Supplementary information for

The first proton sponge-based amino acids: synthesis, acid-base properties and some reactivity

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[b] *Department of Analytical Chemistry, Southern Federal University, Zorge str. 7, 344090 Rostov-on-Don, Russian Federation*

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Potentiometric titration

Protolytic equilibrium constants were estimated by potentiometric alkalymetric titration of hydrobromide **6a** preliminary protonated by 0.1 M aqueous HCl solution. The acidity (pK_a) and protonation ($pK_{BH_2^+}$) constants of the studied amino acid were calculated by the least-squares method according to eq. (1):

$$\lg\frac{(1-a)C_R-[H^+]+[OH^-]}{aC_R+[H^+]-[OH^-]} = pK_a - pH_i\,, \qquad (1)$$

where C_L – the total concentration of proton sponge amino acid, a (degree of neutralization) is found using $a = C_{NaOH}\cdot V_{NaOH}/\upsilon_{spoge}$

0.2 mmol of the compound was dissolved in the ethanol–water 1:1 (v/v) mixture (with addition of 0.2 mmol aqueous HCl) and were titrated with 0.100 M aqueous NaOH. The ionic strength was maintained at 0.100 M by adding KCl. pH-Millivoltmeter (pH-150 M) with a glass and reference electrodes (Ag–AgCl) was used. The electrode was calibrated before each titration. The solution was titrated at least three times, and the reported data represent the average values (maximal deviation for the calculated pK_a values was ±0.05).

[M. S. Chernov'yants, E. V. Khohlov, G. I. Bondarenko and I. V. Burykin, *Spectrochim. Acta*, 2011, **A81**, 640–644.]

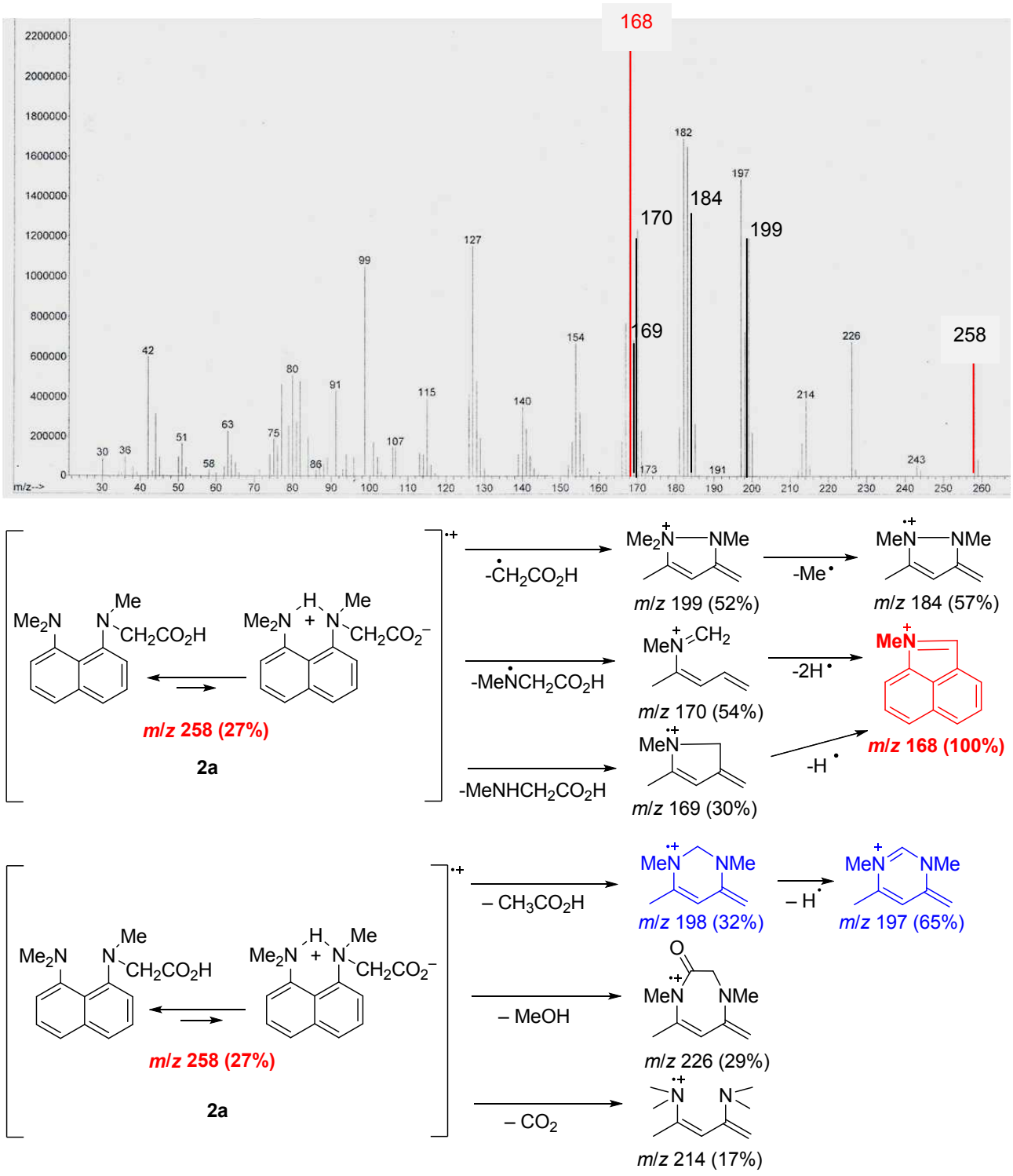
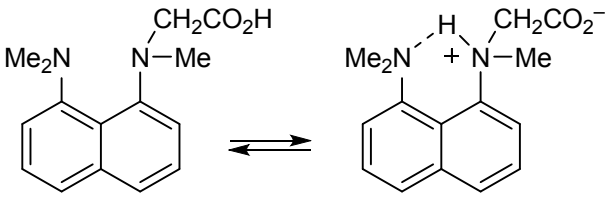


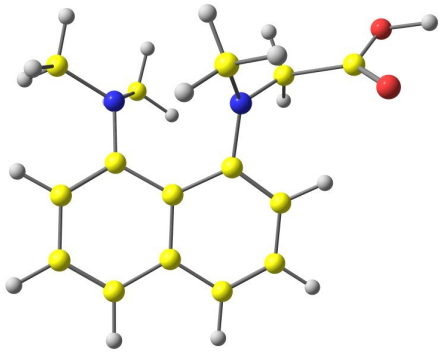
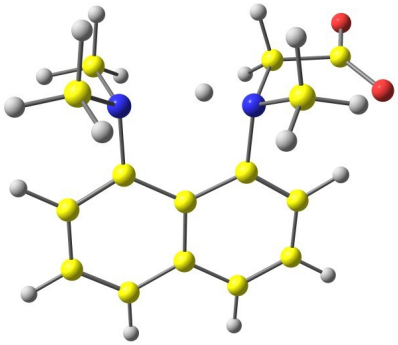
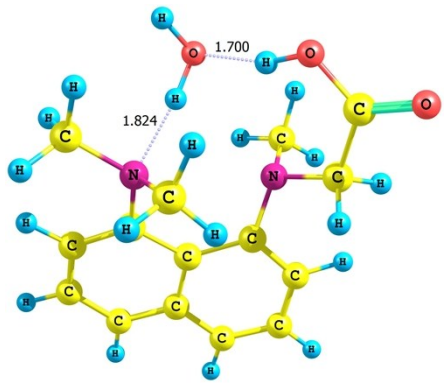
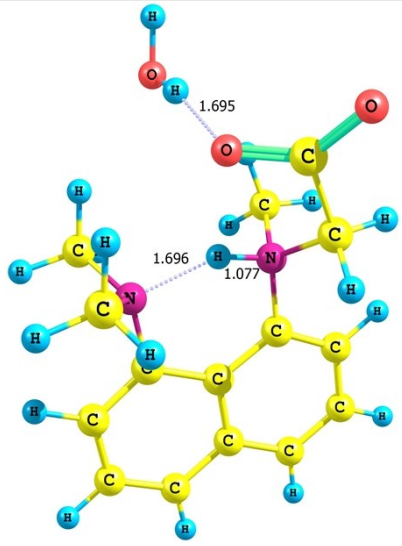
Fig. S1 Mass-spectrum of compound **2a** and the main fragmentation pathways of **2a**$^{+\cdot}$ under electron impact (70 eV).

