2, 111.1 (t, *J* = 154 Hz), 69.1, 67.5 (d, *J* = 166 Hz), 67.3 (d, *J* = 167 Hz), 47.8 (d, *J* = 150 ± 5 Hz), 47.6 (d, *J* = 155 ± 5 Hz) 46.5, 42.4 (d, *J* = 149 Hz), 41.2 (d, *J* = 156 Hz), 30.7, 21.7, 21.6, 18.3, 17.6 (t, *J* = 163 Hz); **IR** (GC, column G, cm^{-1}): $\upsilon_{\text{cyclopropyl C-H or C=C-H}}$ 3085 (w), $\upsilon_{\text{C-H}}$ 2981 (s), $\upsilon_{\text{C=C}}$ 1648 (w), υ_{CH3} 885 (w); **MS** (EI$^+$, column E) *m*/*z* (rel intensity): 212 (13, M$^+$-1), 211 (60), 197 (50), 145 (95), 129 (100), 104 (78).

1-Aza-4β,7β,8β,9α-tetracyclo[7.4.0.0^{3,8}.0^{4,7}]trideca-2,5,11-triene (**S12**)



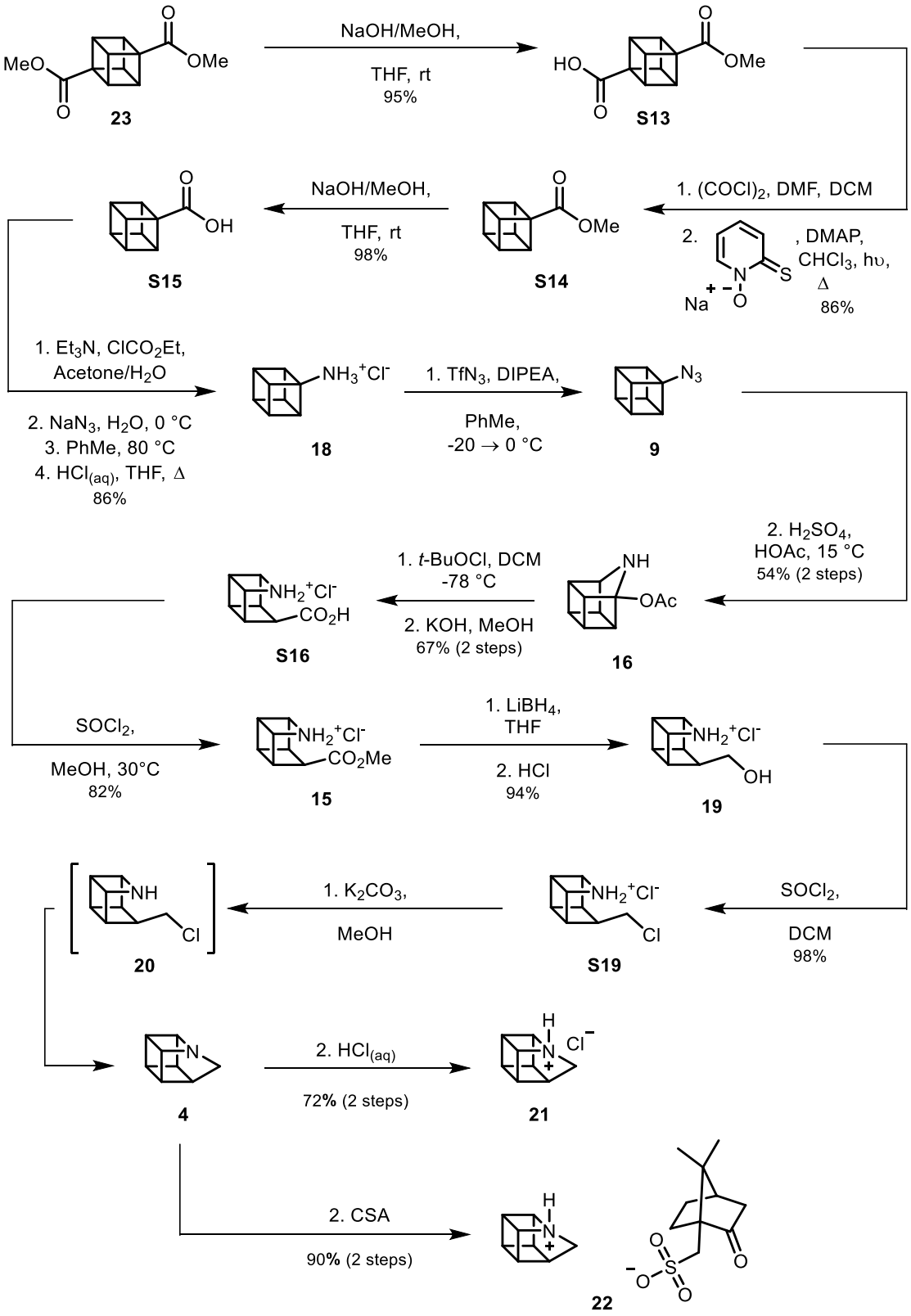
S12

Clear oil, 0.7 mg (5-10% GC yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.82 (H_2, s), 6.00 (H_5, dd), 5.95 (H_6, d), 2.72 (H_{13} or $_{13'}$, d), 2.61 (H_8, br), 2.50 (H_4, br), 2.27 (H_{13} or $_{13'}$, d), 2.15 (H_9, t), 1.75 (H_{10} and $_{10'}$, dt) 1.68 (H_{14} or $_{15}$, br), 1.56 (H_{14} or $_{15}$, br), 1.39 (H_{16}, s), $J_{5,6}$ = 2 Hz, $J_{4,5}$ = 1Hz, $J_{13,13'}$ = 18 Hz, $J_{10,10'}$ = 18 Hz, $J_{9,10}$ = ~8 Hz, $J_{8,9}$ = ≤ 1 Hz; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 177.8, 169.5 (d, *J* = 182 Hz), 142.6 (d, *J* = 170 Hz), 137.9 (d, *J* = 171 Hz), 125.2, 124.9, 60.6 (*d*, 154 Hz), 58.2 (d, *J* = 139 Hz), 58.0 (d, *J* = 131 Hz), 51.5, 37.0 (t, *J* = 125 Hz), 31.3 (t, *J* = 128 Hz), 20.0 (q, *J* = 126 Hz), 19.6 (q, *J* = 125 Hz), 19.5 (q, *J* = 124 Hz); **IR** (GC, column G, cm^{-1}): $\upsilon_{\text{C-H}}$ 2930 (sh), $\upsilon_{\text{C=C}}$ 1595 (w), 1292 (w), $\upsilon_{\text{C=C-H}}$ 780 (m); **MS** (EI$^+$, column E) *m*/*z* (rel intensity): 212 (3, M$^+$-1), 171 (6), 156 (10), 132 (27), 131 (100).

1-Azahomocubane (4)

General Experimental

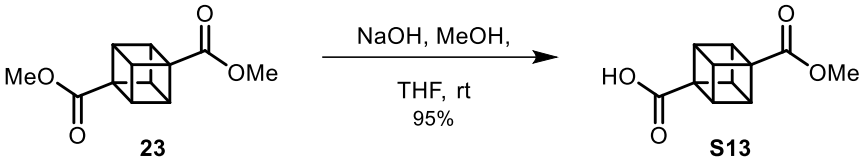
Glassware was oven dried (160 °C) before use with anhydrous solvents and reagents. Tetrahydrofuran was freshly distilled from elemental sodium / benzophenone under an argon atmosphere. Unless started otherwise commercially available chemicals were used without further purification. Dichloromethane, methanol, *N*,*N*-dimethylformamide, triethylamine, and toluene were freshly distilled to dryness over calcium hydride under an argon atmosphere or reduced pressure. *N*,*N*-Diisopropylethylamine was freshly distilled over ninhydrin and then potassium hydroxide under an argon atmosphere. Fresh glacial acetic acid was used from an unopened bottle. Chloroform was purified and dried by first washing with water and then storing over 4 Å molecular sieves. NMR experiments were recorded using a Bruker AS 500 or AV 500 instruments. Chemical shifts (δ) are reported in parts per million (ppm) and referenced internally according to solvent: $CDCl_3$ (^1H δ: 7.26 ppm, ^{13}C δ: 77.2 ppm), C_6D_6 (^1H δ: 7.16 ppm, ^{13}C δ: 128.1 ppm), D_2O (^1H δ: 4.79 ppm, ^{13}C (1,4-dioxane reference) δ: 67.2 ppm), and CD_3OD (^1H δ: 3.31 ppm, ^{13}C δ: 49.0 ppm). Structural assignments were made with additional information from gCOSY, gNOESY, gHSQC, and gHMBC experiments. High resolution electrospray ionization mass spectrometry measurements were obtained on Bruker MicroTOF-Q or Thermo Scientific Orbitrap Elite instruments. Melting points were determined using a Digimelt MPA161 melting point apparatus and are reported uncorrected. Syringe filtration used PhaseSep 13 mm PTFE 0.22 µm syringe filters (Part Number: 2164). Flash column chromatography was undertaken using 230-400 mesh silica gel or neutral ~150 mesh Brockmann I activated aluminum oxide. TLC was performed with Merck precoated silica gel plates (silica gel 60 F_{254}) or neutral aluminum oxide plates (alumina oxide 60 F_{254}). Fractions were initially visualized using UV irradiation and subsequently by heating TLC plates exposed to phosphomolybdic acid stain.



Scheme S2: Synthesis of 1-azahomocubane.

Experimental Procedures

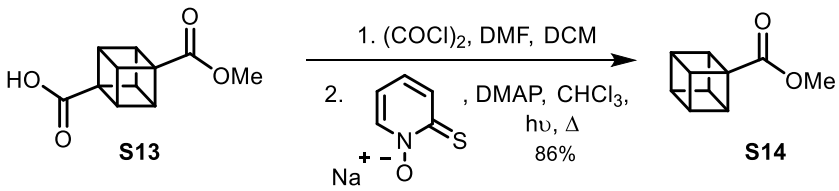
4-Methoxycarbonylcubane-1-carboxylic acid (**S13**)



Following the procedure of Eaton et al.:[6] dimethyl cubane-1,4-dicarboxylate (**23**, 5.01 g, 22.8 mmol) was dissolved in tetrahydrofuran (205 mL) at room temperature. A solution of sodium hydroxide in methanol was then added slowly dropwise (2.10 M, 11.9 mL) and the reaction was left to stir for 18 hours. Following *in vacuo* removal of solvent, the remaining solid was suspended in water (210 mL) and washed with dichloromethane (3 × 105 mL). The aqueous phase was then acidified to pH 2 with hydrochloric acid (10 M) and extracted with dichloromethane (3 × 105 mL). The organic extracts were combined and dried with magnesium sulfate and evaporated to give **S13** (4.44 g, 95%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.27 (s, 6H), 3.71 (s, 3H).

Methyl cubanecarboxylate (**S14**)

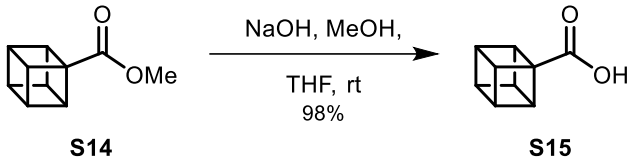


Following the procedure of Ho et al.:[7] anhydrous 4-methoxycarbonylcubane-1-carboxylic acid (**S13**, 4.04 g, 19.6 mmol) was added to anhydrous dichloromethane (130 mL) under an argon atmosphere. Oxalyl chloride (2.01 mL, 23.5 mmol), and a drop of anhydrous *N*,*N*-dimethylformamide, was then added, and the mixture stirred for one hour at room temperature. The solvent was then removed *in vacuo* and the resulting acid chloride placed under high vacuum (<4 mTorr) for one hour. Separately, freshy pestled 2-mercaptopyridine *N*-oxide sodium salt (4.57 g, 30.5 mmol) and *N*,*N*-dimethylpyridin-4-amine (27 mg, 0.22 mmol) were suspended in anhydrous chloroform (200 mL) under an argon atmosphere, and heated to reflux while being irradiated with a 500 W tungsten lamp. The freshly generated acid chloride was subsequently dissolved in anhydrous chloroform (200 mL), and added dropwise to the refluxing mixture. After three hours of reflux, the suspension was washed with water (3 × 130 mL), dried over magnesium

sulfate, and concentrated *in vacuo* to give a brown oil. The brown oil was purified via silica gel column chromatography (10% ethyl acetate / hexanes v/v) to give **S14** (2.74 g, 86%) as sweet-smelling white crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.27–4.23 (m, 3H), 4.03–3.98 (m, 4H), 3.70 (s, 3H).

Cubanecarboxylic acid (**S15**)

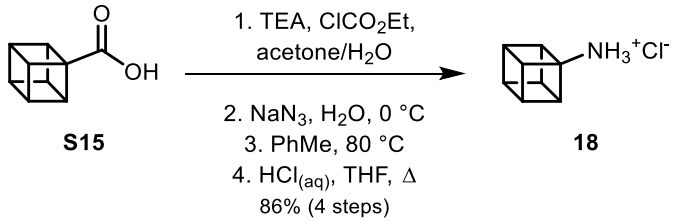


S14 **S15**

Following the procedure of Chalmers et al.:[8] methyl cubane-1-carboxylate (**S14**, 2.74 g, 16.9 mmol) was dissolved in anhydrous tetrahydrofuran (80 mL). A solution of sodium hydroxide in methanol was then added (3.8 M, 12 mL), and the reaction was left to stir for 18 hours at room temperature. The tetrahydrofuran was removed *in vacuo* and the remaining solid was suspended in water (80 mL). Following washes with dichloromethane (3 × 40 mL), the aqueous layer was acidified to pH 2 with hydrochloric acid (10 M) and extracted with dichloromethane (3 × 40 mL). The combined organic phases were dried with magnesium sulfate and evaporated to give **S15** (2.45 g, 98%) as a yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.32–4.28 (m, 3H), 4.06–4.00 (m, 4H).

Aminocubane hydrochloride (**18**)



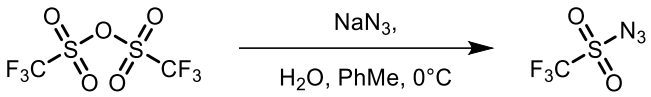
S15 **18**

Adapted from the procedure of Klunder et al.:[9] To an ice-cooled solution of cubanecarboxylic acid (**S15**, 1.08 g, 7.30 mmol) in an acetone/water mix (34 mL/1.2 mL) was added triethylamine (1.2 mL, 8.7 mmol). Ethyl chloroformate (0.85 mL, 8.7 mmol) was then added dropwise over five minutes, and the reaction mixture continued to be stirred for 30 minutes at 0 °C before adding sodium azide (0.72 g, 11 mmol) in water (2.4 mL). After being stirred for two hours at 0 °C, the mixture was poured into ice water (60 mL) and extracted with toluene (4 × 20 mL). The toluene phase was dried over sodium

sulfate and filtered. The dried toluene solution was then heated at 80 °C for one hour before removing the solvent *in vacuo* to give the crude isocyanate as an oil. The isocyanate was dissolved and heated at 65 °C in a tetrahydrofuran (22 mL) and hydrochloric acid (10 M, 3.6 mL) solution. After one hour of heating, the solution was cooled to room temperature, diluted with water (10 mL), and washed with dichloromethane (5 × 6.0 mL). The aqueous phase was then concentrated to a solid and dried under high vacuum (<4 mTorr) overnight to give **18** (0.99 g, 87%) as a white solid.

^{1}H-NMR (300 MHz, D_2O) δ: 4.23-4.21 (m, 3H), 4.03-4.00 (m, 4H).

Triflyl azide (**S7**)

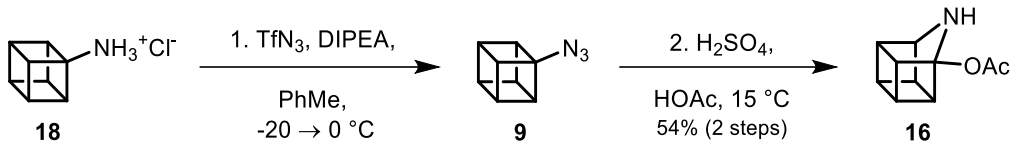


S6 **S7**

[**Note**: Triflyl azide (**S7**) can be explosive as a neat oil and should only be handled as a solution with glassware that contain smooth glass joints or fire polished edges.]

Following the procedure of Titz et al.:[10] sodium azide (545 mg, 8.38 mmol) was dissolved in a vigorously stirred mixture of water (1.4 mL) and toluene (1.4 mL). Behind a blast shield, the mixture was cooled to 0 – 5 °C and triflic anhydride (**S6**, 0.90 mL, 4.2 mmol) was added dropwise. This biphasic mixture was stirred for one hour at 0 – 5 °C and then 30 minutes at 5 – 10 °C. The organic phase was transferred to a separate vessel and kept at 0 °C. The remaining aqueous phase was extracted with toluene (2 × 1.4 mL) and combined with the transferred organic phase. The combined organic phases were then washed with water (2 × 1.4 mL) and saturated aqueous sodium bicarbonate (1 × 1.4 mL) to give a triflyl azide (**S7**) solution (kept below 0 °C and used immediately).

1-Acetoxy-9-azahomocubane (**16**)



18 **9** **16**

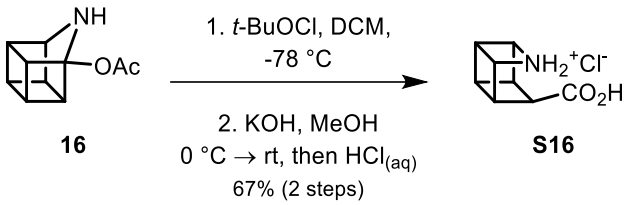
[**Note**: Cubyl azide (**9**) is a volatile impact sensitive oil. Detonation of 4-methylcubyl azide has been observed when a 5 mg sample was touched with the tip of a sharp-edged glass pipette. Cubyl azides are best handled as a solution and only in glassware with smooth glass joints or fire polished edges.[4,5]]

Behind a blast shield, the triflyl azide (**S7**) solution prepared above was diluted with toluene (6.0 mL) and *N*,*N*-diisosopropylethylamine (1.07 mL, 6.14 mmol) was added at -20 °C. To this solution, powdered aminocubane hydrochloride (**18**, 240 mg, 1.54 mmol) was added portionwise over five minutes. The resulting suspension was stirred for an additional 10 minutes before being warmed to 0 °C. After two hours, *t*-butylamine (0.30 mL, 2.9 mmol) was added and the yellow solution was stirred for an additional 15 minutes before being washed with aqueous sodium hydroxide (2.5 M, 3 × 2.0 mL), hydrochloric acid (2.7 M, 3 × 2.0 mL), saturated aqueous sodium bicarbonate (1 × 2.0 mL), and water (1 × 3.0 mL). The organic layer was dried over sodium sulfate and passed through a silica gel plug (25 × 4.5 mm) into a dry flask under an argon atmosphere; the plug was then flushed with toluene (6.0 mL). Following the addition of fresh glacial acetic acid (6.0 mL) to the effluent, a solution of sulfuric acid (5.3% sulfuric acid (98%) / acetic acid v/v), 1.52 mL) was added via syringe pump at 10 – 16 °C over three hours. After complete addition, the solution was warmed to room temperature over 30 minutes and concentrated under a stream of nitrogen. The crude residue was dissolved in aqueous disodium phosphate – monosodium phosphate pH 8 buffer (100 mL) and extracted with dichloromethane (8 × 4.0 mL). The combined organic phases were then concentrated under a stream of nitrogen to give **16** (146 mg, 54%) as a brown oil.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.29 (t, *J* = 5.0 Hz, 1H), 3.44-3.41 (m, 2H), 3.39-3.36 (m, 1H), 3.22-3.19 (m, 1H), 2.98-2.96 (m, 1H), 2.14 (s, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 170.8, 100.9, 56.2, 46.8, 45.2, 38.1, 36.6, 21.5; **HRMS-ESI** calcd for $C_{10}H_{11}NO_2H^+$ $([M+H])^+$: 178.0863; found: 178.0832.

The ^{1}H-NMR spectrum of the cubyl azide (**9**) was also collected while monitoring the acid-induced ring expansion of **9**. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ: 4.18-4.14 (m, 3H), 4.02-3.96 (m, 1H), 3.94-3.88 (m, 3H).

endo-1,2-Seco-1-azacubane-2-carboxylic acid hydrochloride (**S16**)



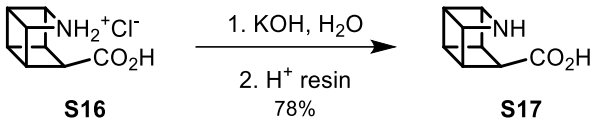
1-Acetoxy-9-azahomocubane (**16**, 133 mg, 751 µmol) was dissolved in anhydrous dichloromethane (3.0 mL) under an argon atmosphere. The solution was cooled to -78 °C before dropwise addition of *t*-butyl hypochlorite[11] (97 µL, 0.85 mmol). After three hours, the yellow solution was brought to room temperature over 30 minutes and gently concentrated under a stream of nitrogen. The resulting oil was dissolved in methanol (4.0 mL) and methanolic potassium hydroxide (1.0 M, 6.0 mL) was added dropwise at 0 °C. After 30 minutes, the solution was brought to room temperature and stirred for an additional two hours. Concentration of the brown reaction mixture *in vacuo* gave a residue, which was dissolved in water (5.0 mL), washed with dichloromethane (5 × 3.0 mL), acidified to pH 2 with hydrochloric acid (10 M), and washed again with dichloromethane (5 × 3.0 mL). The remaining aqueous phase was then concentrated to dryness and the residue was extracted with ethanol to remove inorganic salts. The pooled ethanol extracts were concentrated to give **S16** (94 mg, 67%) as yellow crystals.

m.p. 105.3-107.0 °C (dec.); **^{1}H-NMR** (500 MHz, CD_3OD) δ: 5.03-5.01 (m, 2H), 4.00-3.97 (m, 2H), 3.93-3.91 (m, 1H), 3.72 (t, *J* = 5.6 Hz, 1H), 3.48-3.45 (m, 1H); **^{13}C-NMR** (125 MHz, CD_3OD) δ: 175.1, 64.0, 45.2, 44.3, 41.6, 40.3; **HRMS-ESI** calcd for $C_8H_9NO_2H^+$ $([M-Cl])^+$: 152.0707; found: 152.0703.

The sodium salt was also prepared via the addition of sodium hydroxide (1 mg) to the hydrochloride salt (2 mg) in deuterium oxide (0.6 mL).

Sodium salt – **^{1}H-NMR** (500 MHz, D_2O) δ: 4.38-4.36 (m, 2H), 3.67-3.64 (m, 1H), 3.53-3.50 (m, 2H), 3.28 (t, *J* = 5.6 Hz, 1H), 3.11-3.08 (m, 1H); **^{13}C-NMR** (125 MHz, D_2O (1,4-dioxane reference)) δ: 185.4, 63.9, 47.6, 45.2, 42.4, 36.0; **HRMS-ESI** calcd for $C_8H_9NO_2Na^+$ $([M+Na])^+$: 174.0526; found: 174.0527.

endo-1,2-Seco-1-azacubane-2-carboxylic acid (**S17**)

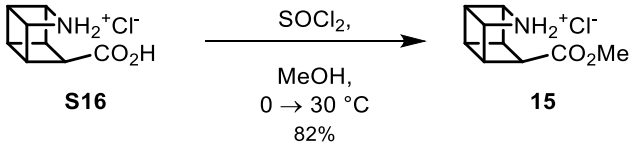


S16 **S17**

Adapted from the procedure of Takano et al.:[12] *endo*-1,2-seco-1-azacubane-2-carboxylic acid hydrochloride (**S16**, 184 mg, 981 µmol) was dissolved in an aqueous potassium hydroxide solution (3 mL, 0.8 M). This solution was then loaded onto a pre-treated resin column (Amberchrom 50WX8, hydrogen form cation exchange resin). Elution with aqueous pyridine (25%) gave **S17** (116 mg, 78%) as a maroon residue.

^{1}H-NMR (500 MHz, CD_3OD) δ: 4.95-4.93 (m, 2H), 3.94–3.91 (m, 2H), 3.89-3.86 (m, 1H), 3.46 (t, *J* = 5.4 Hz, 1H), 3.40-3.37 (m, 1H); **^{13}C-NMR** (125 MHz, CD_3OD) δ: 179.0, 64.8, 48.2, 46.7, 46.6, 41.9; **HRMS-ESI** calcd for $C_8H_9NO_2H^+$ $([M+H])^+$: 152.0707; found: 152.0704.

Methyl *endo*-1,2-seco-1-azacubane-2-carboxylate hydrochloride (**15**)

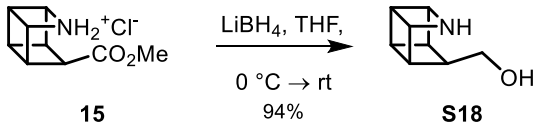


S16 **15**

Adapted from the procedure of Fill et al.:[13] *endo*-1,2-seco-1-azacubane-2-carboxylic acid hydrochloride (**S16**, 49 mg, 0.26 mmol) was dissolved in anhydrous methanol (5.0 mL) and then thionyl chloride (0.15 mL, 2.1 mmol) was added dropwise at 0 °C under an argon atmosphere. Following complete addition, the reaction temperature was brought to 30 °C and stirred for 24 hours. After concentrating *in vacuo*, the dry residue was washed with diethyl ether (3 × 1.0 mL) and toluene (3 × 1.0 mL) before being extracted with tetrahydrofuran (8 × 5.0 mL). The tetrahydrofuran mixture was syringe filtered and the filtrate evaporated under a stream of nitrogen to give **15** (44 mg, 82%) as a yellow oil.

^{1}H-NMR (500 MHz, CD_3OD) δ: 5.02-5.00 (m, 2H), 3.98-3.95 (m, 2H), 3.92-3.91 (m, 1H), 3.80 (s, 3H), 3.77 (t, *J* = 5.3 Hz, 1H), 3.47-3.45 (m, 1H); **^{13}C-NMR** (125 MHz, CD_3OD) δ: 174.8, 65.6, 53.6, 46.7, 45.6, 42.5, 41.7; **HRMS-ESI** calcd for $C_9H_{11}NO_2H^+$ $([M-Cl])^+$: 166.0863; found: 166.0854.

endo-(1,2-Seco-1-azacuban-2-yl)methanol (**S18**)

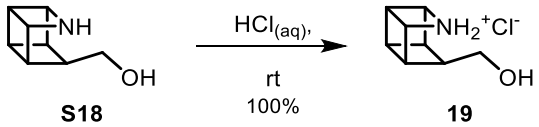


15 **S18**

Methyl *endo*-1,2-seco-1-azacubane-2-carboxylate hydrochloride (**15**, 122 mg, 603 µmol) was dissolved in anhydrous tetrahydrofuran (15 mL), and then a solution of lithium borohydride (2.0 M in tetrahydrofuran, 0.91 mL) was added dropwise at 0 °C under an argon atmosphere. After stirring for four hours at room temperature, aqueous saturated aqueous sodium bicarbonate (3.5 mL) was added at 0 °C, and stirring continued for an additional hour at room temperature. The resulting mixture was then syringe filtered and the tetrahydrofuran removed *in vacuo*. The remaining aqueous solution was diluted with water (4.0 mL) and extracted with dichloromethane (4 × 2.0 mL). The combined organic phases were evaporated, and the dry residue was extracted with acetonitrile (3 × 1.0 mL). Concentrating the pooled extracts under a stream of nitrogen gave **S18** (78 mg, 94%) as a pale-yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.22-4.20 (m, 2H), 3.90 (d, *J* = 3.4 Hz, 2H), 3.84-3.82 (m, 1H), 3.61-3.58 (m, 2H), 3.25-3.22 (m, 1H), 2.75-2.71 (m, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 66.3, 62.0, 47.2, 45.0, 42.2, 38.5; **HRMS-ESI** calcd for $C_8H_{10}NOH^+$ $([M+H])^+$: 138.0914; found: 138.0911.

endo-(1,2-Seco-1-azacuban-2-yl)methanol hydrochloride (**19**)

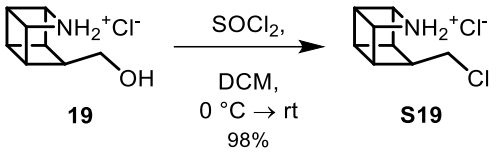


S18 **19**

endo-(1,2-Seco-1-azacuban-2-yl)methanol (**S18**, 79 mg, 0.58 mmol) was dissolved in water (1.0 mL) and acidified to pH 2 with hydrochloric acid (1.0 M). After concentrating *in vacuo*, the dry residue was washed with toluene (3 × 1.0 mL) and extracted with water then syringe filtered. The filtrate was concentrated to a solid and dried under high vacuum (<4 mTorr) to give **19** (100 mg, 100%) as a yellow solid.

m.p. 95.0-96.1 °C (dec.); **^{1}H-NMR** (500 MHz, CD_3OD) δ: 4.85-4.83 (m, 2H), 3.87-3.83 (m, 3H), 3.81 (d, *J* = 3.0 Hz, 2H), 3.39-3.36 (m, 1H), 2.95-2.92 (m, 1H); **^{13}C-NMR** (125 MHz, CD_3OD) δ: 62.1, 59.8, 47.1, 44.7, 42.2, 39.7; **HRMS-ESI** calcd for $C_8H_{10}NOH^+$ $([M-Cl])^+$: 138.0914; found: 138.0910.

endo-2-(Chloromethyl)-1,2-seco-1-azacubane hydrochloride (**S19**)

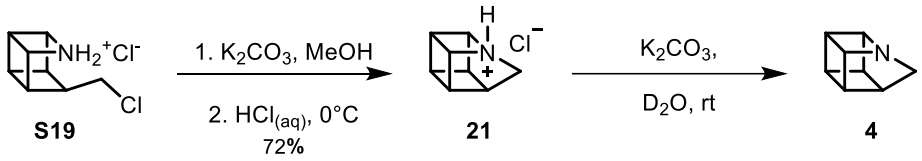


19 **S19**

Adapted from the procedure of Xu et al.:[14] *endo*-(1,2-seco-1-azacuban-2-yl)methanol hydrochloride (**19**, 18 mg, 0.10 mmol) was dissolved in anhydrous dichloromethane (4.5 mL) and thionyl chloride (22 µmol, 0.31 mmol) was added at 0 °C under an argon atmosphere. After stirring for four hours at room temperature, the reaction mixture was concentrated under a stream of nitrogen and the dry residue was washed with hexanes (3 × 1.0 mL). The residue was then extracted in dichloromethane (3 × 1.0 mL) and syringe filtered. Concentrating the filtrate under a stream of nitrogen gave **S19** (19 mg, 98%) as a brown crystalline solid. [**Note**: The product is unstable and storing in solution overnight at room temperature or neat over several days at -24 °C leads to ring closing to **21**.]

^{1}H-NMR (500 MHz, CD_3OD) δ: 4.96-4.94 (m, 2H), 3.97 (d, *J* = 8.4 Hz, 2H), 3.93-3.91 (m, 1H), 3.82-3.79 (m, 2H), 3.36-3.33 (m, 1H), 3.21-3.15 (m, 1H); **^{13}C-NMR** (125 MHz, CD_3OD) δ: 65.9, 46.1, 44.9, 42.4, 42.3, 40.8; **HRMS-ESI** calcd for $C_8H_{10}ClNH^+$ ($[M\text{-}Cl]$)$^+$: 156.0575, 158.0546; found: 156.0577, 158.0548.

1-Azahomocubane hydrochloride (**21**) and 1-Azahomocubane (**4**)



S19 **21** **4**

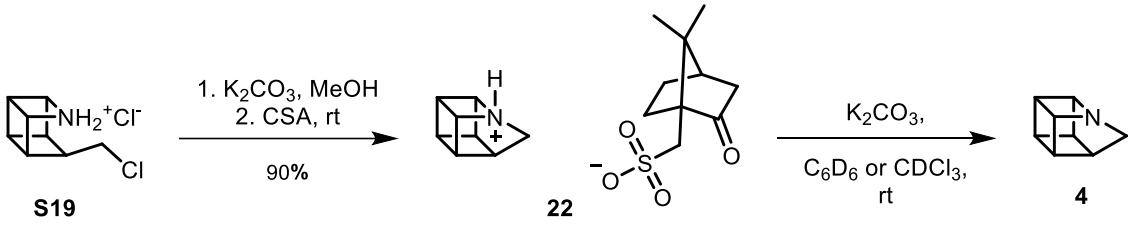
endo-2-(Chloromethyl)-1,2-seco-1-azacubane hydrochloride (**S19**, 17 mg, 87 µmol) was dissolved in methanol (2.0 mL) to which a methanolic potassium carbonate solution (0.10 M, 1.7 mL) was added. After stirring for a minute, the reaction mixture was cooled to 0 °C and hydrochloric acid (1.0 M, 0.48 mL) was added dropwise over five minutes. Following complete addition, the solvent was quickly removed under stream of nitrogen, and the dry residue was washed with toluene (3 × 0.5 mL). The residue was then extracted with dichloromethane (3 × 1.0 mL) and syringe filtered. Concentrating the filtrate under a stream of nitrogen gave **21** (9.8 mg, 72%) as a grey residue. [**Note**: Storing neat at 7 °C leads to product ring opening to **24**.]

^{1}H-NMR (500 MHz, CD_3OD) δ: 5.24-5.21 (m, 2H), 3.99-3.97 (m, 1H), 3.84-3.80 (m, 2H), 3.71-3.69 (m, 1H), 3.46 (s, 2H), 3.39-3.36 (m, 1H); **^{13}C-NMR** (125 MHz, CD_3OD) δ: 73.1, 63.6, 45.4, 43.4, 41.3, 40.2; **^{1}H-NMR** (500 MHz, D_2O) δ: 5.28-5.26 (m, 2H), 4.00-4.00 (m, 1H), 3.86-3.83 (m, 2H), 3.72-3.70 (m, 1H), 3.46 (s, 2H), 3.39-3.37 (m, 1H); **^{13}C-NMR** (125 MHz, D_2O (1,4-dioxane reference)) δ: 72.4, 63.0, 44.4, 42.4, 40.5, 39.4; **HRMS-ESI** calcd for $C_8H_9NH^+$ ([M-Cl])$^+$: 120.0808; found: 120.0809.

The free amine (i.e., 1-azahomocubane **4**) was prepared via adding excess potassium carbonate (5 mg) to the hydrochloride salt (1 mg) in deuterium oxide (0.6 mL), and briefly sonicating the mixture before syringe filtering off undissolved potassium salts.

^{1}H-NMR (500 MHz, D_2O) δ: 4.46-4.46 (m, 2H), 3.62 (t, *J* = 5.3 Hz, 1H), 3.40-3.39 (m, 2H), 3.26-3.25 (m, 1H), 3.17-3.17 (m, 1H), 2.74 (s, 2H); **^{13}C-NMR** (125 MHz, D_2O (1,4-dioxane reference)) δ: 70.2, 66.0, 44.2, 44.2, 39.1, 38.9.

1-Azahomocubane (1*S*)-(+)-camphorsulfonate (**22**) and 1-Azahomocubane (**4**)



S19 **22** **4**

endo-2-(Chloromethyl)-1,2-seco-1-azacubane hydrochloride (**S19**, 30 mg, 0.16 mmol) was dissolved in methanol (2.0 mL) to which methanolic potassium carbonate solution (0.10 M, 0.9 mL) was added. After stirring for a minute, (1*S*)-(+)-camphorsulfonic acid (37 mg, 0.16 mmol) was added followed by small quantities of additional (1*S*)-(+)-camphorsulfonic acid to acidify the reaction below pH 3. The reaction mixture was then concentrated to dryness under a stream of nitrogen and extracted with ethyl acetate (3 × 1.0 mL). Passive evaporation of the pooled ethyl acetate extracts at 7 °C over two weeks caused **22** (50 mg, 90%) to separate out of solution as a brown oil.

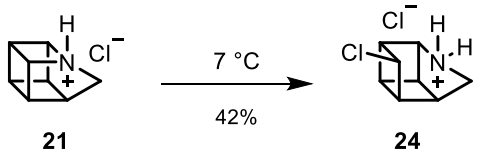
^{1}H-NMR (500 MHz, CD_3OD) δ: 5.25-5.23 (m, 2H), 3.99 (t, *J* = 5.6 Hz, 1H), 3.85-3.81 (m, 2H), 3.72-3.70 (m, 1H), 3.47 (s, 2H), 3.40-3.38 (m, 1H), 3.31 (d, *J* = 9.3 Hz, 1H), 2.79 (d, *J* = 14.7 Hz, 1H), 2.71-2.65 (m, 1H), 2.36 (dt, *J* = 18.4, 3.8 Hz, 1H), 2.08-2.04 (m, 2H), 1.91 (d, *J* = 18.4 Hz, 1H), 1.67-1.61 (m, 1H), 1.46-1.41 (m, 1H), 1.15 (s, 3H), 0.88 (s, 3H); **^{13}C-NMR** (125 MHz, C_6D_6) δ: 216.9, 71.6, 62.3, 58.2, 46.8, 44.0, 42.7, 42.2, 42.1, 39.8, 38.8, 26.4, 24.4, 19.0, 18.7; **HRMS-ESI** calcd for $C_8H_9NH^+$ ([M-$C_{10}H_{15}SO_4$])$^+$: 120.0808; found: 120.0806.

The free amine (i.e., 1-azahomocubane **4**) was prepared via sonicating a solution of the camphorsulfonate salt (3 mg) in deuterated benzene or chloroform (0.6 mL) over

excess potassium carbonate (20 mg) for 10 minutes and then syringe filtering off the potassium salts.

^{1}H-NMR (500 MHz, C_6D_6) δ: 4.29-4.27 (m, 2H), 3.15-3.13 (t, *J* = 5.4 Hz, 1H), 2.96-2.92 (m, 3H), 2.84-2.82 (m, 1H), 2.53 (s, 2H); **^{13}C-NMR** (125 MHz, C_6D_6) δ: 70.7, 67.5, 44.4, 44.1, 39.0, 38.9; **^{15}N-NMR** (^{1}H-^{15}N-HMBC) (700 MHz, C_6D_6) δ: 78.7; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 4.42-4.39 (m, 2H), 3.50 (t, *J* = 5.4 Hz, 1H), 3.31-3.27 (m, 2H), 3.21-3.18 (m, 1H), 3.13-3.09 (m, 1H), 2.69 (s, 2H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 70.6, 67.3, 44.2, 44.0, 38.9, 38.8.

exo-1,2-Seco-2-chloro-1-azahomocubane hydrochloride (**24**)



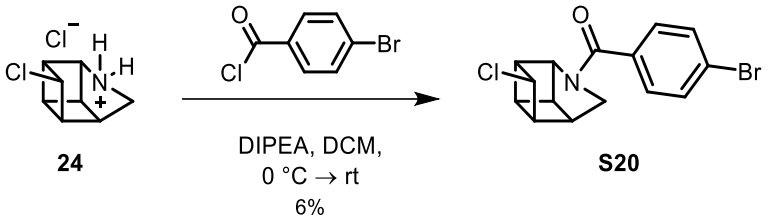
21 **24**

1-Azahomocubane hydrochloride (**21**, 7.7 mg, 49 µmol) was stored neat in a glass vial at 7 °C for three months to give **24** (4.0 mg, 42%) as a yellow residue. **^{1}H-NMR** (500 MHz, CD_3OD) δ: 4.81-4.77 (m, 1H), 4.75 (d, *J* = 0.8 Hz, 1H), 3.91 (d, *J* = 12.7 Hz, 1H), 3.80-3.75 (m, 1H), 3.61-3.58 (m, 2H), 3.52 (dd, *J* = 12.7, 5.6 Hz, 1H), 3.29-3.24 (m, 1H), 3.14-3.10 (m, 1H); **^{13}C-NMR** (125 MHz, CD_3OD) δ: 60.8, 59.7, 53.3, 48.4, 48.4, 45.1, 43.5, 39.0; **HRMS-ESI** calcd for $C_8H_{10}ClNH^+$ $([M\text{-}Cl])^+$: 156.0575, 158.0546; found: 156.0568, 158.0539.

The free amine (i.e., *exo*-1,2-seco-2-chloro-1-azahomocubane) was prepared via adding excess potassium carbonate (10 mg) to the hydrochloride salt (1 mg) in deuterated methanol (0.6 mL) and sonicating the mixture for five minutes before syringe filtering off undissolved potassium salts.

^{1}H-NMR (500 MHz, CD_3OD) δ: 4.63 (d, *J* = 1.5 Hz, 1H), 4.27-4.24 (m, 1H), 3.49-3.45 (m, 1H), 3.37-3.34 (m, 2H), 3.25 (d, *J* = 12.0 Hz, 1H), 3.15 (dd, *J* = 5.6, 12.0 Hz, 1H), 3.01-2.98 (m, 1H), 2.95-2.92 (m, 1H).

(4-Bromophenyl)(*exo*-1,2-seco-2-chloro-1-azahomocuban-1-yl)methanone (**S20**)

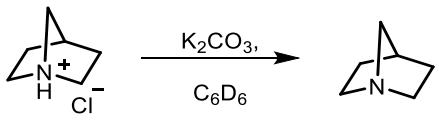


24 **S20**

A dichloromethane solution of *p*-bromobenzoyl chloride (10 mM, 0.30 mL) was added to *exo*-1,2-seco-2-chloro-1-azahomocubane hydrochloride (**24**, 3.0 mg, 16 µmol) in anhydrous dichloromethane (3.0 mL) at 0 °C under an argon atmosphere. Anhydrous *N*,*N*-diisopropylethylamine (10 uL, 71 µmol) was then added, and the reaction was left to stir at room temperature. After two hours, the reaction mixture was washed with saturated aqueous sodium bicarbonate (2 × 1.5 mL), water (2 × 1.5 mL), and brine (1 × 1.5 mL). The solvent was then removed under a stream of nitrogen, and the residue was purified via neutral alumina column chromatography (Pasteur pipette) (dichloromethane, then 5% MeOH / dichloromethane v/v) to give **S20** (0.3 mg, 6%) as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.56 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.70 (d, *J* = 0.9 Hz, 1H), 4.59 (t, *J* = 7.1 Hz, 1H), 3.96 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.89 (d, *J* = 13.2 Hz, 1H), 3.65-3.60 (m, 1H), 3.53-3.50 (m, 1H), 3.44-3.42 (m, 1H), 3.28-3.24 (m, 1H), 3.18-3.14 (m, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 168.4, 135.4, 131.8, 128.7, 125.1, 61.3, 59.9, 53.9, 52.1, 48.2, 44.9, 41.1, 37.6; **HRMS-ESI** calcd for $C_{15}H_{13}BrClNOH^+$ $([M+H])^+$: 337.9942, 339.9922; found: 337.9939, 339.9915.

1-Azabicyclo[2.2.1]heptane (**26**)

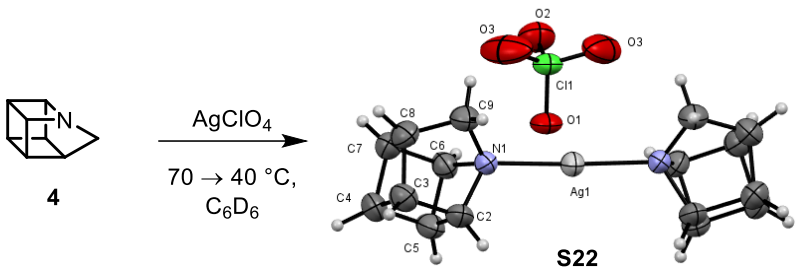


S21 **26**

Commercial 1-azabicyclo[2.2.1]heptane hydrochloride (**S21**, 1.0 mg, 7.5 µmol) was dissolved in deuterated benzene. Excess potassium carbonate (10 mg) was then added, and the mixture was sonicated for five minutes before syringe filtering off undissolved potassium salts to yield a solution of **26** for characterisation.

^{1}H-NMR (500 MHz, C_6D_6) δ: 2.70-2.64 (m, 2H), 2.25-2.19 (m, 2H), 2.16 (t, *J* = 4.4 Hz, 1H), 1.24-1.17 (m, 2H), 0.78-0.73 (m, 2H); **^{13}C-NMR** (125 MHz, C_6D_6) δ: 60.2, 54.8, 36.9, 30.9; **^{15}N-NMR** (^{1}H-^{15}N-HMBC) (700 MHz, C_6D_6) δ: 58.7.

Bis(1-azahomocubane)silver(I) perchlorate (**S22**)



A deuterated benzene solution (100 µL) of silver perchlorate (12 mg, 58 µmol) was added to 1-azahomocubane (**4**, 6.5 mg, 55 µmol) in deuterated benzene (500 µL) and heated at 70 °C for two hours before heating at 40 °C overnight. After cooling to room temperature, the organic solution was washed with brine (200 µL) and dried over sodium sulfate.

^{1}H-NMR (500 MHz, C_6D_6) δ: 4.59-4.57 (m, 4H), 3.12-3.09 (m, 2H), 2.90 (t, *J* = 5.4 Hz, 2H), 2.86 (s, 2H), 2.74-2.71 (m, 4H), 2.49-2.46 (m, 2H); **^{13}C-NMR** (125 MHz, C_6D_6) δ: 74.2. 68.1. 43.3, 42.5. 39.1, 38.4.

Following NMR characterisation, the deuterated benzene solution was stored at 7 °C and slowly evaporated over eight months to yield **S22** as brown crystals.

HRMS-ESI calcd for $C_{16}H_{18}N_2Ag^+$ ([M-ClO_4])$^+$: 345.0521, 347.0518; found: 345.0515, 347.0508.

Supplementary Text

Stability evaluation

1-Azahomocubane (**4**) did not isomerize to the corresponding azanorsnoutane in the presence of catalytic or stoichiometric quantities of silver perchlorate while heating at 40-70 °C for several hours in deuterated benzene. These conditions are reported favourable for homocubane isomerization in the literature.[15,16] Furthermore, after storing for eight months at 7 °C the azahomocubane cage was still intact as evident by X-ray crystallography of the resulting silver complex (**S22**).

Following the NMR-pH titration of 1-azahomocubane, the free amine was recovered from the aqueous solution via deuterated benzene extraction. There was no observable decomposition by ^{1}H-NMR of the caged amine under the aqueous pH range (pH 4-13) investigated over four hours with sodium hydroxide.