DFT quantum-chemical calculations of amino acid 2a (total energies and relative stability in gas phase and selected solvents)



2a **2aZ**

Table S1 Total energies (in a.u.) of neutral (**2a**) and zwitterionic (**2aZ**) forms and their relative stabilities ($\Delta E = E_{2a} - E_{2aZ}$) calculated in the gas phase and in DMSO and H_2O solutions (B3LYP/6–31G**)[a] (the inserts with coloured ball and stick models are for the gas phase with indicated H-bond lengths, Å)

Media	 **2a**	 **2aZ**	ΔE, kcal/mol
Gas phase	–842.40050	–842.37503	–16.0
DMSO	–842.41943	–842.41571	–2.3
H_2O	–842.42000	–842.42319	2.3
Gas phase plus one water molecule[b]	 –918.83235	 –918.82849	–2.4

[a] Gaussian 03, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A.

Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

[b] Calculations of specific solvation with one water molecule as a proton carrier from the carboxylate functionality to the nitrogen atoms. For close examples (NH_3 and CH_3OH as bifunctional catalysts) see: O. N. Burov, M. E. Kletskii and A. V. Gulevskaya, *Russ. Chem. Bull.*, 2013, **62**, 1156–1163; M. E. Kletskii, O. N. Burov, I. L. Dalinger and S. A. Shevelev, *Comp. Theor. Chem.*, 2014, **1033**, 31–42.

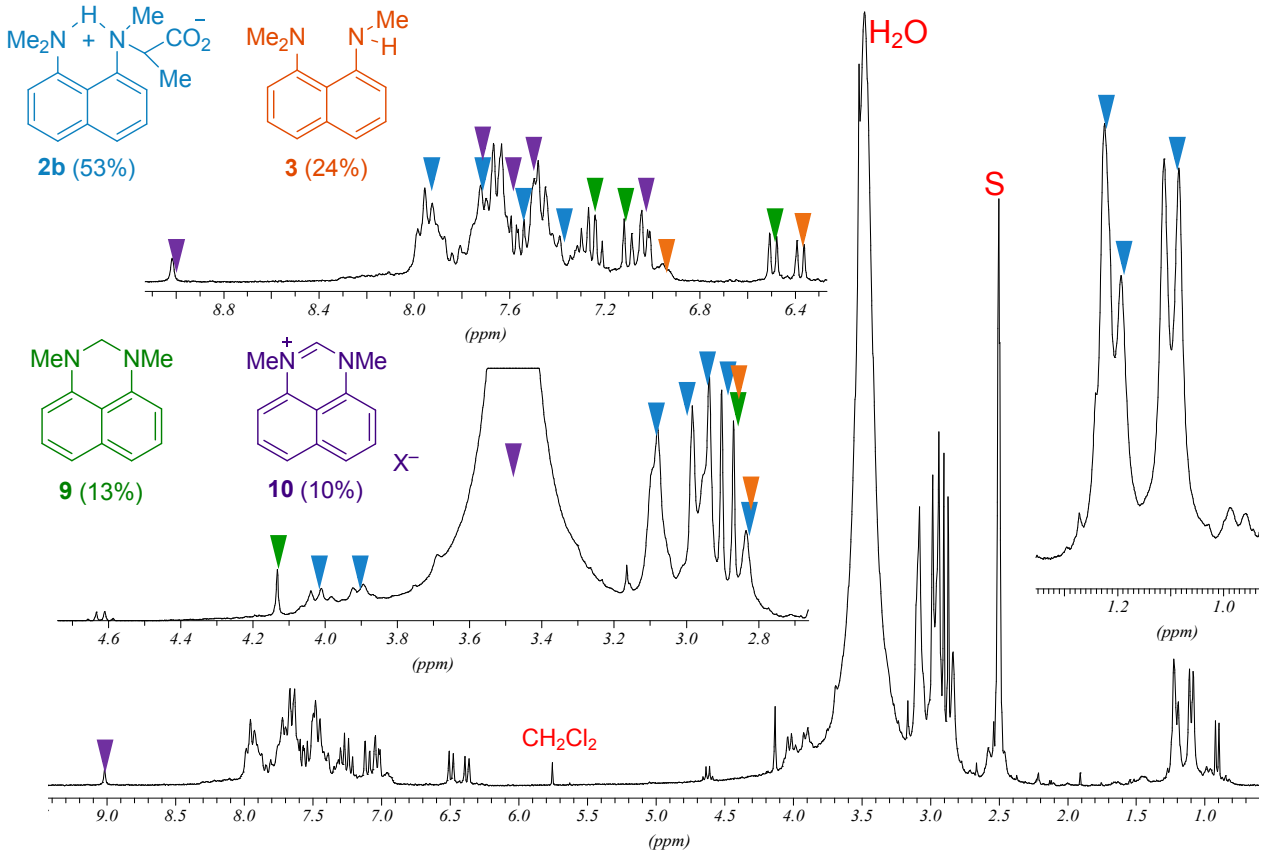


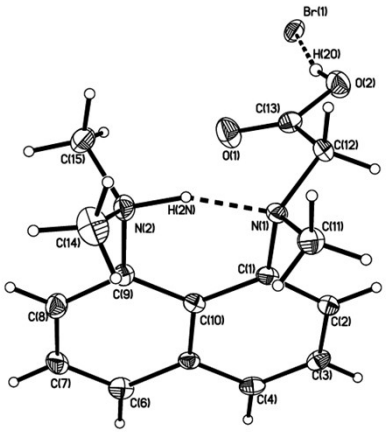
Fig. S2 Thermolysis of **2b** in DMSO-d_6 (6 h at 125 °C, ^{1}H NMR plots with indication of reaction products, 250 MHz; see also Table S2 below).

Table S2 Distribution of reaction products on thermolysis of **2a** and **2b** in DMSO-d_6 (^{1}H NMR yields, %)

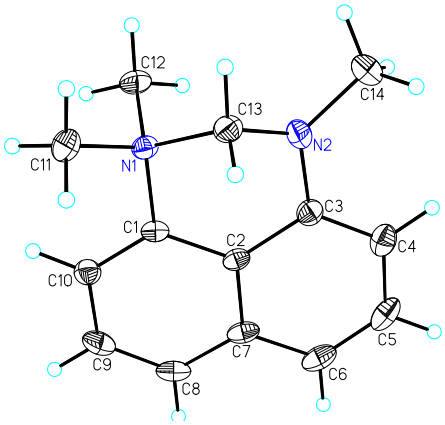
***T*, °C**	***t*, h**	**2a**	**3**	**9**	**10**	***T*, °C**	***t*, h**	**2b**	**3**	**9**	**10**
125	6	59	2	17	22	120	2	82	6	6	6
125	36	30	1	9	54	125	6	53	24	13	10
125[a]	40	9	2	19	65	125	30	6	35	0	59

[a] Additional 4 h with 0.5 equivs. of powdered K_2CO_3 added to low the overall acidity.

Table S3 Crystal data and structure refinement for compounds **6a** and **12a**



6a

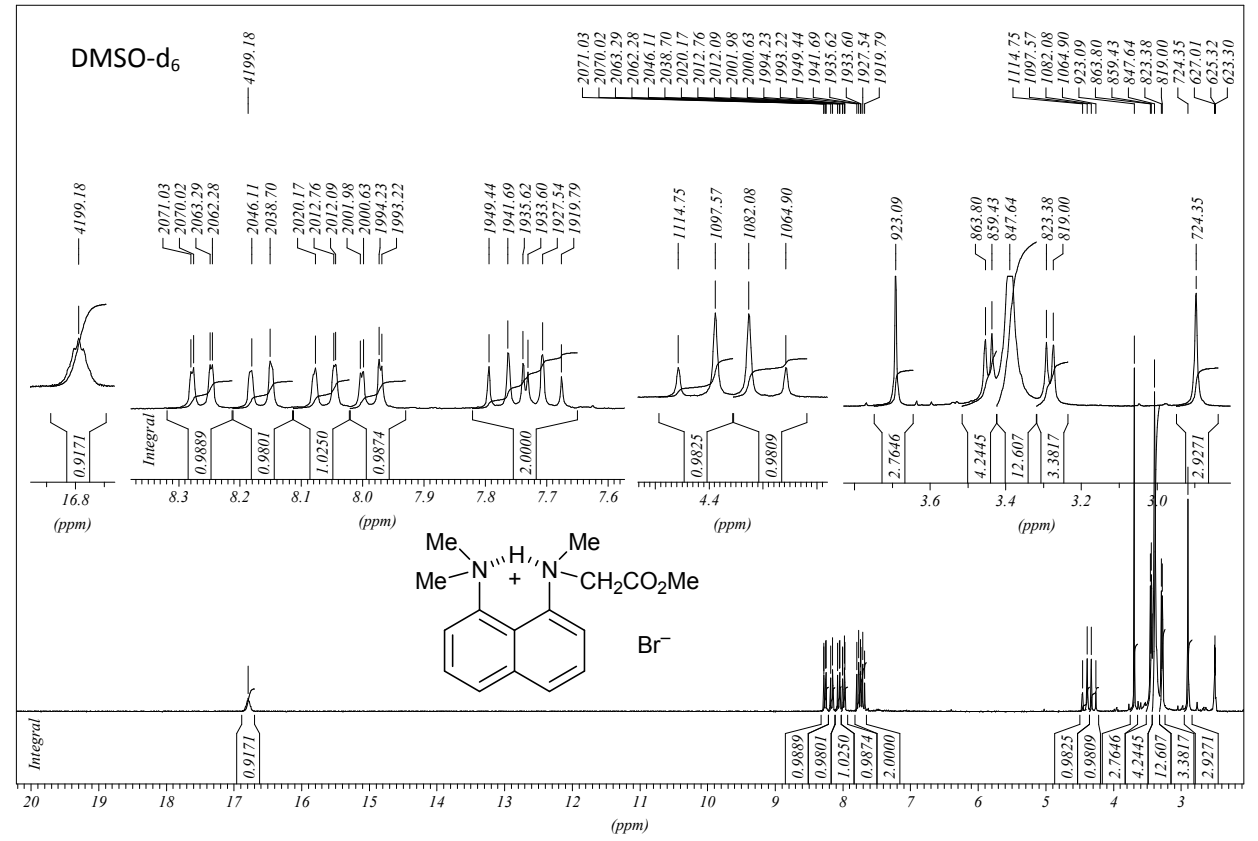


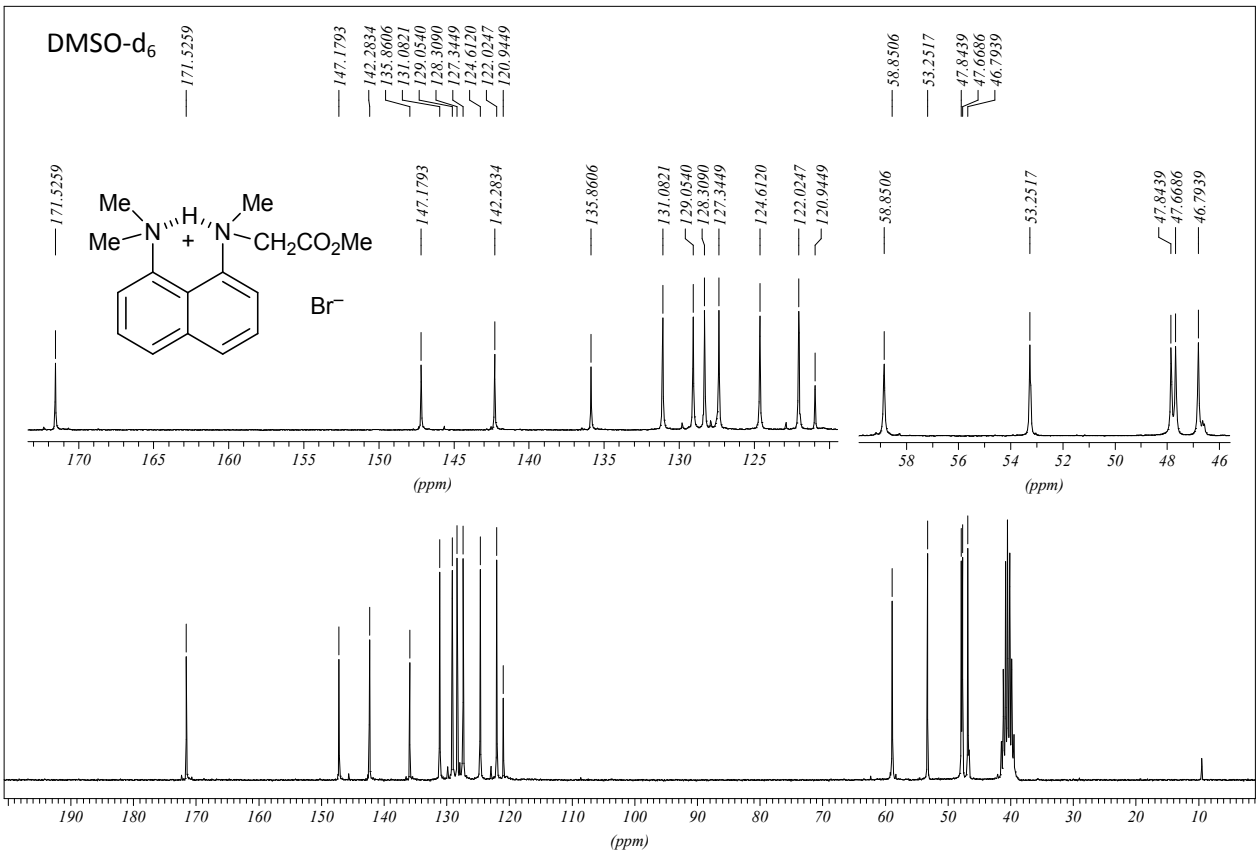
$Br^{-}\cdot 2H_2O$

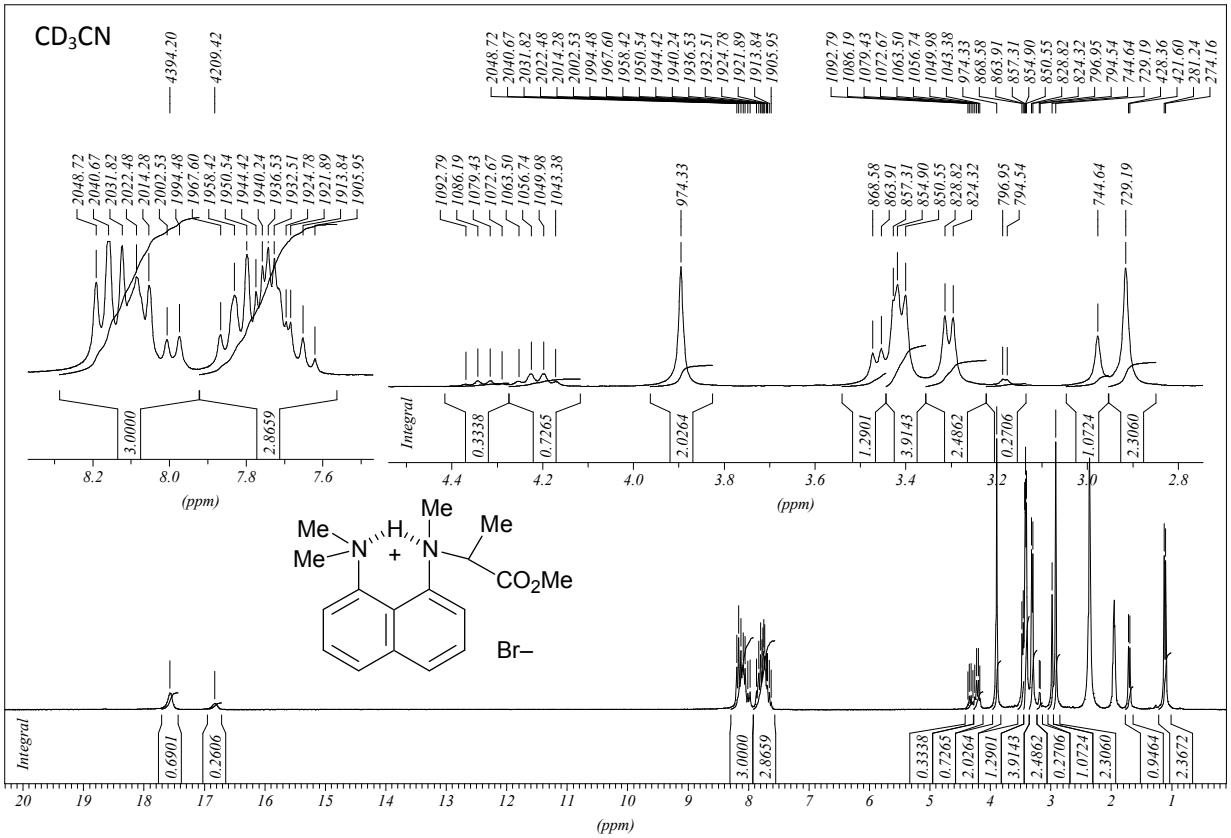
12a

Parameter	**6a**	**12a**
Empirical formula	$C_{15}H_{19}BrN_2O_2$	$C_{14}H_{21}BrN_2O_2$
Formula weight	339.23	329.24
T (K)	100(2)	120(2)
Crystal system	monoclinic	orthorhombic
Space group	$P2_1/c$	$P2_12_12_1$
a (Å)	7.4871(8)	7.0938(3)
b (Å)	12.1721(12)	11.5502(5)
c (Å)	16.4565(17)	18.1965(9)
β (°)	94.653(2)	90
V (Å^3)	1494.8(3)	1490.93(12)
Z, D_c (Mg m^{-3})	4, 1.507	4, 1.467
μ (mm^{-1})	2.753	2.758
Reflections collected/unique	10993/3567	25728/4383
R(int)	0.0629	0.0361
R_1, wR_2 (all data)	0.0580, 0.1213	0.0275, 0.0476
R factor (%)	4.48	2.28
CCDC reference number	1400689	1400690

Copies of ^{1}H and ^{13}C NMR spectra (250 MHz for ^{1}H, 62.9 MHz for ^{13}C)