The free amine (**4**) in deuterated benzene did not show evidence of decomposition while stored for over a month at room temperature in the absence of light and it is believed to be stable for much longer. However, the addition of excess hydrochloric acid (1.0 M) to an aqueous or methanolic solution of 1-azahomocubane was observed to cause ring opening resulting in *exo*-1,2-seco-2-chloro-1-azahomocubane hydrochloride (**24**) at room temperature and in an ice bath. Furthermore, a sample of the 1-azahomocubane hydrochloride salt (**21**) was found fully converted to **24** after storing neat at 7 °C for three months. The sample was not monitored routinely, and it is likely the ring opening occurred much sooner than three months. The hydrochloride salt appeared to be stable indefinitely when stored at -24 °C.

No decomposition was observed following the addition of excess (1*S*)-(+)-camphorsulfonic acid or stoichiometric aqueous triflic acid (0.532 M) to 1-azahomocubane (**4**) at room temperature in deuterated benzene. Furthermore, no decomposition was observed following the addition of excess (1*S*)-(+)-camphorsulfonic acid to a methanolic solution of 1-azahomocubane (**4**). The CSA salt (**22**) showed no signs of decomposition in a solution of ethyl acetate or deuterated benzene while stored at 7 °C for over a month. The CSA salt appeared to be stable indefinitely when stored at -24 °C.

X-Ray Crystallographic Data

Data were acquired on an Oxford Diffraction Gemini Ultra S dual source diffractometer (utilizing Cu-Kα radiation) with the crystal cooled to 190 K by an Oxford Cryosystems Desktop Cooler. The structure was solved with SHELXT and refined with SHELXL[17] within the WinGX interface.[18] All structure diagrams were produced with Mercury[19] with all thermal ellipsoids depicted at the 50% probability level.

The complex cation perchlorate anion and benzene solvent molecule (disordered) occupy a crystallographic mirror plane.

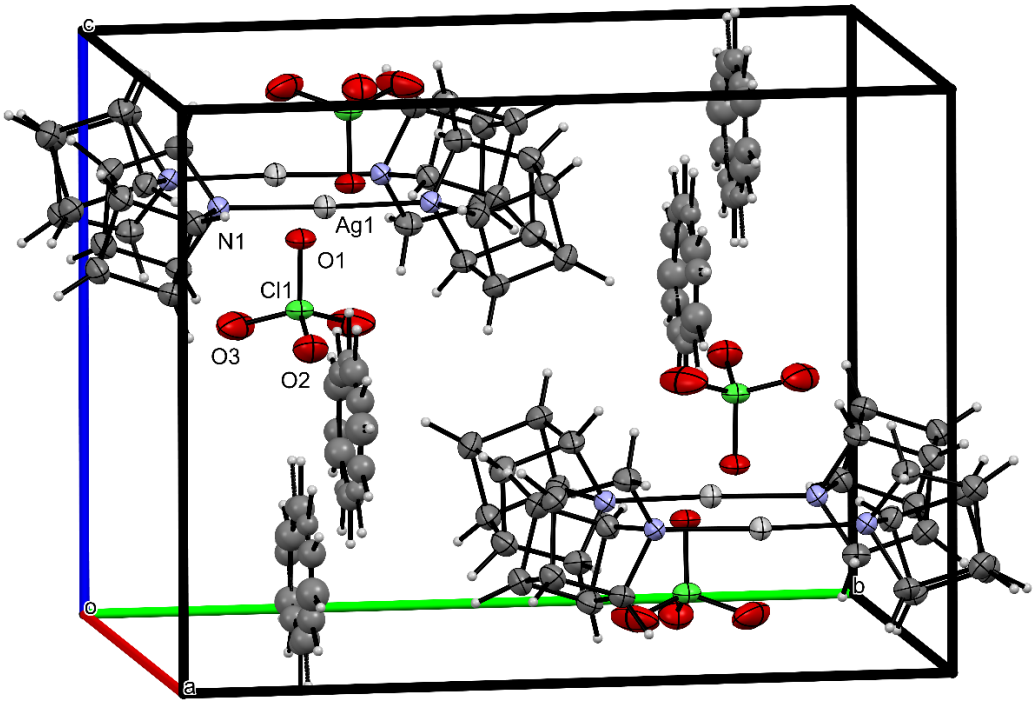


Figure S1: Unit cell of the structure of 1-azahomocubane (**4**) as its 2:1 complex with silver perchlorate and co-crystallized benzene.

Table S2: Crystal data and structure refinement for **S22**.

Identification code	2210agazahomocubane (CCDC 2177501)
Empirical formula	$C_{16}H_{18}AgClN_2O_4 \cdot C_6H_6$
Formula weight	523.75
Temperature	190(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	*P n m a*
Unit cell dimensions	*a* = 11.454(2) Å
	b = 15.519(2) Å
	c = 11.685(1) Å
Volume	2077.1(4) $Å^3$
Z	4
Density (calculated)	1.675 Mg/m^3
Absorption coefficient	9.243 mm^{-1}
F(000)	1064
Crystal size	0.150 x 0.100 x 0.040 mm^3
Theta range for data collection	4.737 to 62.489°.
Index ranges	-12<=h<=13, -17<=k<=17, -13<=l<=12
Reflections collected	10235
Independent reflections	1721 [R(int) = 0.0513]
Completeness to theta = 62.489°	100.0 %
Absorption correction	Analytical
Max. and min. transmission	0.707 and 0.327
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1721 / 12 / 152

Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0538, wR2 = 0.1552
R indices (all data)	R1 = 0.0591, wR2 = 0.1649
Largest diff. peak and hole	2.328 and -0.895 e.$Å^{-3}$

Table S3 Bond lengths [Å] and angles [°] for **S22** (2210agazahomocubane).

N(1)-C(9)	1.484(6)
N(1)-C(2)	1.523(6)
N(1)-C(6)	1.523(6)
N(1)-Ag(1)	2.141(6)
C(2)-C(5)	1.542(8)
C(2)-C(3)	1.556(7)
C(3)-C(8)	1.552(8)
C(3)-C(4)	1.568(9)
C(4)-C(5)	1.548(7)
C(4)-C(7)	1.564(7)
C(5)-C(6)	1.549(6)
C(6)-C(7)	1.556(7)
C(7)-C(8)	1.536(8)
C(8)-C(9)	1.506(7)
C(10)-C(11)	1.374(18)
C(10)-C(15)	1.394(18)
C(11)-C(12)	1.342(19)
C(12)-C(13)	1.390(18)
C(13)-C(14)	1.440(17)
C(14)-C(15)	1.337(19)
C(10')-C(11')	1.373(18)
C(10')-C(15')	1.394(18)
C(11')-C(12')	1.342(19)
C(12')-C(13')	1.389(18)
C(13')-C(14')	1.440(17)
C(14')-C(15')	1.34(2)

Cl(1)-O(2)	1.403(6)
Cl(1)-O(3)#1	1.423(4)
Cl(1)-O(3)	1.423(4)
Cl(1)-O(1)	1.450(5)

C(9)-N(1)-C(2)	105.7(4)
C(9)-N(1)-C(6)	104.9(4)
C(2)-N(1)-C(6)	87.5(4)
C(9)-N(1)-Ag(1)	118.3(3)
C(2)-N(1)-Ag(1)	118.0(3)
C(6)-N(1)-Ag(1)	117.7(3)
N(1)-C(2)-C(5)	91.5(4)
N(1)-C(2)-C(3)	105.1(4)
C(5)-C(2)-C(3)	90.3(4)
C(8)-C(3)-C(2)	101.9(4)
C(8)-C(3)-C(4)	91.2(4)
C(2)-C(3)-C(4)	89.4(4)
C(5)-C(4)-C(7)	90.6(4)
C(5)-C(4)-C(3)	89.6(4)
C(7)-C(4)-C(3)	86.3(4)
C(2)-C(5)-C(4)	90.7(4)
C(2)-C(5)-C(6)	85.9(4)
C(4)-C(5)-C(6)	89.7(4)
N(1)-C(6)-C(5)	91.3(4)
N(1)-C(6)-C(7)	104.6(4)
C(5)-C(6)-C(7)	90.8(4)
C(8)-C(7)-C(6)	102.5(4)

C(8)-C(7)-C(4)	92.0(4)
C(6)-C(7)-C(4)	88.8(4)
C(9)-C(8)-C(7)	105.0(4)
C(9)-C(8)-C(3)	106.0(4)
C(7)-C(8)-C(3)	87.8(4)
N(1)-C(9)-C(8)	99.0(4)
N(1)-Ag(1)-N(1)#1	177.58(19)
C(11)-C(10)-C(15)	122.9(12)
C(12)-C(11)-C(10)	115.7(12)
C(11)-C(12)-C(13)	123.8(12)
C(12)-C(13)-C(14)	119.4(11)
C(15)-C(14)-C(13)	116.3(11)
C(14)-C(15)-C(10)	121.9(12)
C(11')-C(10')-C(15')	123.8(13)
C(12')-C(11')-C(10')	115.4(12)
C(11')-C(12')-C(13')	123.3(12)
C(12')-C(13')-C(14')	120.2(11)
C(15')-C(14')-C(13')	116.0(12)
C(14')-C(15')-C(10')	121.2(12)
O(2)-Cl(1)-O(3)#1	109.4(3)
O(2)-Cl(1)-O(3)	109.4(3)
O(3)#1-Cl(1)-O(3)	110.6(6)
O(2)-Cl(1)-O(1)	109.6(3)
O(3)#1-Cl(1)-O(1)	108.9(2)
O(3)-Cl(1)-O(1)	108.9(2)

Symmetry transformations used to generate equivalent atoms: #1 x,-y+1/2,z

pK_a Determination

^{1}H-NMR experiments were performed on a Bruker AS 500 instrument with suppression of the water resonance. pH measurements were taken with a Hanna HI-1093B pH electrode which can take pH measurements of small volumes (< 200 µL). The portable Hanna 8424 pH meter was calibrated at pH 7 and pH 10 with standard buffers. NMR-pH titrations were conducted on quinuclidine (18 µmol), 1-azabicyclo[2.2.1]heptane (18 µmol), and 1-azahomocubane (16 µmol) in a H_2O/D_2O (9:1) mixture (500 µL). No corrections for the presence of D_2O were made. 1,4-Dioxane was added to each amine solution as an internal NMR reference (^{1}H δ: 3.75 ppm). The quantity of 1,4-dioxane added to each amine solution was 5 µL for quinuclidine and 1-azabicyclo[2.2.1]heptane and 0.3 µL for 1-azahomocubane. The pH of each amine solution was adjusted using a solution of sodium hydroxide (0.532 M, H_2O/D_2O (9:1)). All H_2O/D_2O solutions were prepared from the same stock solution. All NMR-pH titrations began from the respective ammonium salts. 1-Azabicyclo[2.2.1]heptane hydrochloride was purchased from AmBeed Inc. (Catalog No. 1461777). The quinuclidine hydrochloride and 1-azahomocubane triflate salts were prepared following the addition of either excess hydrochloric acid (1.0 M) or stoichiometric aqueous triflic acid (0.532 M) to a benzene solution of the respective free amines, which were concentrated to dryness prior to NMR-pH titration experiments. All NMR-pH titrations were conducted at 21.5 °C.

General Procedure

A H_2O/D_2O (9:1) solution (500 µL) of the hydrogen triflate or hydrochloride salt of the amine (16 or 18 µmol) was prepared in an NMR tube. 1,4-Dioxane (0.3 µL or 5 µL) was added and the NMR tube was sealed with the NMR tube cap before inverting eight times. After collecting the ^{1}H-NMR spectrum, 100 µL of the solution was withdrawn and transferred to a 0.2 mL PCR tube (Quality Scientific Plastics, Catalog No. 431-Q). The pH of this aliquot was taken. The aliquot was returned to the NMR tube. A H_2O/D_2O (9:1) solution of sodium hydroxide (3.0-3.4 µL, 0.532 M) was added directly to the NMR solution and the tube was inverted eight times. After mixing, the ^{1}H-NMR spectrum and pH measurements were collected again. This process continued, adding various quantities (3.0-33.8 µL) of sodium hydroxide (0.532 M), until proton resonances no longer shifted upfield, which indicated that the amine was deprotonated.

The observed chemical shift of a particular resonance (δ_{obs}) is a weighted average of δ_A and δ_{HA}, the chemical shifts of the free base and ammonium salt respectively according to equation (1) where K_a (the acidity constant) is the reciprocal of the amine protonation constant then converted to pK_a.

$$\delta_{obs} = \frac{\delta_A + 10^{(pK_a - pH)}\delta_{HA}}{1 + 10^{(pK_a - pH)}} \qquad (1)$$

Data Analysis

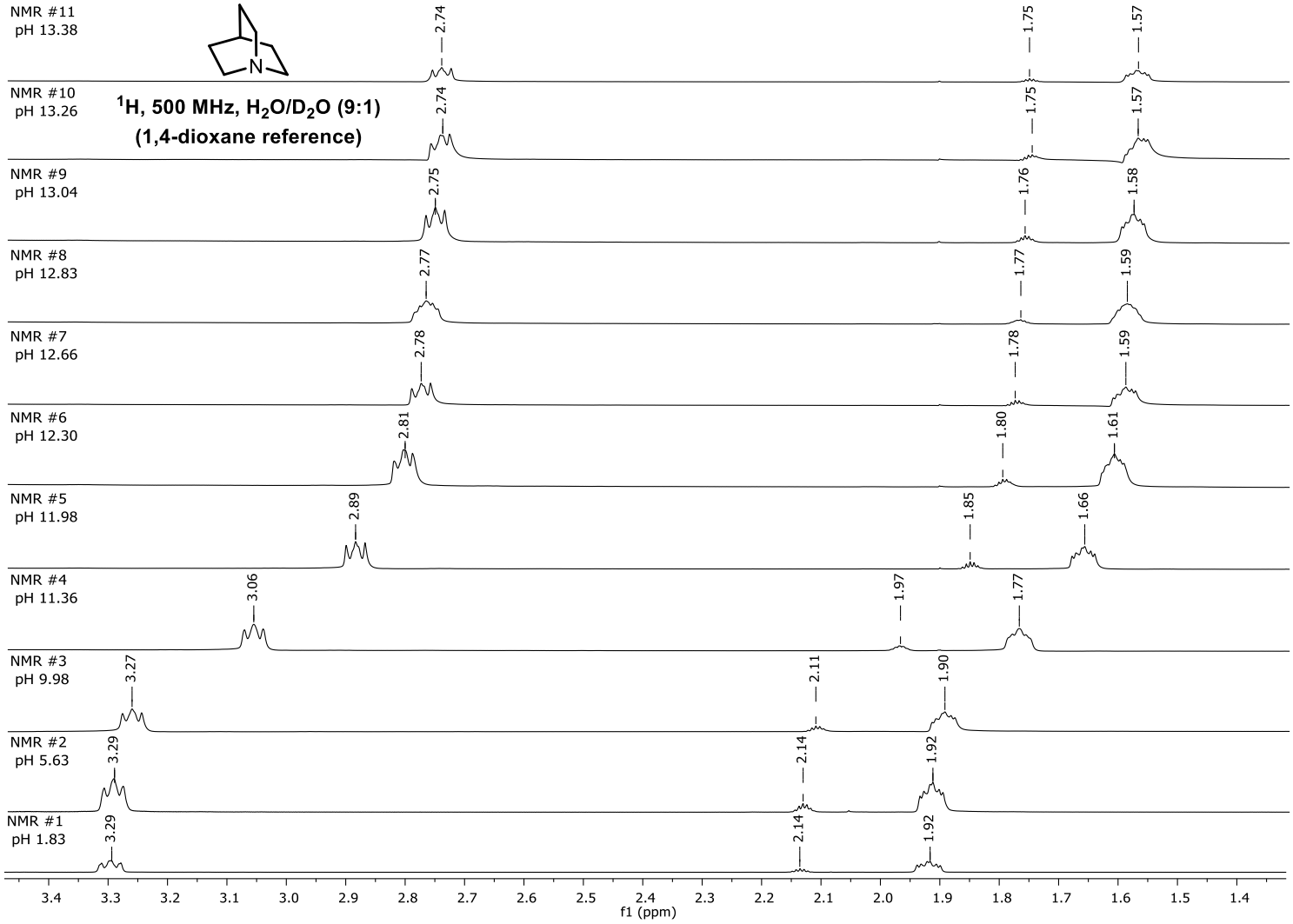


Figure S2: ^{1}H-NMR chemical shifts of quinuclidine at different pH in H_2O/D_2O (9:1).

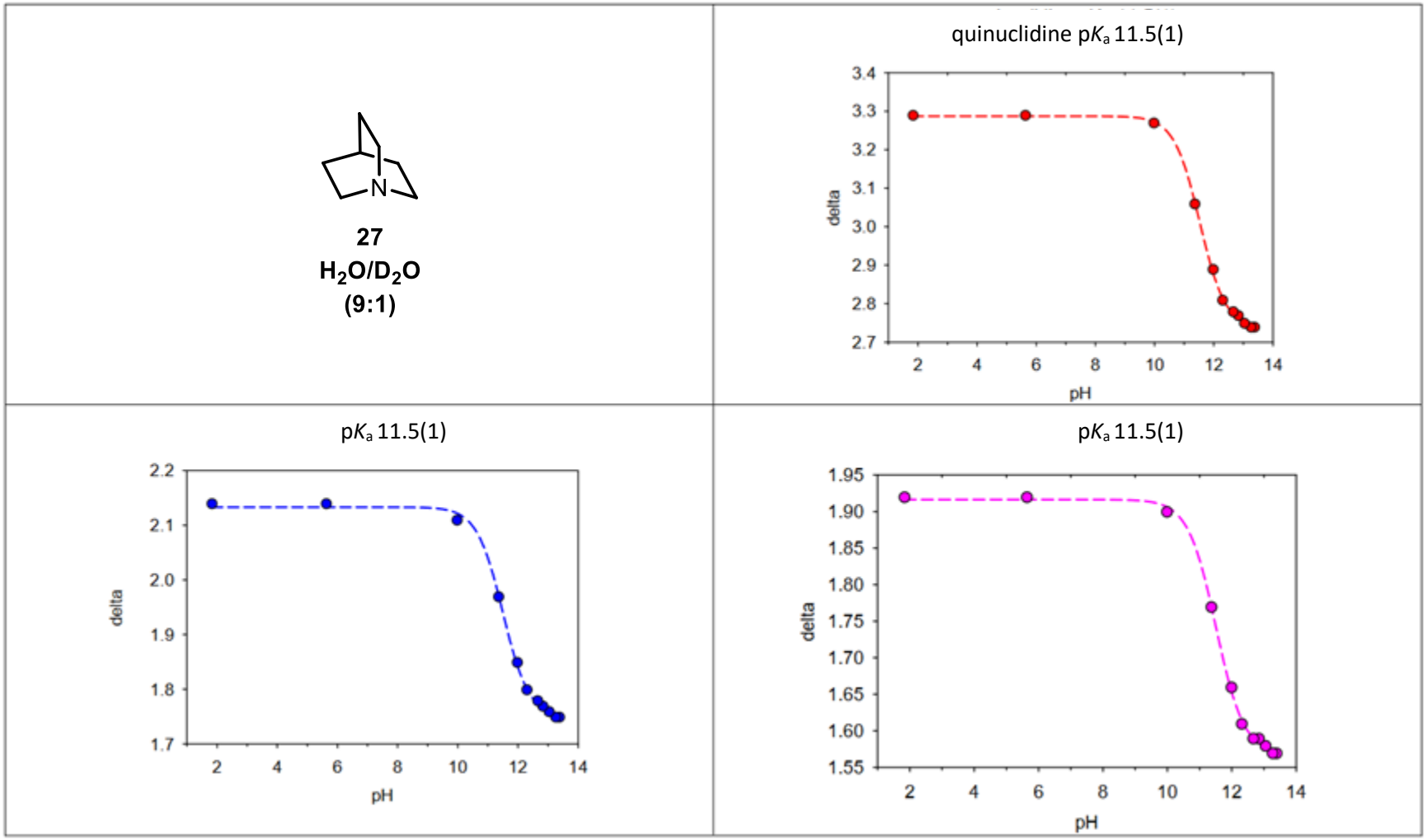


Figure S3: ^{1}H-NMR titration curves of quinuclidine (pK_a = 11.5 ± 0.1).

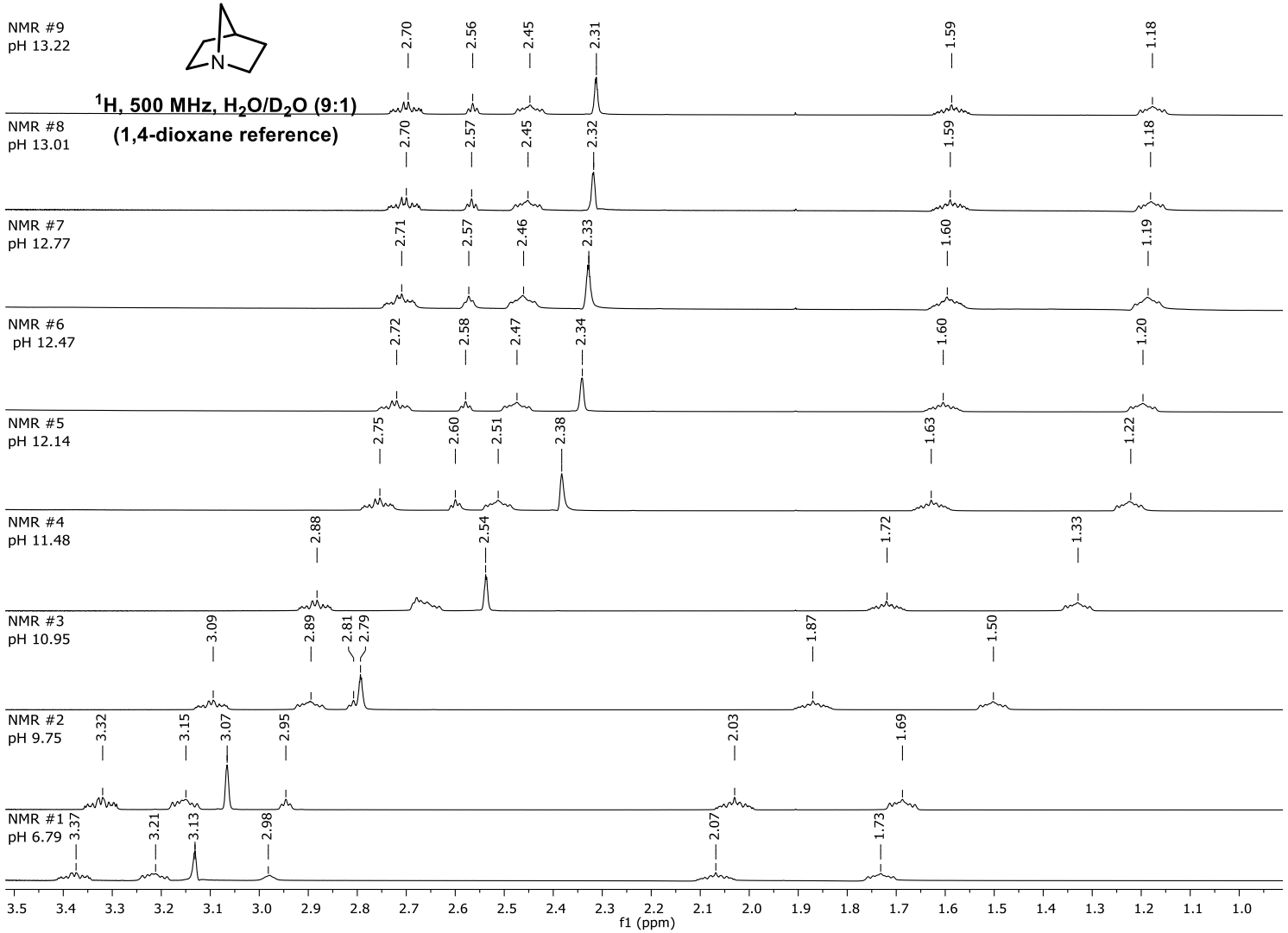


Figure S4: ^{1}H-NMR chemical shifts of 1-azabicyclo[2.2.1]heptane at different pH in H_2O/D_2O (9:1).

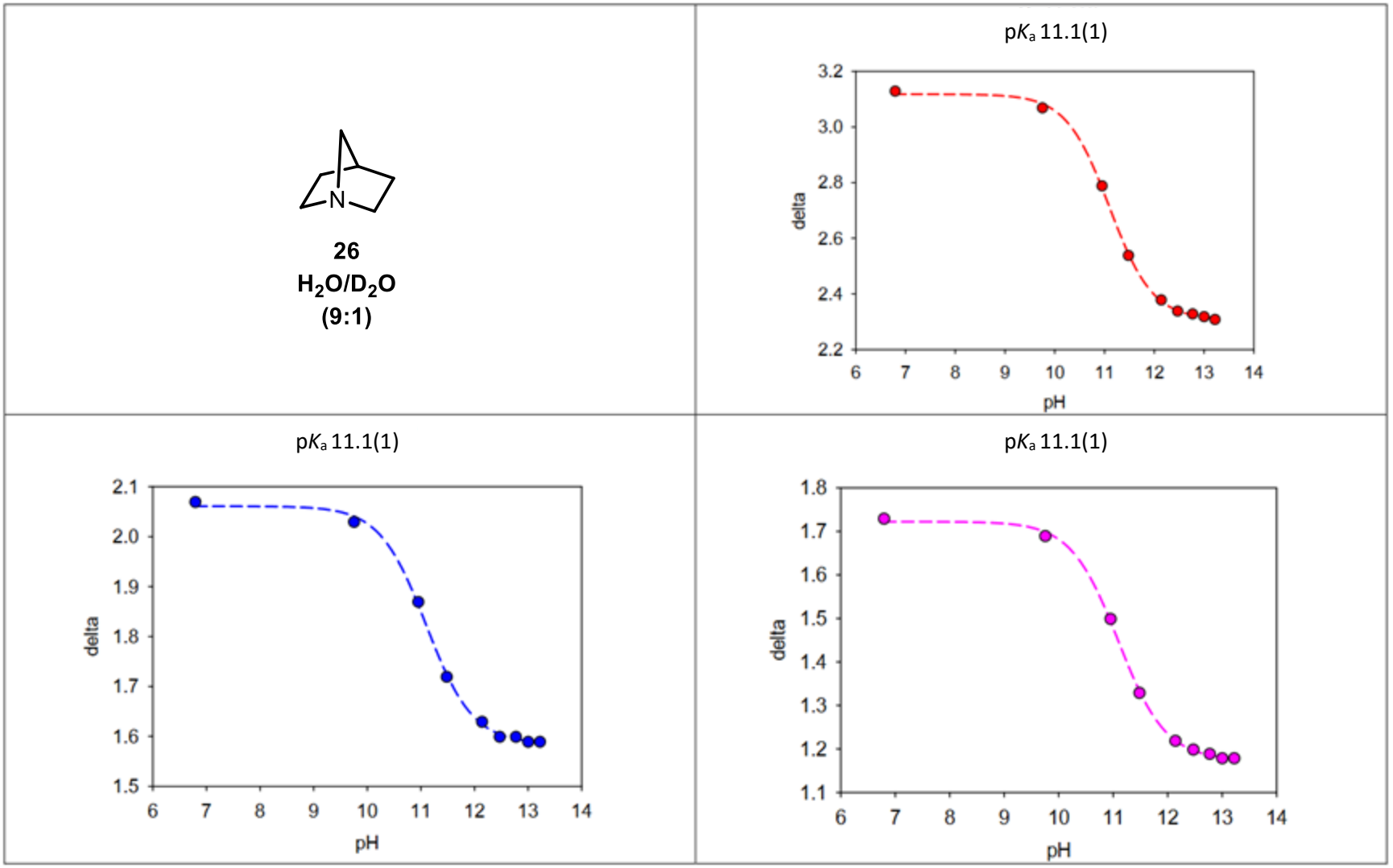


Figure S5: ^{1}H-NMR titration curves of 1-azabicyclo[2.2.1]heptane (pK_a = 11.1 ± 0.1).

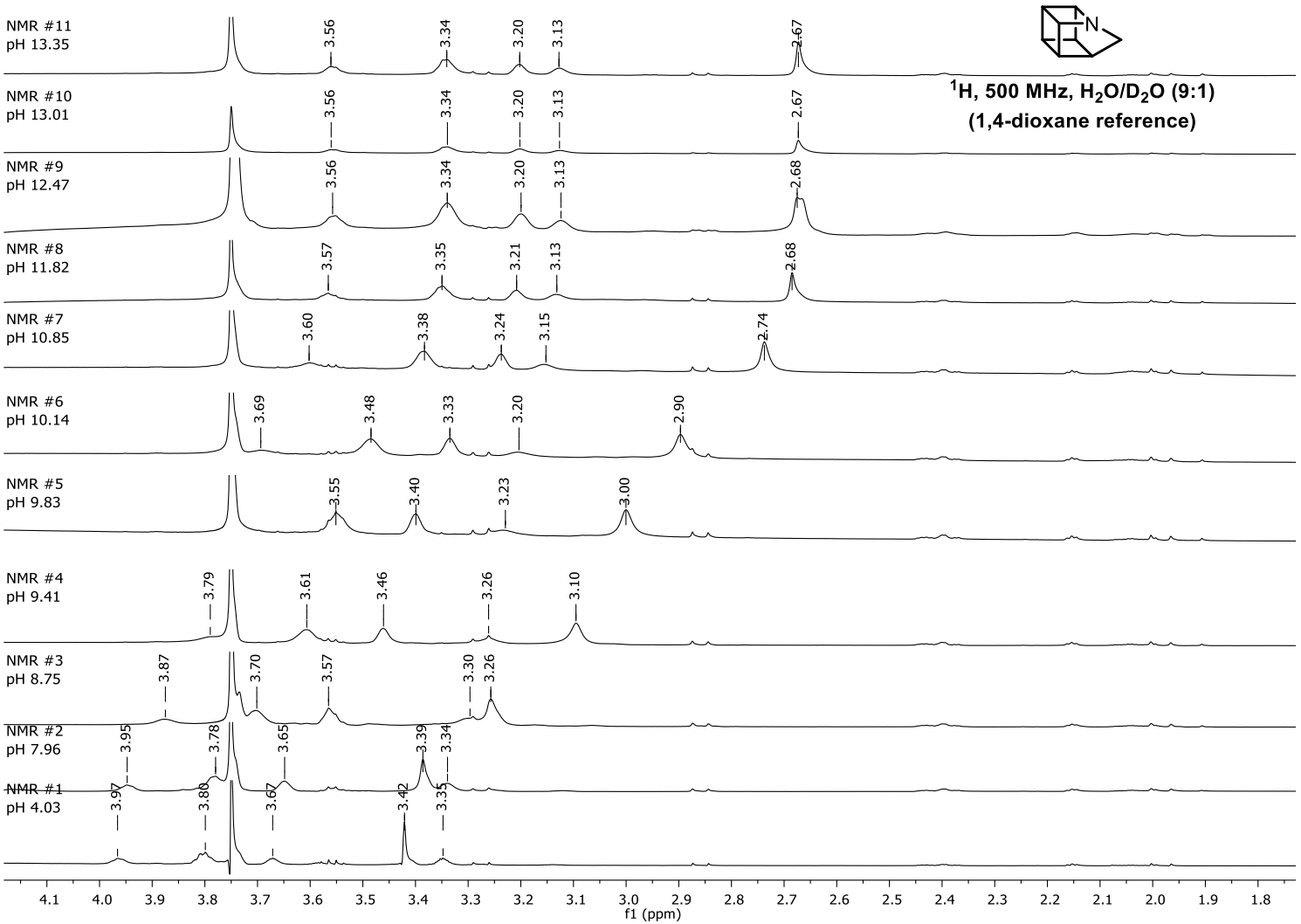


Figure S6: ^{1}H-NMR chemical shifts of 1-azahomocubane at different pH in H_2O/D_2O (9:1).

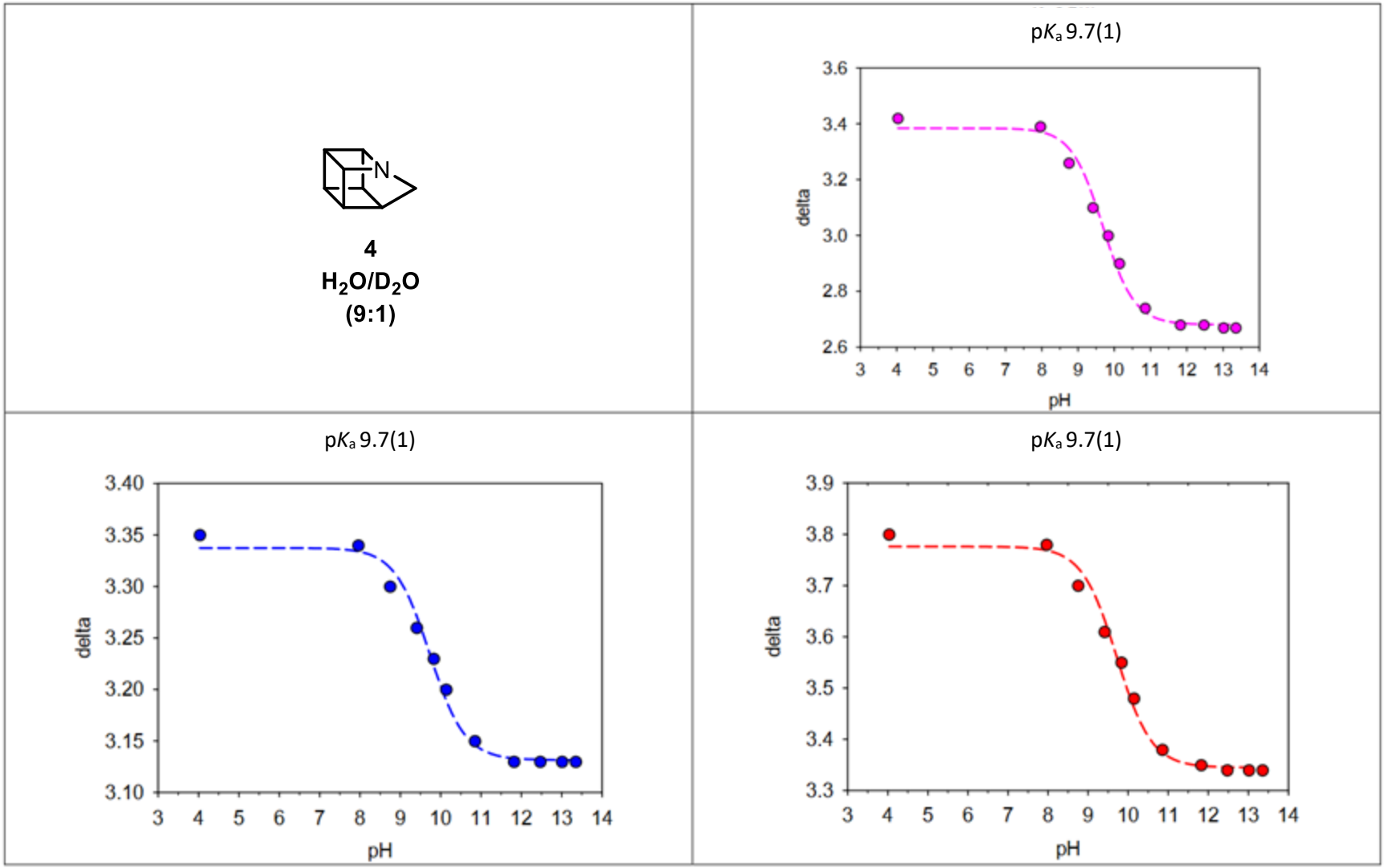


Figure S7: ^{1}H-NMR titration curves of 1-azahomocubane (pK_a = 9.7 ± 0.1).

Proton Affinity

Triethylamine, *N*,*N*-diisopropylamine, piperidine, and quinuclidine were of reagent grade. Methanol was of LCMS grade.

Gas-phase basicity was derived from the kinetic method,[20,21] based on collisional activation of heterogeneous proton-bound cluster ions (*i.e.*, $[A\text{--}H\text{--}B_i]^+$). The observed ratio of product ions ($[AH^+]/[B_iH^+]$) is related to the difference in gas phase basicity between 1-azahomocubane (A) and each reference compound (B_i). Reference bases were carefully chosen for their structural and thermochemical similarities to 1-azahomocubane. The proton affinity of 1-azahomocubane was determined using an updated version of the kinetic method,[22,23] whereby cluster ion dissociation at multiple collision energies allows the enthalpic and entropic contributions to be isolated.

Mass spectra were acquired with an LTQ-XL linear ion-trap mass spectrometer (Thermo Fisher Scientific, Bremen, Germany) equipped with an electrospray ionisation (ESI) source. Instrument settings were optimised to maximise the formation of proton-bound dimers. The source voltage was set to 3.5 kV, capillary voltage 4 V, tube lens 25 V and ion transfer capillary temperature 150 °C. Sheath and auxiliary gas flows (N_2) were set to 5 and 2 (arbitrary units), respectively.

1-Azahomocubane hydrochloride (**21**) and reference bases were prepared individually at ~500 µM in methanol. Equal volumes of two solutions were mixed and infused into the ESI source at 10 µL/min to form the required cationic proton-bound dimers. The dimer ions were isolated with an isolation window of 10 Da and subjected to collision-induced dissociation (CID) in the presence of helium bath gas at various activation energies (normalised collision energy 4-10). Tandem mass spectra presented herein represent the accumulation of at least 50 scans. For summary of gas phase basicity and proton affinity of reference amines see Table S1.

Proton-bound dimer ions of 1-azahomocubane and each reference amine were prepared by electrospray ionization of mixed solutions in methanol. Upon isolation and collisional activation, the dimer dissociated into its constituents, with the abundance ratio of protonated 1-azahomocubane and the protonated reference amine indicating the relative proton affinity of the two species. As shown in Figure S8, formation of protonated 1-azahomocubane (*m/z* 120) is preferred when paired with piperidine (PA = 954 kJ mol^{-1}) or *N*,*N*-diisopropylamine (PA = 972 kJ mol^{-1}). Conversely, 1-azahomocubane is the minor product ion when paired with triethylamine (PA = 982 kJ mol^{-1}) or quinuclidine (PA = 983 kJ mol^{-1}). Thus, it is evident from these bracketing experiments that the PA of 1-azahomocubane is between 972 and 982 kJ mol^{-1}.

To accurately determine the enthalpic and entropic contributions to the gas phase basicity of 1-azahomocubane, the experiments are repeated at multiple collision energies. In Figure S9, the natural logarithm of the product ion abundance ratio is plotted against the difference between proton affinity of the reference amine (PA_i) and the average proton affinity of all reference amines (PA_{avg}). The slope of each best-fit line is equal to $-1/RT_{eff}$, where R is the ideal gas constant and T_{eff} is the effective temperature parameter. The y-intercept of each line is equal to $\{[PA(A) - PA_{avg}] - T_{eff}\Delta\Delta S\}/RT_{eff}$.

The y-intercept of each best-fit line in Figure S9 is subsequently plotted against the corresponding negative slope ($1/RT_{eff}$). The slope of the line plotted in Figure S10 is equal to [PA(A) – PA_{avg}], which ultimately yields the proton affinity of 1-azahomocubane as 975.4 kJ mol^{-1}. An uncertainty in the proton affinity of 8 kJ mol^{-1} was assigned, which is predominantly a function of the uncertainty in the proton affinities of the reference base set.[23]

The proton affinity of the bridgehead bicyclic amine 1-azabicyclo[2.2.1]heptane (**26**) is hitherto unknown, so cannot be used as a reference compound for determining the PA of 1-azahomocubane. Therefore, direct PA comparisons between 1-azabicyclo[2.2.1]heptane (**26**) and 1-azabicyclo[2.2.2]octane (**27**) or 1-azahomocubane (**4**) were also investigated. As shown in Figure S11, formation of protonated 1-azabicyclo[2.2.1]heptane (*m/z* 98) is preferred when paired with 1-azahomocubane (experimental PA = 975 kJ mol^{-1}), but not when paired with 1-azabicyclo[2.2.2]octane (experimental PA = 983 kJ mol^{-1}). Analysis by the kinetic method reveals a gas-phase PA of 980 (±8) kJ mol^{-1}, consistent with theoretical calculations (Table 1, main text).

Table S1: Summary of reference bases gas phase basicity and proton affinity.[24]

Reference base	*m/z* $[B_i+H]^+$	*m/z* $[A+B_i+H]^+$	Gas phase basicity (GB) (kJ mol^{-1})	Proton affinity (PA) (kJ mol^{-1})
Piperidine	86	205	921.0	954.0
Diisopropylamine	102	221	938.6	971.9
Triethylamine	102	221	951.0	981.8
Quinuclidine	112	231	952.5	983.3
			Average (PA_{avg})	972.8

Uncertainty in all values considered to be ± 8 kJ mol^{-1}.[24]

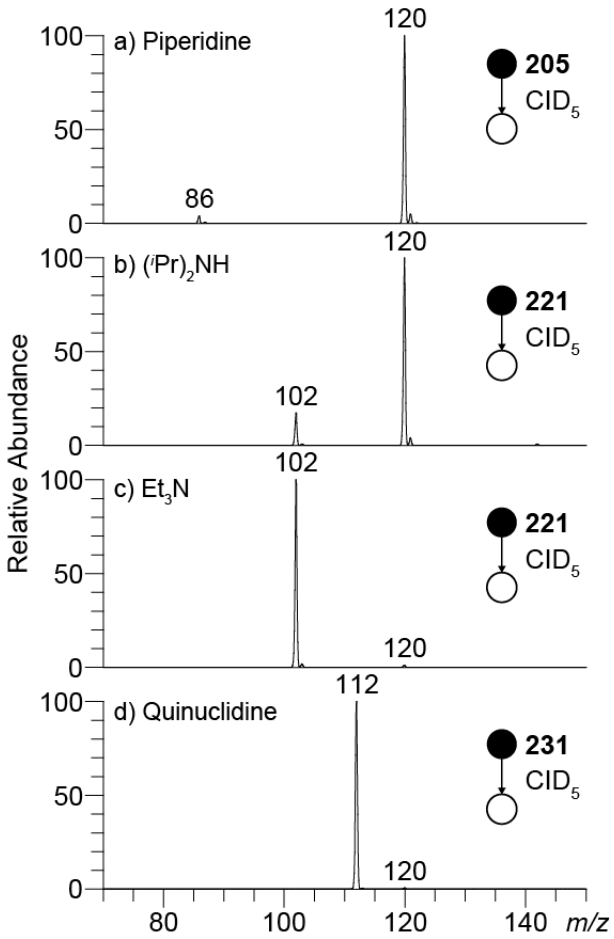


Figure S8: Mass spectra resulting from collision-induced dissociation of proton-bound dimer ions of 1-azahomocubane with different reference amines. Spectra were acquired with the normalised collision energy (NCE) set to 5% (CID_5) and an isolation window of 10 Da.

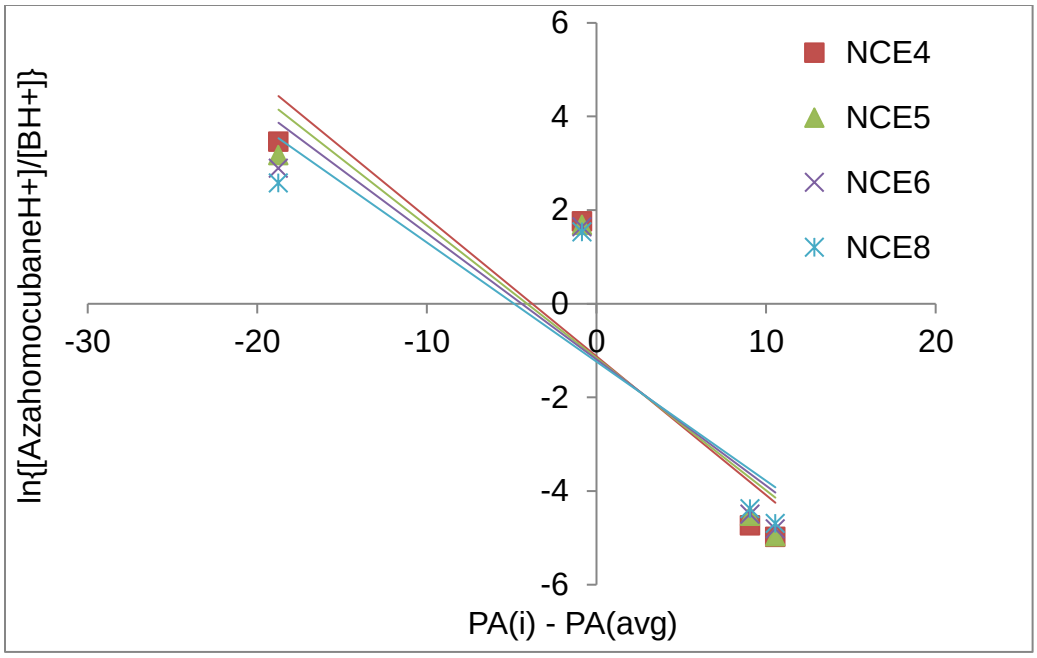


Figure S9: Plot of $\ln([AH]^+/[B_iH]^+)$ versus $(PA_i - PA_{avg})$. Each series represents a different normalised collision energy.

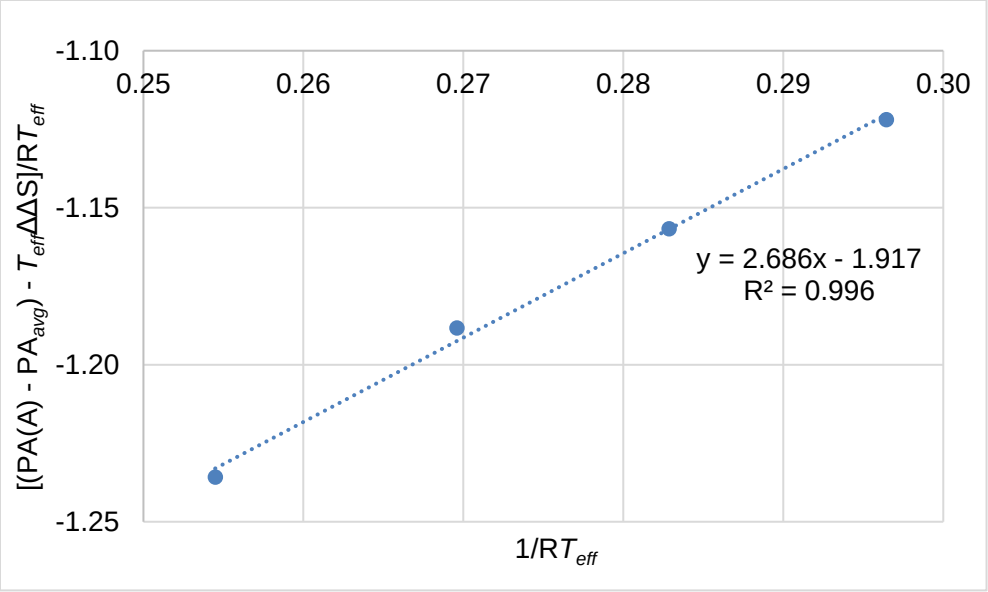


Figure S10: Plotting the (negative) slope against the y-intercept of each series from Figure S9 yields [PA(A) – PA$_{avg}$] as the slope.

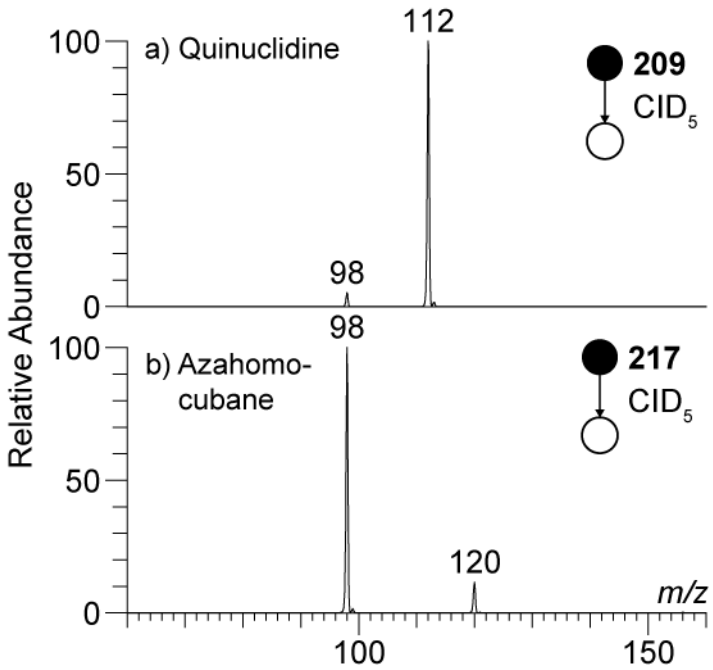


Figure S11: Mass spectrum resulting from collision-induced dissociation of proton-bound dimer ions of 1-azabicyclo[2.2.1]heptane (*m/z* 98) with a) quinuclidine (*i.e.*, 1-azabicyclo[2.2.2]octane, *m/z* 112); and b) 1-azahomocubane (*m/z* 120). Data were acquired with the normalised collision energy (NCE) set to 5% (CID_5) and an isolation window of 10 Da.

Proton Affinity and Vertical Ionization Energy Calculations

Proton affinity (PA) computations were undertaken using the Gaussian 16 suite of software.[25] Molecular structures and electronic energies were optimized using the dispersion correction hybrid-density functional method, M06-2X(GD),[26] in combination with the triple-zeta basis set, 6-311++G(d,p). Minimum energy structures were confirmed as minima on the potential energy surface by computation of vibrational frequencies that also enabled the determination of zero-point energy and thermal corrections at 298 K. Computed proton affinity are presented as the enthalpy of the reaction of the base B, with a proton in the gas phase, *i.e.*, PA = DH_{298} [$B + H^+ \rightarrow AH^+$]. Vertical ionization energies (IE) were calculated by a single-point energy determination of the optimized structure of the neutral amine on the radical cation potential energy surface. A summary of computational results is provided in Table S4. Agreement between computed and known experimental proton affinities is illustrated in Figure S12, and provides an empirical correction for the proton affinities of 1-azacubane (**3**) and 1-azabicyclo[2.2.1]heptane for which direct experimental values were not available. A summary of the computed structures and energies are provided as an archive.

Table S4: A summary of the computed proton affinity (PA) and ionization energies (IE). Experimental values of PA are listed and were either measured in the present study[A] or obtained from the literature [27]. Literature values for IE[28,29] are also listed for comparison.

	Proton affinity	Reaction Energy	Proton Affinity	Vertical Ionization Energy	Adiabatic Ionization Energy	Vertical Ionization Energy	VIE -AIE
	Expt. (298 K)	Calcd. (0 K)	Calcd. (298 K)	Expt.	Calcd. (0 K)	Calcd. (0 K)	Calcd. (0 K)
Amines	kJ/mol	kJ/mol	kJ/mol	eV	eV	eV	eV
1-Azahomocubane (**4**)	975[A]	963.5	968.3	-	8.18	8.61	0.43
1-Azacubane (**3**)	-	963.7	968.5	-	7.96	8.04	0.08
Quinuclidine (**27**)	983.3	971.1	978.3	8.06	7.63	8.05	0.42
Triethylamine (**S26**)	981.8	971.1	976.0	8.08	7.33	8.14	0.81
Piperidine (**S28**)	954.0	975.8	948.3	8.65	7.99	8.76	0.77
N,N-Diisopropylamine (**S27**)	971.9	960.5	965.1	8.40	7.87	8.52	0.65
1-Azabicyclo[2.2.1]heptane (**26**)	980[A]	968.5	973.1	-	8.22	8.72	0.49

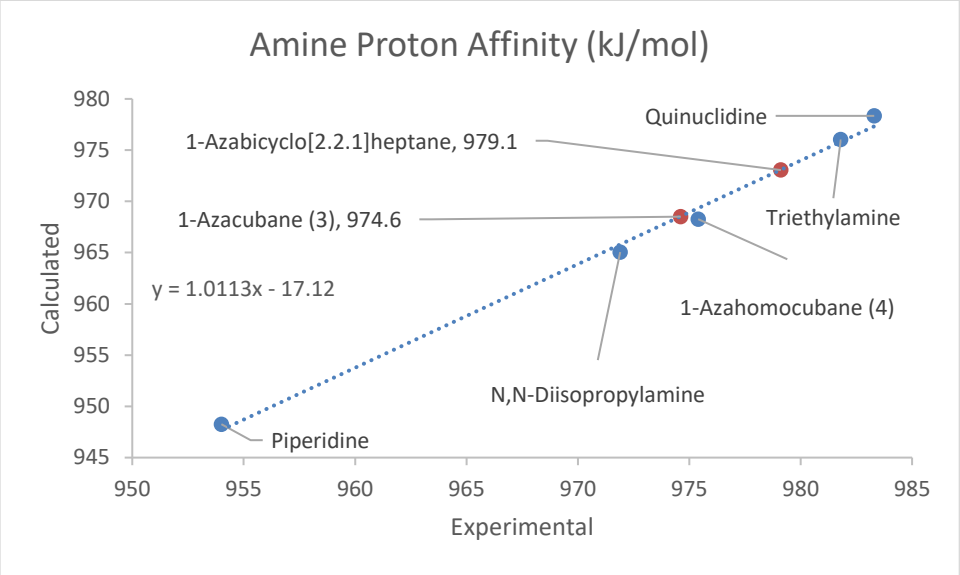
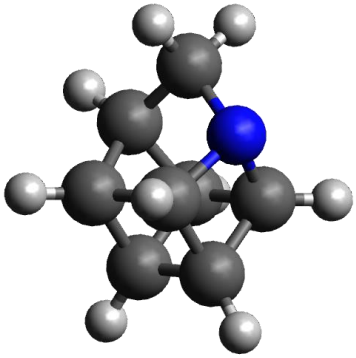
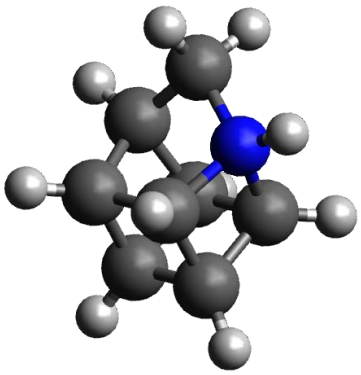
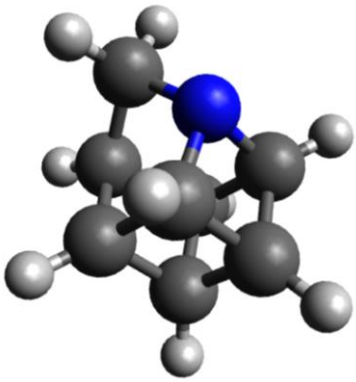
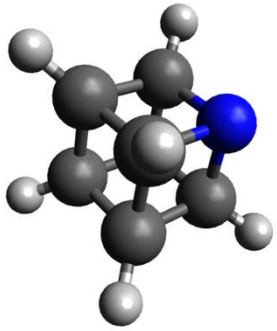
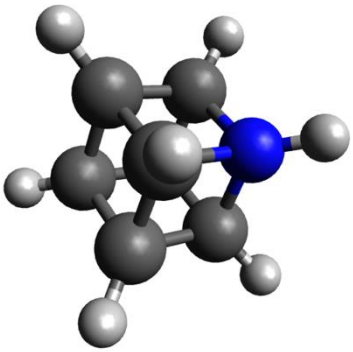


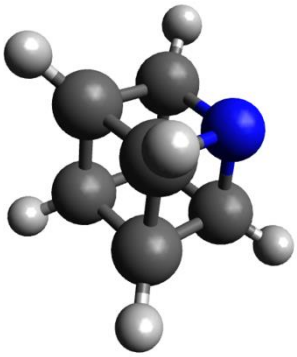
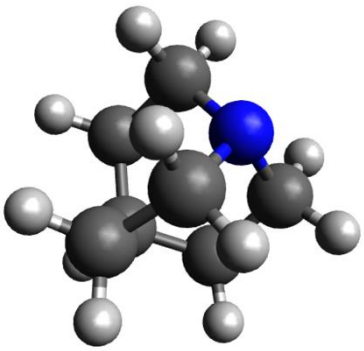
Figure S12: Plot of the experimentally determined and computed proton affinity of the amines investigated in this study (blue circles). The plot demonstrates strong agreement in the relative ordering of amine proton affinity with a small systematic underestimation of PA (5-7 kJ mol^{-1}) at the level of theory used. Trendline enables an empirical correction to the computed PA for 1-azacubane (**3**) and 1-azabicyclo[2.2.1]heptane (red circles) for which direct experimental values were not available.

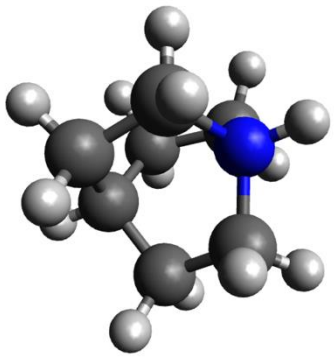
Table S5: Computational Chemistry Archive for Proton Affinity and Vertical Ionization Energy

1-Azahomocubane (4)  Charge = 0 Multiplicity = 1 *E* (0K) = -364.8186524 H (298K) = -364.658414	C 0.4705660000 0.5949190000 1.0547810000 C 0.4456220000 1.4823190000 -0.2280460000 C 1.1957790000 0.3761210000 -1.0258850000 C 1.1986610000 -0.5286450000 0.2327530000 C -1.0169810000 0.1974640000 0.8666520000 C -0.9240690000 0.8105050000 -0.5553410000 C -0.1557760000 -0.3192160000 -1.3308570000 N 0.1147550000 -1.3912580000 -0.3263040000 C -0.9893370000 -1.3179150000 0.6401480000 H 0.8697660000 0.8993500000 2.0194600000 H 0.6442890000 2.5497120000 -0.2573570000 H 2.0187170000 0.5020820000 -1.7221270000 H 2.0604260000 -1.0403130000 0.6566110000 H -1.7475710000 0.6160450000 1.5555500000 H -1.7689540000 1.3071370000 -1.0266780000 H -0.5072960000 -0.6437600000 -2.3082070000 H -0.7454380000 -1.8879540000 1.5405000000 H -1.9093300000 -1.7085780000 0.1974240000
 Charge = +1 Multiplicity = 1 *E* (0K) = -365.1997056 H (298K) = -365.024846	C 0.4869520000 0.5527300000 1.0374580000 C 0.4427100000 1.4774250000 -0.2229730000 C 1.1996640000 0.3975560000 -1.0487260000 C 1.2357250000 -0.5213150000 0.1973000000 C -1.0056880000 0.1676820000 0.8460090000 C -0.9213840000 0.7962860000 -0.5719410000 C -0.1506130000 -0.2815140000 -1.3866630000 N 0.0827140000 -1.3819410000 -0.3408990000 C -1.0380690000 -1.3360090000 0.6470640000 H 0.8912450000 0.8195610000 2.0086180000 H 0.6294730000 2.5444410000 -0.2253300000 H 2.0182720000 0.5364840000 -1.7455720000 H 2.0830540000 -1.0794430000 0.5841250000 H -1.7233980000 0.5955200000 1.5388790000 H -1.7739570000 1.2803880000 -1.0373200000

	H -0.4896550000 -0.6342900000 -2.3560470000 H -0.7717600000 -1.9191740000 1.5296930000 H -1.9497520000 -1.7158640000 0.1838580000 H 0.3418350000 -2.2989760000 -0.7065370000
 Charge = +1 Multiplicity = 2 Vertical *E* (0K) = -364.502404304 *E* (0K) = -364.5160616 H (298K) = -364.357706	C 0.4625940000 0.5931550000 1.0627500000 C 0.4204240000 1.4648220000 -0.2087810000 C 1.2119520000 0.3727810000 -1.0397070000 C 1.2357360000 -0.5254060000 0.2117870000 C -1.0341680000 0.1950030000 0.8806620000 C -0.9334870000 0.8088700000 -0.5495230000 C -0.1287070000 -0.3141040000 -1.3636380000 N 0.0851630000 -1.2835800000 -0.2861280000 C -1.0330490000 -1.3196160000 0.6776150000 H 0.9086830000 0.8625060000 2.0150490000 H 0.6432590000 2.5263330000 -0.2596640000 H 2.0313840000 0.5439400000 -1.7270470000 H 2.0798300000 -1.0557880000 0.6469690000 H -1.7568200000 0.6303100000 1.5650030000 H -1.7640280000 1.2752940000 -1.0701230000 H -0.4948520000 -0.6572100000 -2.3287620000 H -0.7526650000 -1.8999170000 1.5564360000 H -1.9274180000 -1.7193800000 0.2001770000

1-Azacubane (3)  Charge = 0 Multiplicity = 1 *E* (0K) = -325.4408508 H (298K) = -325.311783	C 0.4525580000 0.6027710000 -1.0661090000 C 1.3882490000 -0.6346680000 1.1093240000 N -0.4257310000 -0.0293360000 0.0000270000 C 1.3513460000 1.2858390000 -0.0003770000 C 0.4525940000 0.6033790000 1.0657730000 C 2.2785620000 0.0225750000 -0.0000320000 C 0.4879900000 -1.2429060000 0.0003580000 C 1.3882130000 -0.6353000000 -1.1089840000 H -0.0193790000 1.0857740000 -1.9190110000 H 1.7524120000 -1.1409770000 1.9989560000 H 1.6859500000 2.3194820000 -0.0006800000 H -0.0193160000 1.0868670000 1.9184160000 H 0.0443710000 -2.2362060000 0.0006450000 H 1.7523480000 -1.1421150000 -1.9983390000 H 3.3644290000 0.0433080000 -0.0000560000
 Charge = +1 Multiplicity = 1 *E* (0K) = -325.8212957 H (298K) = -325.678309	C 0.4734050000 0.6344320000 -1.1072480000 C 1.3542890000 -0.6257220000 1.0987480000 N -0.4209190000 -0.0011160000 -0.0283730000 C 1.3514010000 1.2914460000 -0.0085210000 C 0.4488230000 0.6348800000 1.0704410000 C 2.2693130000 0.0205250000 0.0020250000 C 0.4763280000 -1.2516120000 -0.0180700000 C 1.3793330000 -0.6261910000 -1.1149130000 H -0.0075580000 1.1152500000 -1.9530710000 H 1.6775130000 -1.1393320000 1.9967050000 H 1.6722280000 2.3266600000 -0.0049050000 H -0.0512010000 1.1159440000 1.9049850000 H -0.0026040000 -2.2255350000 -0.0232140000 H 1.7223880000 -1.1392110000 -2.0058830000 H 3.3526120000 0.0292220000 0.0137180000 H -1.4416880000 -0.0091150000 -0.0400670000

 Charge = +1 Multiplicity = 2 Vertical *E* (0K) = -325.145551097 *E* (0K) = -325.1459984 H (298K) = -325.019257	C 0.4736850000 0.6222430000 -1.0989180000 C 1.3816580000 -0.6425060000 1.1224270000 N -0.3116460000 -0.0271210000 0.0000240000 C 1.3442820000 1.3010940000 -0.0003820000 C 0.4737220000 0.6228690000 1.0985710000 C 2.2441190000 0.0219100000 -0.0000320000 C 0.5102320000 -1.2806760000 0.0003680000 C 1.3816220000 -0.6431450000 -1.1220830000 H -0.0143940000 1.1001680000 -1.9440030000 H 1.7177900000 -1.1527390000 2.0183010000 H 1.6508100000 2.3412400000 -0.0006840000 H -0.0143300000 1.1012750000 1.9433990000 H 0.0499660000 -2.2650010000 0.0006540000 H 1.7177250000 -1.1538900000 -2.0176770000 H 3.3293530000 0.0427660000 -0.0000550000
Quinuclidine  Charge = 0 Multiplicity = 1 *E* (0K) = -329.2443407 H (298K) = -329.040451	C 0.7755600000 1.4216280000 -0.2246980000 C -0.7700880000 1.3294580000 -0.3692970000 N -1.2672320000 0.0001680000 -0.0005490000 C -0.7705810000 -0.3451460000 1.3352000000 C 0.7750720000 -0.5161320000 1.3434020000 C 1.3121070000 0.0000450000 0.0002240000 C 0.7757470000 -0.9053550000 -1.1186180000 C -0.7701030000 -0.9838550000 -0.9673800000 H 1.0509050000 2.0564890000 0.6228630000 H 1.2252900000 1.8612310000 -1.1189080000 H -1.0779790000 1.5204230000 -1.4006960000 H -1.2699910000 2.0694620000 0.2601720000 H -1.2704200000 -1.2604520000 1.6609590000 H -1.0789930000 0.4523780000 2.0163080000 H 1.0505850000 -1.5675200000 1.4694350000 H 1.2242520000 0.0385260000 2.1714750000 H 2.4038960000 0.0000060000 0.0004730000 H 1.2249280000 -1.8997840000 -1.0518010000 H 1.0518920000 -0.4891870000 -2.0921490000 H -1.0787620000 -1.9725200000 -0.6175860000 H -1.2694300000 -0.8082130000 -1.9231760000



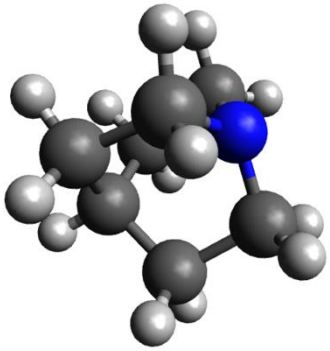
Charge = +1

Multiplicity = 1

E (0K) = -329.6303471

H (298K) = -329.410723

C 0.7837110000 1.3525180000 -0.4278950000
C -0.7316270000 1.3141980000 -0.1562860000
N -1.1414090000 -0.1286080000 0.0214880000
C -0.6124020000 -0.6594990000 1.3328050000
C 0.8899300000 -0.3311850000 1.4122420000
C 1.3918880000 0.0086690000 0.0008590000
C 0.9112530000 -1.0812850000 -0.9688990000
C -0.6161060000 -0.9611000000 -1.1240370000
H 1.2275880000 2.1768820000 0.1306530000
H 0.9775050000 1.5328820000 -1.4870500000
H -1.3225310000 1.7220050000 -0.9759310000
H -1.0072130000 1.8281430000 0.7652490000
H -0.8094240000 -1.7320930000 1.3325250000
H -1.1930820000 -0.1961340000 2.1299130000
H 1.4239650000 -1.1900780000 1.8192940000
H 1.0619660000 0.5105270000 2.0859080000
H 2.4791250000 0.0675840000 -0.0079780000
H 1.1801050000 -2.0688220000 -0.5889240000
H 1.3812580000 -0.9680020000 -1.9460580000
H -1.1257400000 -1.9235070000 -1.0878500000
H -0.9067640000 -0.4436840000 -2.0389770000
H -2.1606150000 -0.1839160000 0.0298590000



Charge = +1

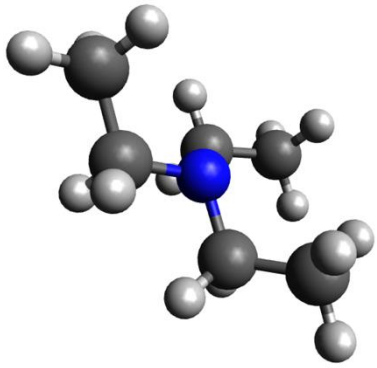
Multiplicity = 2

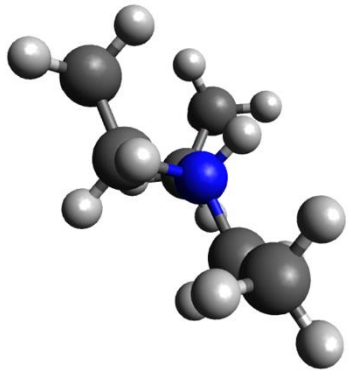
Vertical *E* (0K) = -328.948776912

E (0K) = -328.9637925

H (298K) = -328.760081

C 0.7931680000 1.4254690000 -0.2119120000
C -0.7822080000 1.3465770000 -0.3934250000
N -1.1228940000 0.0000740000 -0.0005830000
C -0.7827910000 -0.3327400000 1.3620900000
C 0.7926700000 -0.5291380000 1.3403850000
C 1.3137140000 0.0000620000 0.0002120000
C 0.7934510000 -0.8962600000 -1.1283450000
C -0.7821600000 -1.0134040000 -0.9701250000
H 1.0256710000 2.0593280000 0.6447450000
H 1.2167380000 1.8851150000 -1.1050670000
H -1.0767290000 1.4997980000 -1.4303430000
H -1.2923350000 2.0598050000 0.2531380000
H -1.2928950000 -1.2493350000 1.6564300000
H -1.0777470000 0.4886380000 2.0130750000
H 1.0252810000 -1.5879230000 1.4609220000
H 1.2156870000 0.0145130000 2.1853120000
H 2.4062690000 0.0000330000 0.0005000000
H 1.2164890000 -1.8997880000 -1.0796460000
H 1.0264800000 -0.4715070000 -2.1055750000
H -1.0775120000 -1.9879620000 -0.5848220000
H -1.2916920000 -0.8097070000 -1.9113150000

Triethylamine  Charge = 0 Multiplicity = 1 *E* (0K) = -292.3391557 H (298K) = -292.121727	C 1.1020880000 0.2920110000 -0.6029480000 C 2.3241140000 -0.1756440000 0.1824370000 N 2.8290450000 0.8504300000 1.1042770000 C 2.4609720000 0.5795280000 2.4907000000 C 0.9552210000 0.5309480000 2.7177010000 C 4.2705860000 1.0464680000 0.9544760000 C 4.7994810000 2.2707190000 1.6932700000 H 0.7622450000 -0.4874470000 -1.2900900000 H 1.3546440000 1.1820010000 -1.1822950000 H 0.2767530000 0.5507980000 0.0608580000 H 3.1164480000 -0.4319670000 -0.5265340000 H 2.0979830000 -1.1045990000 0.7264610000 H 2.8730690000 1.3759440000 3.1120510000 H 2.9173120000 -0.3684360000 2.8351100000 H 0.4902050000 1.4552640000 2.3687210000 H 0.7448790000 0.4163580000 3.7829900000 H 0.4890320000 -0.3079040000 2.1973340000 H 4.4652520000 1.1792970000 -0.1124470000 H 4.8306360000 0.1476810000 1.2739010000 H 4.1723780000 3.1375290000 1.4738770000 H 5.8185210000 2.4872680000 1.3664790000 H 4.8290740000 2.1285510000 2.7742470000



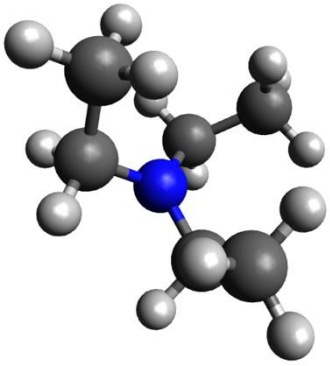
Charge = +1

Multiplicity = 1

E (0K) = -292.7241283

H (298K) = -292.491120

C 1.1993610000 0.6020260000 0.2269830000
C 2.4204110000 -0.0902860000 -0.3512560000
N 2.9354290000 -1.1854510000 0.5684320000
C 2.5419130000 -2.5673330000 0.1059740000
C 1.0411450000 -2.7430090000 -0.0322200000
C 4.4272460000 -1.0578420000 0.7792010000
C 4.9850420000 -2.0485390000 1.7839940000
H 0.8753820000 1.3839790000 -0.4603540000
H 1.4359660000 1.0817310000 1.1800390000
H 0.3648510000 -0.0842250000 0.3721200000
H 3.2369960000 0.6182010000 -0.4846230000
H 2.2189510000 -0.5557950000 -1.3160650000
H 2.9386340000 -3.2652490000 0.8410140000
H 3.0644970000 -2.7237710000 -0.8401340000
H 0.5255180000 -2.5403690000 0.9094380000
H 0.8436680000 -3.7825910000 -0.2952580000
H 0.6132300000 -2.1186470000 -0.8164770000
H 4.5880930000 -0.0328900000 1.1159130000
H 4.8806850000 -1.1696580000 -0.2076970000
H 4.4170920000 -2.0368690000 2.7181550000
H 6.0071070000 -1.7524840000 2.0221800000
H 5.0224060000 -3.0666390000 1.3994490000
H 2.4932730000 -1.0423960000 1.4822700000



Charge = +1

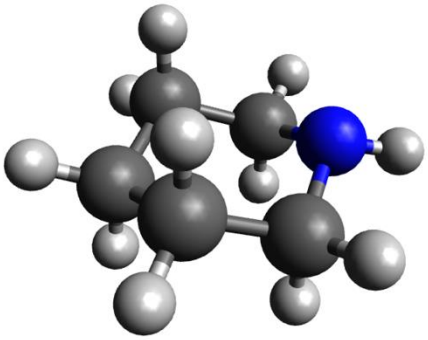
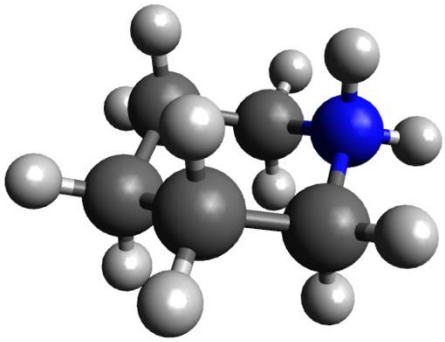
Multiplicity = 2

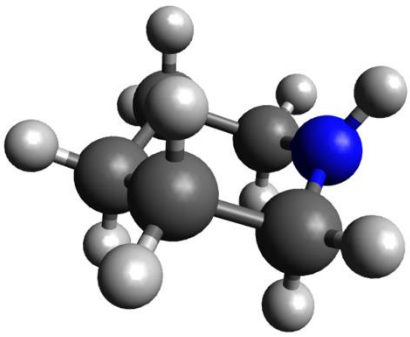
Vertical *E* (0K) = -292.040173876

E (0K) = -292.0697647

H (298K) = -291.852334

C 0.7931680000 1.4254690000 -0.2119120000
C -0.7822080000 1.3465770000 -0.3934250000
N -1.1228940000 0.0000740000 -0.0005830000
C -0.7827910000 -0.3327400000 1.3620900000
C 0.7926700000 -0.5291380000 1.3403850000
C 1.3137140000 0.0000620000 0.0002120000
C 0.7934510000 -0.8962600000 -1.1283450000
C -0.7821600000 -1.0134040000 -0.9701250000
H 1.0256710000 2.0593280000 0.6447450000
H 1.2167380000 1.8851150000 -1.1050670000
H -1.0767290000 1.4997980000 -1.4303430000
H -1.2923350000 2.0598050000 0.2531380000
H -1.2928950000 -1.2493350000 1.6564300000
H -1.0777470000 0.4886380000 2.0130750000
H 1.0252810000 -1.5879230000 1.4609220000
H 1.2156870000 0.0145130000 2.1853120000
H 2.4062690000 0.0000330000 0.0005000000
H 1.2164890000 -1.8997880000 -1.0796460000
H 1.0264800000 -0.4715070000 -2.1055750000
H -1.0775120000 -1.9879620000 -0.5848220000
H -1.2916920000 -0.8097070000 -1.9113150000

Piperidine  Charge = 0 Multiplicity = 1 *E* (0K) = -251.8509514 H (298K) = -251.684191	C 0.8606470000 1.1657840000 -0.4432630000 C -0.6492880000 1.2606320000 -0.2394600000 N -1.1714540000 -0.0483200000 0.1440960000 C -0.6130590000 -0.5067630000 1.4133550000 C 0.8982260000 -0.6712280000 1.2742690000 C 1.5370410000 0.6462330000 0.8278180000 H 1.2604770000 2.1450270000 -0.7198330000 H 1.0568320000 0.4776540000 -1.2715160000 H -1.1398390000 1.5751750000 -1.1631720000 H -0.8563000000 2.0270000000 0.5292370000 H -1.0779620000 -1.4596670000 1.6754010000 H -0.8185160000 0.2045950000 2.2335670000 H 1.0961200000 -1.4471610000 0.5280780000 H 1.3248350000 -1.0039970000 2.2242870000 H -2.1826300000 -0.0214360000 0.1950050000 H 1.4197450000 1.3898790000 1.6258560000 H 2.6105280000 0.5182270000 0.6673800000
 Charge = +1 Multiplicity = 1 *E* (0K) = -252.225106 H (298K) = -252.043004	C 0.8669580000 1.1571060000 -0.4520770000 C -0.6378910000 1.2898640000 -0.2787900000 N -1.2128130000 -0.0395830000 0.1575790000 C -0.5992210000 -0.5485590000 1.4431430000 C 0.9055610000 -0.6794800000 1.2678590000 C 1.5300290000 0.6461140000 0.8283430000 H 1.2588840000 2.1354560000 -0.7346010000 H 1.0803060000 0.4806980000 -1.2877740000 H -1.1478390000 1.5755910000 -1.1985650000 H -0.8947950000 2.0008720000 0.5089660000 H -1.0834980000 -1.4959660000 1.6788330000 H -0.8563740000 0.1854900000 2.2093790000 H 1.1210710000 -1.4642390000 0.5335840000 H 1.3250680000 -1.0165360000 2.2170650000 H -2.2274460000 0.0367180000 0.2618150000 H 1.4155380000 1.3892000000 1.6245080000 H 2.6003110000 0.5171490000 0.6665700000 H -1.0472680000 -0.7292400000 -0.5825130000



Charge = +1

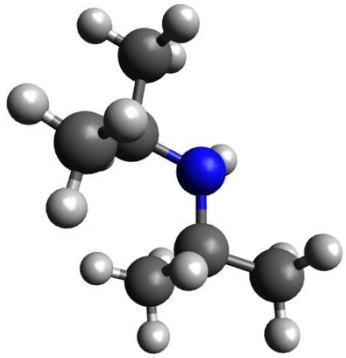
Multiplicity = 2

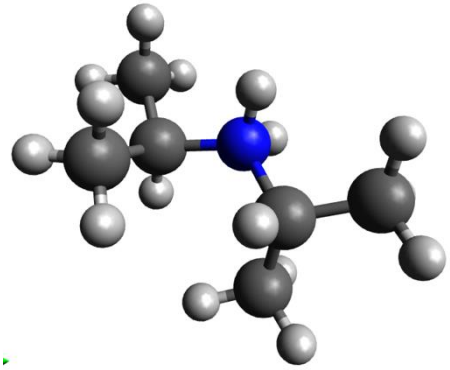
Vertical *E* (0K) = -251.529422933

E (0K) = -251.5561596

H (298K) = -251.390562

C 0.8371180000 1.1653520000 -0.4467310000
C -0.6963410000 1.3614560000 -0.1654940000
N -1.1916210000 0.1084500000 0.3120990000
C -0.6594220000 -0.4407680000 1.5197800000
C 0.8747460000 -0.6751150000 1.2742310000
C 1.5224850000 0.6189030000 0.7988830000
H 1.2235680000 2.1424450000 -0.7409600000
H 0.9536200000 0.4855040000 -1.2942940000
H -1.2364630000 1.6631620000 -1.0603750000
H -0.8097470000 2.1064450000 0.6273710000
H -1.1746840000 -1.3651810000 1.7718760000
H -0.7725170000 0.2981110000 2.3183570000
H 0.9936520000 -1.4727920000 0.5368440000
H 1.2882230000 -1.0253890000 2.2213130000
H -1.6750310000 -0.5100680000 -0.3388340000
H 1.5036860000 1.3659610000 1.5982900000
H 2.5741300000 0.4251570000 0.5687470000

***N*,*N*-Diisopropylamine**  Charge = 0 Multiplicity = 1 *E* (0K) = -292.3558948 H (298K) = -292.138884	C 1.0948730000 0.0707730000 0.1620730000 N 0.6395710000 -0.6919230000 1.3266560000 C 0.5151920000 1.4773000000 0.2651450000 H 2.1845900000 0.1503920000 0.2365890000 C 1.0056480000 -2.1077630000 1.3898060000 C 2.5234930000 -2.2625120000 1.3987430000 C 0.3980990000 -2.6966510000 2.6583240000 C 0.7453970000 -0.5632750000 -1.1887310000 H -0.3713610000 -0.6071080000 1.3992660000 H 0.7731170000 1.9252640000 1.2257700000 H -0.5766000000 1.4454550000 0.1825290000 H 0.8914750000 2.1156140000 -0.5366020000 H 0.6081550000 -2.6706260000 0.5296070000 H 2.9501440000 -1.6565540000 2.2026860000 H 2.9744110000 -1.9488860000 0.4547340000 H 2.7944640000 -3.3072910000 1.5651080000 H 0.8061360000 -2.1891600000 3.5355620000 H 0.6157910000 -3.7641670000 2.7332830000 H -0.6883620000 -2.5726440000 2.6669150000 H -0.3383600000 -0.6932460000 -1.2770740000 H 1.2156650000 -1.5408870000 -1.3151660000 H 1.0788210000 0.0750950000 -2.0106560000



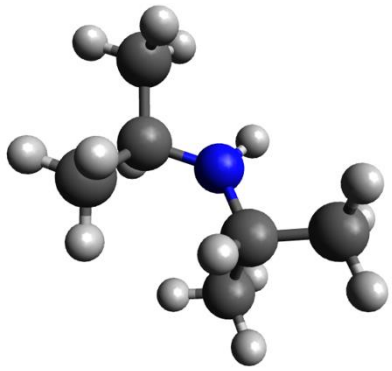
Charge = +1

Multiplicity = 1

E (0K) = -292.7362536

H (298K) = -292.504094

N 0.6387950000 -0.7016870000 1.2729260000
C 1.1362460000 0.1039220000 0.0825550000
C 0.5695460000 1.5098950000 0.2114490000
C 1.0408660000 -2.1645350000 1.3825560000
C 2.5542430000 -2.2868800000 1.3416860000
C 0.4328780000 -2.7121620000 2.6651130000
C 0.7325710000 -0.5844910000 -1.2097670000
H 0.9435550000 -0.2270250000 2.1297330000
H 2.2218620000 0.1268970000 0.1879720000
H -0.3856990000 -0.6503730000 1.2809950000
H 0.8402480000 1.9761090000 1.1617300000
H -0.5196230000 1.5073800000 0.1122700000
H 0.9726260000 2.1331400000 -0.5868600000
H 0.5880810000 -2.6499130000 0.5167380000
H 3.0191580000 -1.6935650000 2.1349560000
H 2.9758180000 -1.9902670000 0.3808910000
H 2.8237900000 -3.3295910000 1.5117830000
H 0.8722330000 -2.2349260000 3.5456490000
H 0.6382070000 -3.7806450000 2.7311890000
H -0.6516450000 -2.5828930000 2.6930050000
H -0.3514410000 -0.7255240000 -1.2593220000
H 1.2241660000 -1.5481580000 -1.3456390000
H 1.0187240000 0.0521810000 -2.0473780000



Charge = +1

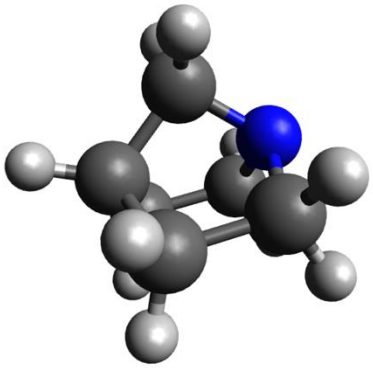
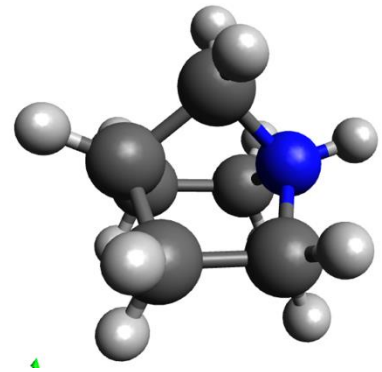
Multiplicity = 2

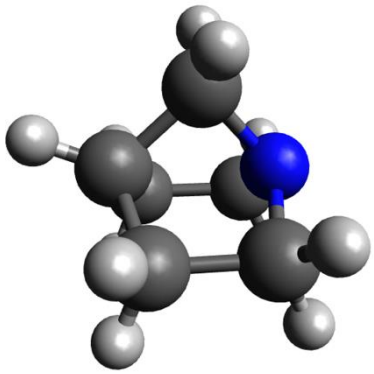
Vertical *E* (0K) = -292.043084588

E (0K) = -292.0654004

H (298K) = -291.849538

C 1.0669360000 0.0402470000 0.1417900000
N 0.4459380000 -0.9333650000 1.0091380000
C 0.4606040000 1.4173860000 0.3816570000
H 2.1366440000 0.0292380000 0.3618130000
C 0.9723290000 -2.2258760000 1.4104660000
C 2.4854870000 -2.3149720000 1.2826260000
C 0.4541870000 -2.5524740000 2.8160530000
C 0.8572350000 -0.4470440000 -1.3176350000
H -0.5290170000 -0.7534920000 1.2639280000
H 0.6056150000 1.7435430000 1.4120390000
H -0.6070870000 1.4212070000 0.1467640000
H 0.9480940000 2.1380580000 -0.2749050000
H 0.4989580000 -2.9323530000 0.7021830000
H 2.9739740000 -1.6025460000 1.9514130000
H 2.8327590000 -2.1514760000 0.2621700000
H 2.7935010000 -3.3172060000 1.5798660000
H 0.8916710000 -1.8733970000 3.5496080000
H 0.7473770000 -3.5710230000 3.0684360000
H -0.6346980000 -2.4929410000 2.8715320000
H -0.2056020000 -0.4694720000 -1.5631740000
H 1.2908210000 -1.4341720000 -1.4784720000
H 1.3546350000 0.2693300000 -1.9727310000

1-Azabicyclo[2.2.1]heptane  Charge = 0 Multiplicity = 1 *E* (0K) = -289.9315396 H (298K) = -289.758232	C 0.3614000000 1.1148220000 -0.2238050000 N -0.8702900000 0.3256420000 -0.0270850000 C -0.6173250000 -0.2626430000 1.3063680000 C 0.9218100000 -0.5350760000 1.3711320000 C 1.3687420000 -0.0341290000 -0.0121350000 C 0.8573830000 -1.0384390000 -1.0580520000 C -0.6794640000 -0.7468780000 -1.0278520000 H -1.2230900000 -1.1599340000 1.4363400000 H -0.9204310000 0.4604910000 2.0655740000 H 1.1612790000 -1.5889800000 1.5240340000 H 1.3903880000 0.0385700000 2.1736670000 H 2.4261130000 0.2135130000 -0.0914410000 H 1.1004390000 -2.0688880000 -0.7924210000 H 1.2778380000 -0.8349700000 -2.0452400000 H -1.2813230000 -1.6155390000 -0.7592430000 H -1.0288460000 -0.3819910000 -1.9953080000 H 0.3882820000 1.5476200000 -1.2261680000 H 0.4350840000 1.9104520000 0.5207080000
 Charge = +1 Multiplicity = 1 *E* (0K) = -290.3150429 H (298K) = -290.126489	C 0.3884820000 1.1431840000 -0.2229020000 N -0.8480370000 0.3034650000 -0.0130850000 C -0.6236930000 -0.2865410000 1.3634660000 C 0.9075620000 -0.5220110000 1.3826840000 C 1.3446610000 -0.0303140000 -0.0105420000 C 0.8336380000 -1.0260750000 -1.0694910000 C -0.6965880000 -0.7832610000 -1.0567920000 H -1.2286320000 -1.1855710000 1.4600800000 H -0.9507630000 0.4499340000 2.0960240000 H 1.1572910000 -1.5696220000 1.5433950000 H 1.3728360000 0.0649490000 2.1738860000 H 2.4006750000 0.2108970000 -0.0919050000 H 1.0857330000 -2.0551680000 -0.8182430000 H 1.2457170000 -0.8042640000 -2.0533630000 H -1.2961240000 -1.6401980000 -0.7572490000 H -1.0732860000 -0.3902020000 -1.9999880000 H 0.3813530000 1.5650410000 -1.2274410000 H 0.4345700000 1.9266960000 0.5327950000 H -1.7322840000 0.8071930000 -0.0898070000

 Charge = +1 Multiplicity = 2 Vertical *E* (0K) = -289.61152183 *E* (0K) = -289.6294112 H (298K) = -289.456181	C 0.4001090000 1.1401910000 -0.2299290000 N -0.7432300000 0.2339530000 -0.0114440000 C -0.6345710000 -0.2795850000 1.3523810000 C 0.9263850000 -0.5226120000 1.3914240000 C 1.3774670000 -0.0430060000 -0.0107640000 C 0.8600220000 -1.0359530000 -1.0812680000 C -0.6992030000 -0.7797800000 -1.0631330000 H -1.2409290000 -1.1736750000 1.4704700000 H -0.9495470000 0.4922940000 2.0542270000 H 1.1579770000 -1.5711870000 1.5721000000 H 1.3700440000 0.0790290000 2.1836280000 H 2.4341210000 0.1983310000 -0.0891840000 H 1.0925730000 -2.0723080000 -0.8410790000 H 1.2565880000 -0.8044720000 -2.0689750000 H -1.3022560000 -1.6403670000 -0.7861710000 H -1.0567760000 -0.3459280000 -1.9966720000 H 0.3858240000 1.5511890000 -1.2374880000 H 0.4333890000 1.9175290000 0.5309480000

Geometry Optimization and Ring Strain Calculations

DFT calculations were conducted with Gaussian 16 (Version A.03),[25] high accuracy wavefunction calculations were implemented in ORCA (Version 5.0.1).[30,31] Geometry optimisation and frequency calculations were performed at the M062X-D3/Def2TZVPP level of theory.[26,32] M06-2X (with Grimme's empirical dispersion correction)[33] has been shown to be one of the most robust hybrid methods for general thermochemistry calculations.[34] The nature of all minima were confirmed through inspection of the calculated frequencies (0 imaginary). Single point energy calculations were performed at the DLPNO-CCSD(T)-F12D/cc-pVDZ-F12 level of theory,[35,36] which approximates the canonical "gold standard" CCSD(T) energy through a series of well controlled approximations. Explicit correlation with the F12D ansatz was utilised to provide values close to the basis set limit.[37,38] Coulomb and exchange integral steps were accelerated using the RIJCOSX approximation.[39] Appropriate auxiliary basis sets were used as required (cc-pVDZ-F12-CABS, cc-pVTZ/C, def2/J) (Figures S13 and S14, and Table S7).

The predicted proton affinity for azahomocubane at the DLPNO-CCSD(T)-F12D/cc-pVDZ-F12//M062X-D3/Def2TZVPP level of theory was calculated to be 969 kJ/mol. This result is within the uncertainty of the experimental method (975.4 ± 8 kJ/mol), and corroborates the values calculated at the M062X level of theory.

Determination of ring strain:

Hypohomodesmotic reactions[40] for the transformation of 1-azahomocubane into the appropriate, equivalently substituted fragments (trimethylamine, isobutane and propane) were conducted to gauge the magnitude of ring strain in the system. Enthalpy of reaction (ΔH) at the M062X-D3/Def2TZVPP level of theory yielded a value of 110.37 kcal/mol (Figure S13). As expected, this is lower than cubane itself (169 kcal/mol)[41] and reflect the considerable strain release that occurs on homologation of the cubane system. Note that we make no reference to experimental values in our determination.

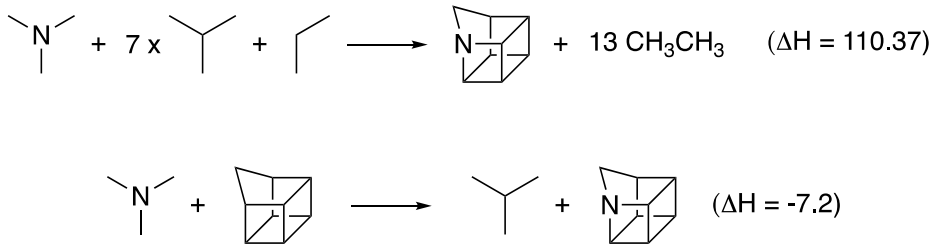


Figure S13: Hypohomodesmotic reactions of the azahomocubane system (**4**). Calculated at the M062X-D3/Def2TZVPP level of theory (kcal/mol).