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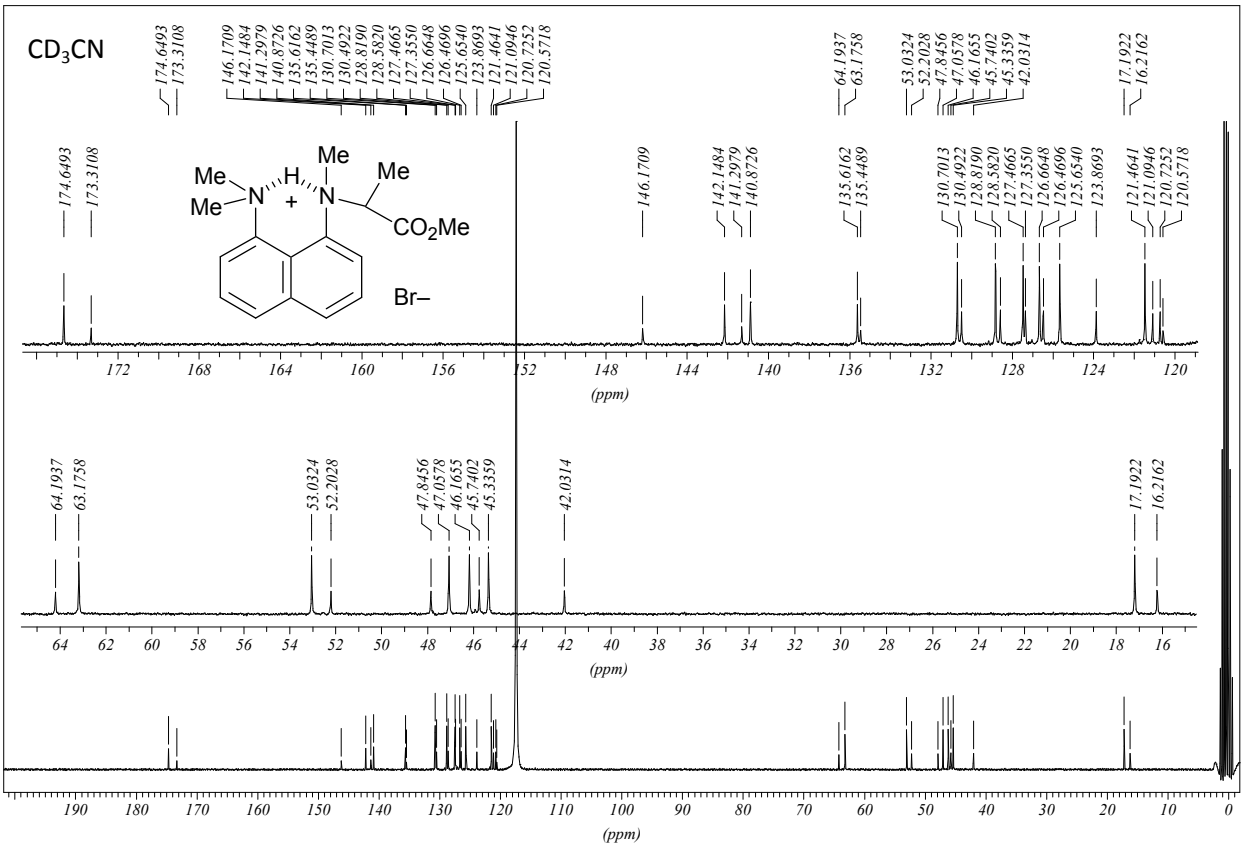
H
+
N
Me
Me
CO2Me
Br–
(ppm)
Integral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N
H
+
N
Me
Me
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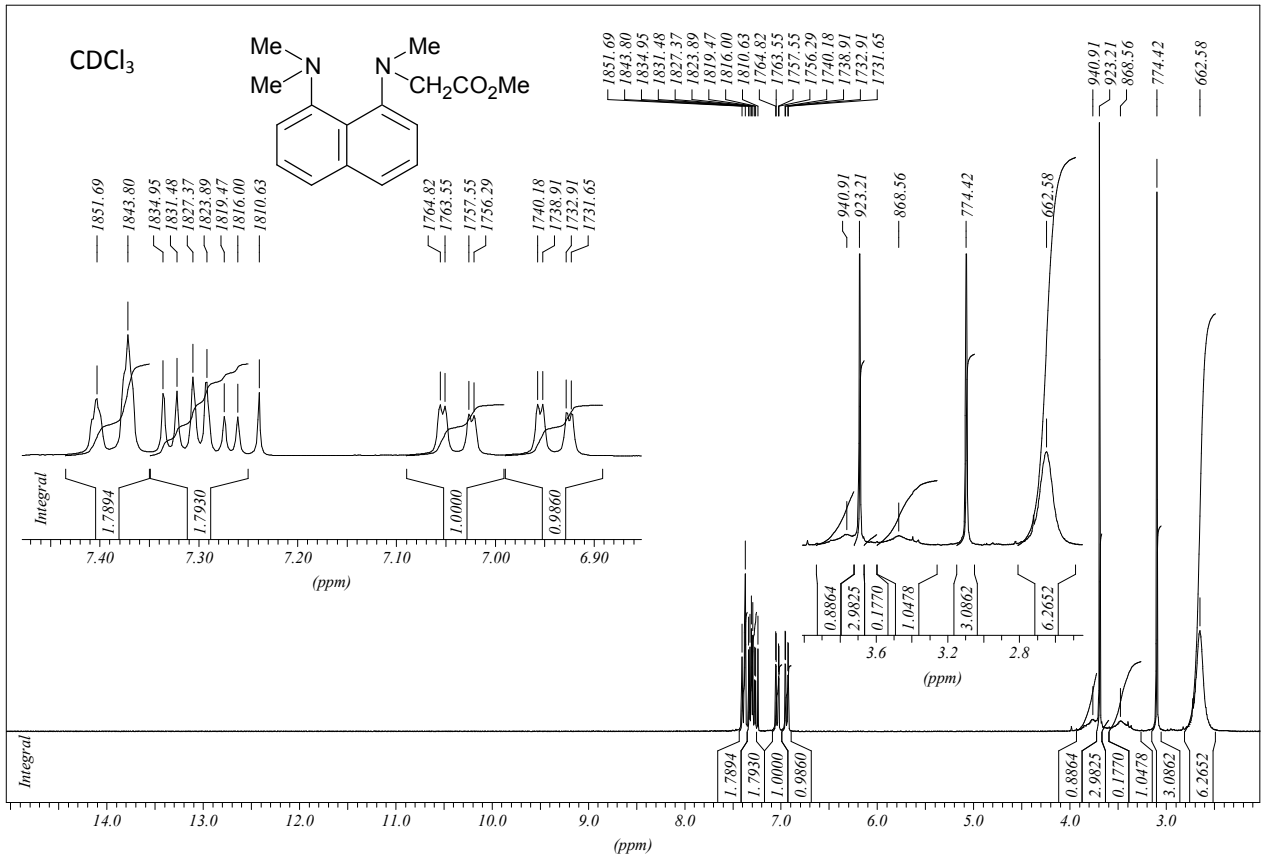
Br–
(ppm)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Me
N
Me
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1819.47
1816.00
1810.63
1764.82
1763.55
1757.55
1756.29
1740.18
1738.91
1732.91
1731.65
940.91
923.21
868.56
774.42
662.58
Integral
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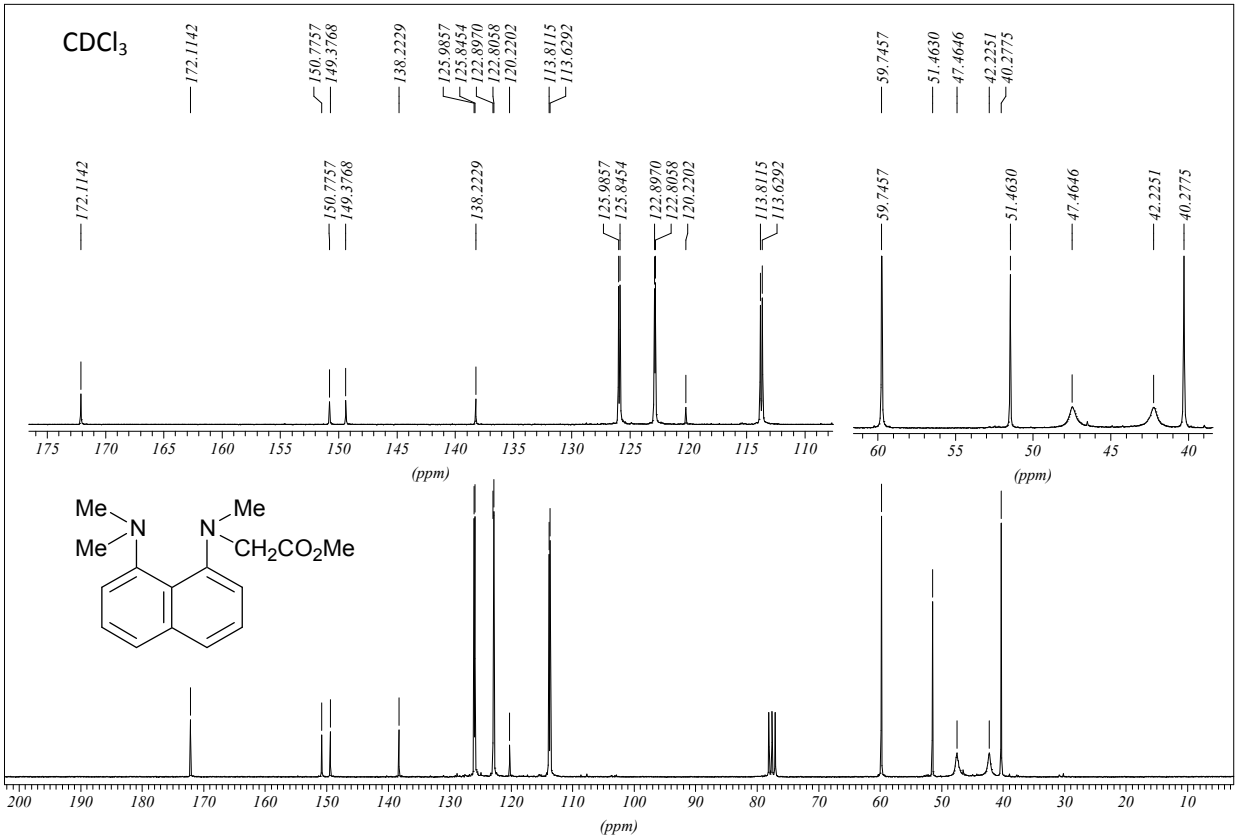
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113.8115
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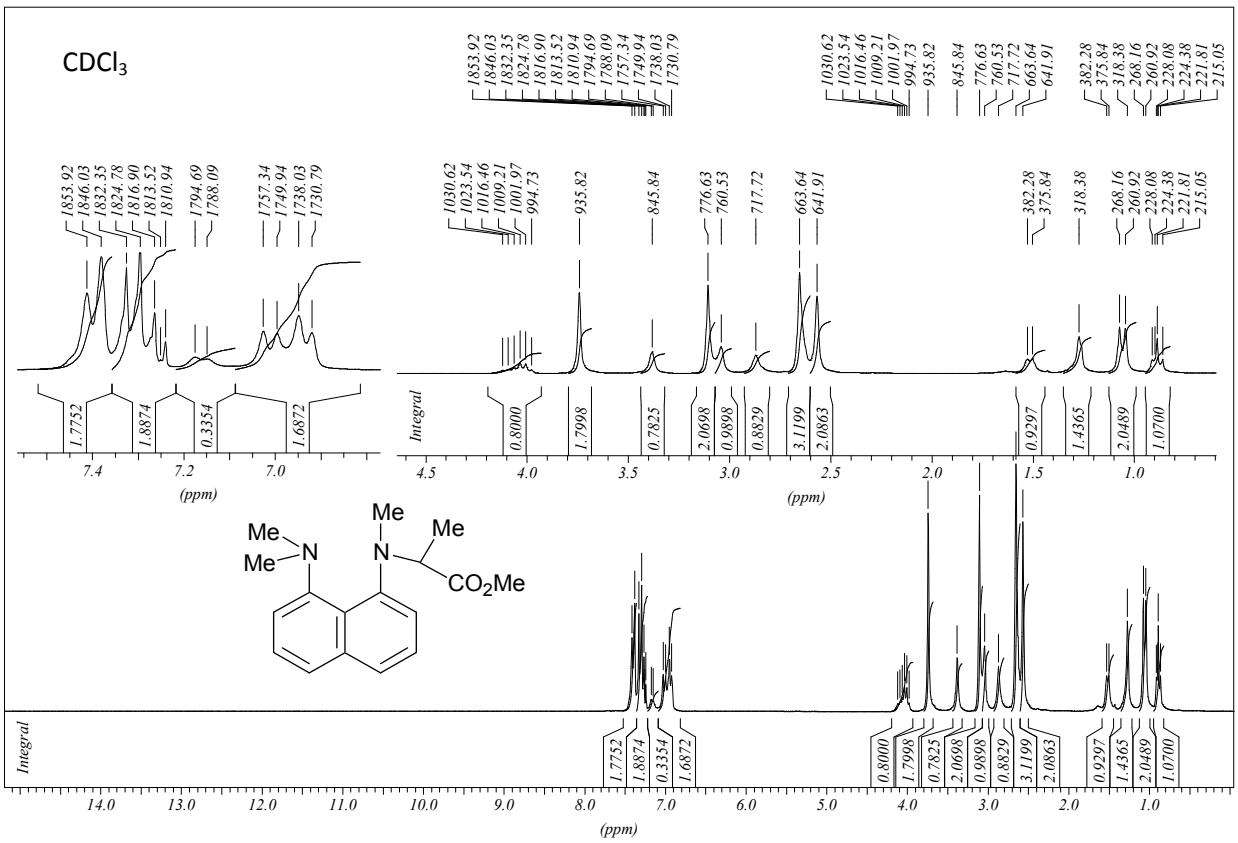