Table S6: Second Order Perturbation Theory Analysis

Compound	**Second Order Perturbation Theory Analysis of Fock Matrix in NBO Basis (kcal/mol)**
Azabicyclo[2.2.1]heptane (**26**)	N π → C1-C2 σ*: 7.28 (“2” bridgehead) N π → C2-H5 σ*: 2.44 (“2” CH) N π → C10-C15 σ*: 4.67 (“1” bridgehead) N π → C10-H16 σ*: 1.12 (“1” distal CH) N π → C15-H17 σ*: 0.91 (“1” proximal CH)
Quinuclidine (**27**)	N π → C1-C2 σ*: 9.84 N π → C2-H4 σ*: 1.08 N π → C2-H5 σ*: 2.34
Azahomocubane (**4**)	N π → C1-C3 σ*: 5.80 N π → C3-C7 σ*: 2.85 N π → C11-C15 σ*: 4.58 N π → C11-H18 σ*: 0.90 (“basket handle” distal CH) N π → C15-H16 σ*: 0.78 (“basket handle” proximal CH)
Azacubane (**3**)	N π → C1-H13 σ*: 2.14

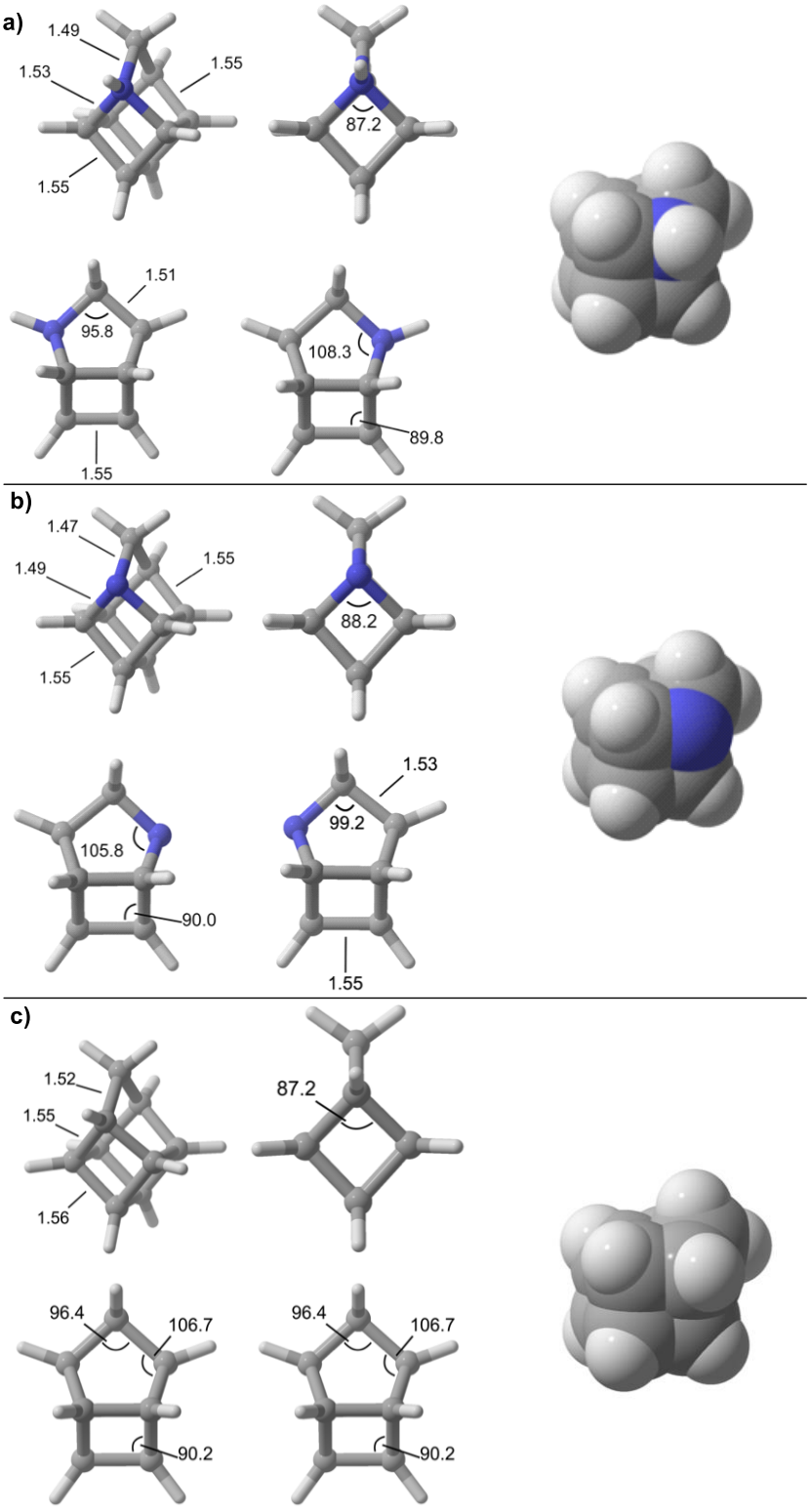


Figure S14: Calculated geometries for protonated azahomocubane (**4+H**), azahomocubane (**4**) and homocubane (**1**) in Ångstroms and degrees. All calculations performed at the M062X-D3/Def2TZVPP level of theory.

Table S7. Calculated Geometries

Azahomocubane

C	0.22703	0.78994	-1.06799
C	1.36051	0.78508	-0.00004
C	0.22579	-0.77773	-1.03780
C	1.37392	-0.76876	-0.00023
C	0.22603	-0.77788	1.03785
H	2.23705	-1.42346	-0.00031
H	0.20184	-1.33576	-1.96962
N	-0.77429	-1.16240	-0.00014
C	0.22721	0.78941	1.06815
H	2.22527	1.43903	0.00040
C	-0.84480	1.11762	0.00015
H	0.20199	-1.33689	1.96907
H	0.26694	1.30711	-2.02153
H	0.26717	1.30722	2.02135
C	-1.77853	-0.09389	0.00004
H	-2.40471	-0.15915	-0.89128
H	-2.40479	-0.15928	0.89131
H	-1.27366	2.11529	0.00073

E = -364.8577564

H = -364.697408

G = -364.732192

$E_{CCSD(T)}$ = -364.2832867

Azahomocubane_H

C	0.29100	0.78357	-1.07383
C	1.42289	0.73094	-0.00022
C	0.23109	-0.76800	-1.05697
C	1.35814	-0.82135	-0.00004
C	0.23132	-0.76781	1.05715
H	2.17916	-1.52593	0.00001
H	0.14489	-1.35719	-1.96257
N	-0.84350	-1.04527	0.00003
C	0.29129	0.78368	1.07374
H	2.31574	1.34070	-0.00034
C	-0.75355	1.18366	0.00005
H	0.14525	-1.35712	1.96267
H	0.34755	1.28404	-2.03289
H	0.34806	1.28436	2.03267
C	-1.80529	0.09426	0.00010
H	-2.42031	0.05367	-0.89745
H	-2.42031	0.05360	0.89763
H	-1.09878	2.21062	0.00010
H	-1.23814	-1.98360	0.00011

E = -365.2398917

H = -365.06489

G = -365.099839

$E_{CCSD(T)}$ = -364.6668837

Homocubane

C	0.22703	0.78994	-1.06799
C	1.36051	0.78508	-0.00004
C	0.22579	-0.77773	-1.03780
C	1.37392	-0.76876	-0.00023
C	0.22603	-0.77788	1.03785
H	2.23705	-1.42346	-0.00031
H	0.20184	-1.33576	-1.96962
C	-0.77429	-1.16240	-0.00014
C	0.22721	0.78941	1.06815
H	2.22527	1.43903	0.00040
C	-0.84480	1.11762	0.00015
H	0.20199	-1.33689	1.96907
H	0.26694	1.30711	-2.02153
H	0.26717	1.30722	2.02135
C	-1.77853	-0.09389	0.00004

H	-2.40471	-0.15915	-0.89128
H	-2.40479	-0.15928	0.89131
H	-1.27366	2.11529	0.00073
H	-1.27336	-2.10888	-0.00028

E = -348.8230637
H = -348.651223
G = -348.686257

Ethane

C	-0.76192	0.00001	-0.00000
C	0.76192	-0.00001	0.00000
H	-1.15648	-0.70491	-0.73140
H	-1.15647	0.98588	-0.24475
H	-1.15647	-0.28098	0.97616
H	1.15647	0.28098	-0.97616
H	1.15647	-0.98588	0.24475
H	1.15648	0.70491	0.73140

E = -79.8067647
H = -79.727239
G = -79.754779

Isobutane

C	-0.00001	-0.00001	-0.38023
C	-1.44133	-0.14407	0.09622
C	0.84544	-1.17617	0.09622
C	0.59589	1.32025	0.09622
H	-0.00003	-0.00001	-1.47433
H	-1.47972	-0.14811	1.18824
H	-1.88485	-1.07576	-0.25698
H	-2.06038	0.68163	-0.25664
H	0.86805	-1.20749	1.18825
H	1.87409	-1.09433	-0.25690
H	0.43997	-2.12513	-0.25676
H	0.61180	1.35543	1.18825
H	0.01071	2.17021	-0.25682
H	1.62042	1.44358	-0.25684

E = -158.424848
H = -158.285926
G = -158.320086

Propane

C	0.00000	0.59043	0.00000
C	1.26384	-0.26027	-0.00000
C	-1.26384	-0.26027	0.00000
H	-0.00000	1.24520	-0.87394
H	0.00000	1.24520	0.87394
H	1.29672	-0.90436	-0.88036
H	1.29672	-0.90436	0.88036
H	2.16411	0.35385	0.00000
H	-1.29672	-0.90436	-0.88036
H	-2.16411	0.35385	-0.00000
H	-1.29672	-0.90436	0.88037

E = -119.114719
H = -119.005251
G = -119.036353

Trimethylamine

N	-0.00001	-0.00002	-0.38699
C	0.09231	1.37349	0.06211
C	-1.23569	-0.60680	0.06211
C	1.14337	-0.76668	0.06210
H	0.09773	1.45257	1.16271
H	-0.75535	1.94466	-0.31613
H	1.00877	1.82609	-0.31621
H	-1.30679	-0.64199	1.16271
H	-1.30663	-1.62639	-0.31639

H	-2.08580	-0.03918	-0.31598
H	1.20952	-0.81067	1.16270
H	2.06175	-0.31822	-0.31648
H	1.07698	-1.78674	-0.31596

E = -174.4481927

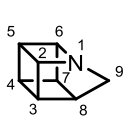
H = -174.32067

G = -174.354

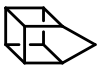
^{13}C-^{1}H Coupling Constants and ^{15}N Chemical Shifts

$^{1}J_{CH}$ coupling and ^{15}N-NMR experiments were recorded using a 700 MHz Bruker Avance III HD spectrometer equipped with a TCI cryoprobe. $^{1}J_{CH}$ coupling constants were determined using the Bruker pulse sequence "shsqcetgpsisp2.2" which was used to improve the resolution in the indirect dimension. Shaped pulses were applied in the indirect dimension which covered the carbon chemical shifts of interest. The ^{13}C decoupling was disabled during the acquisition so the $^{1}J_{CH}$ coupling constant were observable after the 2D Fourier transform, as a double in the ^{1}H dimension. ^{15}N chemical shifts were determined using the "hmbcf3gpndqf" Bruker pulse sequence with the long-range coupling constant (^{n}J) of 4 Hz. The Bruker "xiref" macro was used to reference the indirect dimension in the ^{15}N experiments (Table S8).

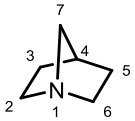
Table S8: One-bond proton-carbon coupling constants (Hz) and ^{15}N chemical shifts (ppm). ^{15}N-NMR chemical shifts collected in C_6D_6 except lit. piperidine chemical shift collected in $CDCl_3$.[42] Position in parentheses.



4

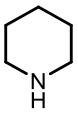


S23

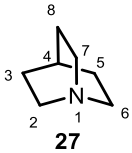


26

S24

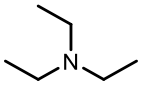


S28

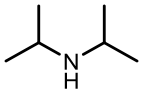


27

S25



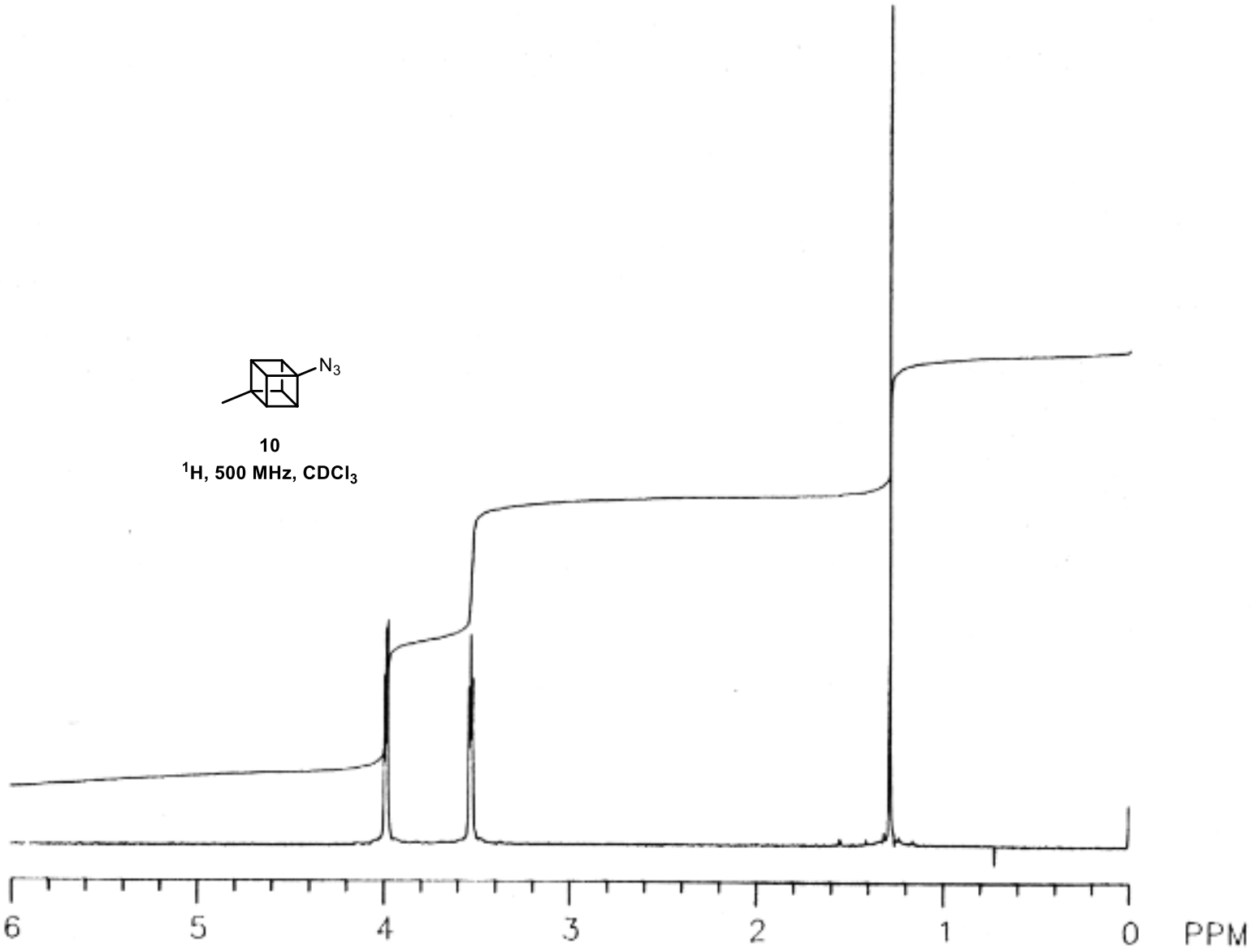
S26



S27

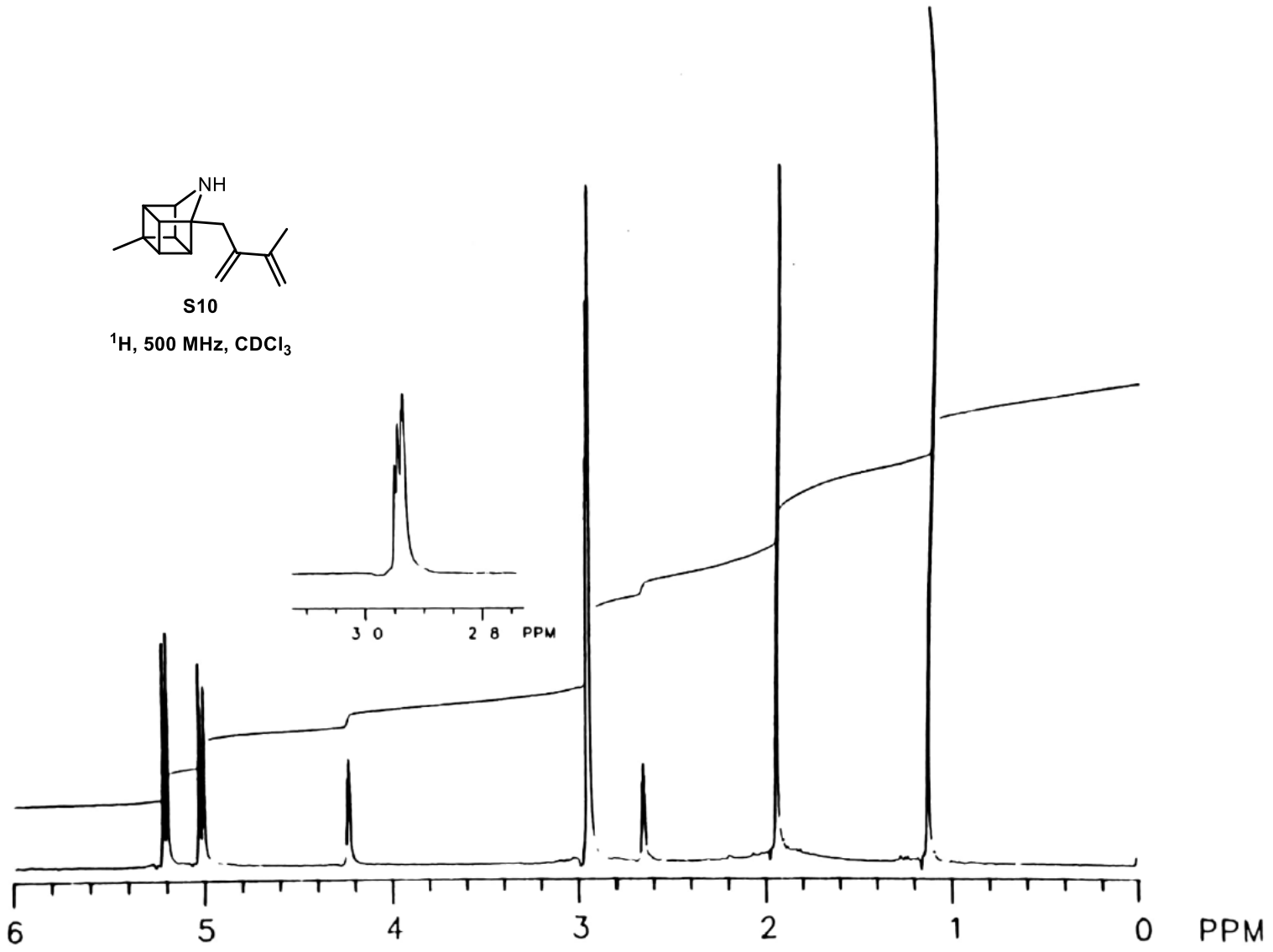
COMPOUND	$^1J_{CH}$						^{15}N
1-Azahomocubane (4)	146.7 (8)	162.4 (2/6)	156.1 (3/7)	155.8 (4)	162.3 (5)	139.2 (9)	78.7
Homocubane (S23)[43]	146 (1/8)	152 (2/3/6/7)	—	157 (4/5)	—	129 (9)	—
Δ	+0.7	+10.4	+4.1	-1.2	+5.3	+10.2	—
1-Azabicyclo[2.2.1]heptane (26)	143.0 (4)	140.4 (2/6)	131.6 (3/5)	141.0 (7)	—	—	58.7
Bicyclo[2.2.1]heptane (S24)[44]	140.1 (1/4)	130.3 (2/3/5/6)	—	131.3 (7)	—	—	—
Δ	+2.9	+10.1	+1.3	+9.7	—	—	—
Quinuclidine (27)	137.5 (4)	135.3 (2/6/7)	127.1 (3/5/8)	—	—	—	15.0
Bicyclo[2.2.2]octane (S25)[44]	134.3 (1/4)	125.7 (2/3/5/6/7/8)	—	—	—	—	—
Δ	+3.2	+9.6	+1.4	—	—	—	—
Triethylamine (S26)	—	—	—	—	—	—	47.7
Diisopropylamine (S27)	—	—	—	—	—	—	76.3
Piperidine (S28)[42]	—	—	—	—	—	—	49.8

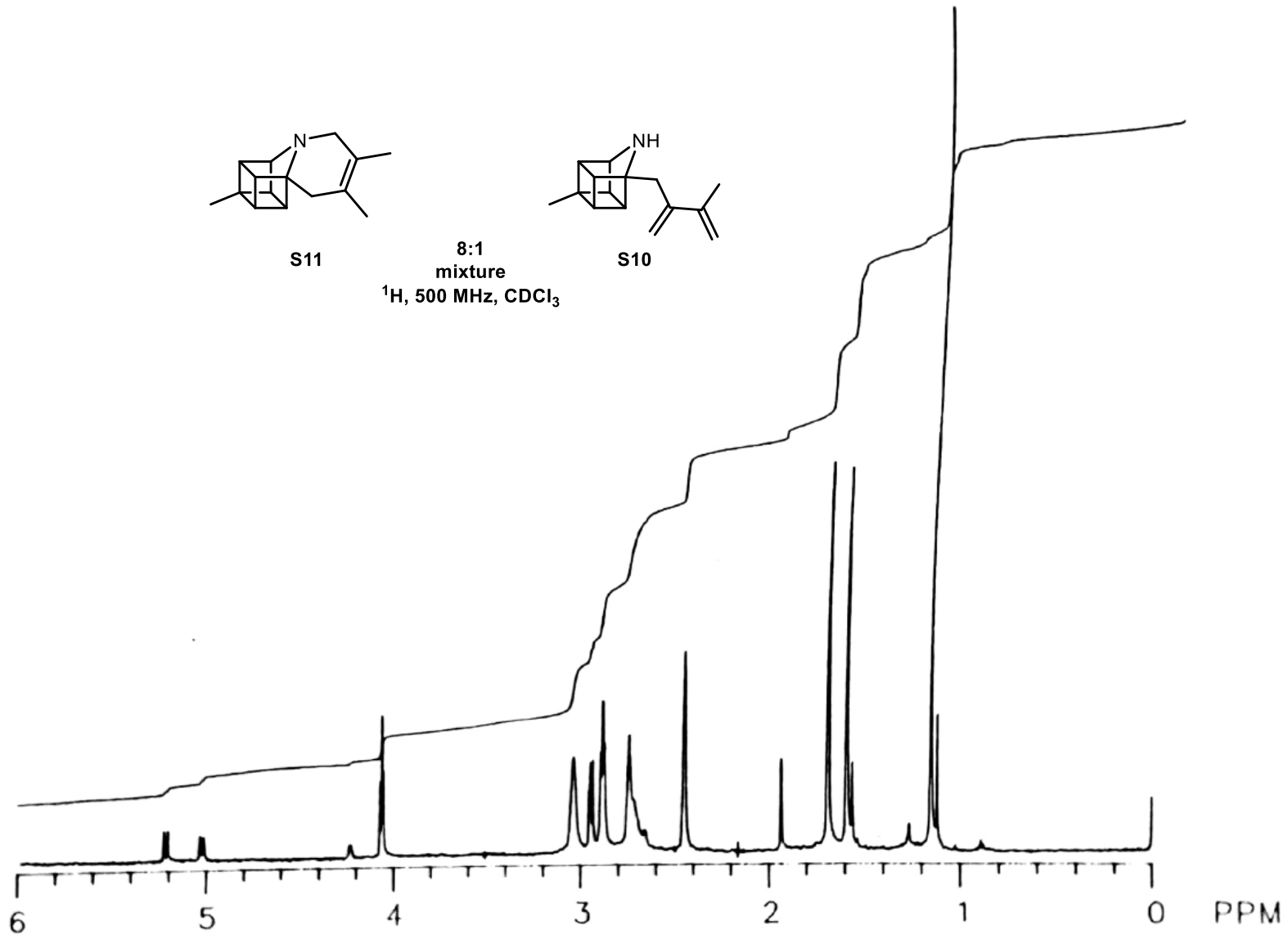
NMR spectra

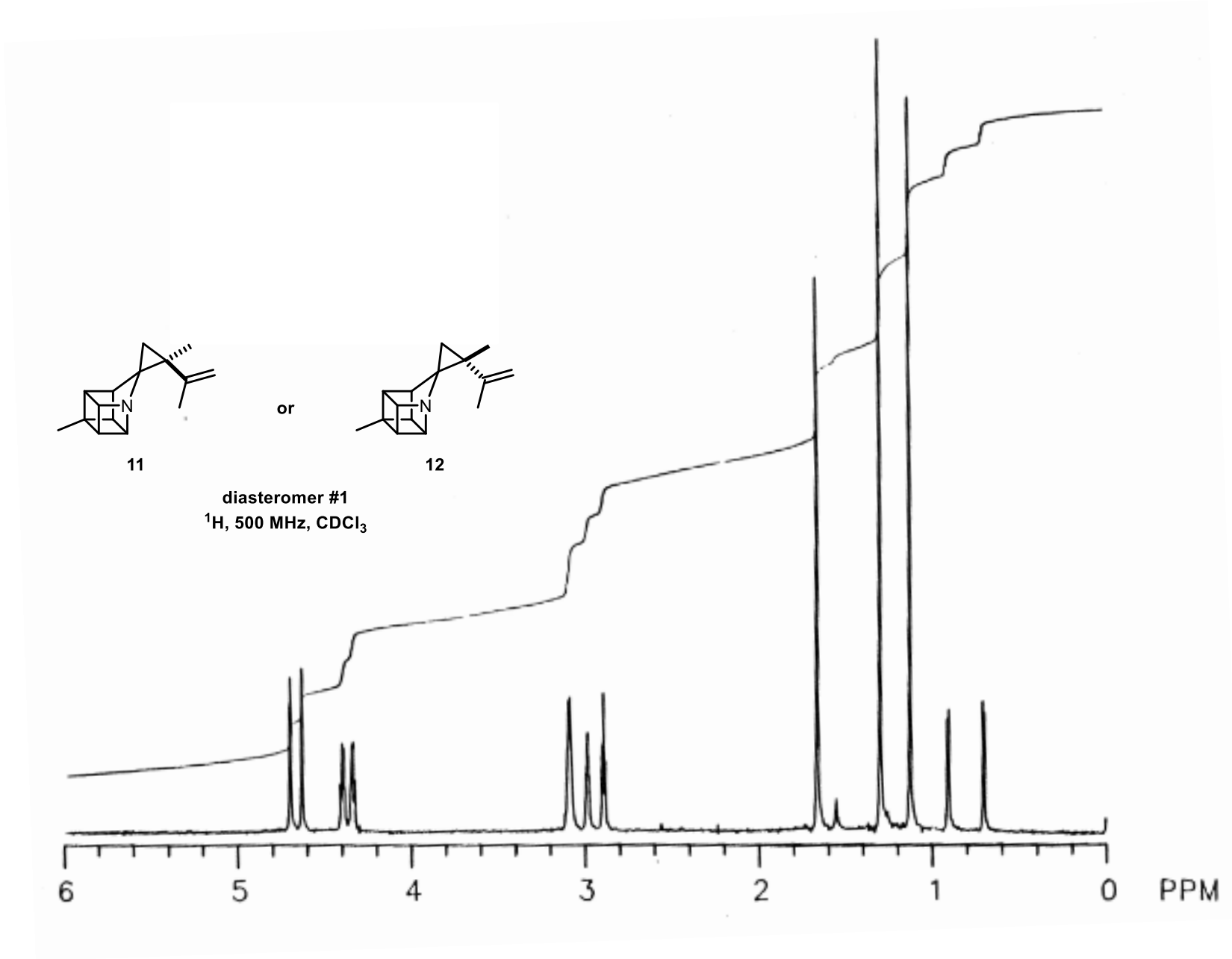


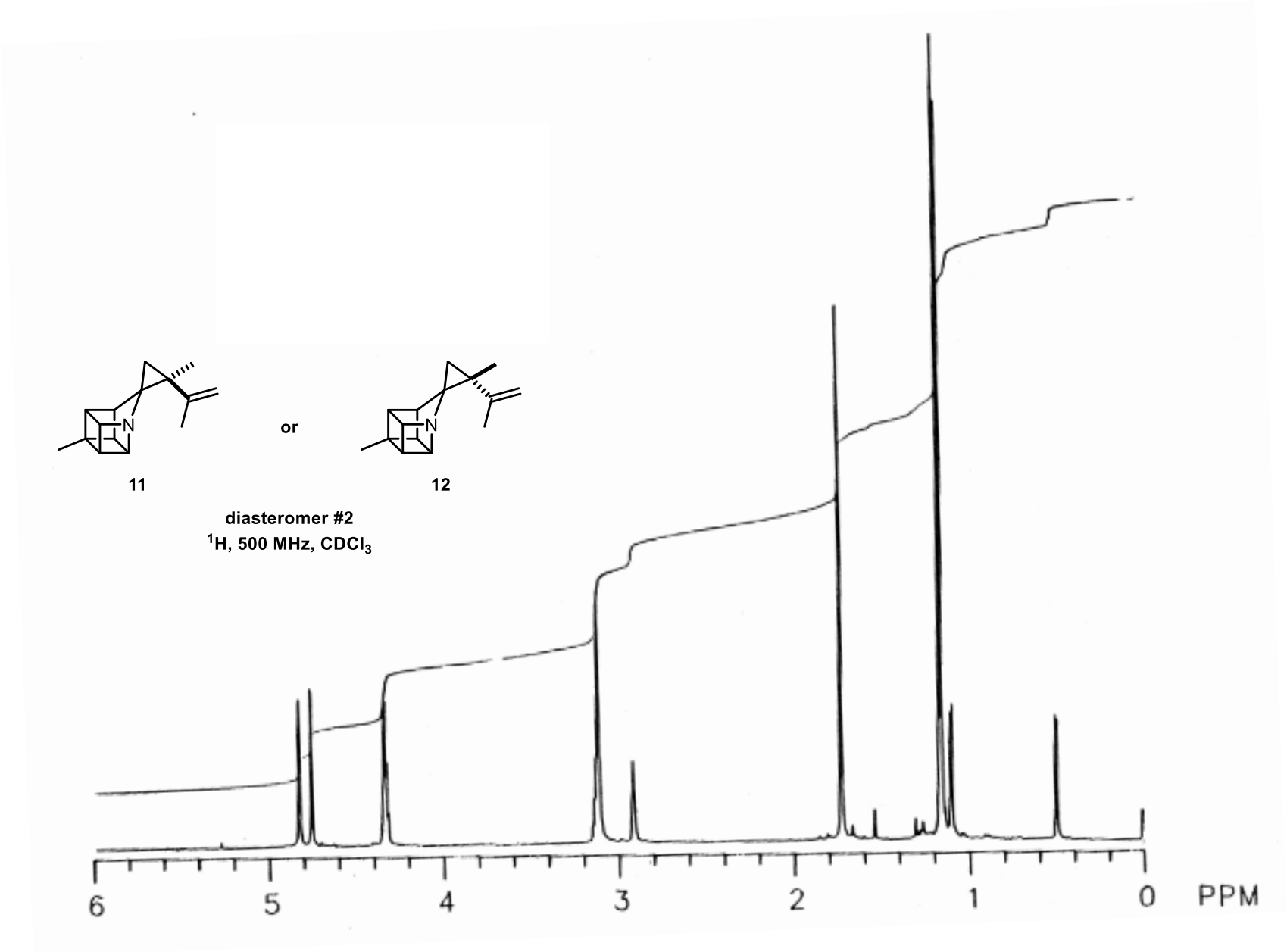
10

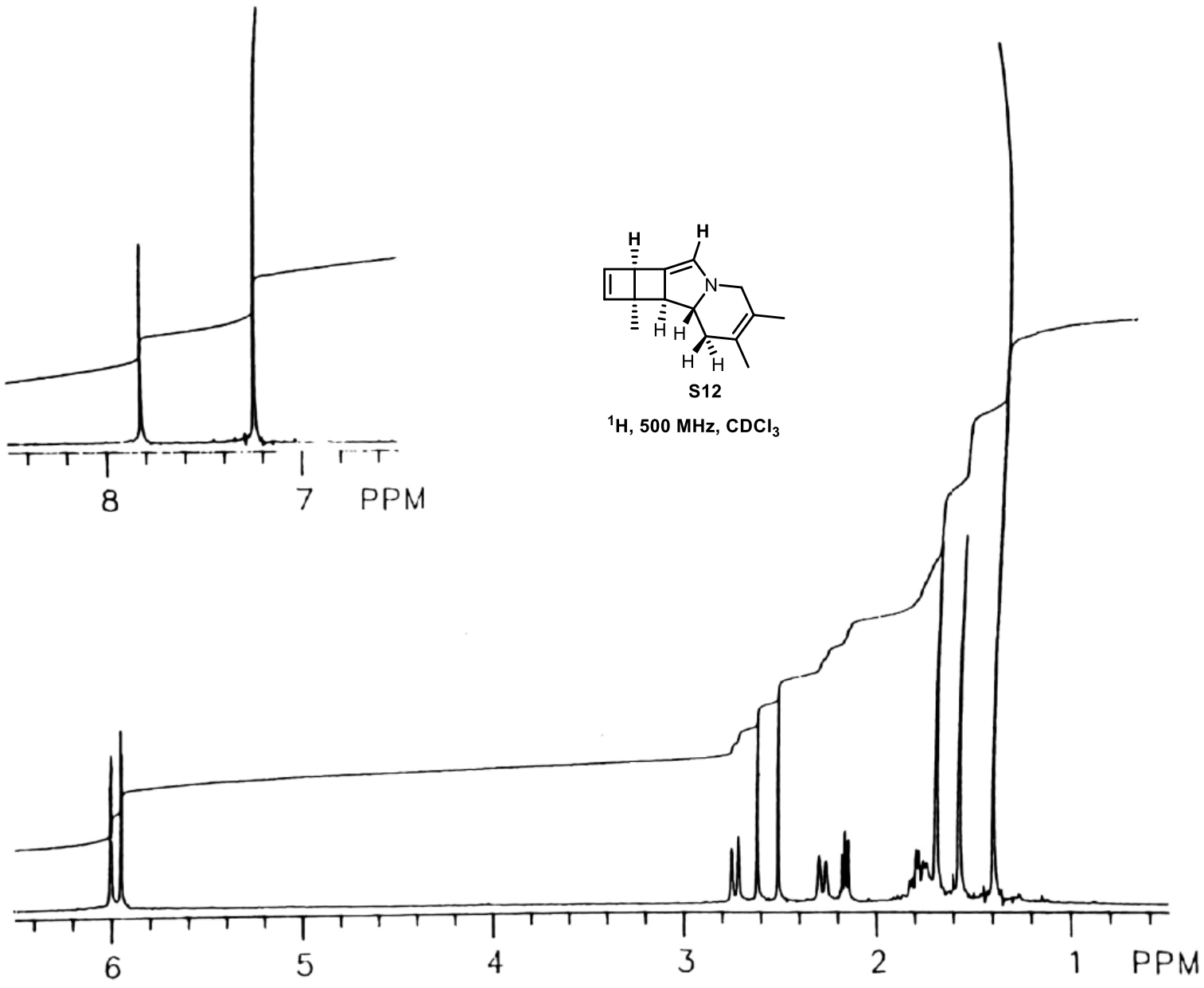
^{1}H, 500 MHz, $CDCl_3$


NH
S10
1H, 500 MHz, CDCl3
3 0
2 8
PPM
6
5
4
3
2
1
0
PPM


N
NH
S11
8:1
mixture
^{1}H, 500 MHz, CDCl$_3$
S10
6
5
4
3
2
1
0
PPM

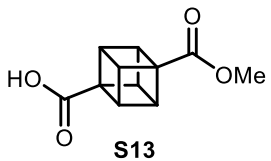

or
11
12
diasteromer #1
^{1}H, 500 MHz, $CDCl_3$
6
5
4
3
2
1
0
PPM


or
11
12
diasteromer #2
^{1}H, 500 MHz, $CDCl_3$
6
5
4
3
2
1
0
PPM



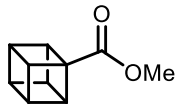
S12

^{1}H, 500 MHz, $CDCl_3$



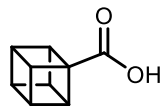
S13

^{1}H, 300 MHz, $CDCl_3$



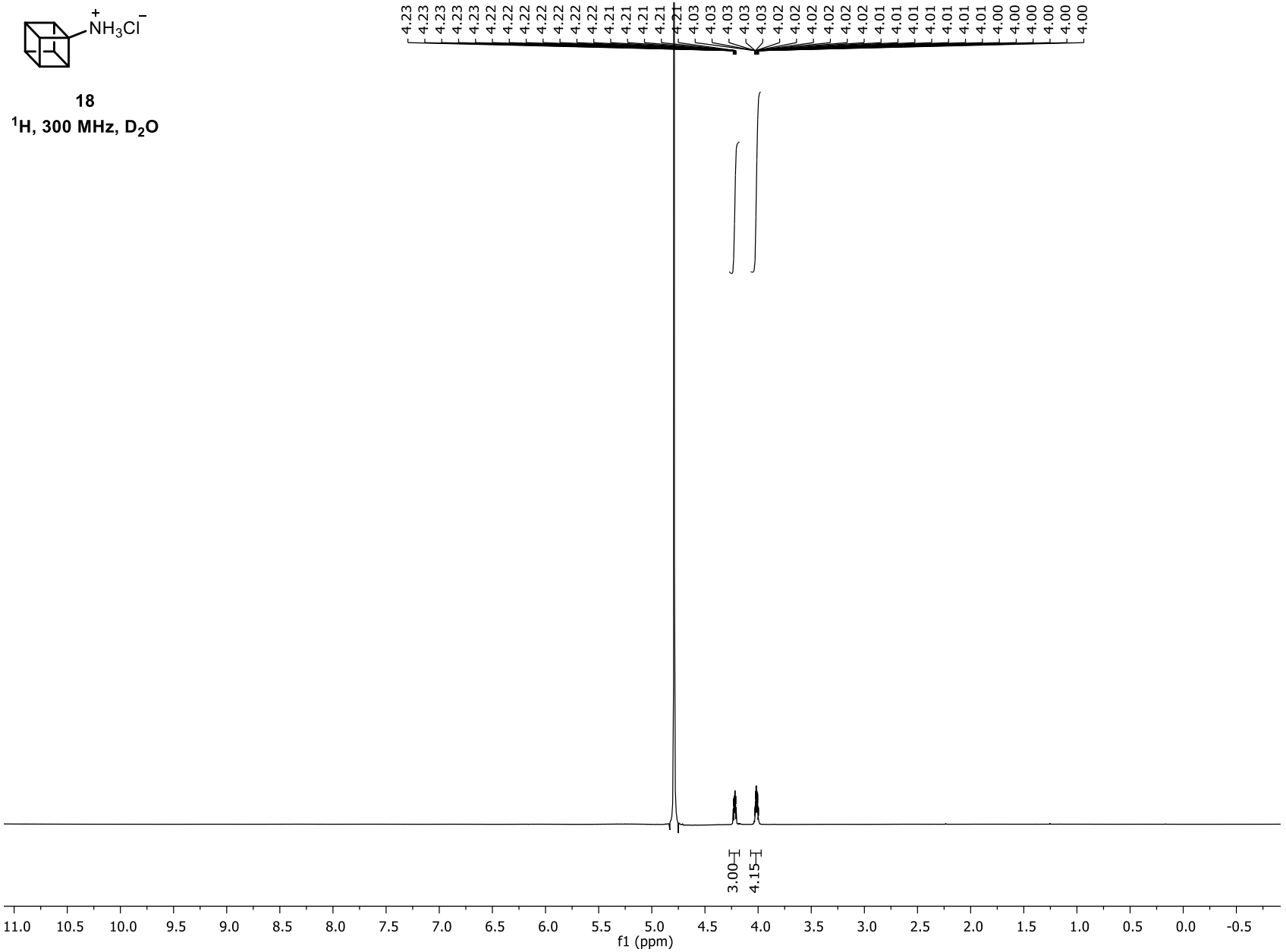
S14

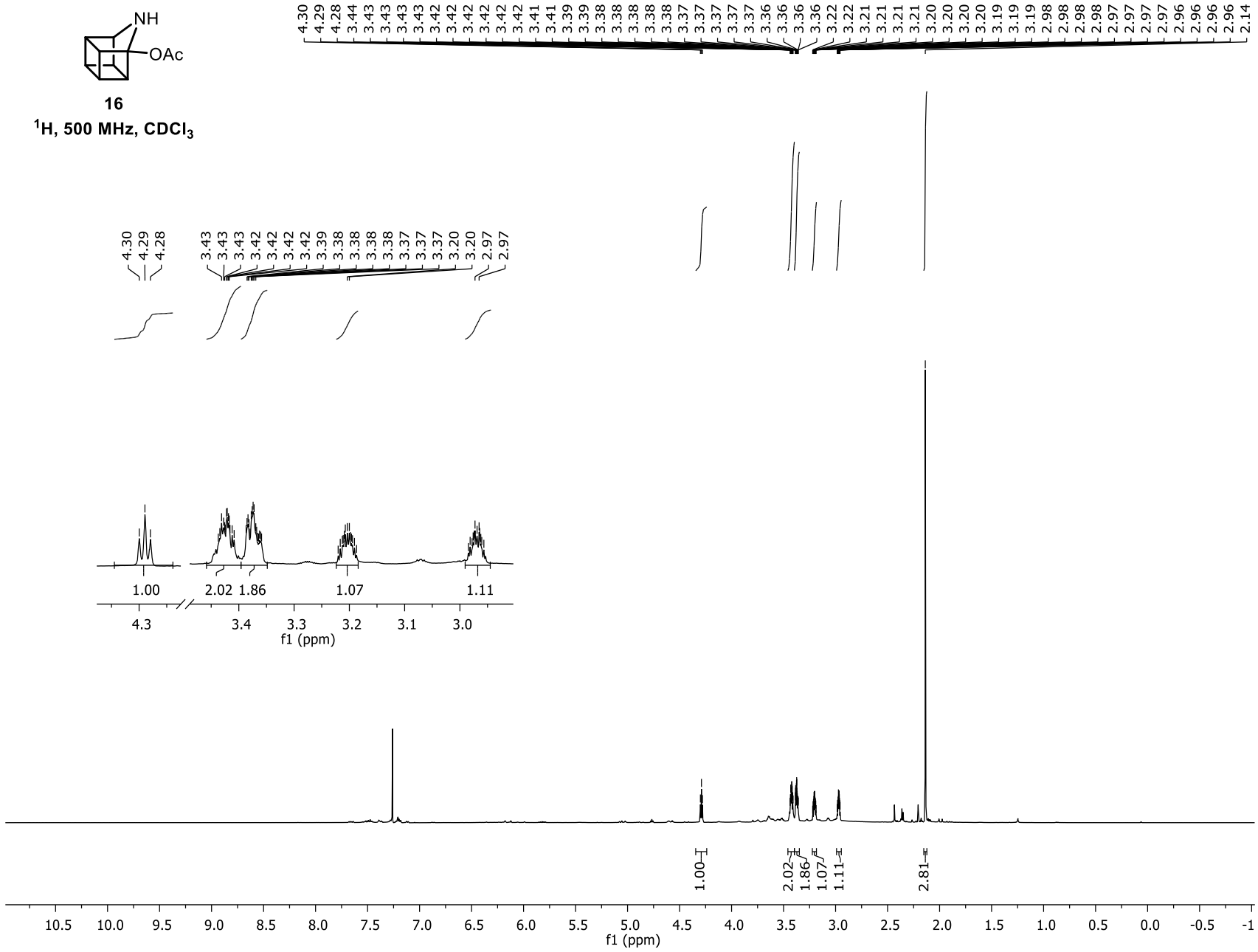
^{1}H, 300 MHz, $CDCl_3$

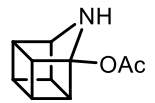


S15

^{1}H, 300 MHz, $CDCl_3$


NH3Cl
18
1H, 300 MHz, D2O
4.23 4.23 4.23 4.23 4.23 4.22 4.22 4.22 4.22 4.22 4.22 4.21 4.21 4.21 4.21 4.21 4.03 4.03 4.03 4.03 4.02 4.02 4.02 4.02 4.02 4.01 4.01 4.01 4.01 4.01 4.01 4.00 4.00 4.00 4.00 4.00
3.00
4.15
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


NH
OAc
16
1H, 500 MHz, CDCl3
4.30 4.29 4.28 4.44 3.43 3.43 3.43 3.42 3.42 3.42 3.42 3.41 3.41 3.39 3.39 3.38 3.38 3.38 3.38 3.37 3.37 3.37 3.37 3.36 3.36 3.36 3.22 3.22 3.21 3.21 3.21 3.20 3.20 3.20 3.19 3.19 2.98 2.98 2.98 2.97 2.97 2.97 2.96 2.96 2.96 2.14
4.30 4.29 4.28
3.43 3.43 3.43 3.42 3.42 3.42 3.42 3.39 3.38 3.38 3.38 3.38 3.37 3.37 3.37 3.20 3.20 2.97 2.97
1.00 2.02 1.86 1.07 1.11
4.3 3.4 3.3 3.2 3.1 3.0
f1 (ppm)
1.00 2.02 1.86 1.07 1.11 2.81
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)