Me
N
Me
N
Me
CH2CO2Me
(ppm)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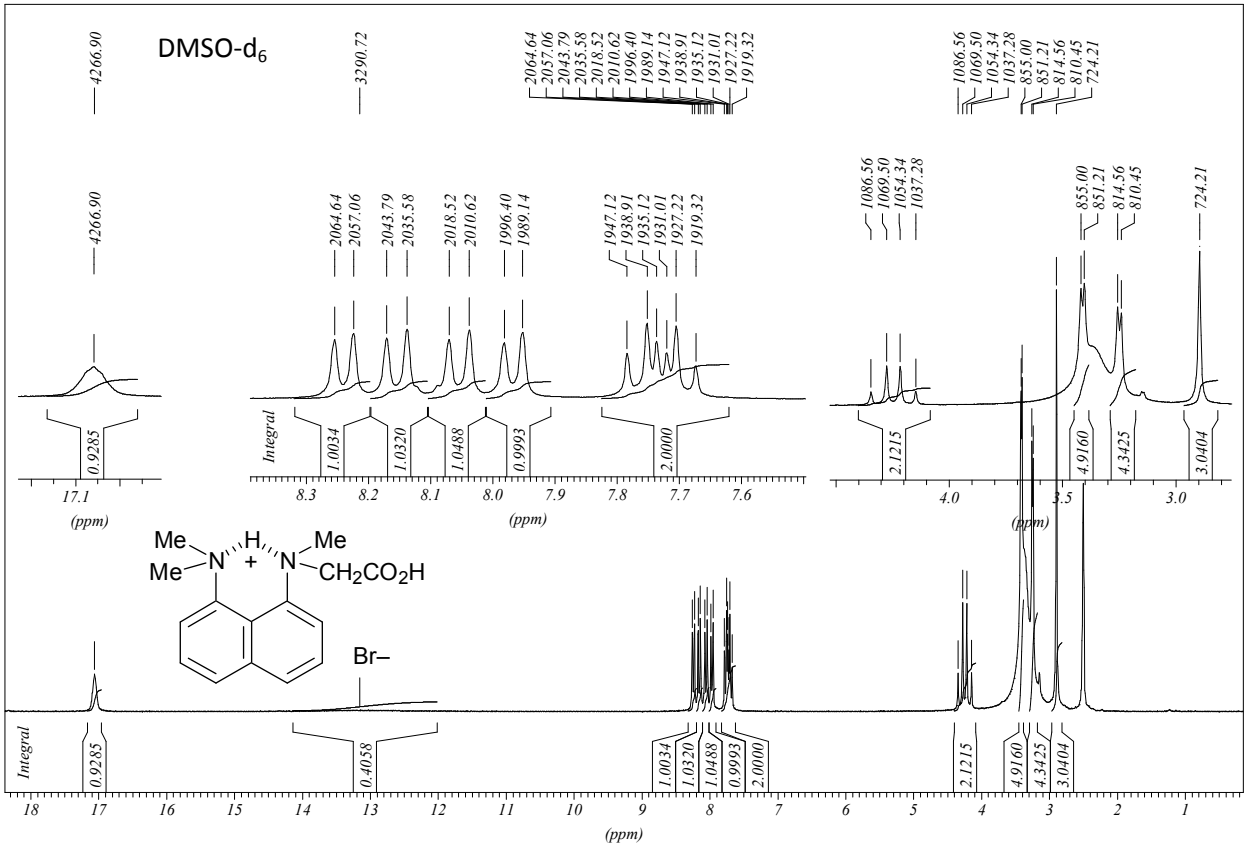
Me
N
Me
N
Me
CO2Me
(ppm)
Integral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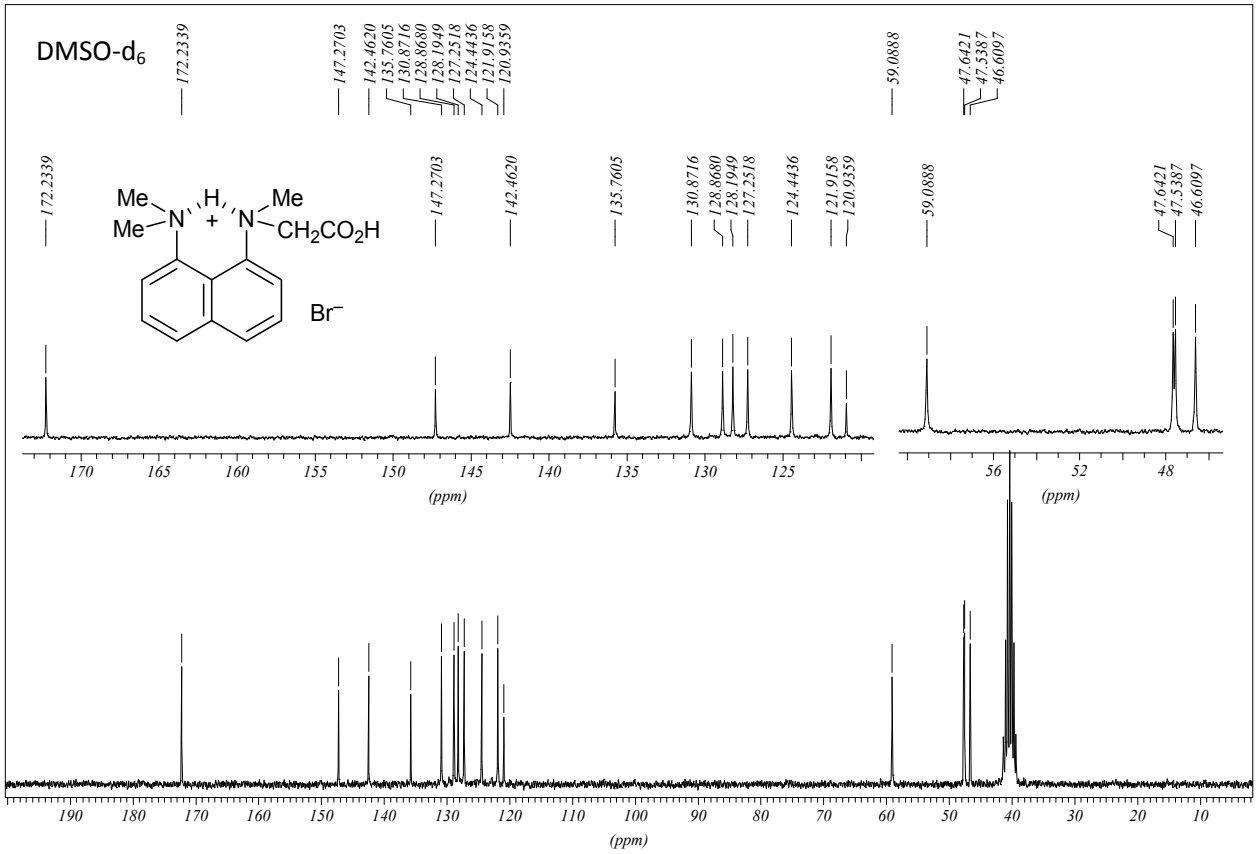
H
+
N
Me
CH2CO2H
Br–
(ppm)
Integral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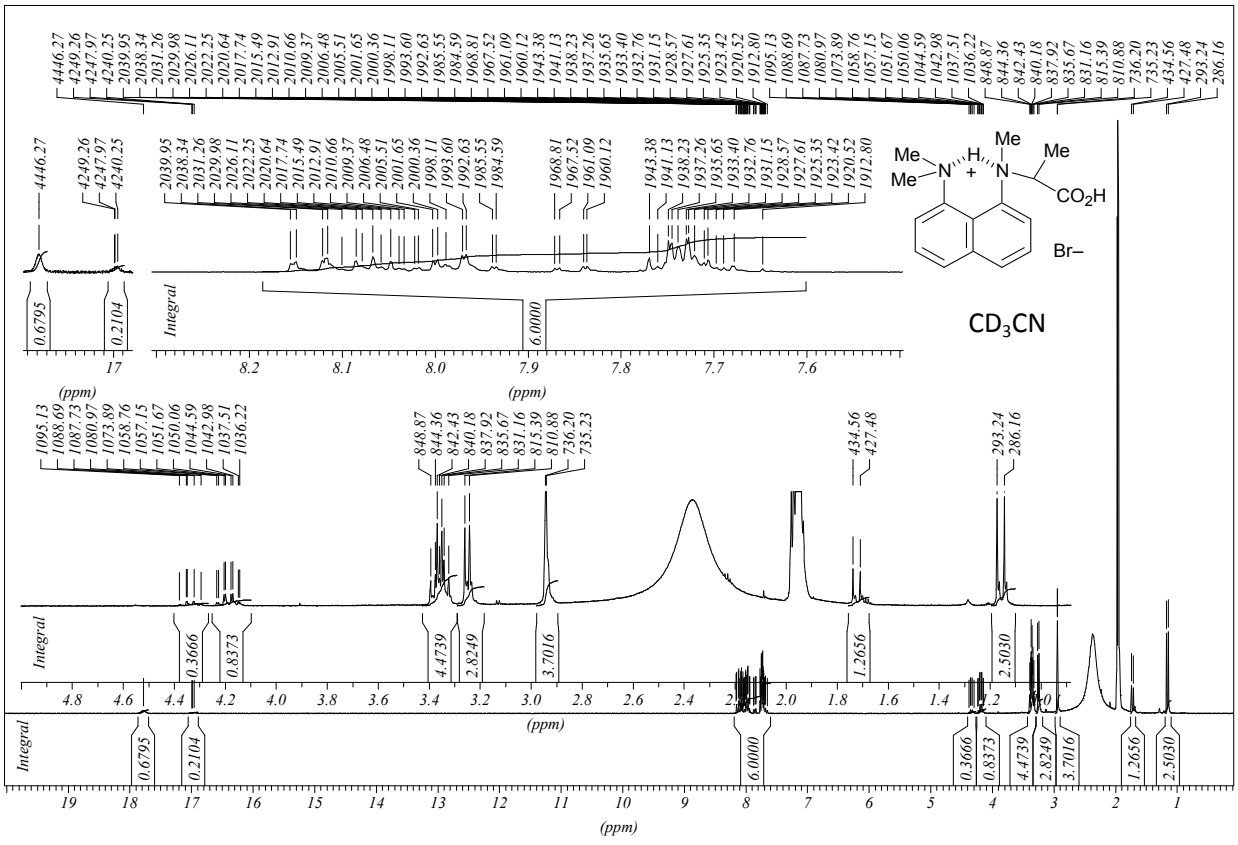
H
+
N
Me
CH2CO2H
Br–
(ppm)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Me
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CO2H
Br–
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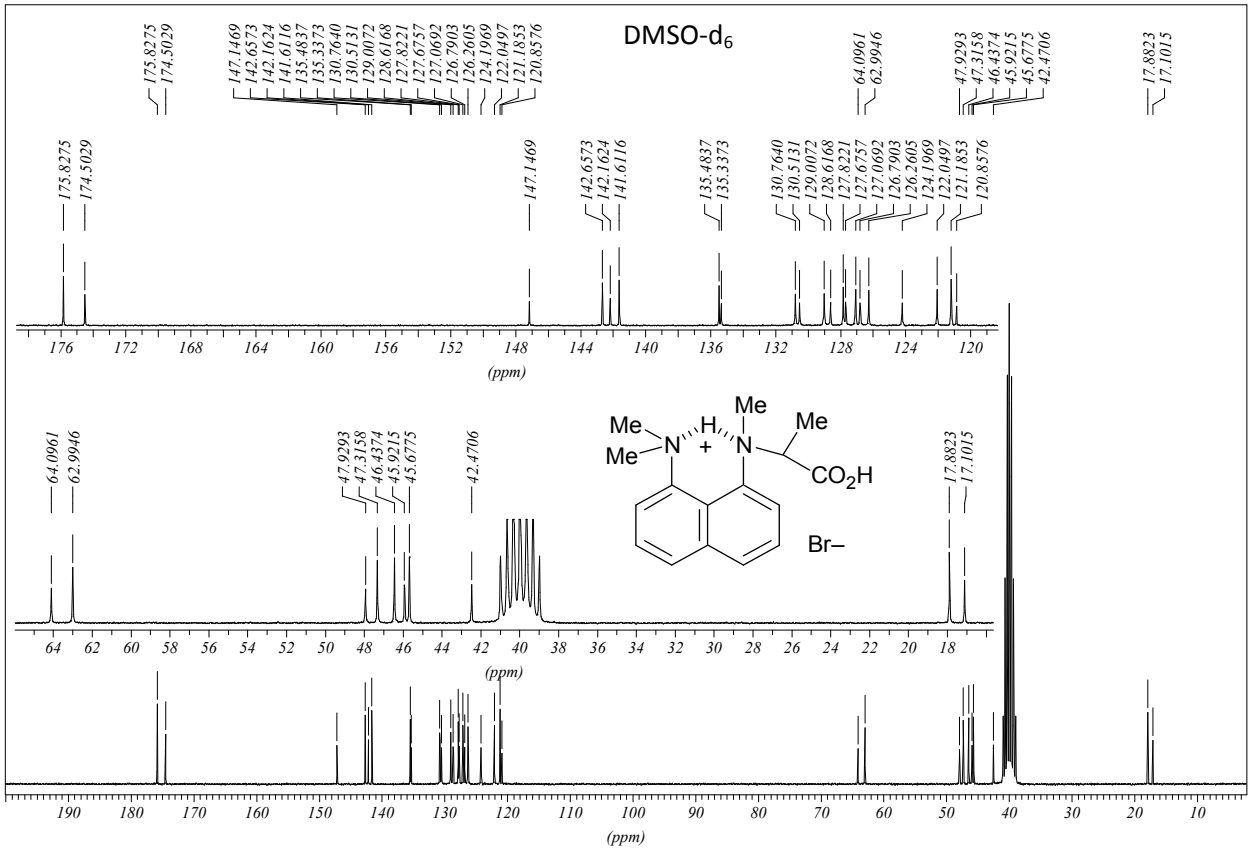
Integral
(ppm)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Me
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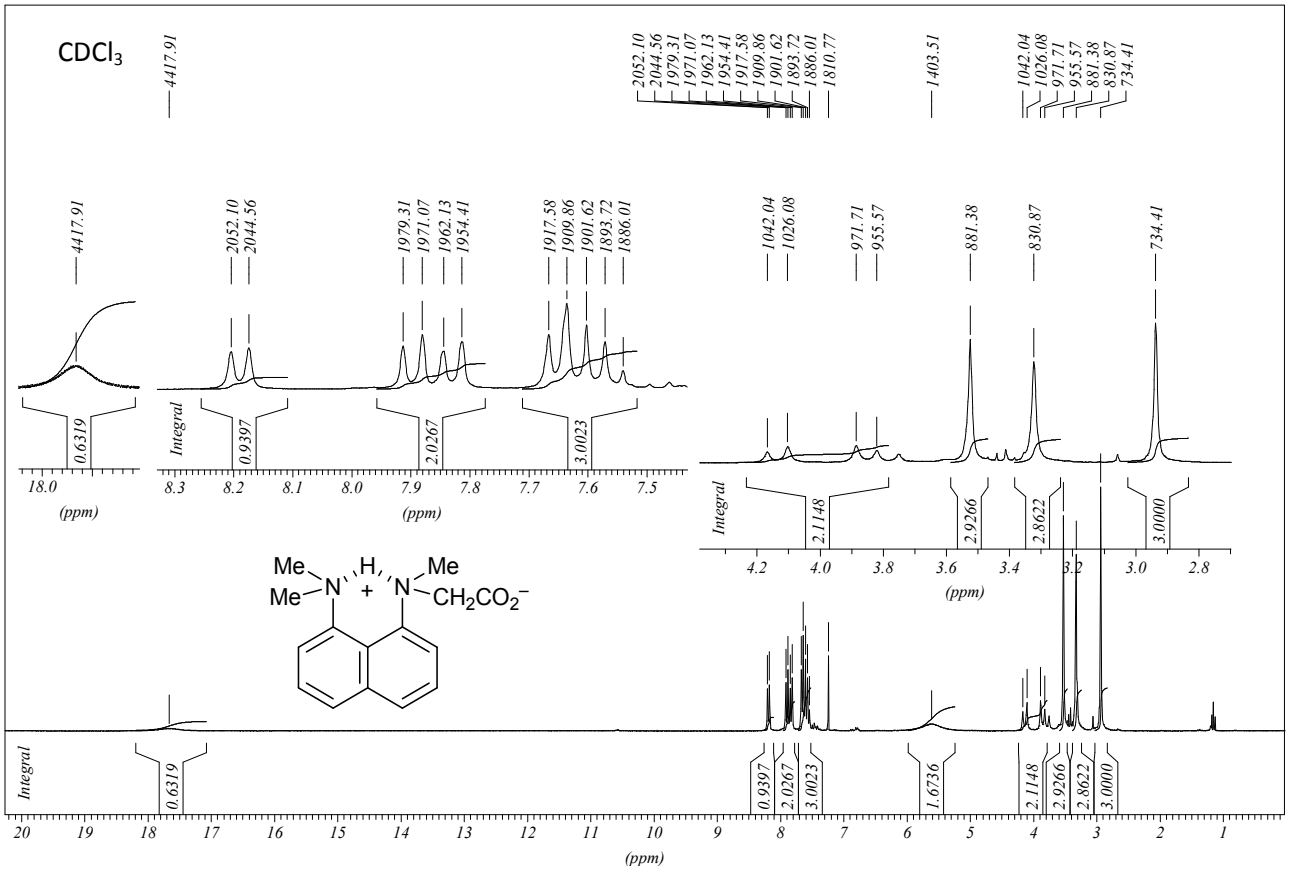