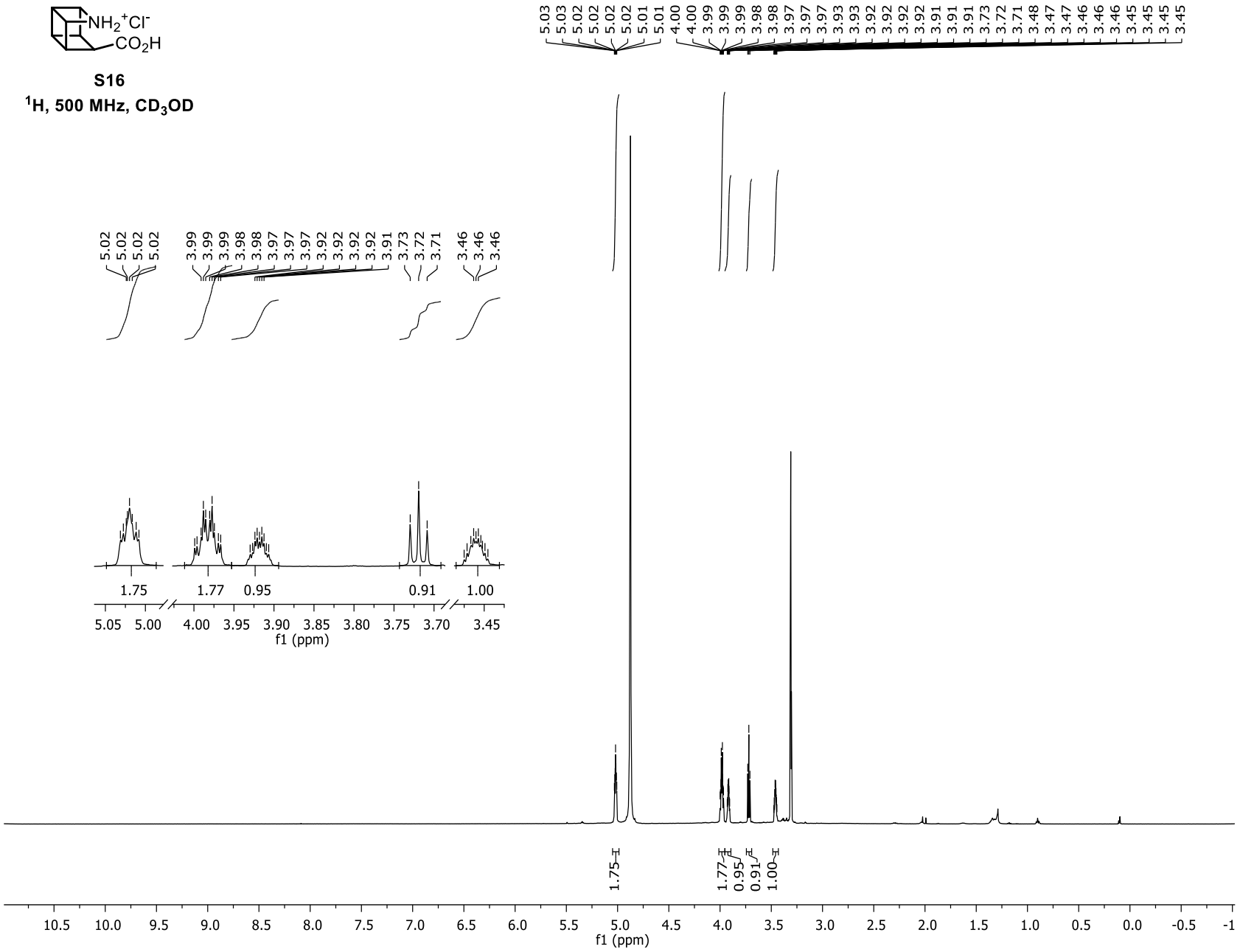
16

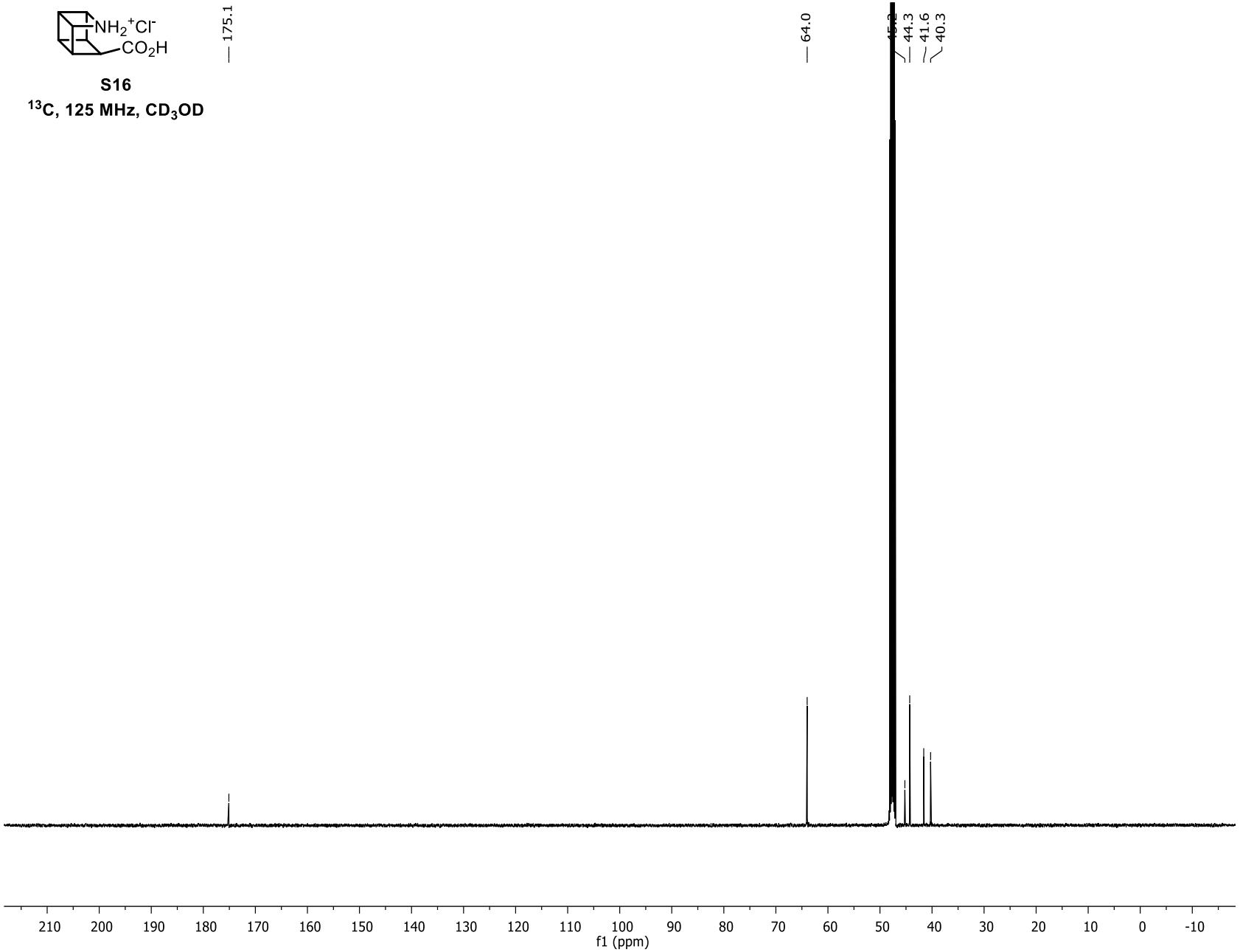
^{13}C, 125 MHz, $CDCl_3$

9

(Mixture of 9 and 16)

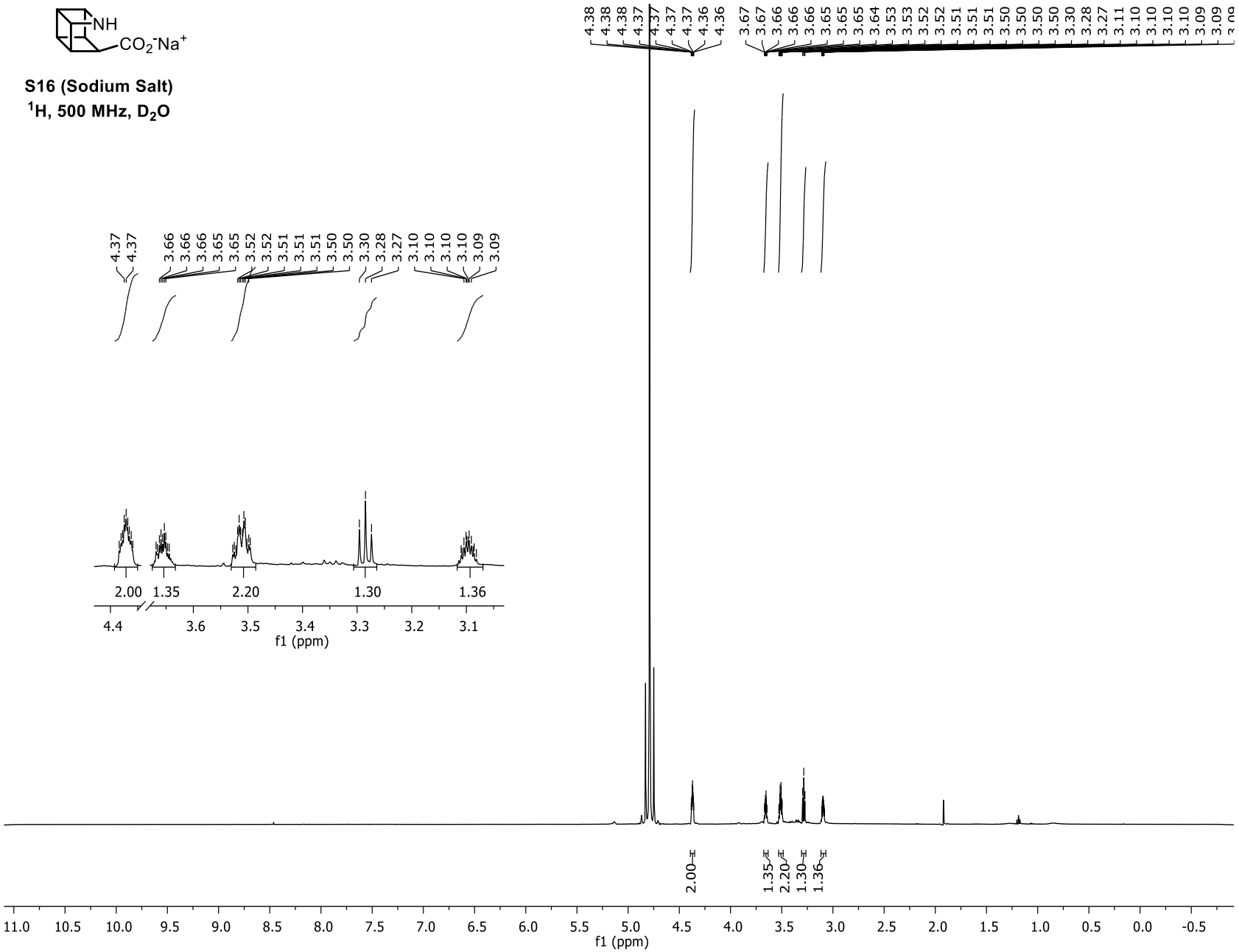
^{1}H, 300 MHz, $CDCl_3$

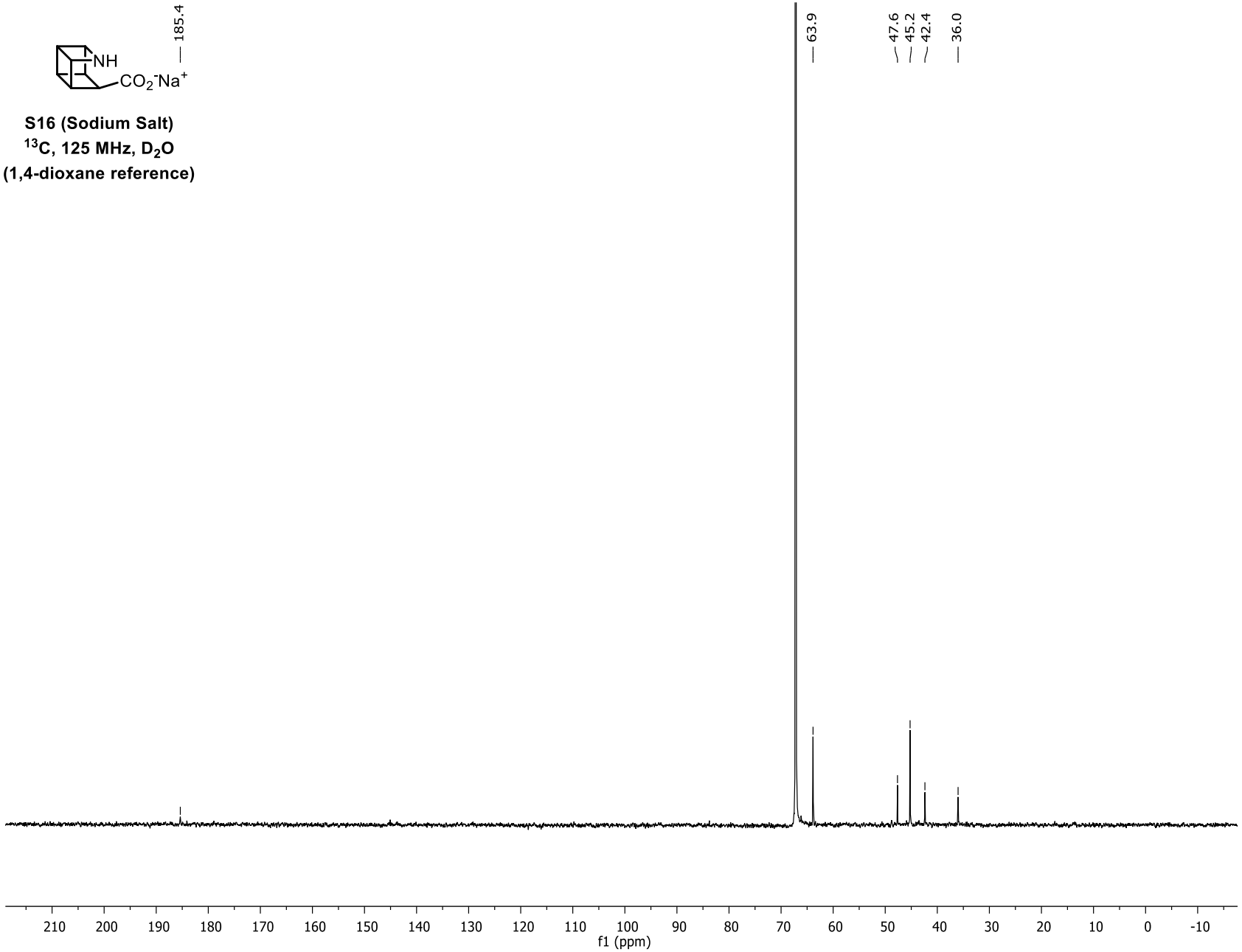

NH2+Cl-
CO2H
S16
1H, 500 MHz, CD3OD
f1 (ppm)



S16

^{13}C, 125 MHz, CD_3OD

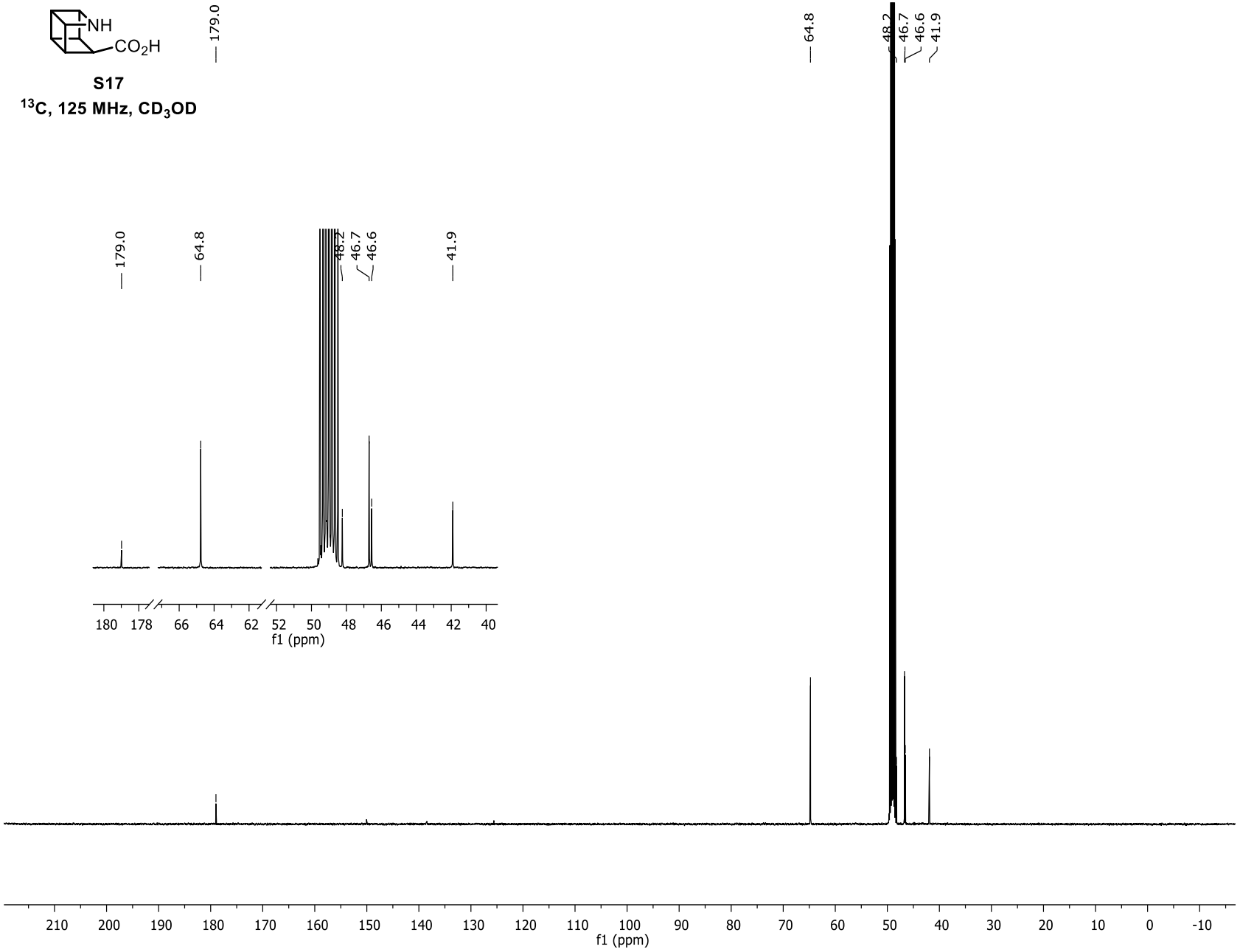

NH
CO2-Na+
S16 (Sodium Salt)
1H, 500 MHz, D2O
4.38 4.38 4.38 4.37 4.37 4.37 4.37 4.36 4.36
3.67 3.67 3.66 3.66 3.66 3.65 3.65 3.65 3.64 3.53 3.53 3.52 3.52 3.51 3.51 3.51 3.50 3.50 3.50 3.30 3.28 3.27 3.11 3.10 3.10 3.10 3.09 3.09
4.37 4.37
3.66 3.66 3.66 3.65 3.65 3.52 3.52 3.51 3.51 3.51 3.50 3.50
3.30 3.28 3.27
3.10 3.10 3.10 3.09 3.09
2.00 1.35 2.20 1.30 1.36
4.4 3.6 3.5 3.4 3.3 3.2 3.1
f1 (ppm)
2.00 1.35 2.20 1.30 1.36
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

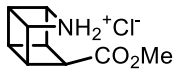


S16 (Sodium Salt)
^{13}C, 125 MHz, D_2O
(1,4-dioxane reference)

S17

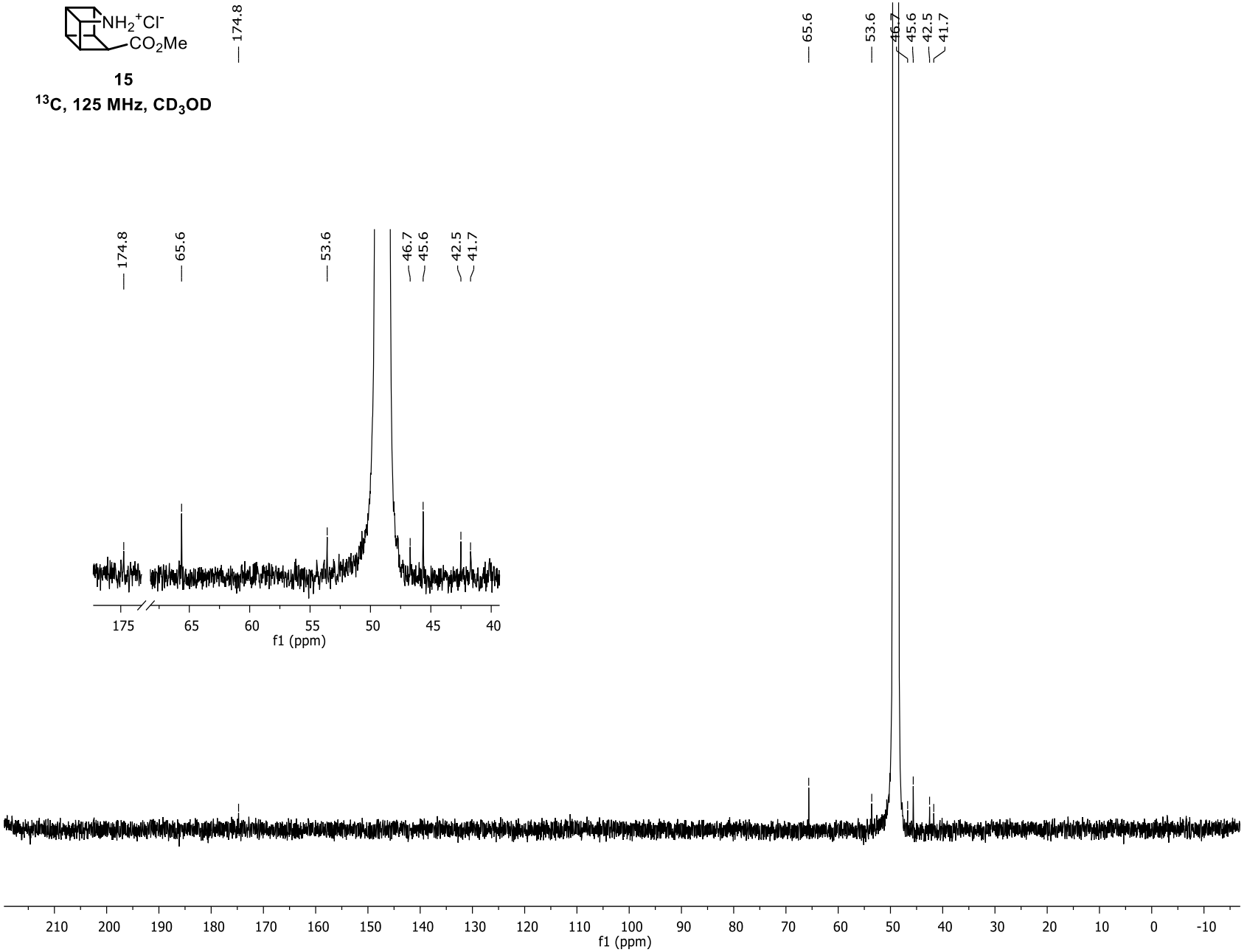
^{1}H, 500 MHz, CD_3OD

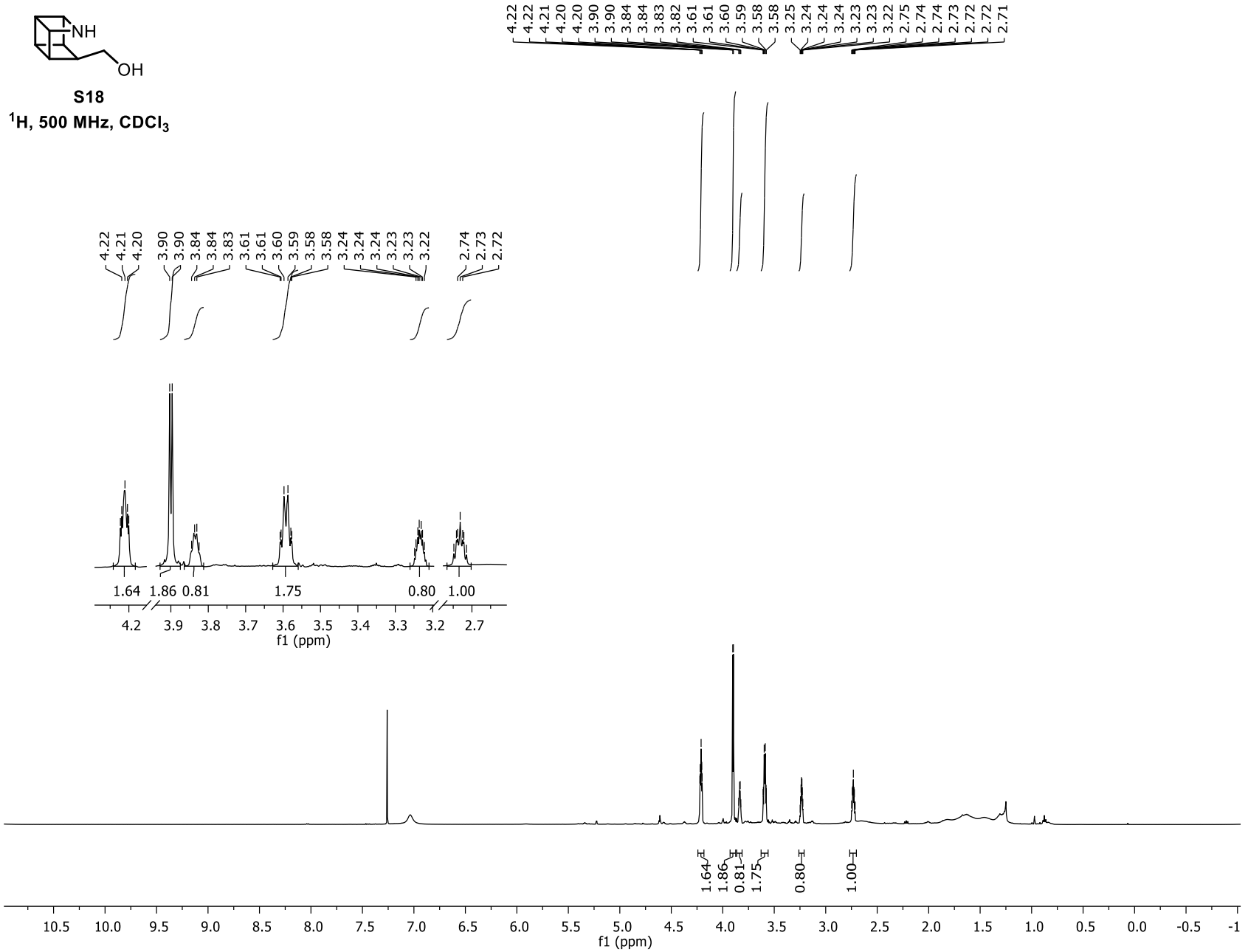

NH
CO2H
S17
13C, 125 MHz, CD3OD
179.0
64.8
48.2
46.7
46.6
41.9
f1 (ppm)

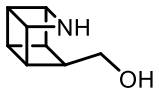


15

^{1}H, 500 MHz, CD_3OD

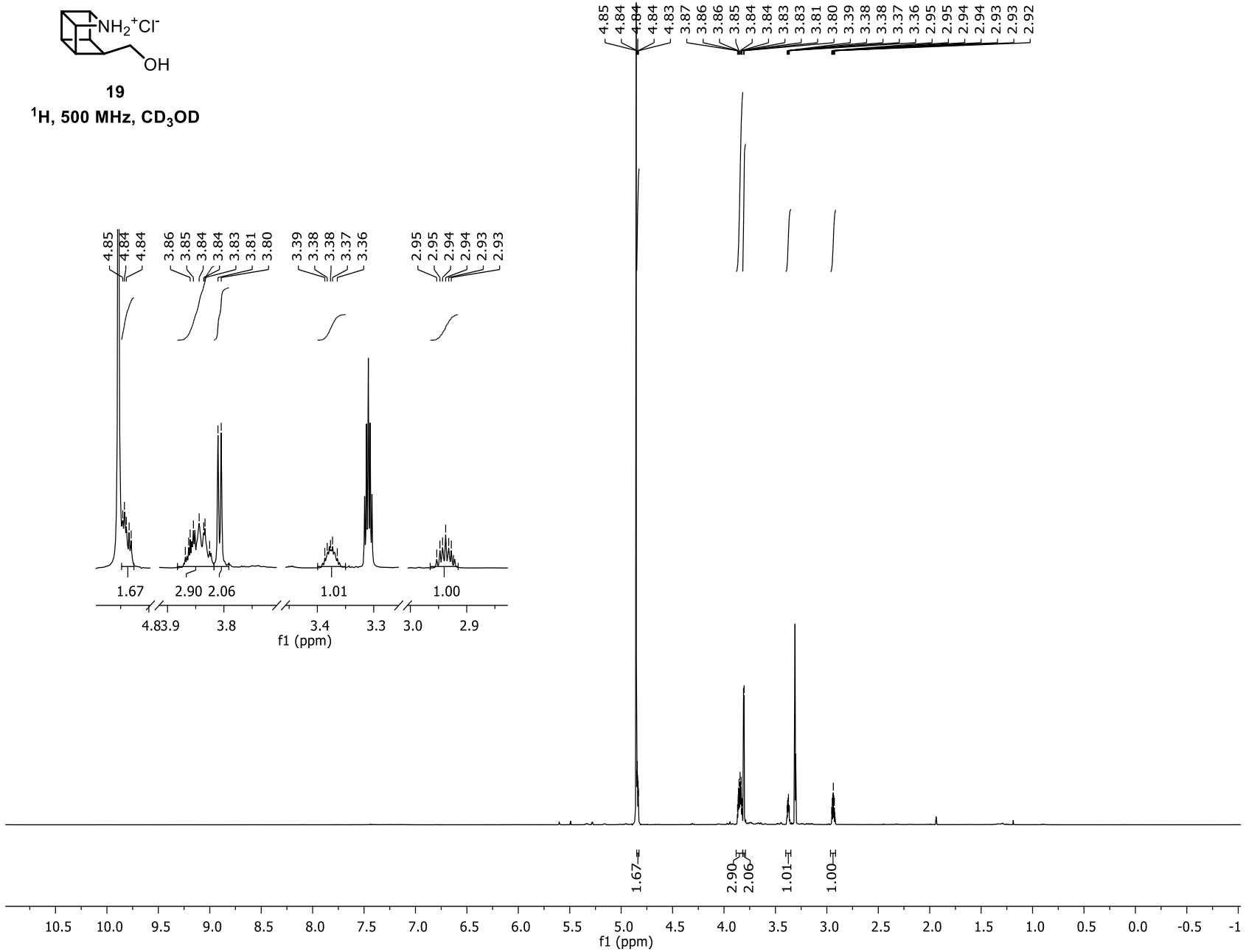

NH2+Cl-
CO2Me
15
13C, 125 MHz, CD3OD
174.8
65.6
53.6
46.7
45.6
42.5
41.7
f1 (ppm)

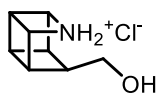

NH
OH
S18
1H, 500 MHz, CDCl3
4.22 4.22 4.21 4.20 4.20 3.90 3.90 3.84 3.84 3.83 3.82 3.61 3.60 3.59 3.58 3.58 3.25 3.24 3.24 3.24 3.23 3.23 3.22 2.75 2.74 2.74 2.73 2.72 2.72 2.71
4.22 4.21 4.20 3.90 3.90 3.84 3.84 3.83 3.61 3.61 3.60 3.59 3.58 3.58 3.24 3.24 3.24 3.23 3.23 3.22 2.74 2.73 2.72
1.64 1.86 0.81 1.75 0.80 1.00
4.2 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 2.7
f1 (ppm)
1.64 1.86 0.81 1.75 0.80 1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)



S18

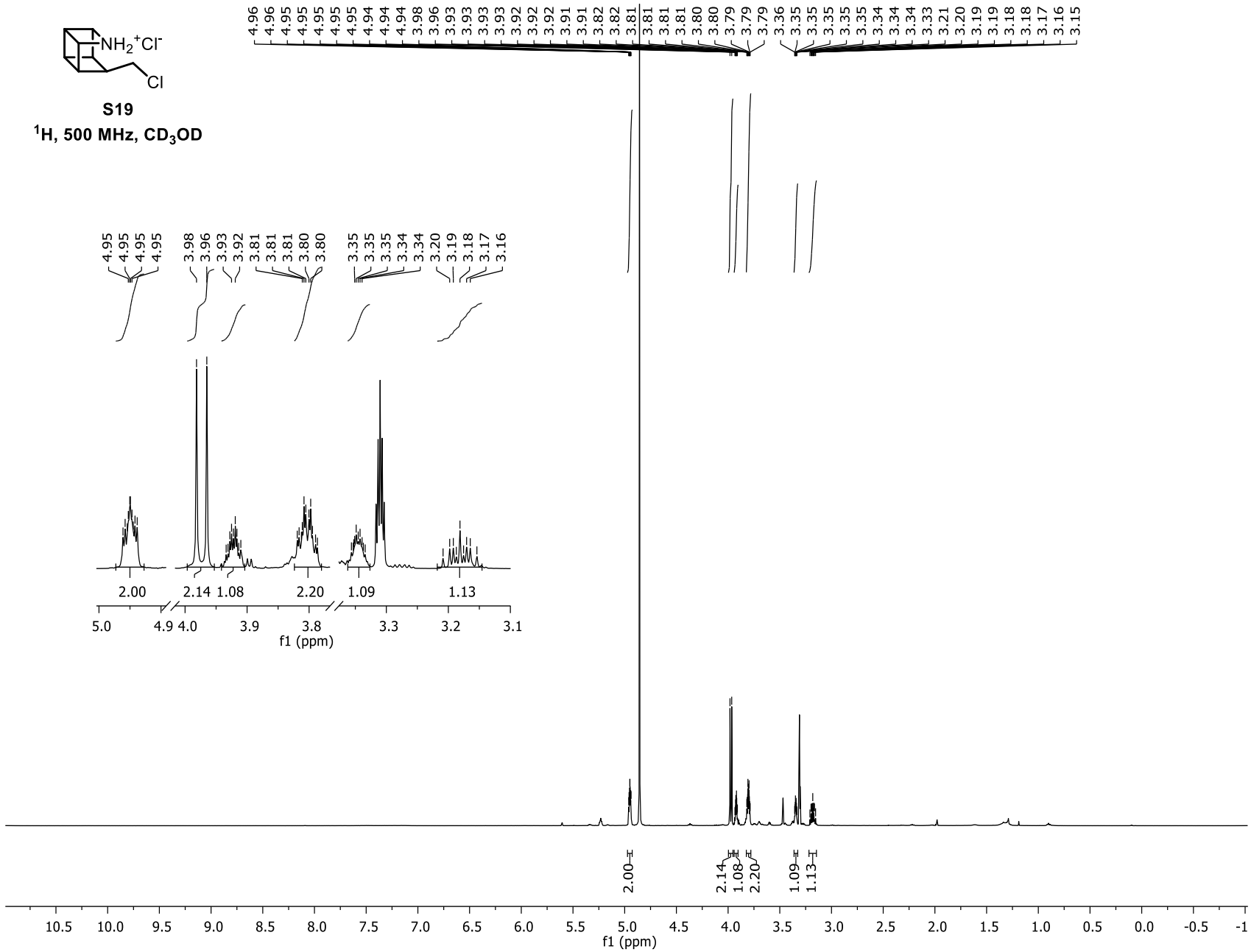
^{13}C, 125 MHz, $CDCl_3$

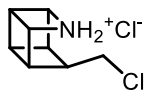

NH2+Cl-
OH
19
1H, 500 MHz, CD3OD
4.85 4.84 4.84 4.84 4.83 3.87 3.86 3.86 3.85 3.84 3.84 3.83 3.83 3.81 3.80 3.39 3.38 3.38 3.37 3.36 2.95 2.95 2.94 2.94 2.93 2.93 2.92
1.67 2.90 2.06 1.01 1.00
f1 (ppm)



19

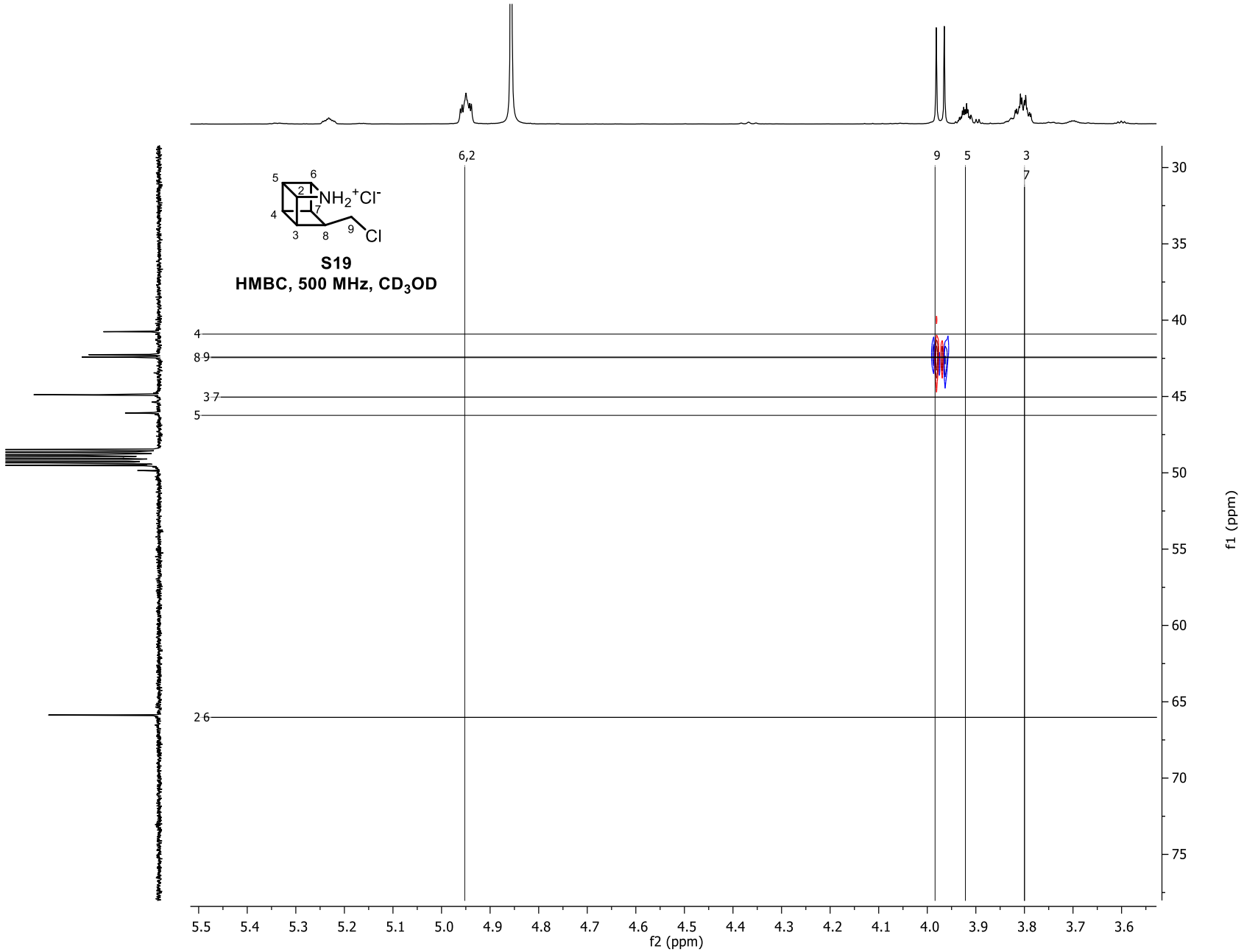
^{13}C, 125 MHz, CD_3OD

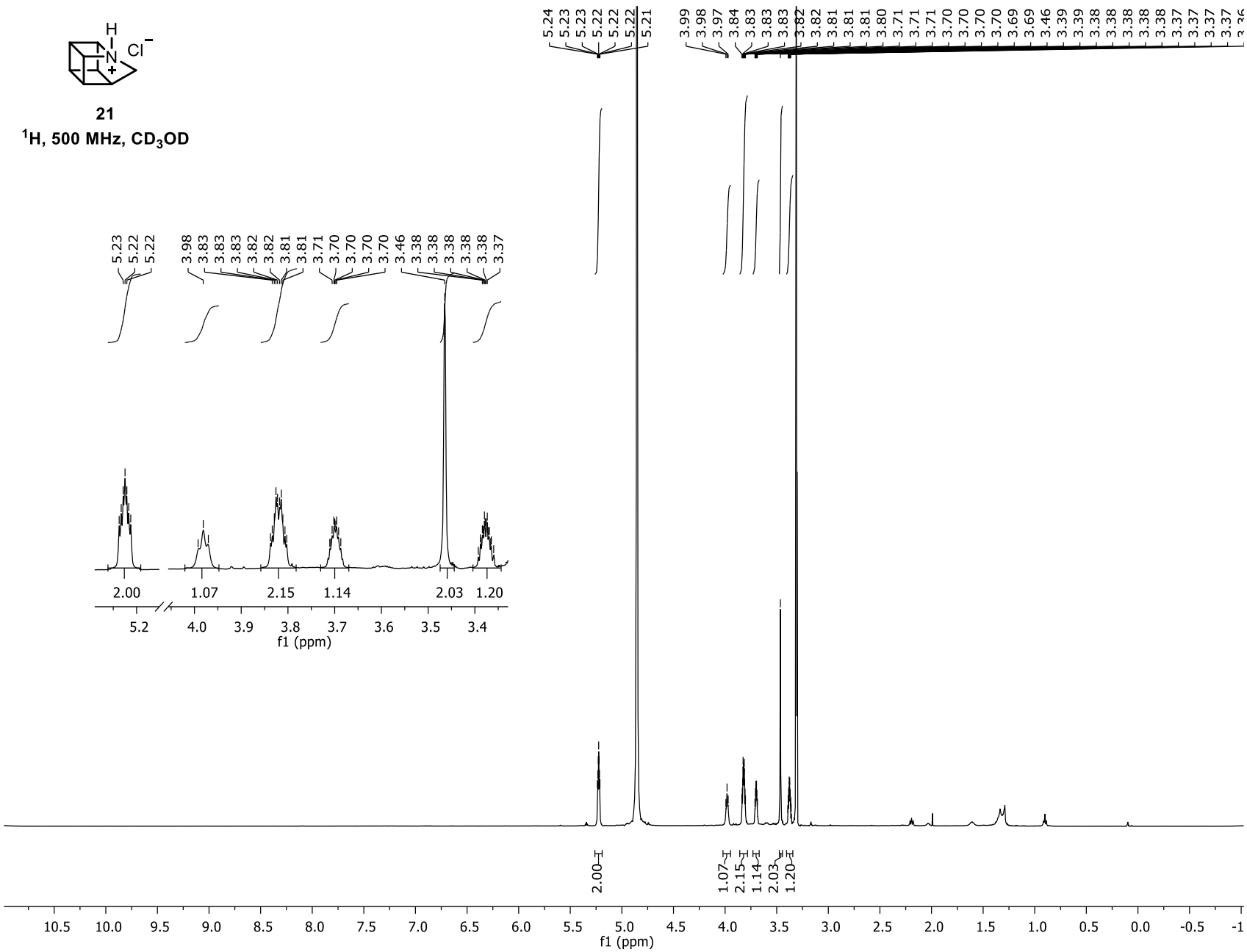

NH2+Cl-
Cl
S19
1H, 500 MHz, CD3OD
4.96 4.96 4.95 4.95 4.95 4.95 4.94 4.94 4.94 3.98 3.96 3.93 3.93 3.93 3.92 3.92 3.92 3.91 3.91 3.82 3.82 3.81 3.81 3.81 3.80 3.80 3.79 3.79 3.79 3.36 3.35 3.35 3.35 3.35 3.34 3.34 3.34 3.33 3.21 3.20 3.19 3.19 3.18 3.18 3.17 3.16 3.15
4.95 4.95 4.95 4.95
3.98 3.96 3.93 3.92 3.81 3.81 3.81 3.80 3.80
3.35 3.35 3.35 3.34 3.34
3.20 3.19 3.18 3.17 3.16
2.00 2.14 1.08 2.20 1.09 1.13
5.0 4.9 4.0 3.9 3.8 3.3 3.2 3.1
f1 (ppm)
2.00 2.14 1.08 2.20 1.09 1.13
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

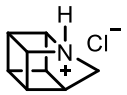


S19

^{13}C, 125 MHz, CD_3OD

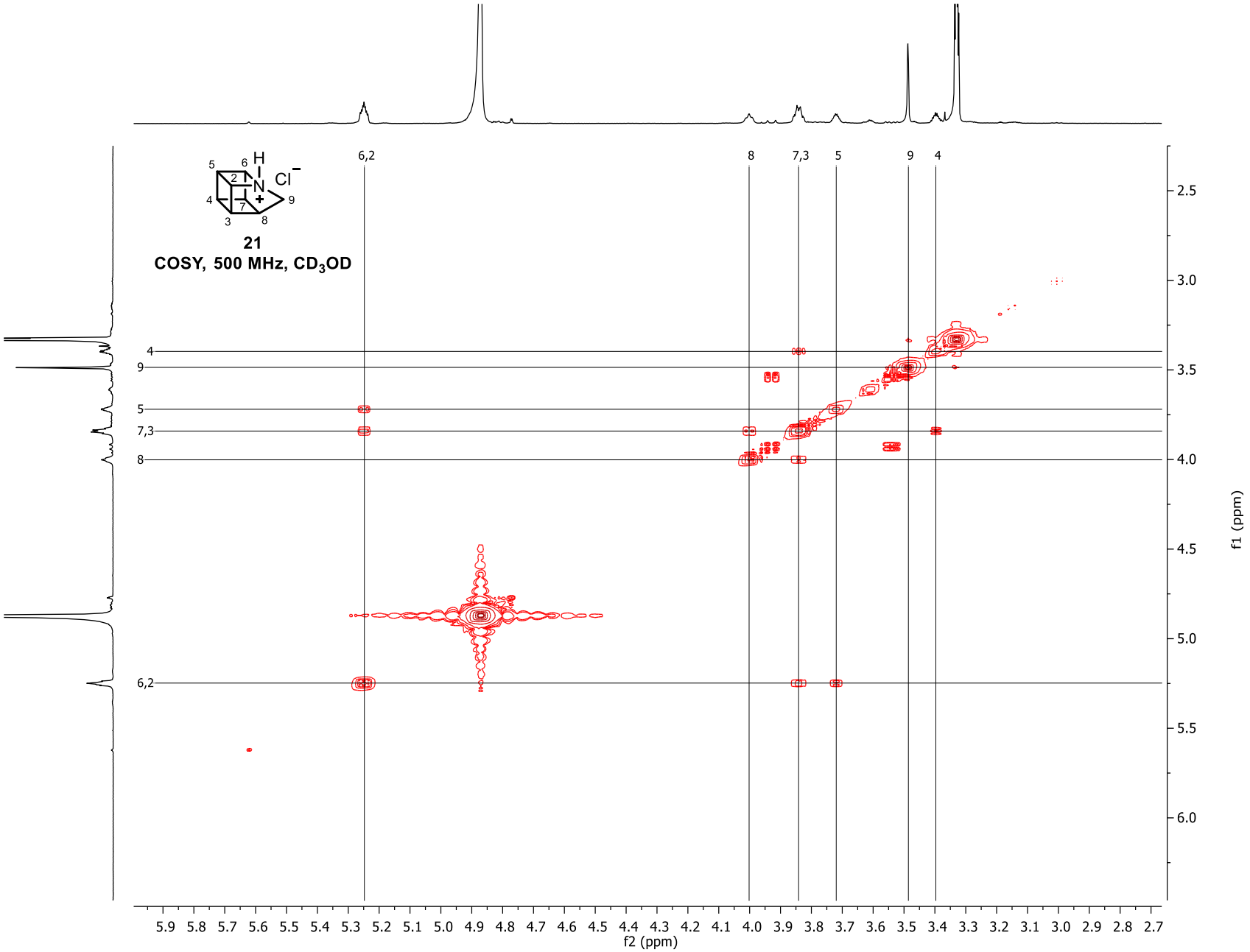

S19
HMBC, 500 MHz, CD3OD
NH2+Cl-
Cl
6,2
9
5
3
7
4
8 9
3 7
5
2 6
f2 (ppm)
f1 (ppm)

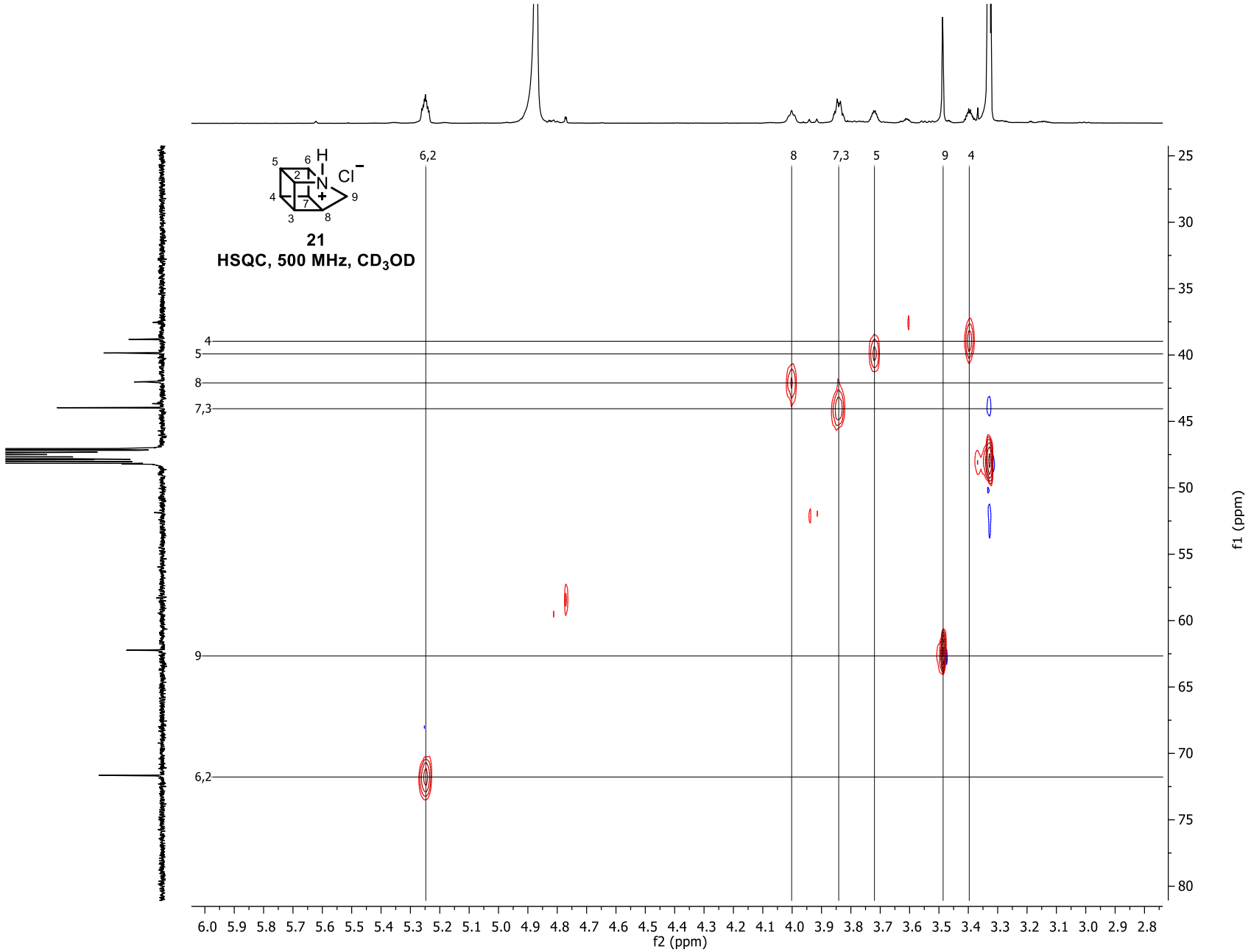

21
1H, 500 MHz, CD3OD
f1 (ppm)

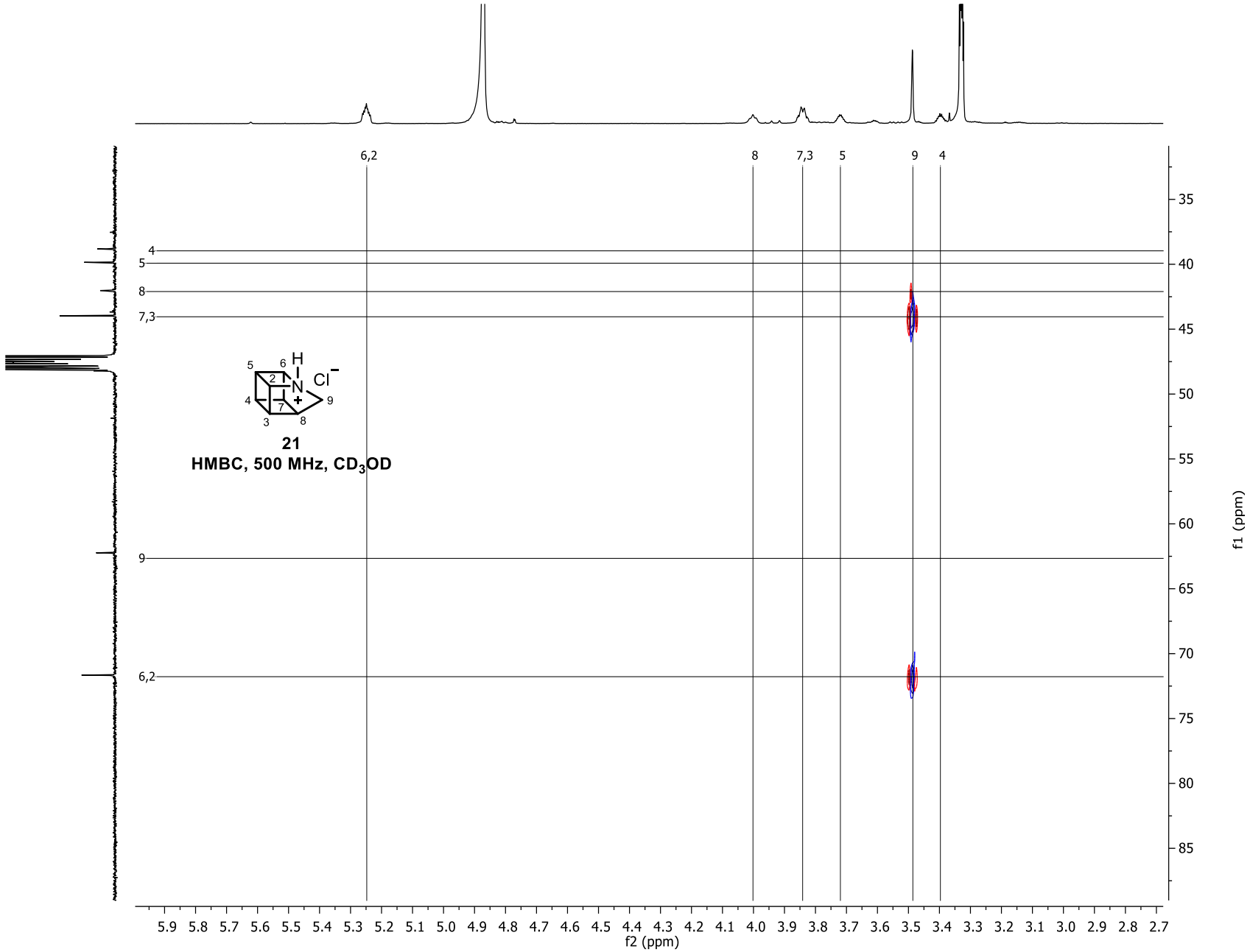


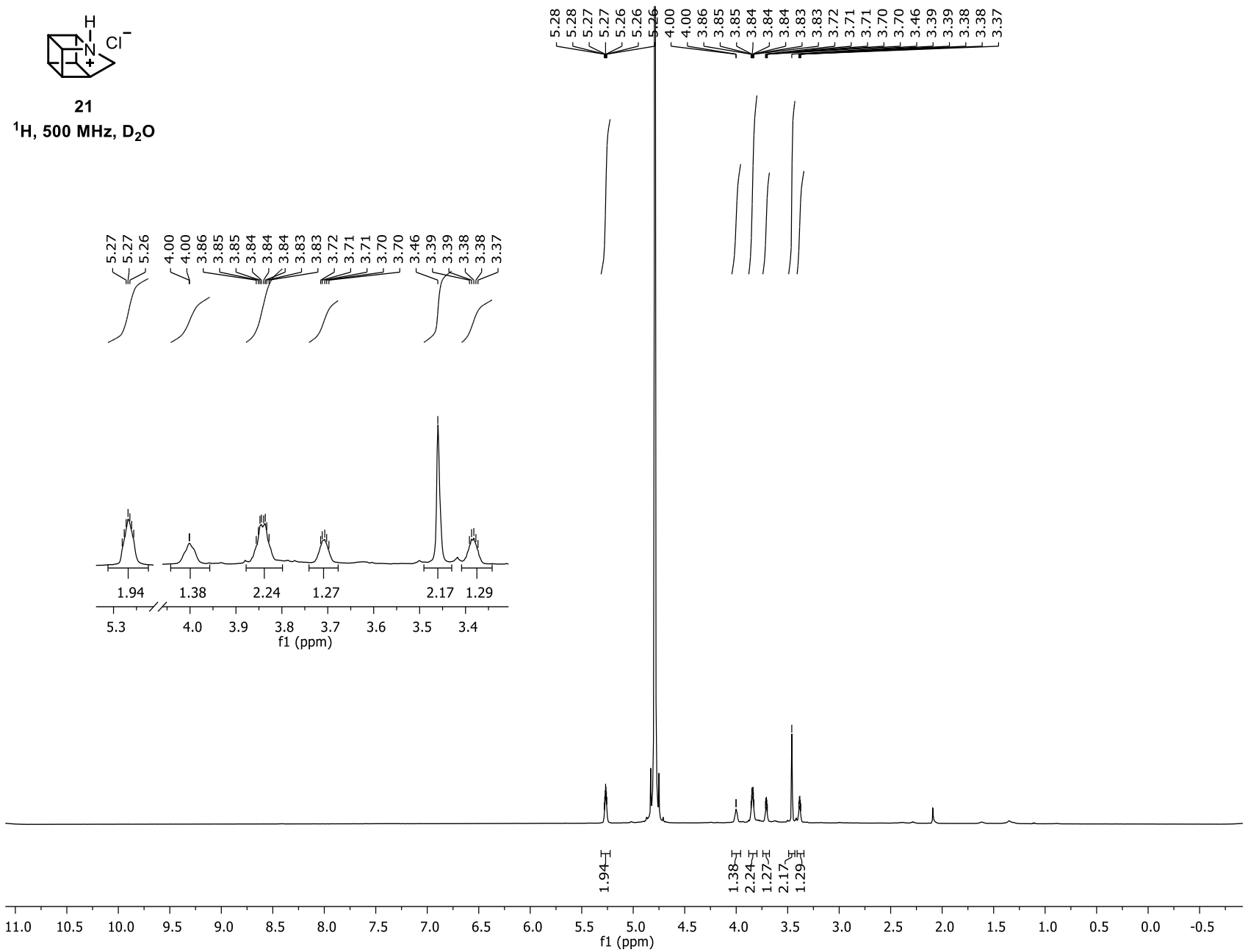
21

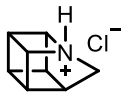
^{13}C, 125 MHz, CD_3OD


21
COSY, 500 MHz, CD3OD
6,2
8
7,3
5
9
4
4
9
5
7,3
8
6,2
f2 (ppm)
f1 (ppm)


21
HSQC, 500 MHz, CD3OD
6,2
8
7,3
5
9
4
f2 (ppm)
f1 (ppm)


6,2
8
7,3
5
9
4
4
5
8
7,3
9
6,2
21
HMBC, 500 MHz, CD3OD
f2 (ppm)
f1 (ppm)

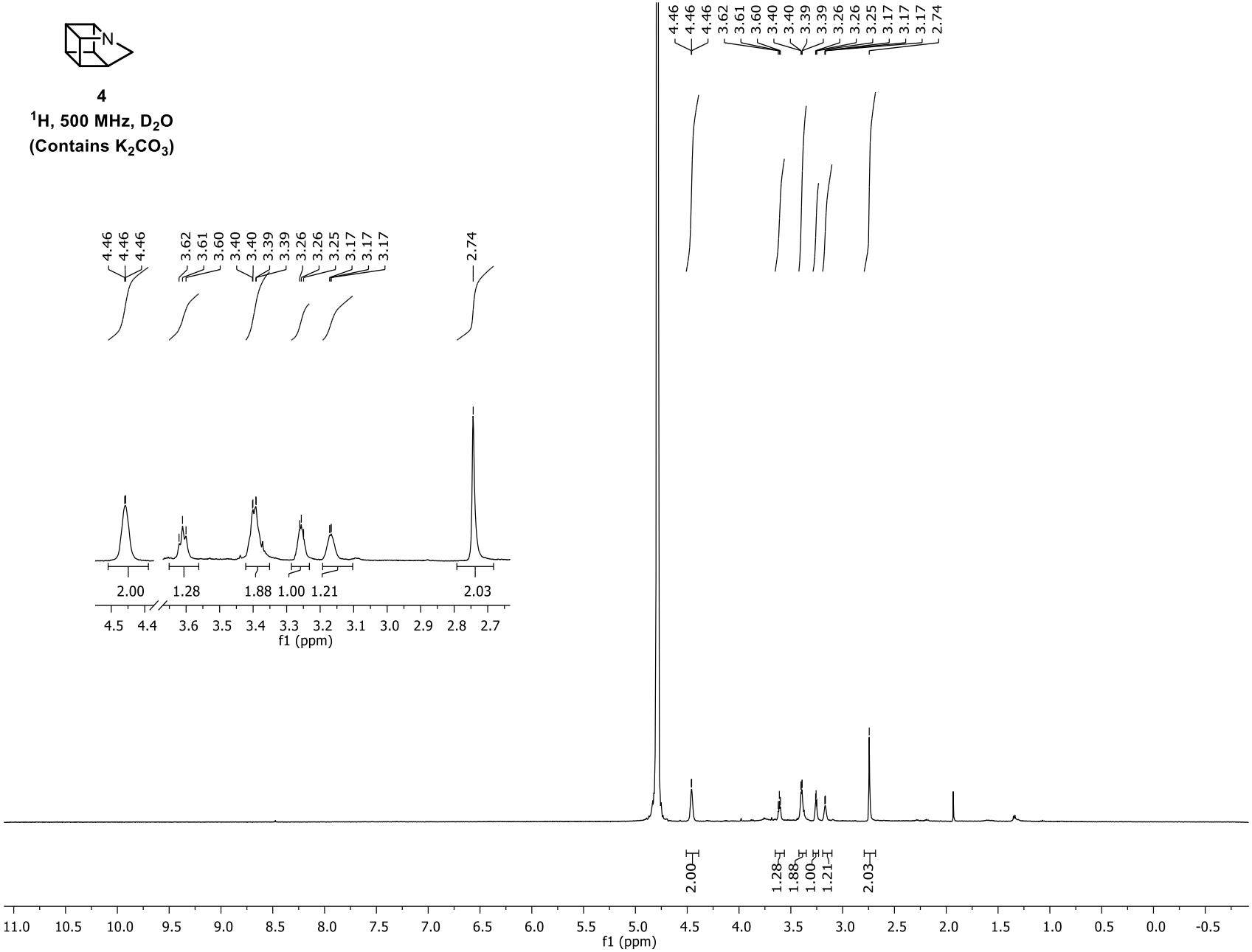

21
1H, 500 MHz, D2O
5.28 5.28 5.27 5.27 5.26 5.26 5.26 4.00 4.00 3.86 3.85 3.85 3.84 3.84 3.84 3.83 3.83 3.72 3.71 3.71 3.70 3.70 3.46 3.39 3.39 3.38 3.38 3.37
1.94 1.38 2.24 1.27 2.17 1.29
f1 (ppm)

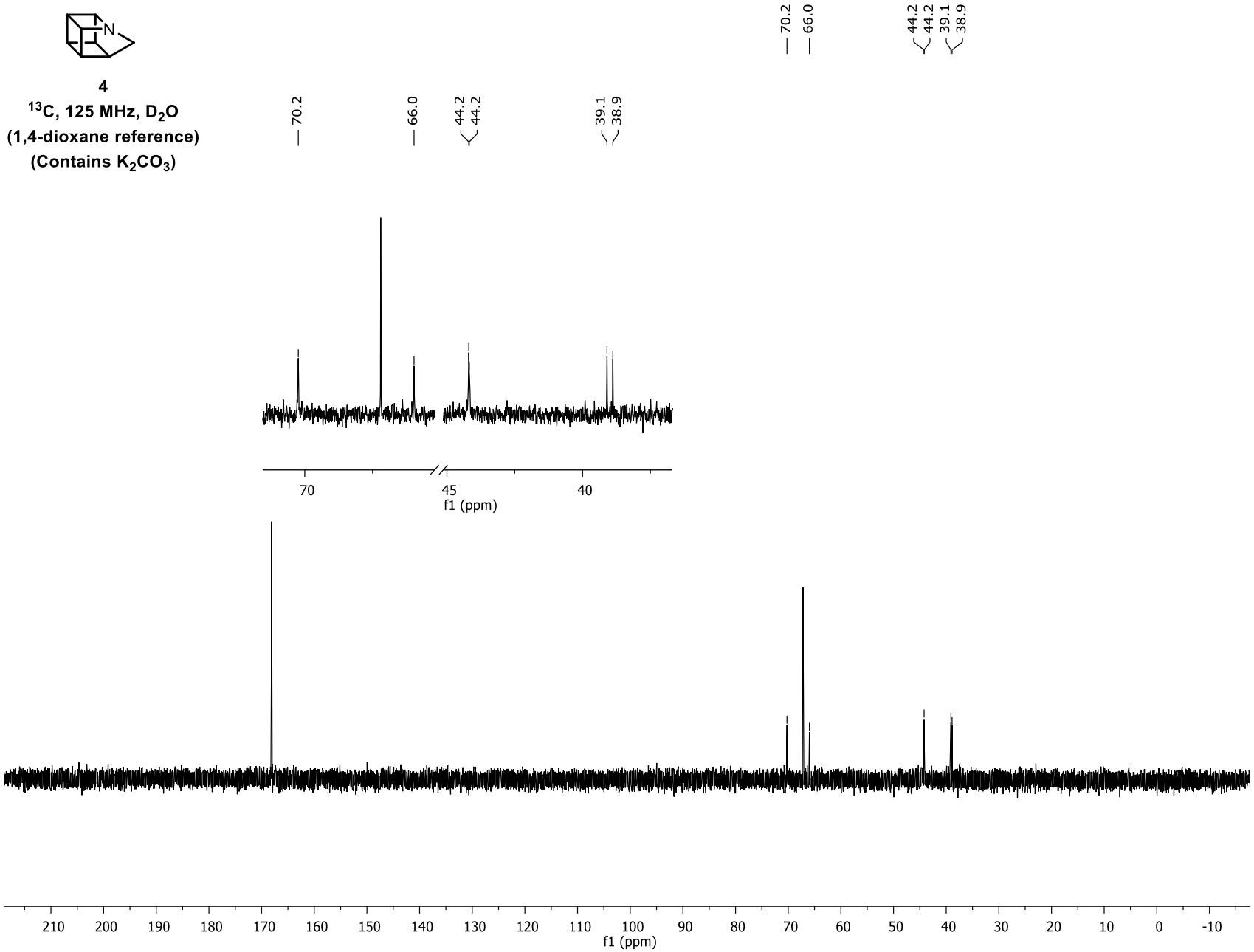


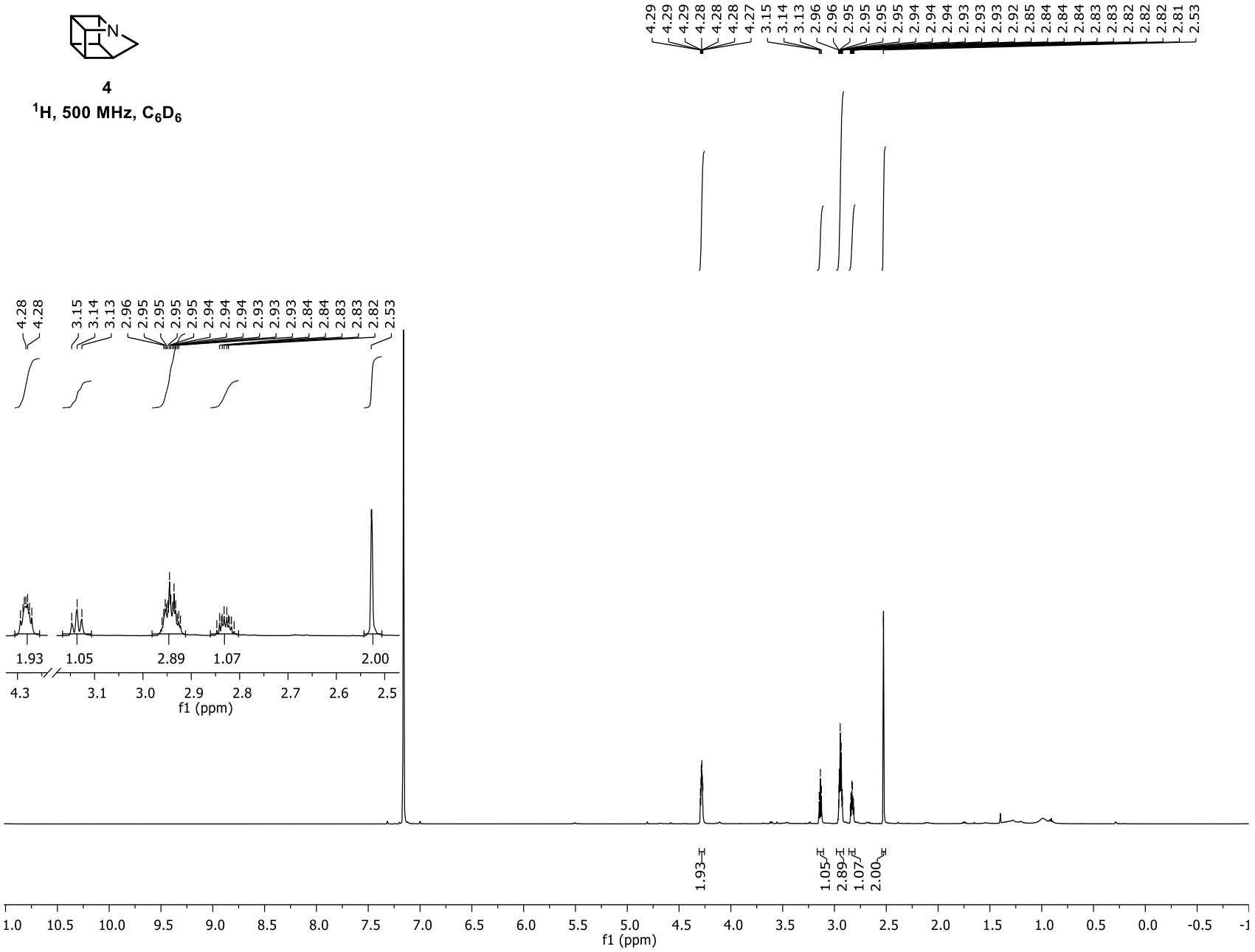
21

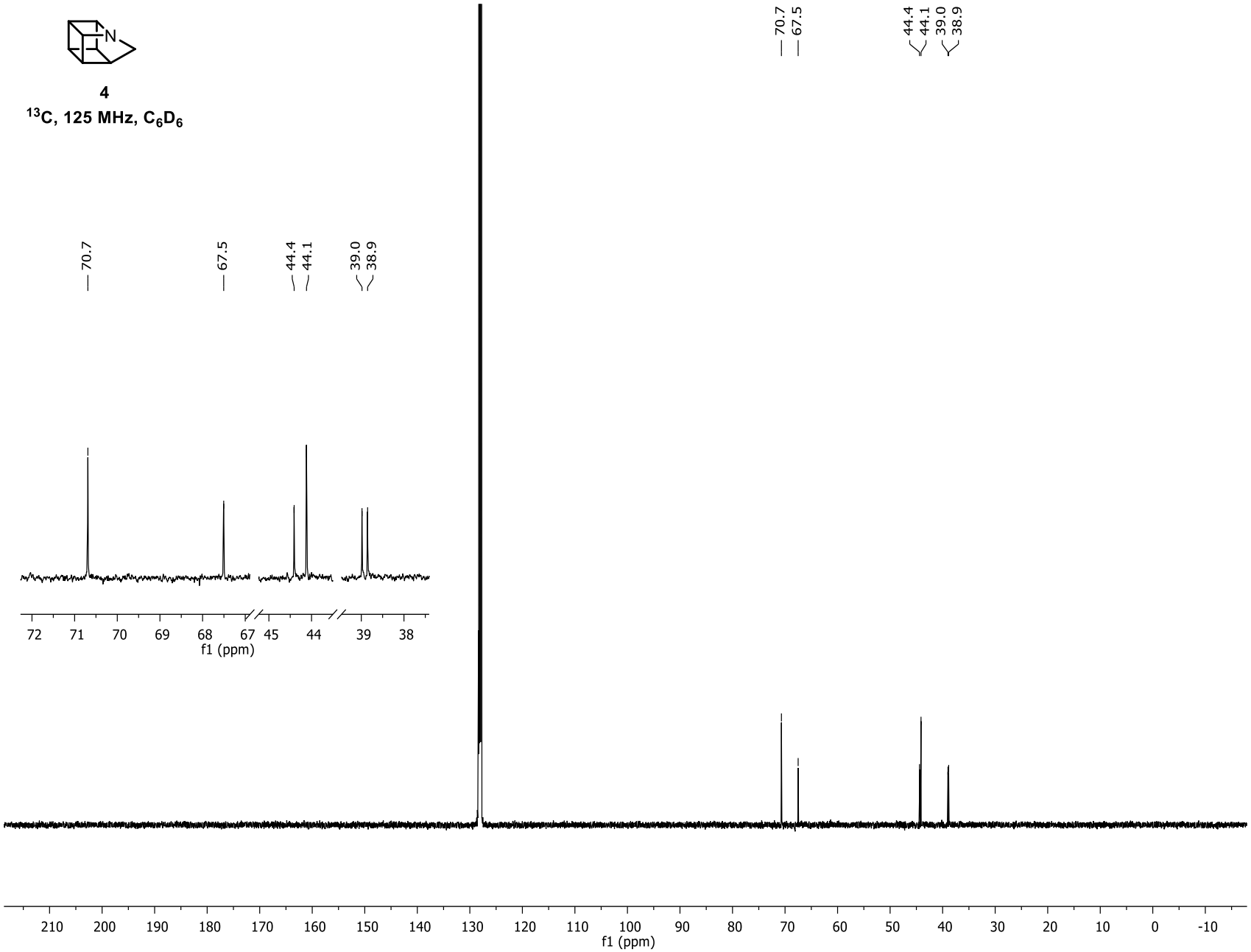
^{13}C, 125 MHz, D_2O

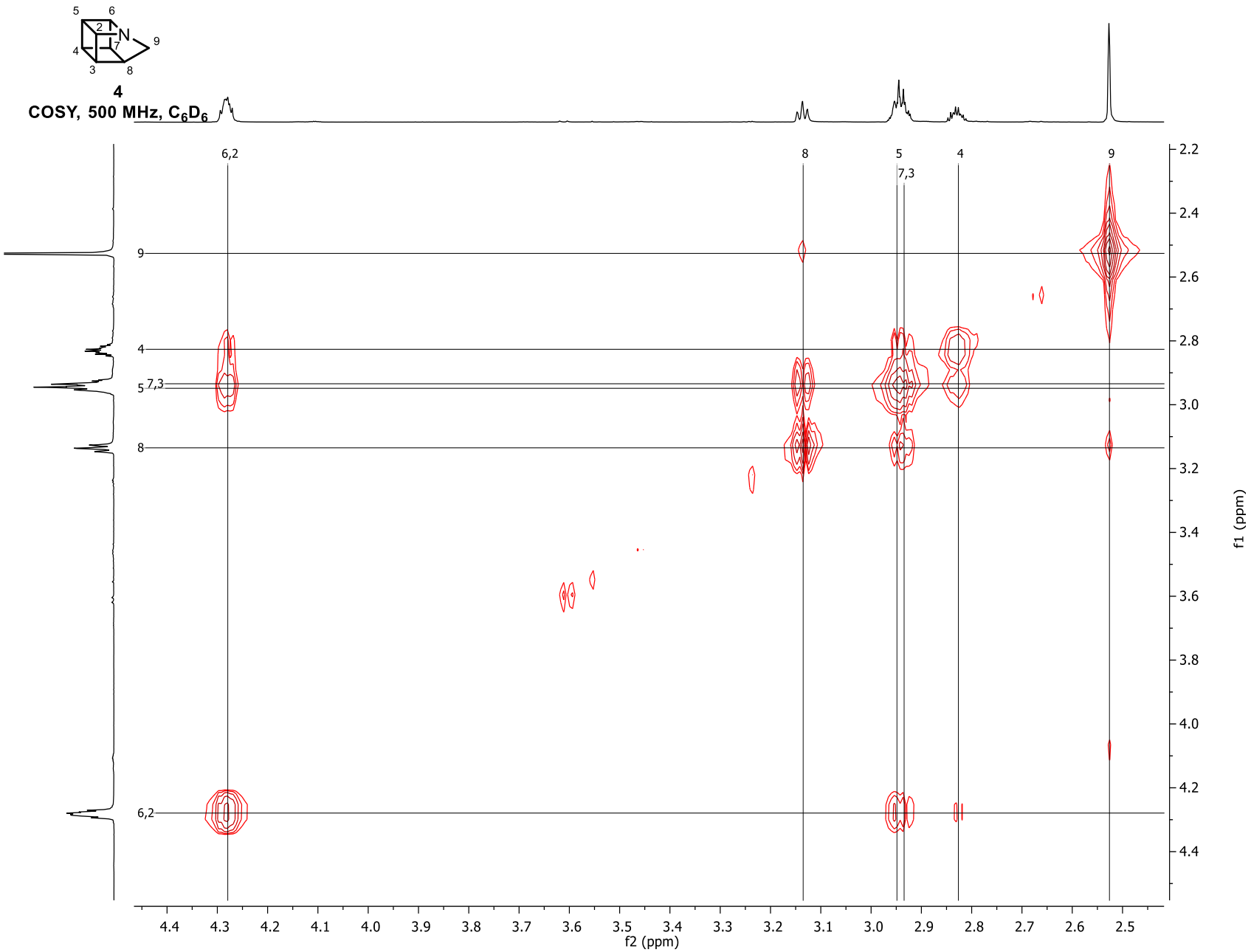
(1,4-dioxane reference)

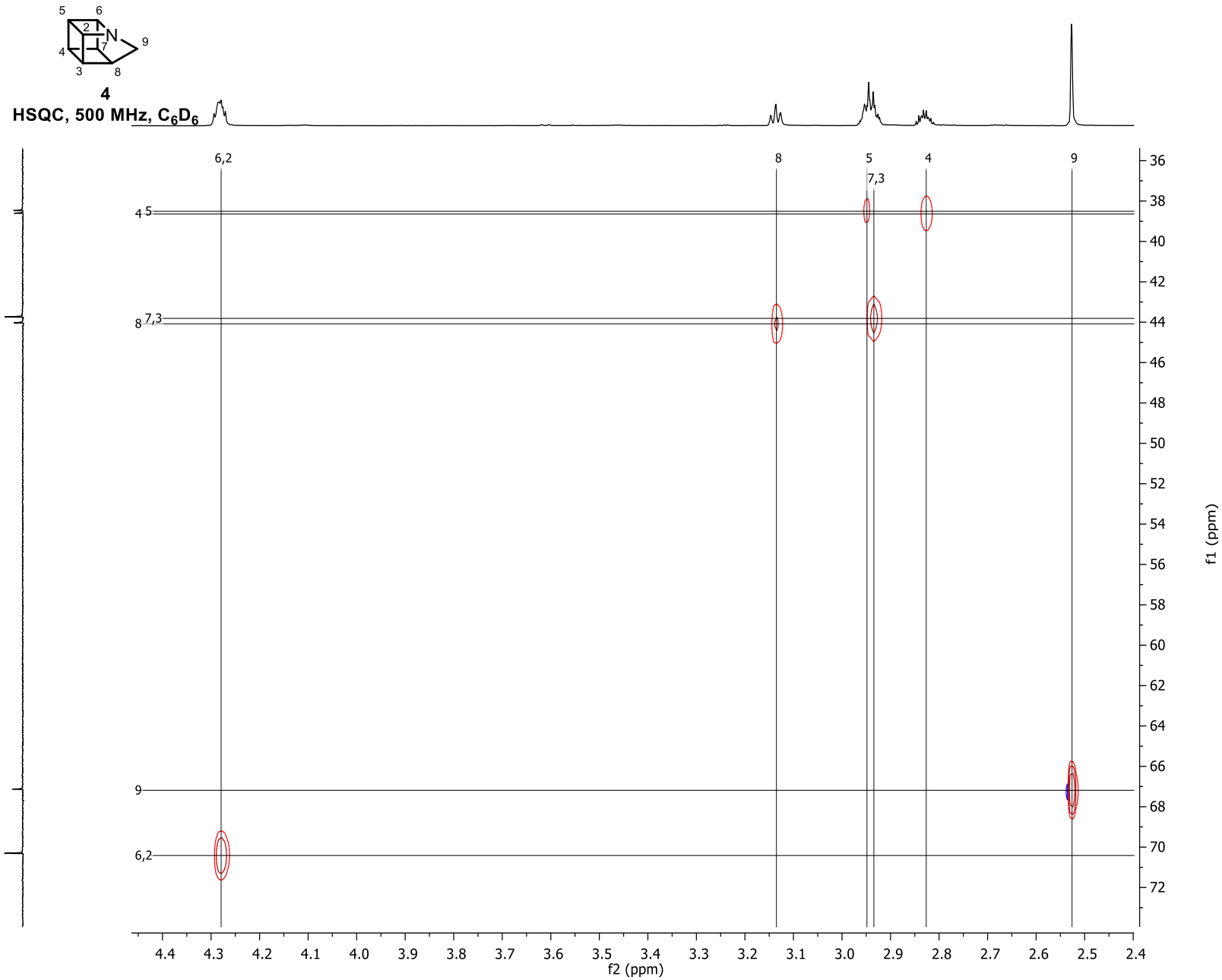

4
1H, 500 MHz, D2O
(Contains K2CO3)
4.46
4.46
4.46
3.62
3.61
3.60
3.40
3.40
3.39
3.39
3.26
3.25
3.17
3.17
3.17
2.74
2.00
1.28
1.88
1.00
1.21
2.03
f1 (ppm)

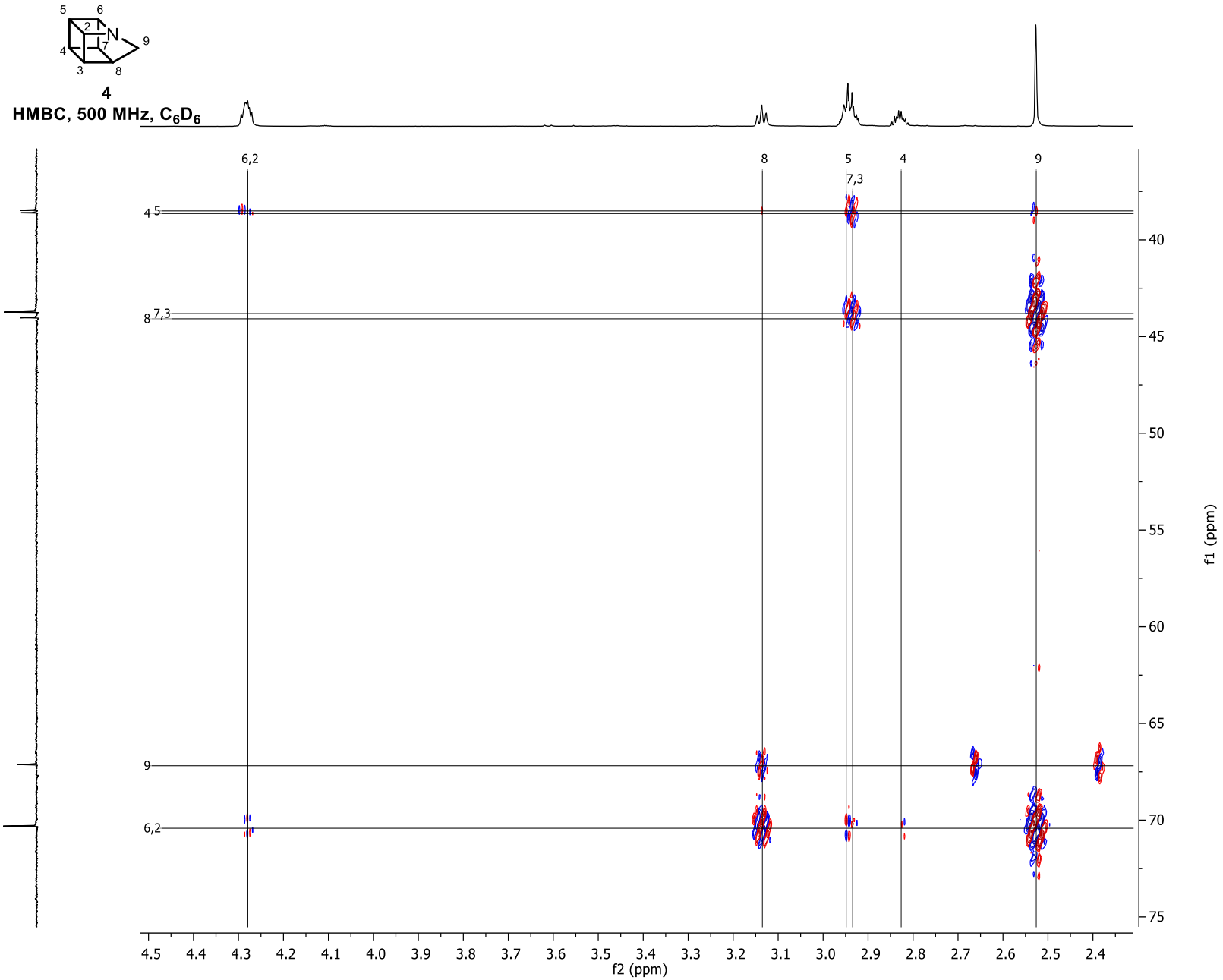

4
13C, 125 MHz, D2O
(1,4-dioxane reference)
(Contains K2CO3)
70.2
66.0
44.2
44.2
39.1
38.9
70
45
40
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

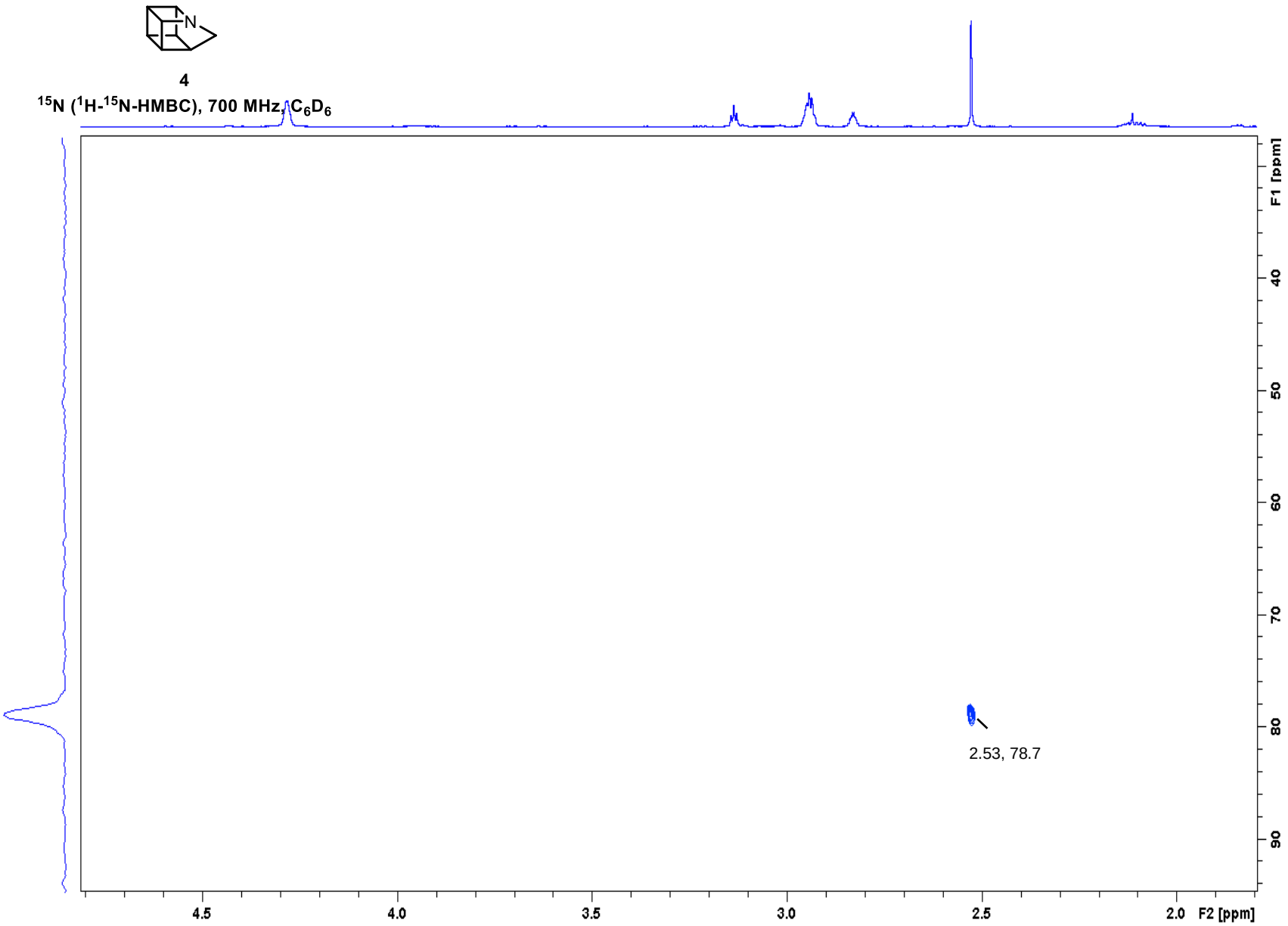

N
4
^{1}H, 500 MHz, C_6D_6
4.29 4.29 4.29 4.28 4.28 4.27 3.15 3.14 3.13 2.96 2.96 2.95 2.95 2.95 2.94 2.94 2.94 2.93 2.93 2.92 2.85 2.84 2.84 2.84 2.83 2.83 2.82 2.82 2.82 2.81 2.53
4.28 4.28 3.15 3.14 3.13 2.96 2.95 2.95 2.95 2.94 2.94 2.94 2.93 2.93 2.84 2.84 2.83 2.83 2.82 2.53
1.93 1.05 2.89 1.07 2.00
4.3 3.1 3.0 2.9 2.8 2.7 2.6 2.5
f1 (ppm)
1.93 1.05 2.89 1.07 2.00
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

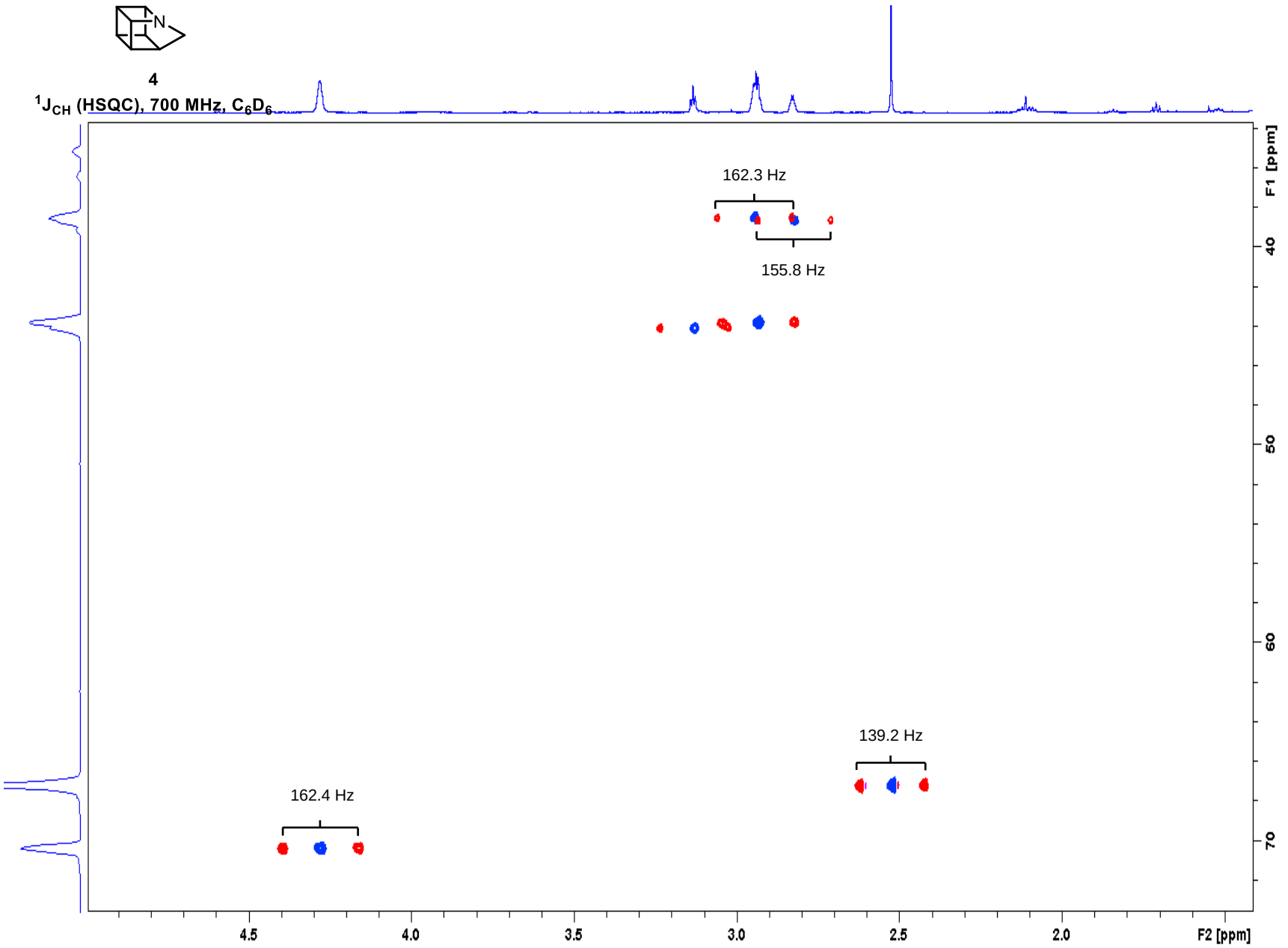

4
13C, 125 MHz, C6D6
70.7
67.5
44.4
44.1
39.0
38.9
f1 (ppm)

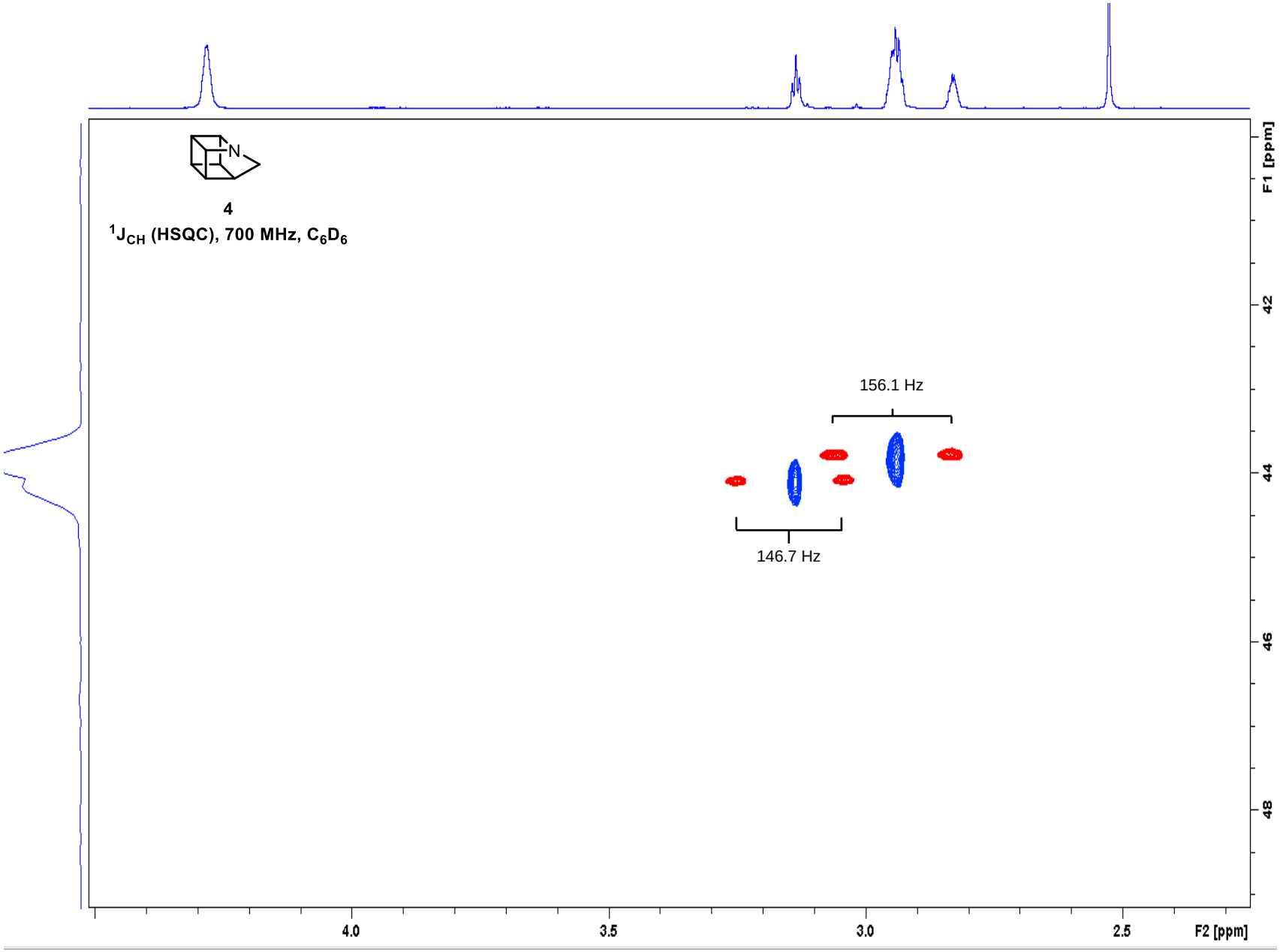

4
COSY, 500 MHz, C6D6
6,2
8
5
7,3
4
9
f2 (ppm)
f1 (ppm)

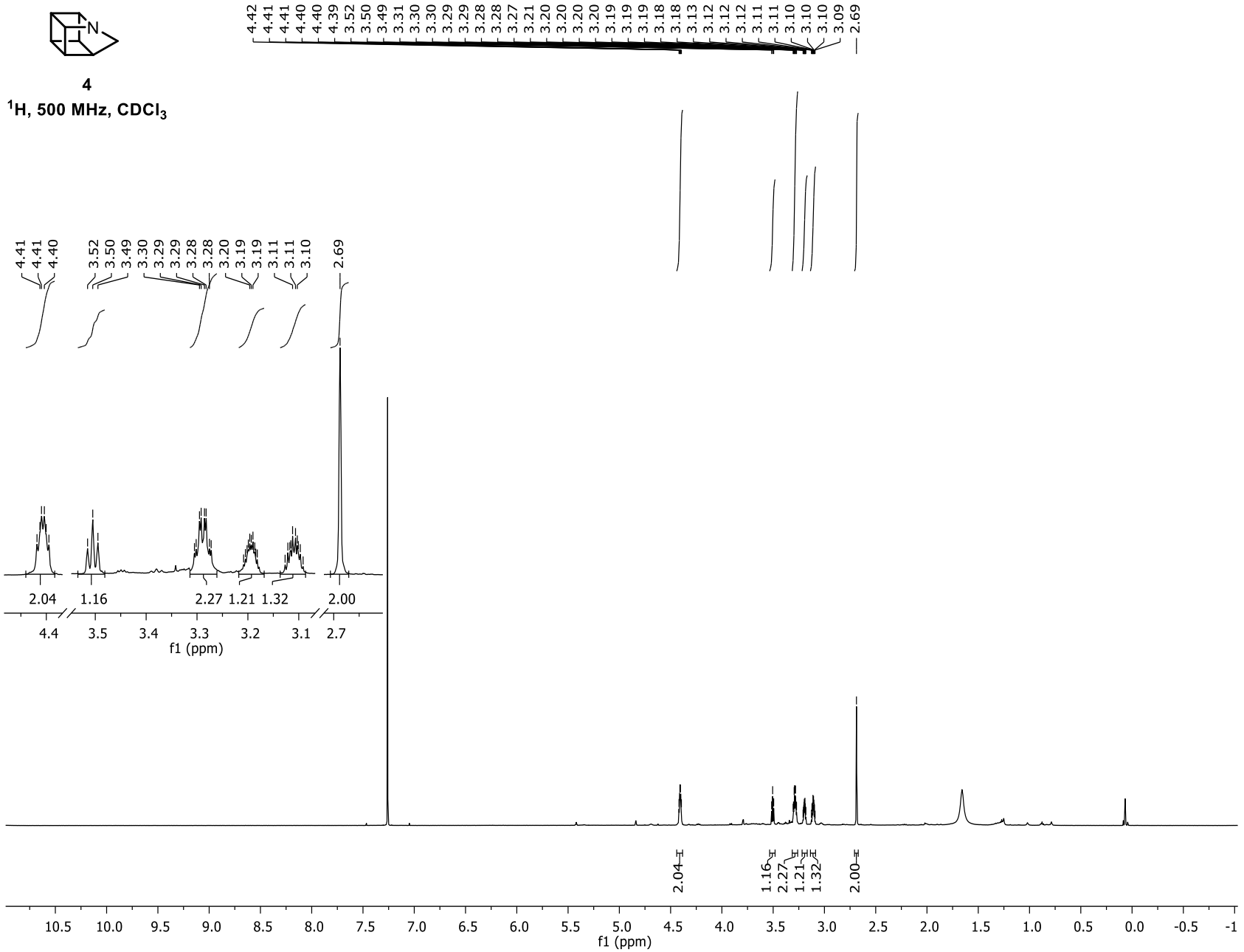

4
HSQC, 500 MHz, C6D6
6,2
8
5
7,3
4
9
4 5
8 7,3
9
6,2
f2 (ppm)
f1 (ppm)

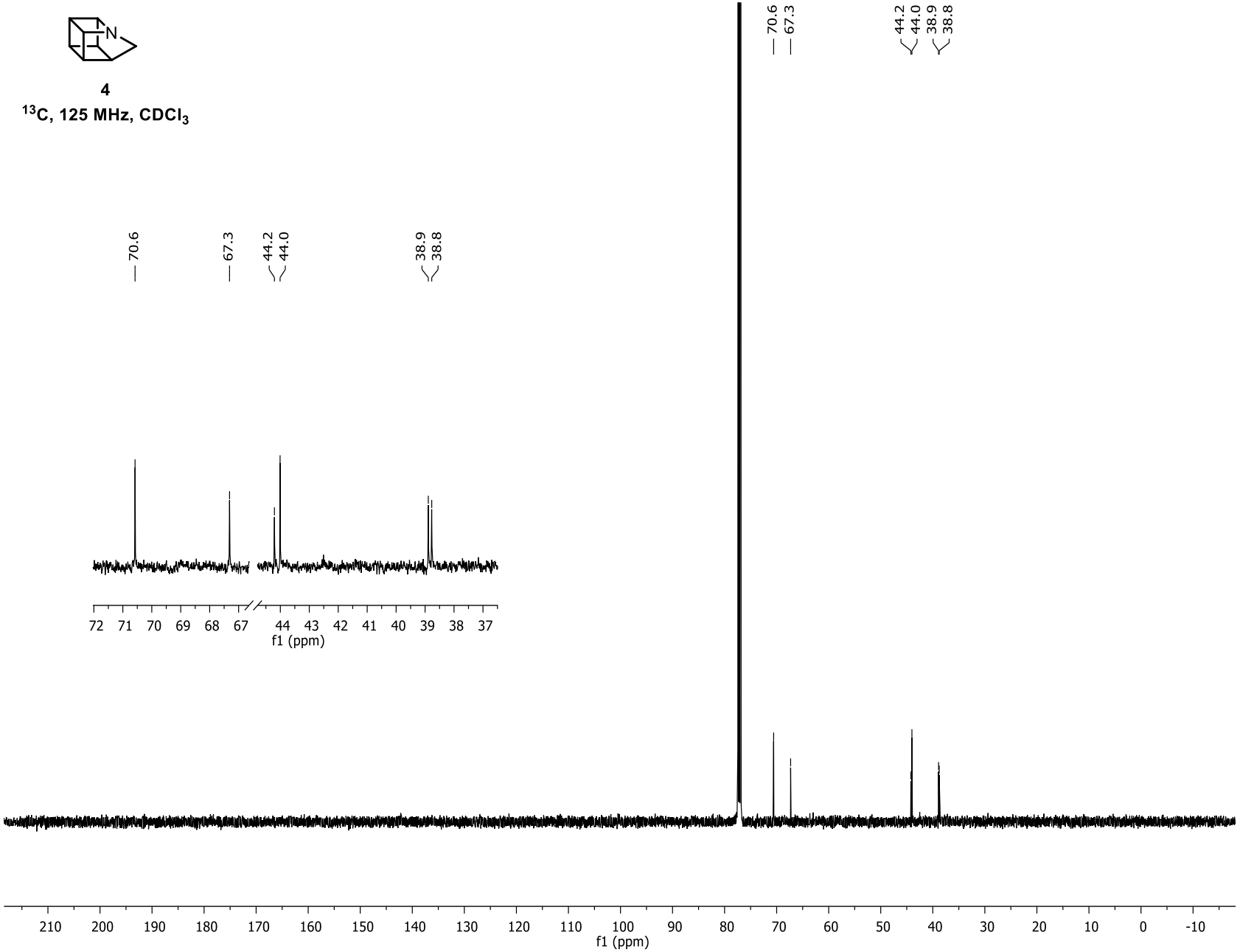

5 6
2
N
4
7
9
3 8
4
HMBC, 500 MHz, C6D6
6,2
8
5
7,3
4
9
4 5
8 7,3
9
6,2
40
45
50
55
60
65
70
75
f1 (ppm)
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4
f2 (ppm)

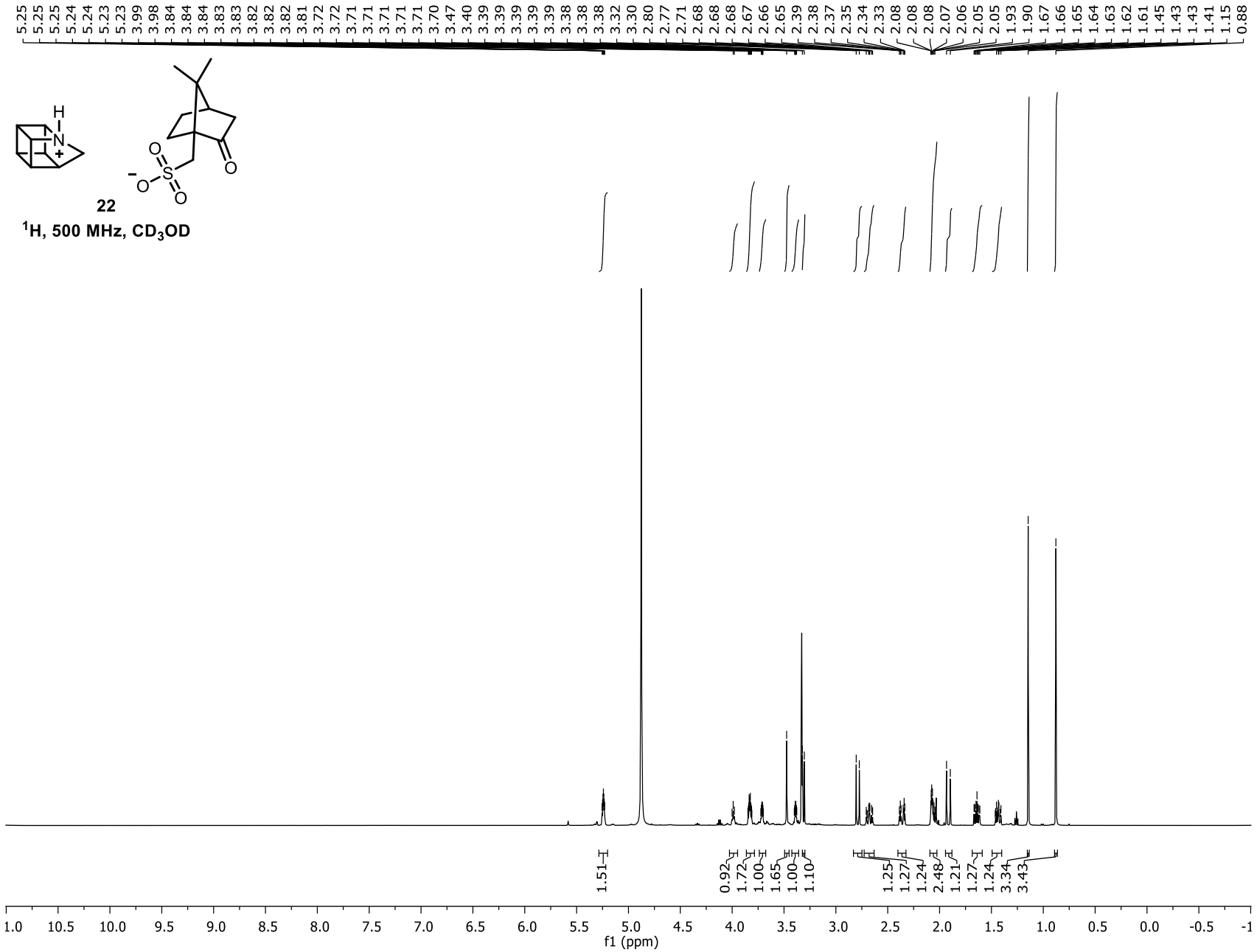

4
15N (1H-15N-HMBC), 700 MHz, C6D6
2.53, 78.7
F1 [ppm]
40
50
60
70
80
90
4.5
4.0
3.5
3.0
2.5
2.0
F2 [ppm]

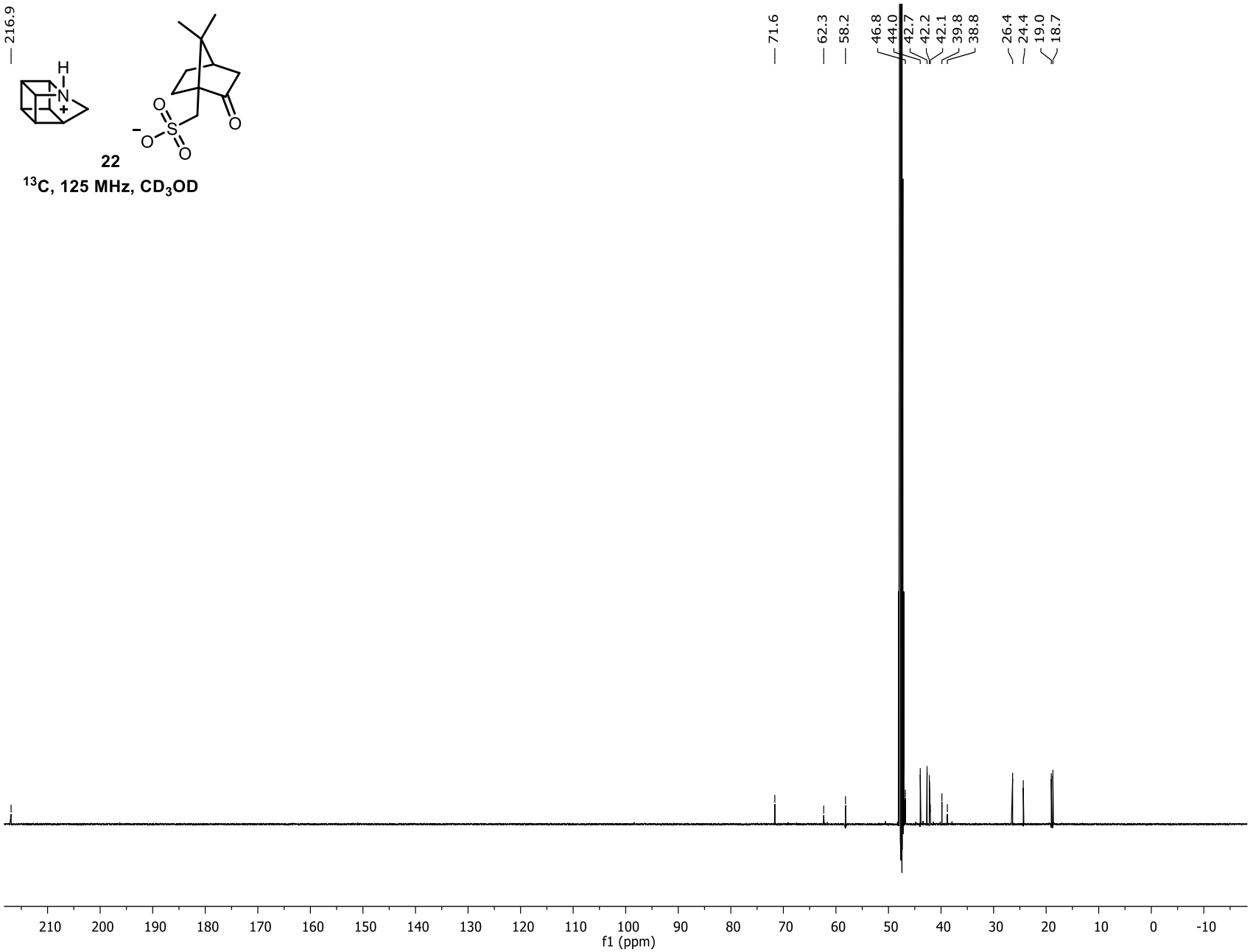

N
4
$^{1}J_{CH}$ (HSQC), 700 MHz, C_6D_6
162.3 Hz
155.8 Hz
139.2 Hz
162.4 Hz
F1 [ppm]
40
50
60
70
4.5
4.0
3.5
3.0
2.5
2.0
F2 [ppm]


N
4
$^{1}J_{CH}$ (HSQC), 700 MHz, C_6D_6
156.1 Hz
146.7 Hz
F1 [ppm]
42
44
46
48
4.0
3.5
3.0
2.5
F2 [ppm]


4
1H, 500 MHz, CDCl3
4.42 4.41 4.41 4.40 4.40 4.39 3.52 3.50 3.49 3.31 3.30 3.30 3.29 3.29 3.28 3.28 3.27 3.21 3.20 3.20 3.20 3.20 3.19 3.19 3.18 3.18 3.13 3.12 3.12 3.12 3.11 3.11 3.10 3.10 3.10 3.09 2.69
4.41 4.41 4.40 3.52 3.50 3.49 3.30 3.29 3.29 3.28 3.28 3.20 3.19 3.19 3.11 3.11 3.10 2.69
2.04 1.16 2.27 1.21 1.32 2.00
4.4 3.5 3.4 3.3 3.2 3.1 2.7
f1 (ppm)
2.04 1.16 2.27 1.21 1.32 2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

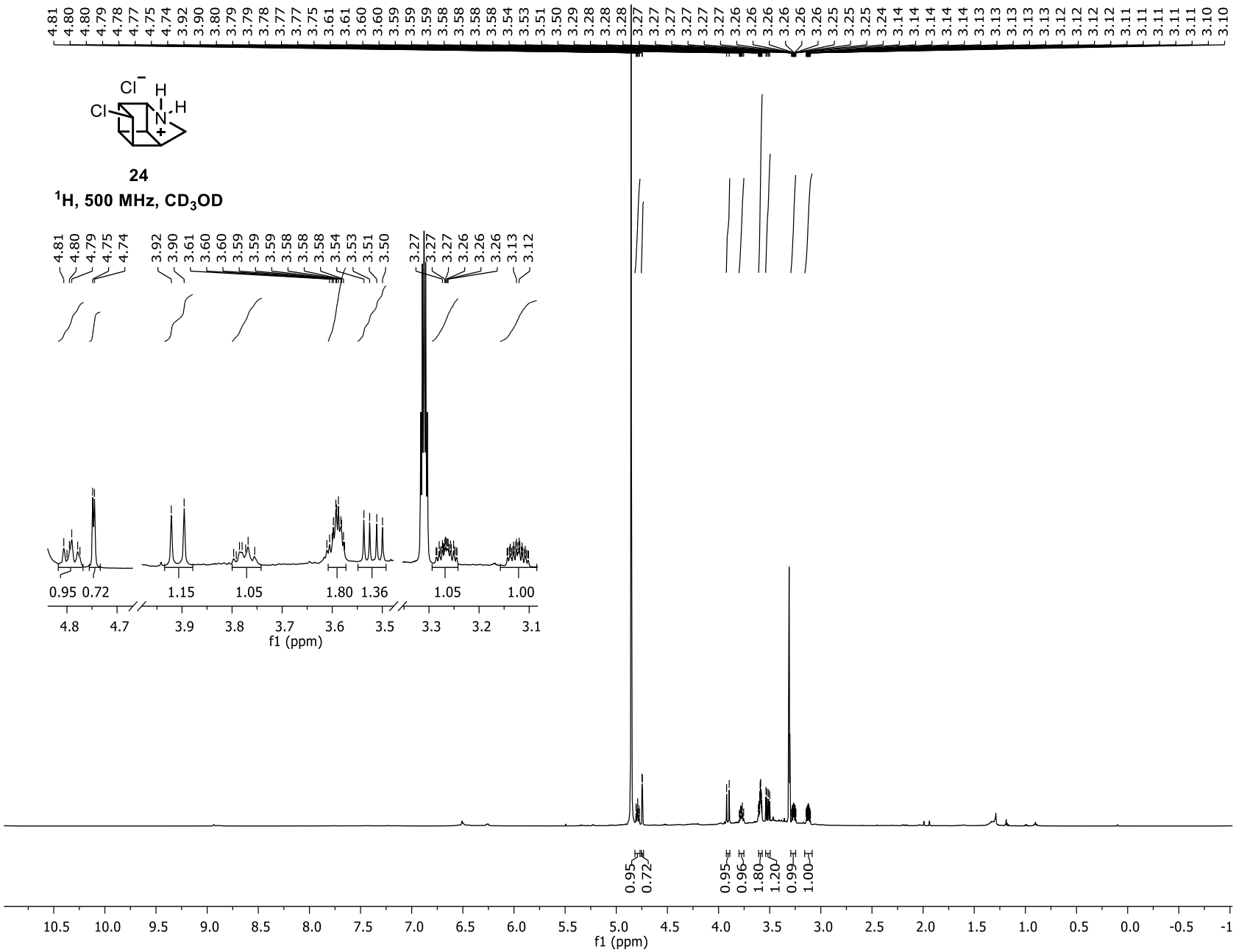

4
13C, 125 MHz, CDCl3
70.6
67.3
44.2
44.0
38.9
38.8
f1 (ppm)

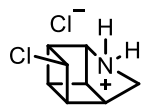

5.25 5.25 5.25 5.24 5.24 5.23 5.23 3.99 3.98 3.84 3.84 3.84 3.83 3.83 3.82 3.82 3.82 3.81 3.72 3.72 3.71 3.71 3.71 3.71 3.70 3.47 3.40 3.39 3.39 3.39 3.39 3.39 3.38 3.38 3.38 3.32 3.30 2.80 2.77 2.71 2.68 2.68 2.67 2.66 2.65 2.39 2.38 2.37 2.35 2.34 2.33 2.08 2.08 2.08 2.07 2.06 2.05 2.05 1.93 1.90 1.67 1.66 1.65 1.64 1.63 1.62 1.61 1.45 1.43 1.43 1.41 1.15 0.88
22
1H, 500 MHz, CD3OD
1.51 0.92 1.72 1.00 1.65 1.00 1.10 1.25 1.27 1.24 2.48 1.21 1.27 1.24 3.34 3.43
f1 (ppm)



22

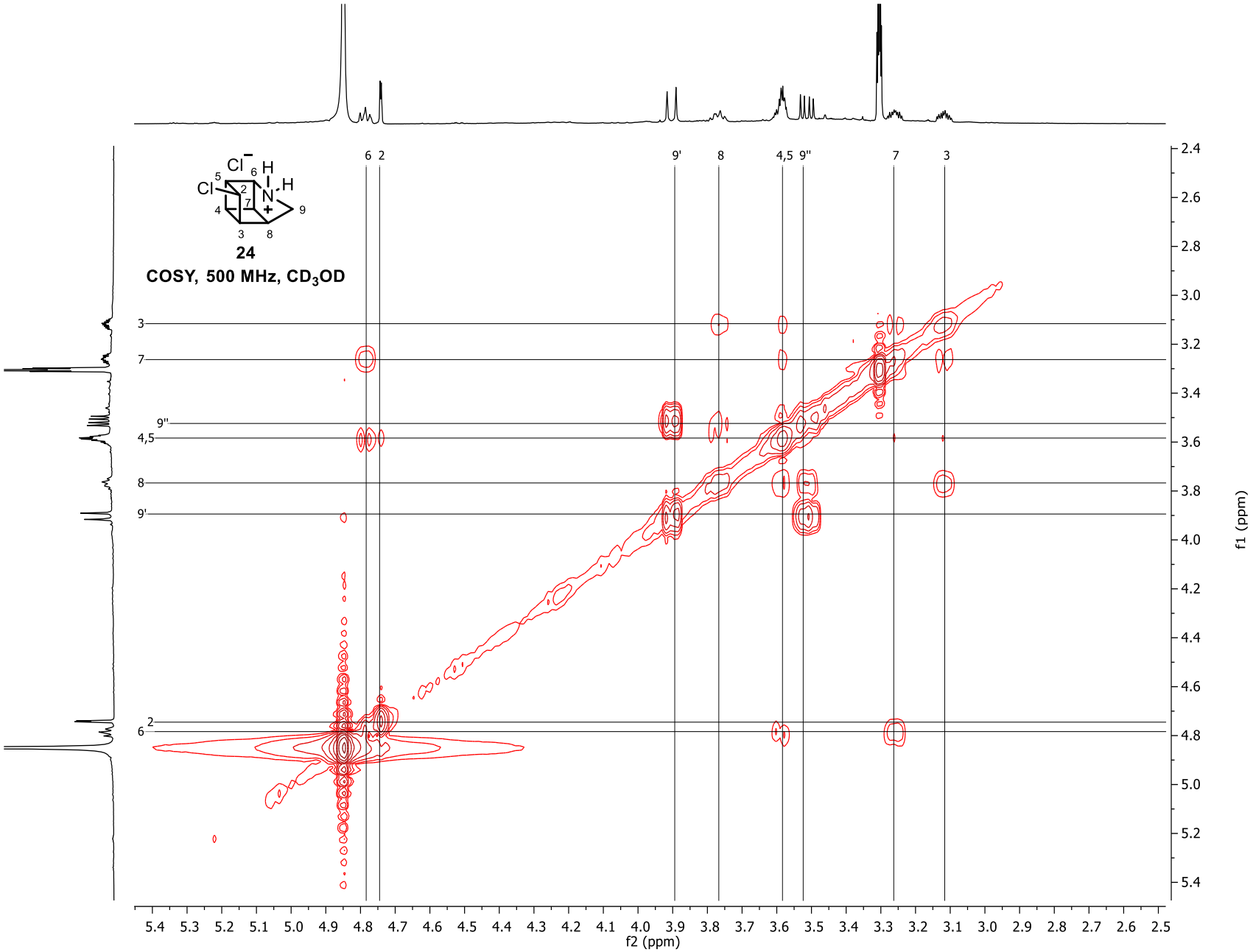
^{13}C, 125 MHz, CD_3OD

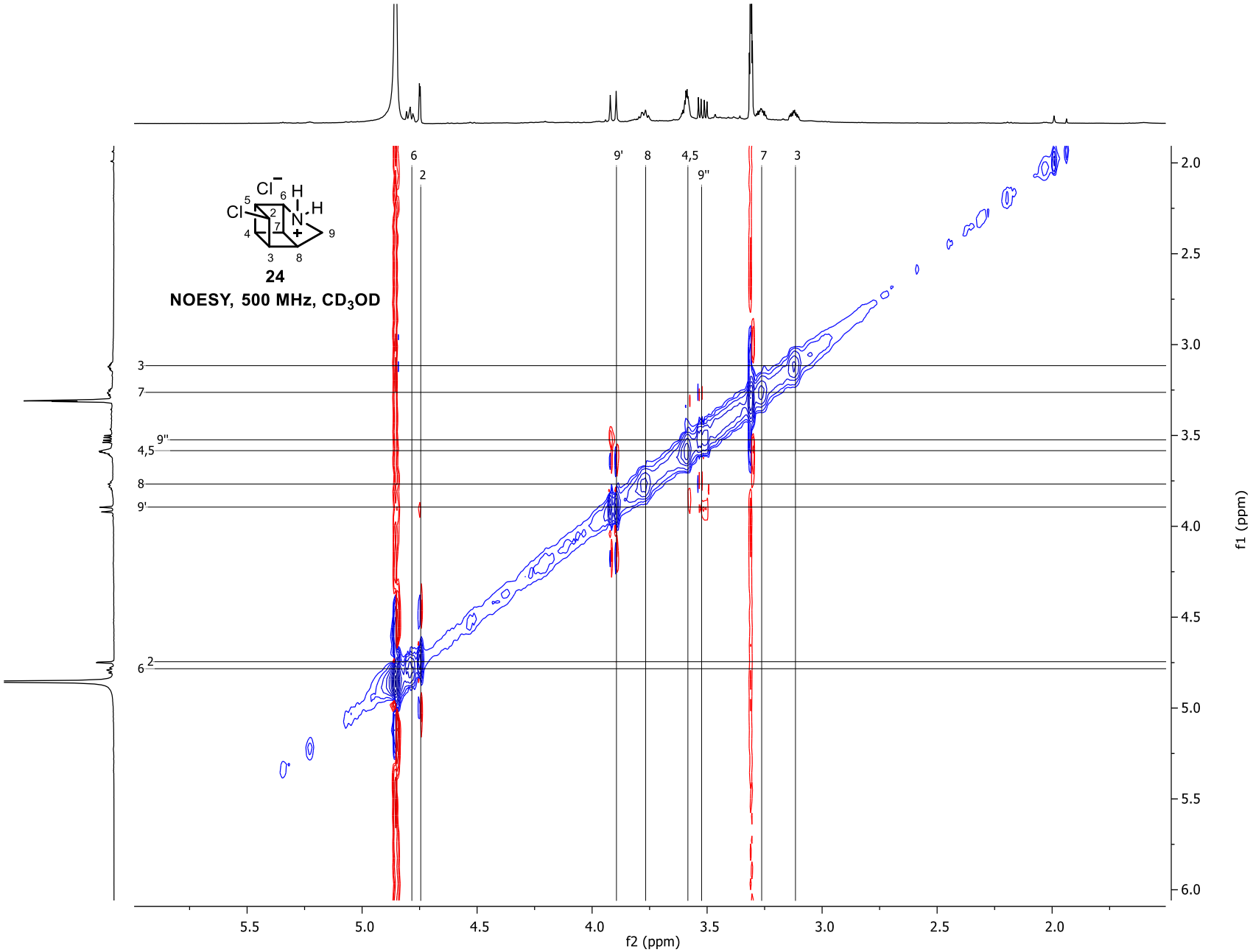

Cl⁻
H
Cl
N
H
+
24
¹H, 500 MHz, CD3OD
4.81 4.80 4.80 4.79 4.78 4.77 4.75 4.74 3.92 3.90 3.80 3.79 3.79 3.78 3.77 3.77 3.75 3.61 3.61 3.60 3.60 3.59 3.59 3.59 3.58 3.58 3.58 3.54 3.53 3.51 3.50 3.29 3.28 3.28 3.27 3.27 3.27 3.27 3.27 3.27 3.26 3.26 3.26 3.26 3.25 3.25 3.25 3.24 3.14 3.14 3.14 3.14 3.13 3.13 3.13 3.13 3.12 3.12 3.12 3.11 3.11 3.11 3.11 3.10 3.10
0.95 0.72 1.15 1.05 1.80 1.36 1.05 1.00
4.8 4.7 3.9 3.8 3.7 3.6 3.5 3.3 3.2 3.1
f1 (ppm)
0.95 0.72 0.95 0.96 1.80 1.20 0.99 1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

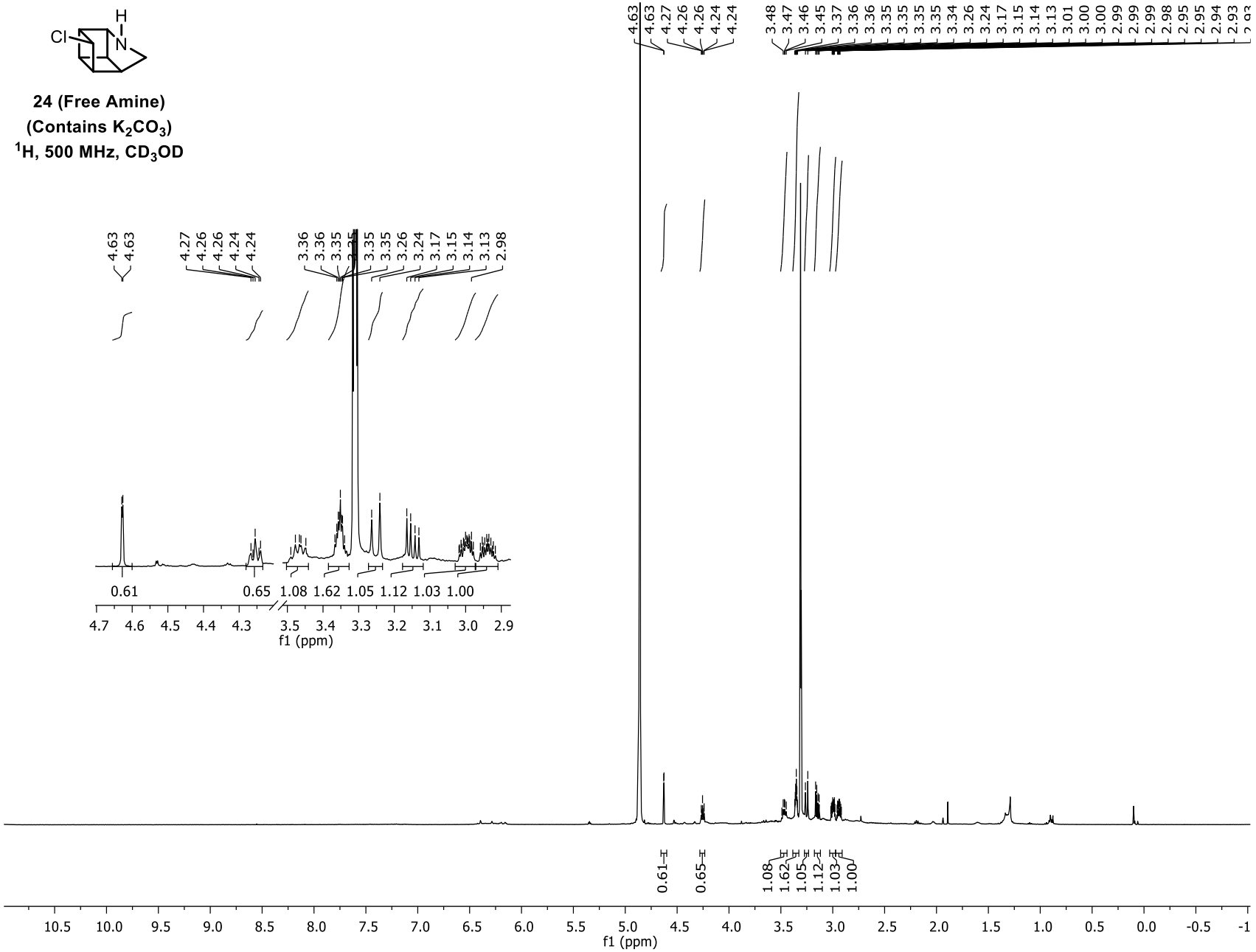


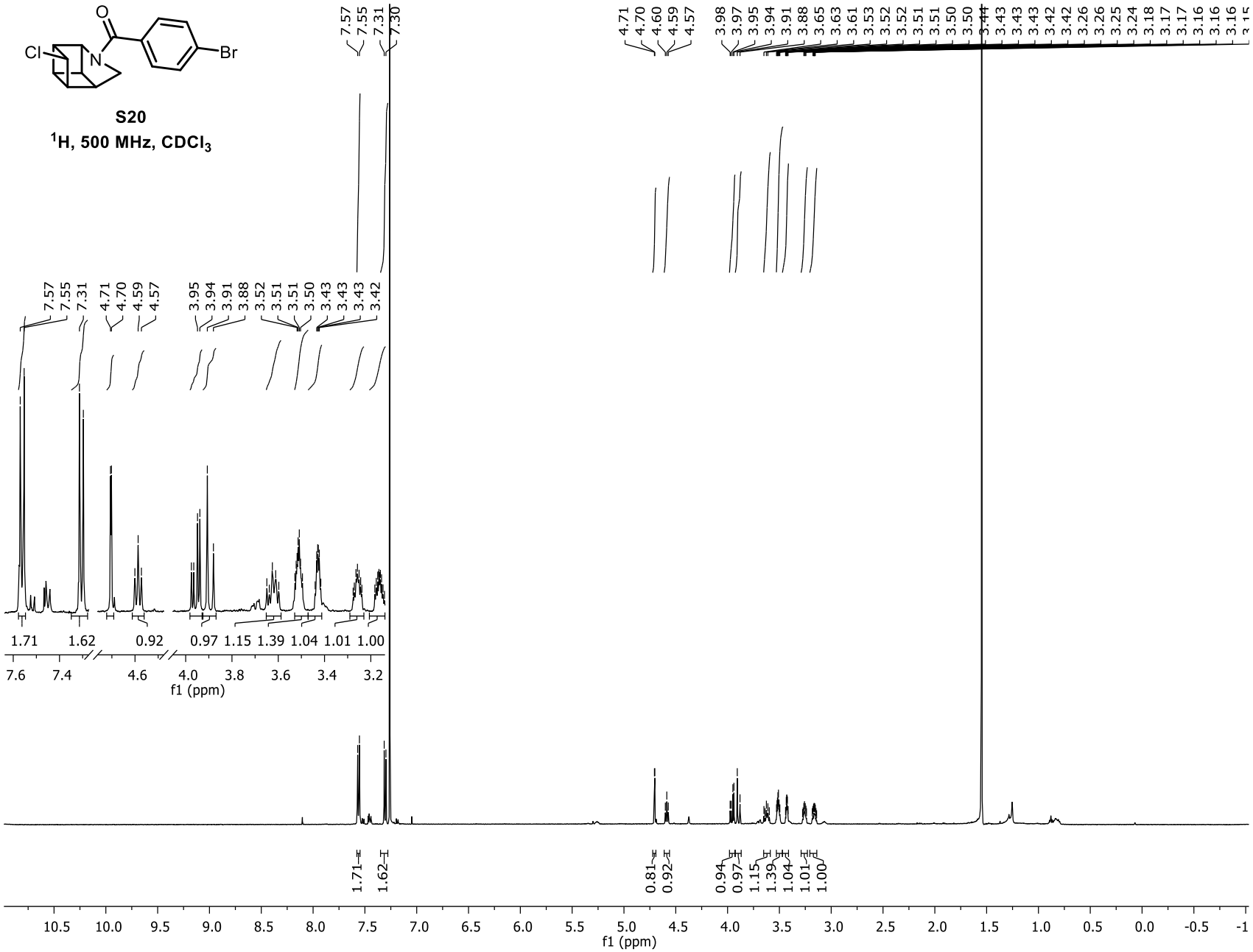
24

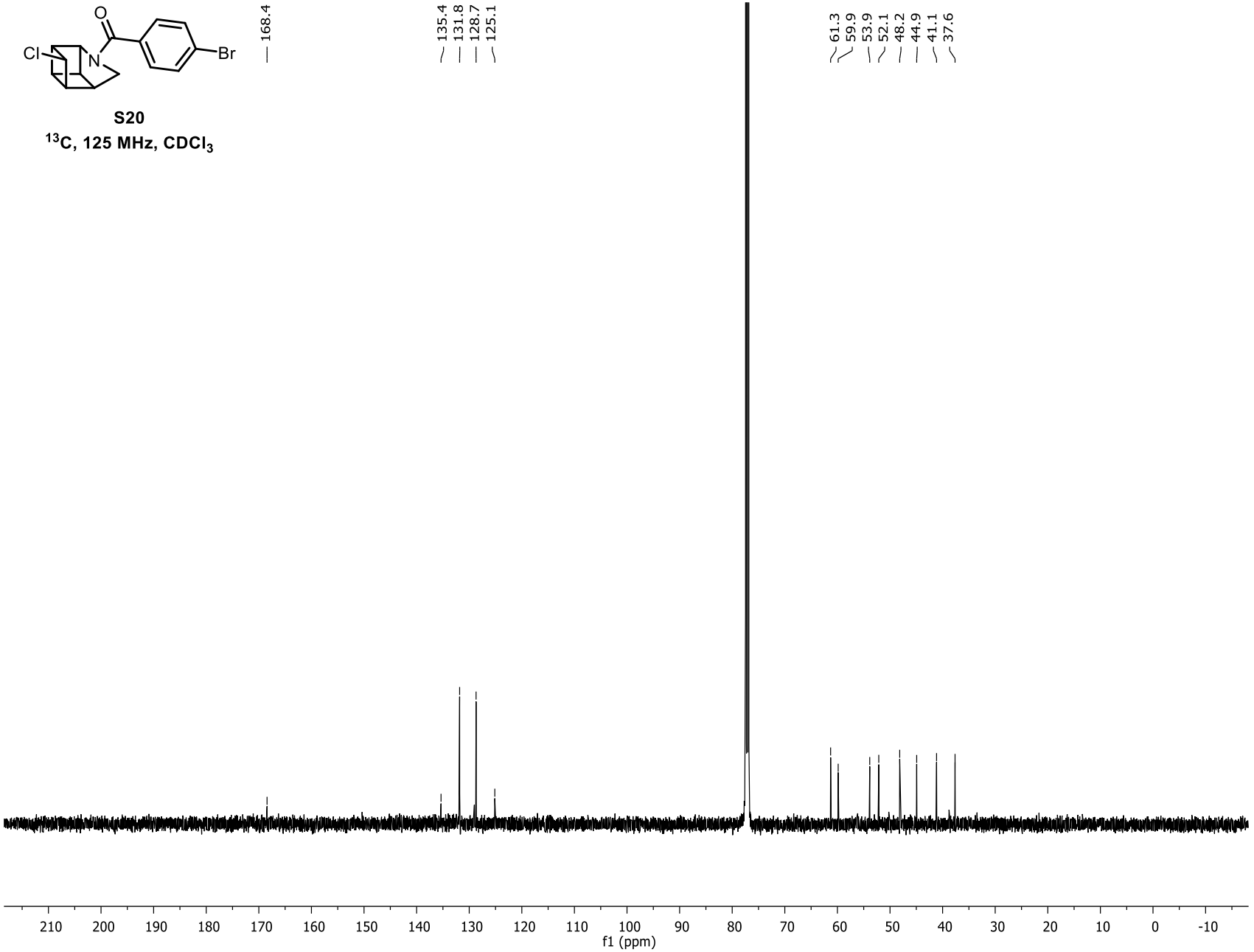
^{13}C, 125 MHz, CD_3OD


24
COSY, 500 MHz, CD3OD
f2 (ppm)
f1 (ppm)


24
NOESY, 500 MHz, CD3OD
f2 (ppm)
f1 (ppm)

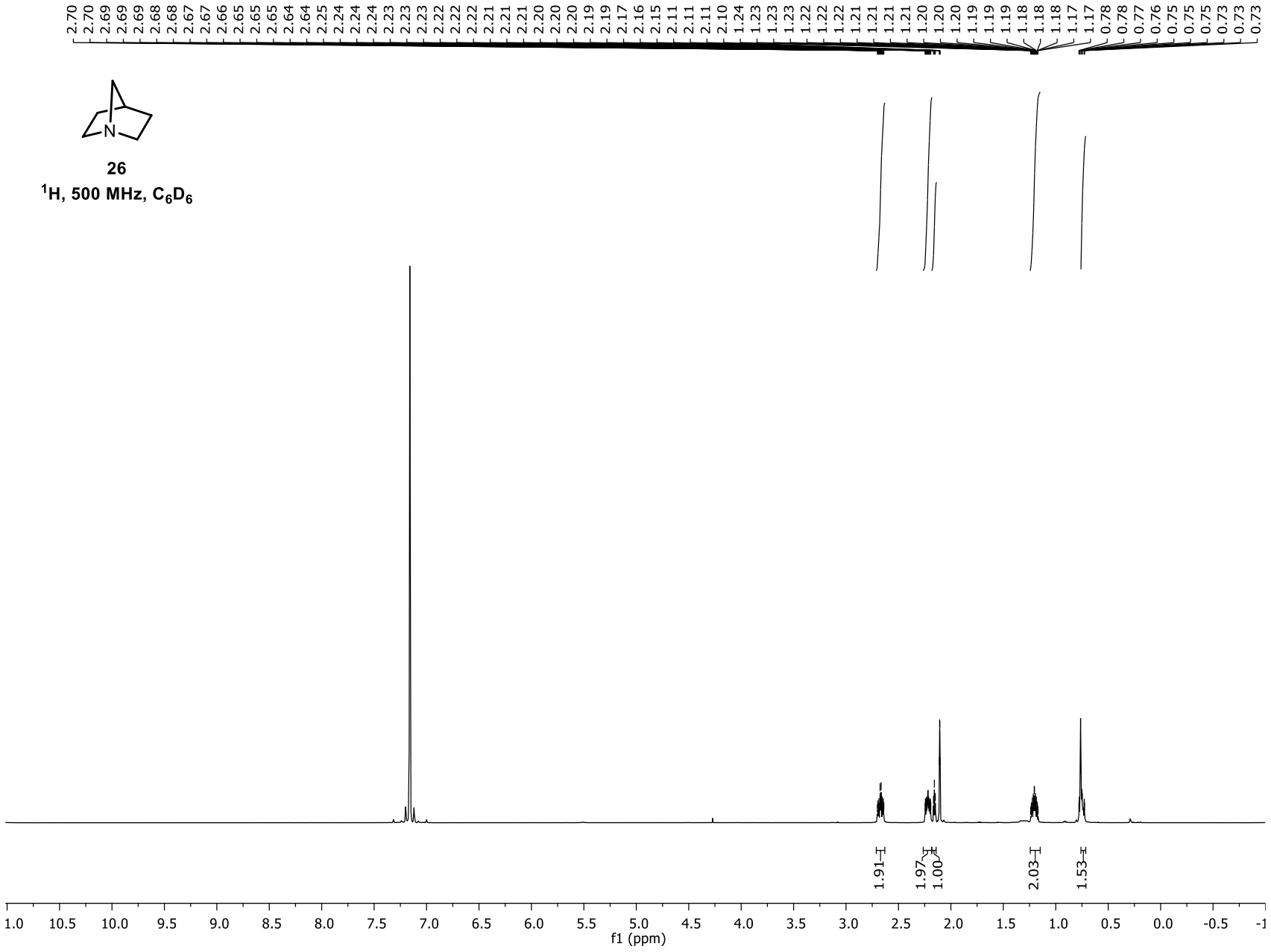

24 (Free Amine)
(Contains K_2CO_3)
^{1}H, 500 MHz, CD_3OD
f1 (ppm)

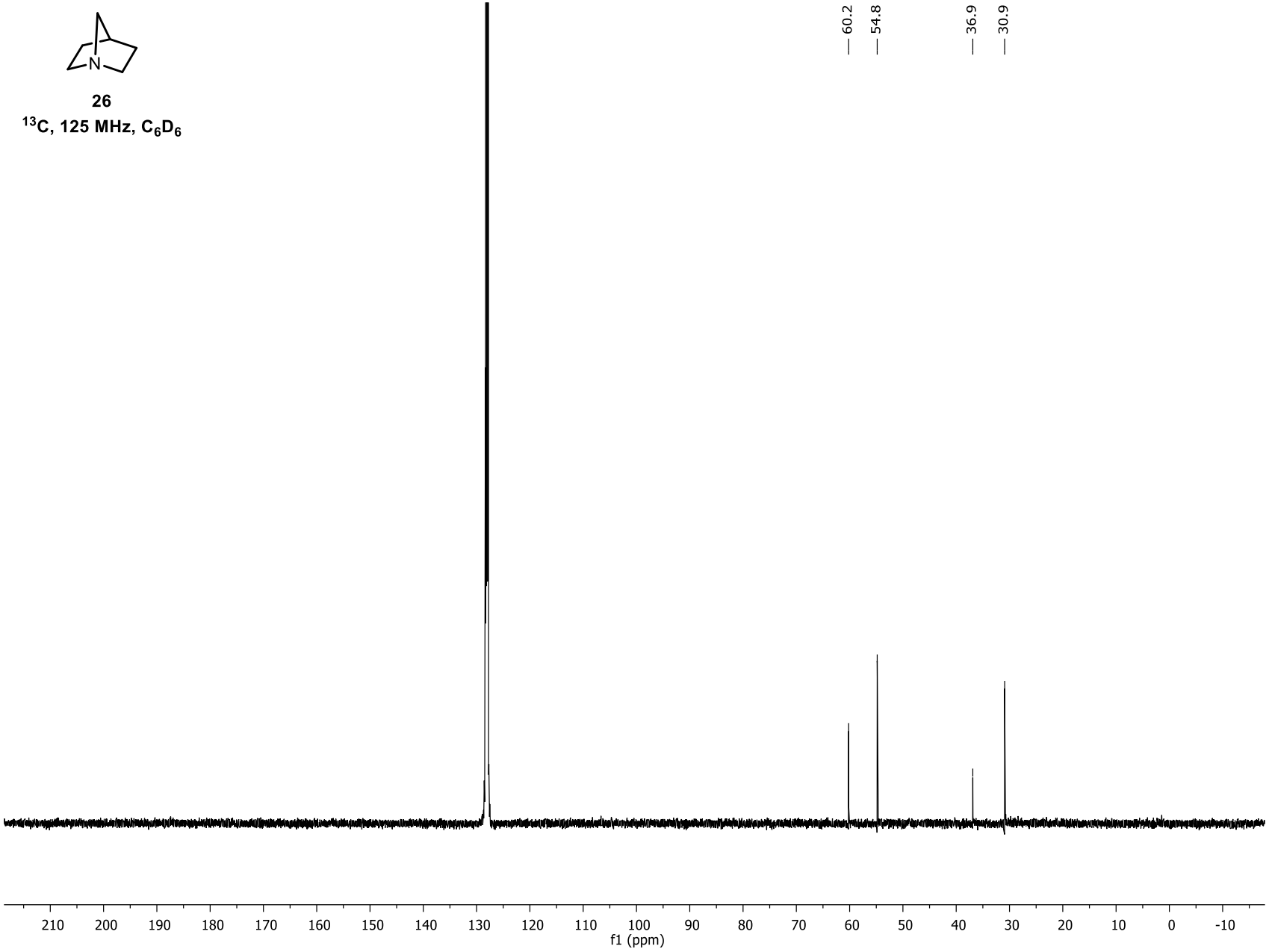

S20
1H, 500 MHz, CDCl3
Cl
N
O
Br
f1 (ppm)

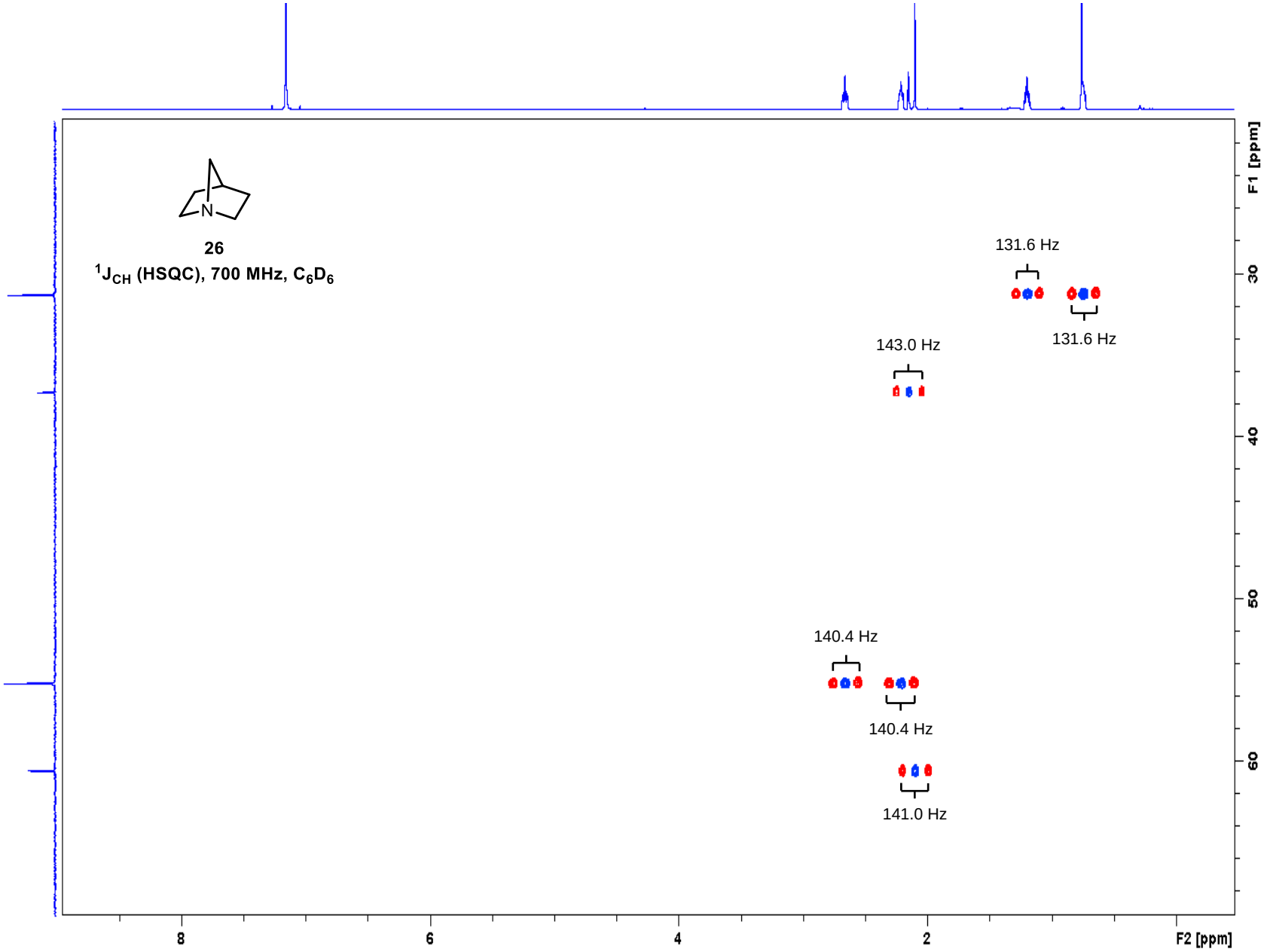


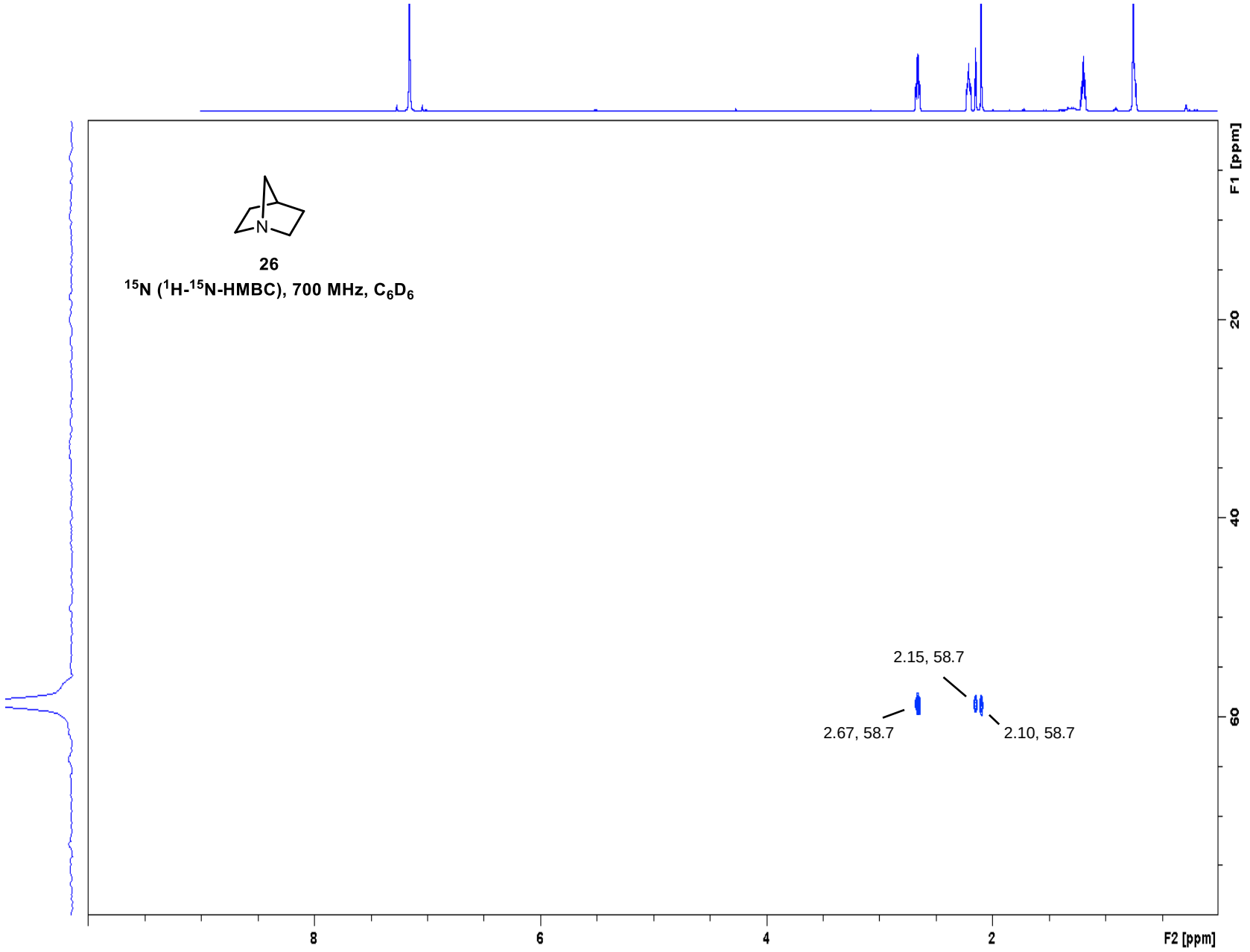
S20

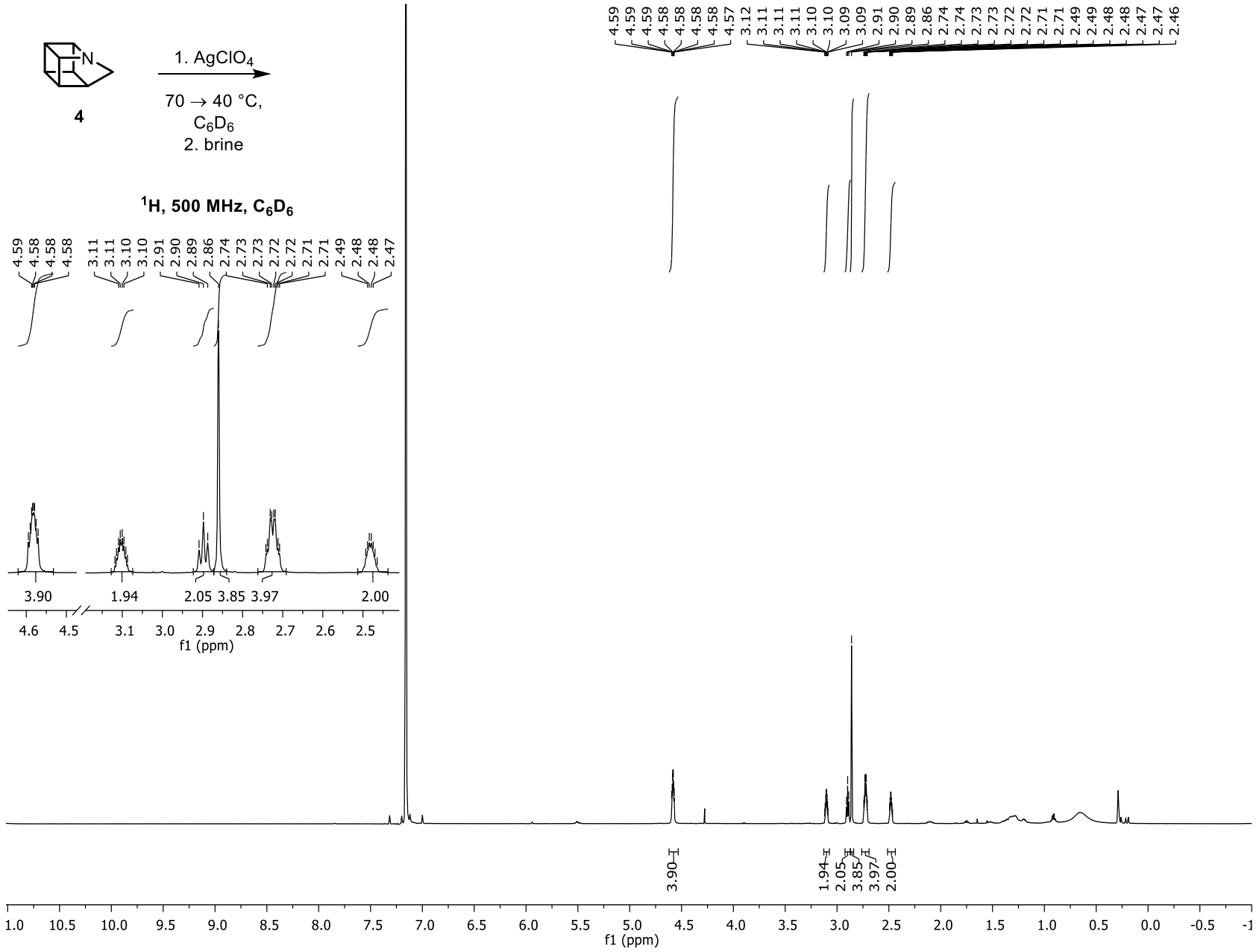
^{13}C, 125 MHz, $CDCl_3$

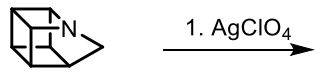

2.70 2.70 2.69 2.69 2.69 2.68 2.68 2.67 2.67 2.66 2.65 2.65 2.65 2.64 2.64 2.25 2.24 2.24 2.24 2.23 2.23 2.22 2.22 2.22 2.21 2.21 2.21 2.20 2.20 2.20 2.19 2.19 2.17 2.16 2.15 2.11 2.11 2.11 2.10 1.24 1.23 1.23 1.23 1.22 1.22 1.21 1.21 1.21 1.21 1.20 1.20 1.20 1.19 1.19 1.19 1.18 1.18 1.18 1.17 1.17 0.78 0.78 0.77 0.76 0.75 0.75 0.75 0.73 0.73
N
26
1H, 500 MHz, C6D6
1.91
1.97
1.00
2.03
1.53
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


26
^{13}C, 125 MHz, C_6D_6
60.2
54.8
36.9
30.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


26
$^{1}J_{CH}$ (HSQC), 700 MHz, C_6D_6
131.6 Hz
131.6 Hz
143.0 Hz
140.4 Hz
140.4 Hz
141.0 Hz
F1 [ppm]
30
40
50
60
8
6
4
2
F2 [ppm]


N
26
15N (1H-15N-HMBC), 700 MHz, C6D6
2.15, 58.7
2.67, 58.7
2.10, 58.7
F1 [ppm]
20
40
60
8
6
4
2
F2 [ppm]

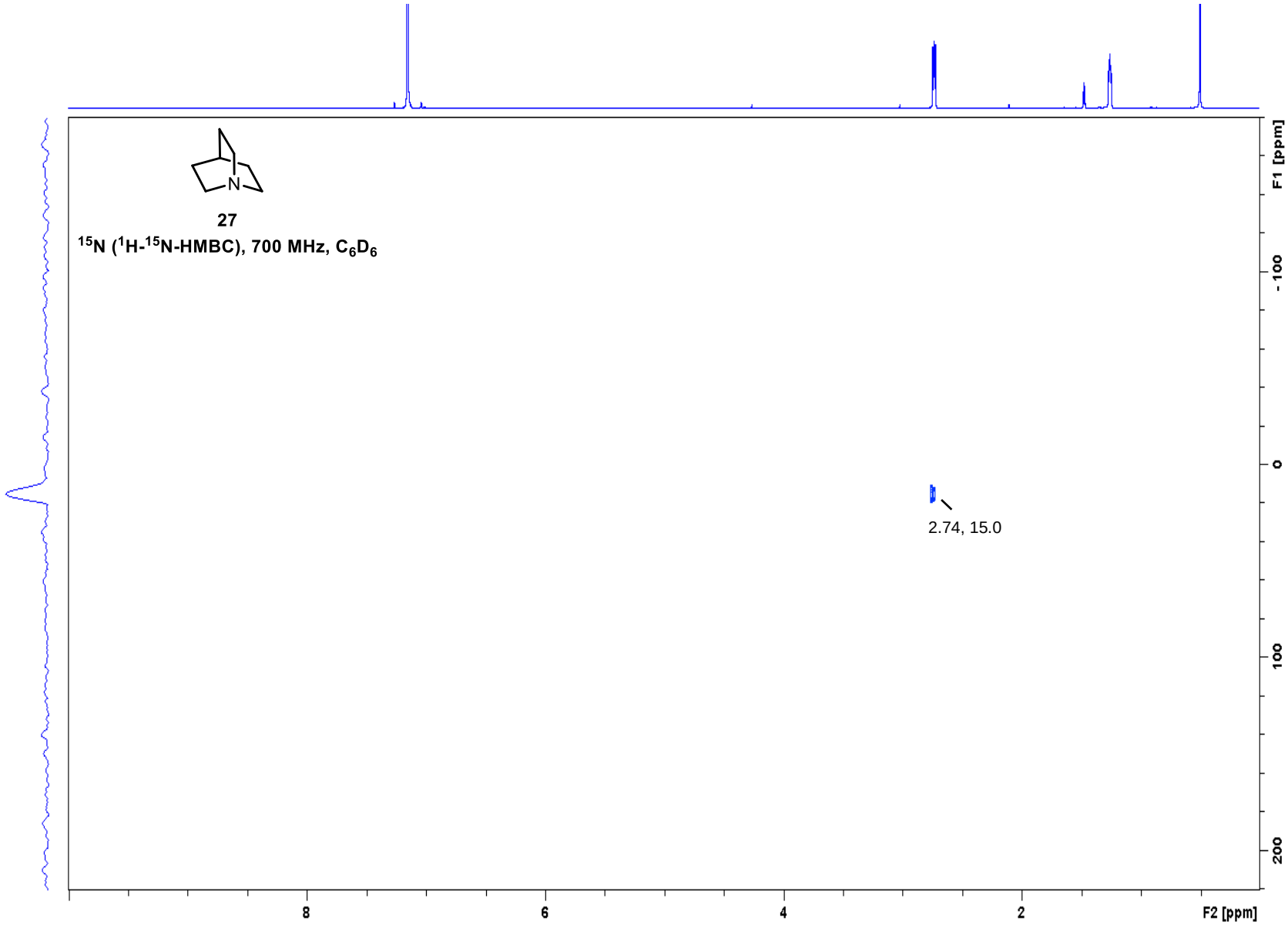

4
1. AgClO4
70 → 40 °C,
C6D6
2. brine
1H, 500 MHz, C6D6
f1 (ppm)

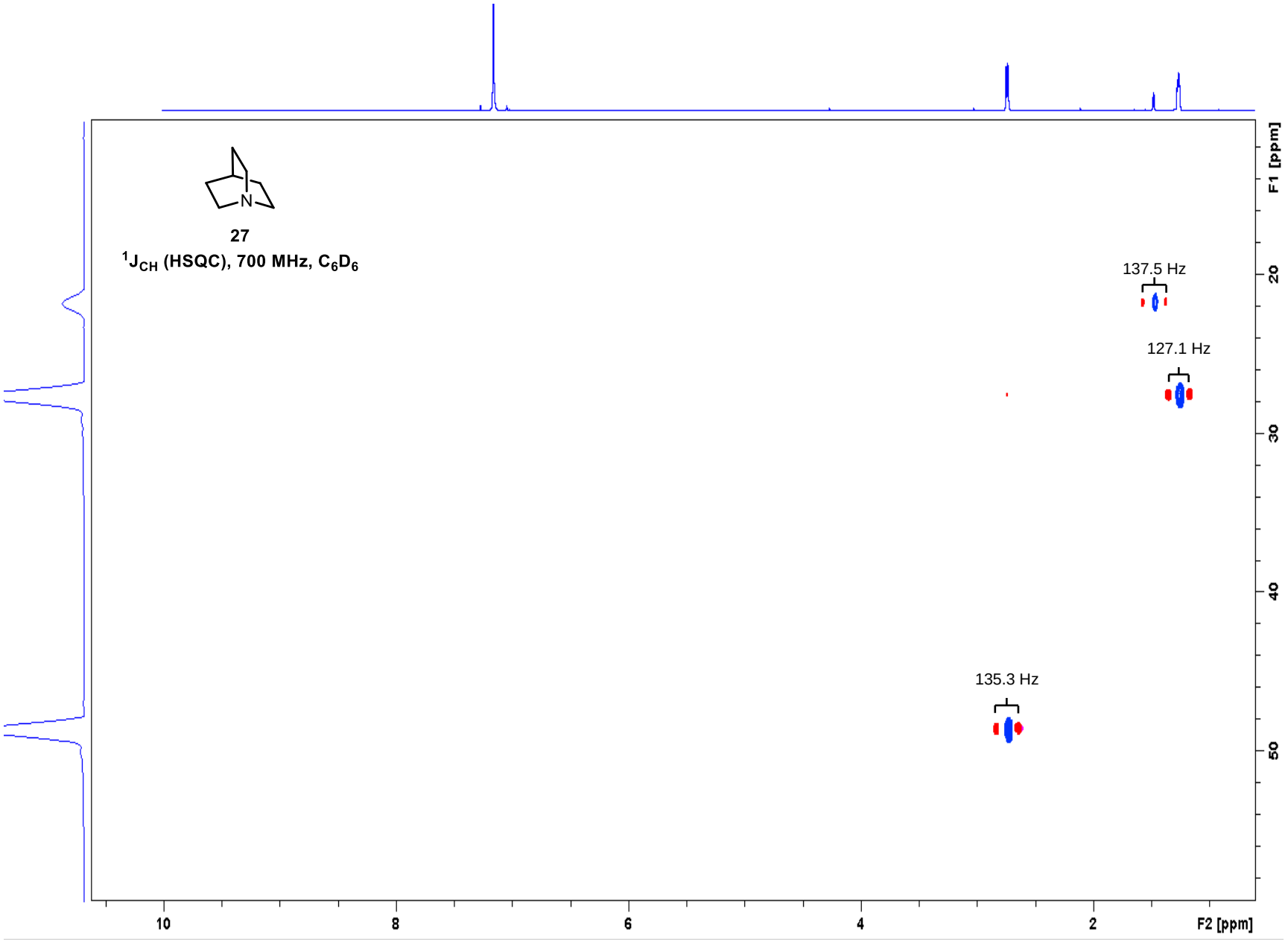


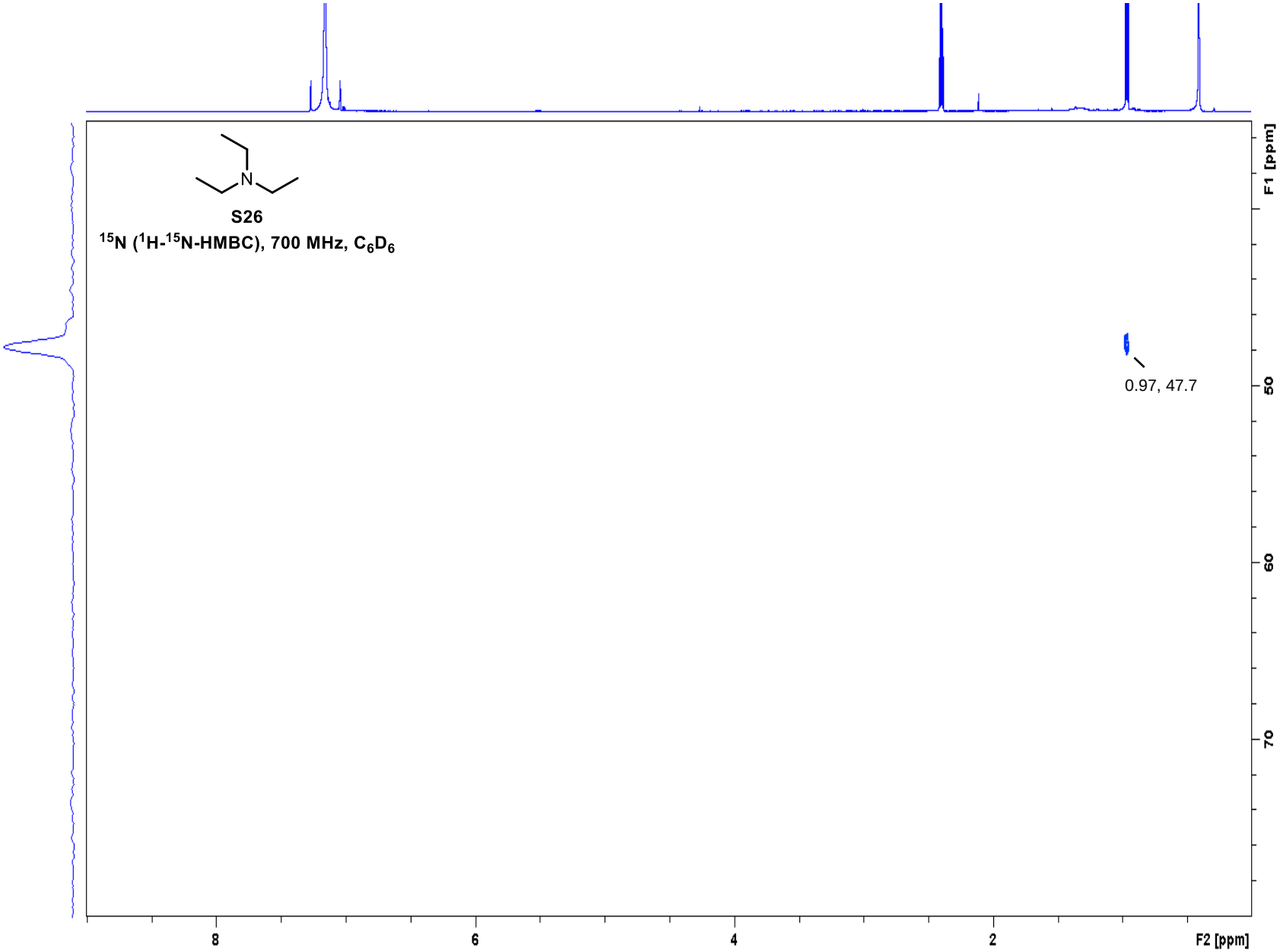
4

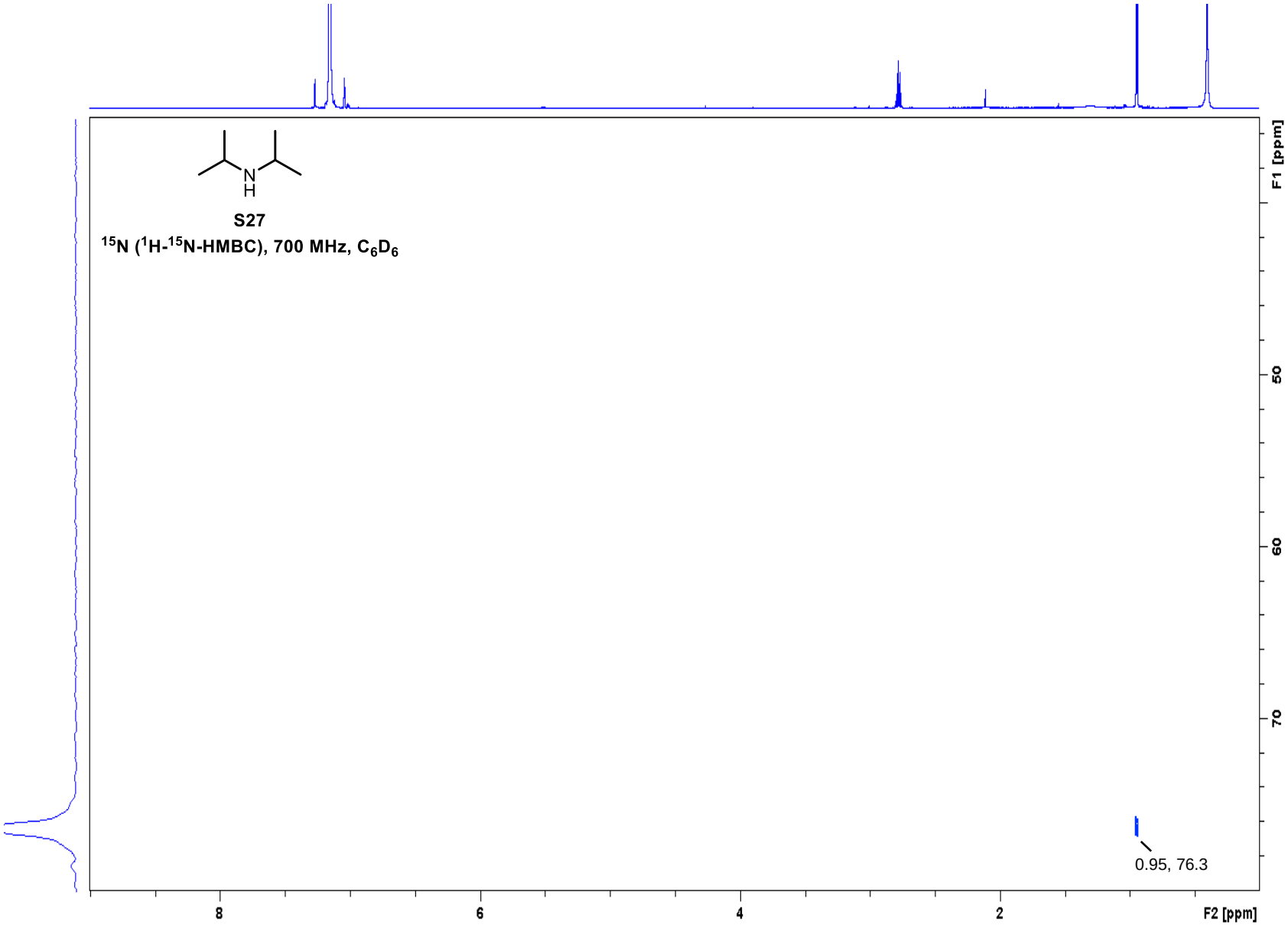
70 → 40 °C,
C_6D_6
2. brine

^{13}C, 125 MHz, C_6D_6


27
15N (1H-15N-HMBC), 700 MHz, C6D6
2.74, 15.0
F1 [ppm]
- 100
0
100
200
8
6
4
2
F2 [ppm]


27
$^{1}J_{CH}$ (HSQC), 700 MHz, C_6D_6
137.5 Hz
127.1 Hz
135.3 Hz
F1 [ppm]
20
30
40
50
10
8
6
4
2
F2 [ppm]


S26
^{15}N (^{1}H-^{15}N-HMBC), 700 MHz, C_6D_6
0.97, 47.7
F1 [ppm]
50
60
70
8
6
4
2
F2 [ppm]


S27
15N (1H-15N-HMBC), 700 MHz, C6D6
0.95, 76.3
F1 [ppm]
F2 [ppm]
8
6
4
2
50
60
70

References

1 J. T. Edward, P. G. Farrell and G. E. Langford, Proton magnetic resonance spectra of cubane derivatives. I. Syntheses and spectra of mono- and 1,4-disubstituted cubanes, *J. Am. Chem. Soc.*, 1976, **98**, 3075–3085.

2 P. E. Eaton, B. K. R. Shankar, G. D. Price, J. J. Pluth, E. E. Gilbert, J. Alster and O. Sandus, Synthesis of 1,4-dinitrocubane, *J. Org. Chem.*, 1984, **49**, 185–186.

3 C. J. Cavender and V. J. Shiner, Trifluoromethanesulfonyl azide. Its reaction with alkyl amines to form alkyl azides, *J. Org. Chem.*, 1972, **37**, 3567–3569.

4 P. E. Eaton and R. E. Hormann, Azidocubanes. 1. Photolysis: formation of a homoprismyl nitrile, *J. Am. Chem. Soc.*, 1987, **109**, 1268–1269.

5 P. E. Eaton, A. M. Fisher and R. E. Hormann, Azidocubanes; 2. Acid-Induced Rearrangement: Formation of 9-Azahomocubanes, *Synlett*, 1990, **1990**, 737–738.

6 P. E. Eaton, N. Nordari, J. Tsanaktsidis and S. P. Upadhyaya, Barton Decarboxylation of Cubane-1,4-dicarboxylic Acid: Optimized Procedures for Cubanecarboxylic Acid and Cubane, *Synthesis*, 1995, **1995**, 501–502.

7 J. Ho, J. Zheng, R. Meana-Pañeda, D. G. Truhlar, E. J. Ko, G. P. Savage, C. M. Williams, M. L. Coote and J. Tsanaktsidis, Chloroform as a Hydrogen Atom Donor in Barton Reductive Decarboxylation Reactions, *J. Org. Chem.*, 2013, **78**, 6677–6687.

8 B. A. Chalmers, H. Xing, S. Houston, C. Clark, S. Ghassabian, A. Kuo, B. Cao, A. Reitsma, C.-E. P. Murray, J. E. Stok, G. M. Boyle, C. J. Pierce, S. W. Littler, D. A. Winkler, P. V. Bernhardt, C. Pasay, J. J. De Voss, J. McCarthy, P. G. Parsons, G. H. Walter, M. T. Smith, H. M. Cooper, S. K. Nilsson, J. Tsanaktsidis, G. P. Savage and C. M. Williams, Validating Eaton's Hypothesis: Cubane as a Benzene Bioisostere, *Angew. Chem. Int. Ed.*, 2016, **55**, 3580–3585.

9 A. J. H. Klunder and B. Zwanenburg, Chemistry of strained polycyclic compounds—III: Synthesis of cubane and homocubane alcohols, *Tetrahedron*, 1972, **28**, 4131–4138.

10 A. Titz, Z. Radic, O. Schwardt and B. Ernst, A safe and convenient method for the preparation of triflyl azide, and its use in diazo transfer reactions to primary amines, *Tetrahedron Lett.*, 2006, **47**, 2383–2385.

11 M. J. Mintz and C. Walling, *t*-Butyl Hypochlorite, *Org. Synth.*, 1969, **49**, 9.

12 Y. Takano, Y. Kashiyama, N. O. Ogawa, Y. Chikaraishi and N. Ohkouchi, Isolation and desalting with cation-exchange chromatography for compound-specific nitrogen isotope analysis of amino acids: application to biogeochemical samples, *Rapid Commun. Mass Spectrom.*, 2010, **24**, 2317–2323.

13 T. P. Fill, H. F. Pallini, Z. U. Din, I. D. Jurberg, J. V. da Silva and E. Rodrigues-Filho, Conjugation of antifungal benzoic acid derivatives as a path for detoxification in Penicillium brasilianum, an endophyte from Melia azedarach, *Bioorganic Chem.*, 2018, **81**, 367–372.

14 F. Xu, B. Simmons, R. A. Reamer, E. Corley, J. Murry and D. Tschaen, Chlorination/Cyclodehydration of Amino Alcohols with $SOCl_2$: An Old Reaction Revisited, *J. Org. Chem.*, 2008, **73**, 312–315.

15 L. A. Paquette, J. S. Ward, R. A. Boggs and W. B. Farnham, Valence isomerization of homocubanes. Reversible complex formation and kinetic substituent effects operating during silver(I)-induced bond reorganization, *J. Am. Chem. Soc.*, 1975, **97**, 1101–1112.

16 L. A. Paquette, R. S. Beckley and W. B. Farnham, Silver(I) ion catalyzed rearrangements of strained .sigma. bonds. XXVII. Kinetic analysis of the silver(I)-catalyzed 1,8-bishomocubane-snoutane rearrangement, *J. Am. Chem. Soc.*, 1975, **97**, 1089–1100.
17 G. M. Sheldrick, A short history of SHELX, *Acta Crystallogr. A*, 2008, **64**, 112–122.
18 L. J. Farrugia, WinGX suite for small-molecule single-crystal crystallography, *J. Appl. Crystallogr.*, 1999, **32**, 837–838.
19 C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. McCabe, E. Pidcock, M. Platings, G. P. Shields, J. S. Stevens, M. Towler and P. A. Wood, Mercury 4.0: from visualization to analysis, design and prediction, *J. Appl. Crystallogr.*, 2020, **53**, 226–235.
20 R. G. Cooks and P. S. H. Wong, Kinetic Method of Making Thermochemical Determinations: Advances and Applications, *Acc. Chem. Res.*, 1998, **31**, 379–386.
21 S. A. McLuckey, D. Cameron and R. G. Cooks, Proton affinities from dissociations of proton-bound dimers, *J. Am. Chem. Soc.*, 1981, **103**, 1313–1317.
22 P. B. Armentrout, Entropy measurements and the kinetic method: A statistically meaningful approach, *J. Am. Soc. Mass Spectrom.*, 2000, **11**, 371–379.
23 A. F. Kuntz, A. W. Boynton, G. A. David, K. E. Colyer and J. C. Poutsma, The proton affinity of proline analogs using the kinetic method with full entropy analysis, *J. Am. Soc. Mass Spectrom.*, 2002, **13**, 72–81.
24 E. P. L. Hunter and S. G. Lias, Evaluated Gas Phase Basicities and Proton Affinities of Molecules: An Update, *J. Phys. Chem. Ref. Data*, 2009, **27**, 413.
25 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, Williams, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman and D. J. Fox, 2016.
26 Y. Zhao and D. G. Truhlar, The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals, *Theor. Chem. Acc.*, 2008, **120**, 215–241.
27 E. P. L. Hunter and S. G. Lias, Evaluated Gas Phase Basicities and Proton Affinities of Molecules: An Update, *J. Phys. Chem. Ref. Data*, 1998, **27**, 413–656.
28 A. de Meijere, V. Chaplinski, F. Gerson, P. Merstetter and E. Haselbach, Radical Cations of Trialkylamines: ESR Spectra and Structures, *J. Org. Chem.*, 1999, **64**, 6951–6959.

29 A. E. Lyuts, V. Z. Gabdrakipov, I. A. Shlygina and V. A. Petropavlov, Photoelectron spectra of saturated nitrogen-containing organic compounds, *J. Struct. Chem.*, 1987, **27**, 629–651.
30 F. Neese, The ORCA program system, *WIREs Comput. Mol. Sci.*, 2012, **2**, 73–78.
31 F. Neese, Software update: the ORCA program system, version 4.0, *WIREs Comput. Mol. Sci.*, 2018, **8**, e1327.
32 F. Weigend and R. Ahlrichs, Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297–3305.
33 S. Grimme, J. Antony, S. Ehrlich and H. Krieg, A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu, *J. Chem. Phys.*, 2010, **132**, 154104.
34 L. Goerigk, A. Hansen, C. Bauer, S. Ehrlich, A. Najibi and S. Grimme, A look at the density functional theory zoo with the advanced GMTKN55 database for general main group thermochemistry, kinetics and noncovalent interactions, *Phys. Chem. Chem. Phys.*, 2017, **19**, 32184–32215.
35 C. Riplinger, P. Pinski, U. Becker, E. F. Valeev and F. Neese, Sparse maps—A systematic infrastructure for reduced-scaling electronic structure methods. II. Linear scaling domain based pair natural orbital coupled cluster theory, *J. Chem. Phys.*, 2016, **144**, 024109.
36 T. H. Dunning, Gaussian basis sets for use in correlated molecular calculations. I. The atoms boron through neon and hydrogen, *J. Chem. Phys.*, 1989, **90**, 1007–1023.
37 L. Kong, F. A. Bischoff and E. F. Valeev, Explicitly Correlated R12/F12 Methods for Electronic Structure, *Chem. Rev.*, 2012, **112**, 75–107.
38 S. Ten-no and J. Noga, Explicitly correlated electronic structure theory from R12/F12 ansätze, *WIREs Comput. Mol. Sci.*, 2012, **2**, 114–125.
39 F. Neese, F. Wennmohs, A. Hansen and U. Becker, Efficient, approximate and parallel Hartree–Fock and hybrid DFT calculations. A ‘chain-of-spheres’ algorithm for the Hartree–Fock exchange, *Chem. Phys.*, 2009, **356**, 98–109.
40 S. E. Wheeler, K. N. Houk, P. v. R. Schleyer and W. D. Allen, A Hierarchy of Homodesmotic Reactions for Thermochemistry, *J. Am. Chem. Soc.*, 2009, **131**, 2547–2560.
41 X.-W. Fan, X.-H. Ju, Q.-Y. Xia and H.-M. Xiao, Strain energies of cubane derivatives with different substituent groups, *J. Hazard. Mater.*, 2008, **151**, 255–260.
42 Z. Zeng, A. M. A. Qasem, T. J. Woodman, M. G. Rowan and I. S. Blagbrough, Impacts of Steric Compression, Protonation, and Intramolecular Hydrogen Bonding on the ^{15}N NMR Spectroscopy of Norditerpenoid Alkaloids and Their Piperidine-Ring Analogues, *ACS Omega*, 2020, **5**, 14116–14122.
43 J. E. Hamlin and K. J. Toyne, The ^{13}C and ^{1}H N.M.R. spectra of homocubane, norsnoutane and their 9-keto- and 9,9-ethylenedioxy-derivatives, and a novel route to functionalised brendanes, *J. Chem. Soc. Perkin 1*, 1981, 2731–2736.
44 E. W. Della, P. T. Hine and H. K. Patney, Carbon-13 spectral parameters of some polycyclic hydrocarbons, *J. Org. Chem.*, 1977, **42**, 2940–2941.