CO2H
Br–
(ppm)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Integral
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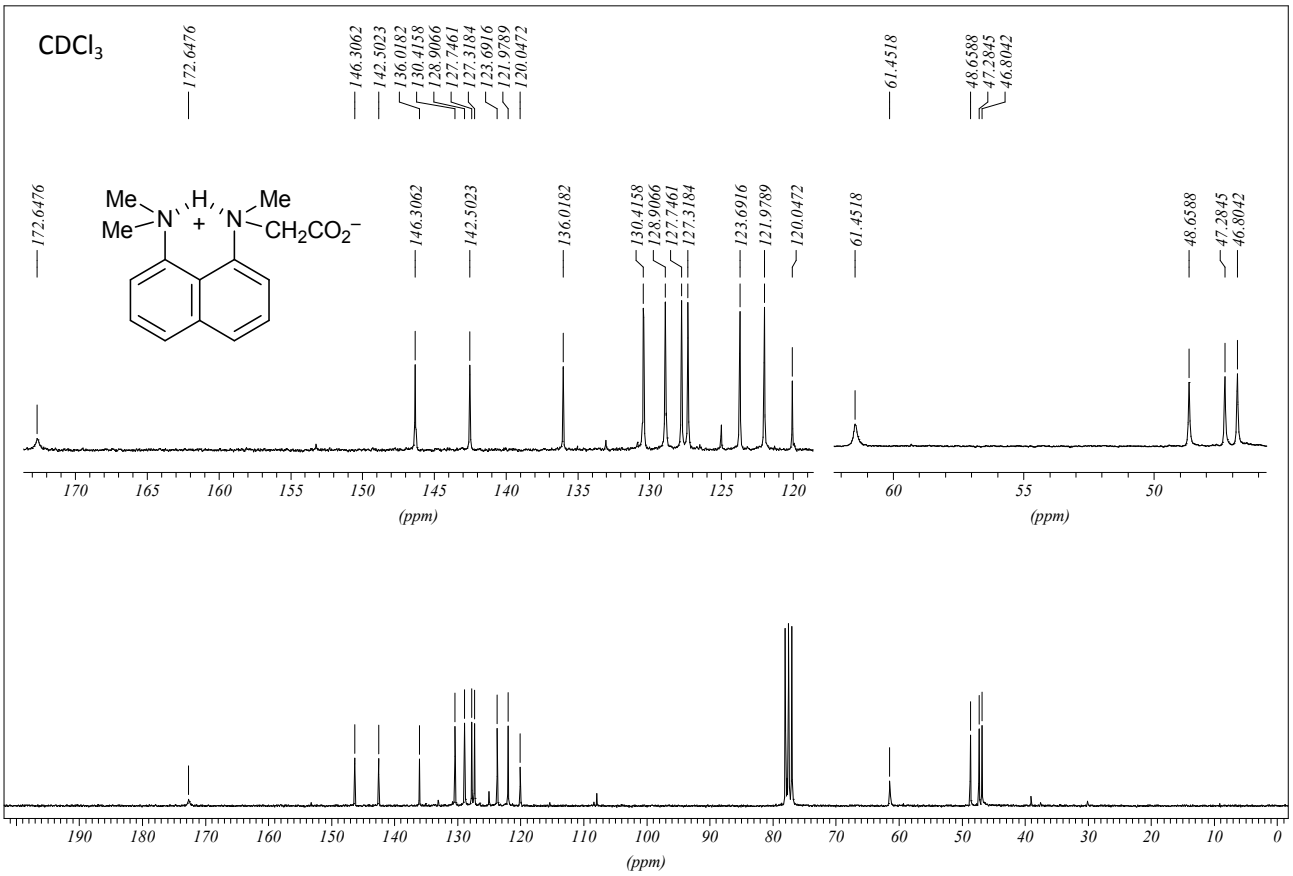
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120.0472
61.4518
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47.2845
46.8042
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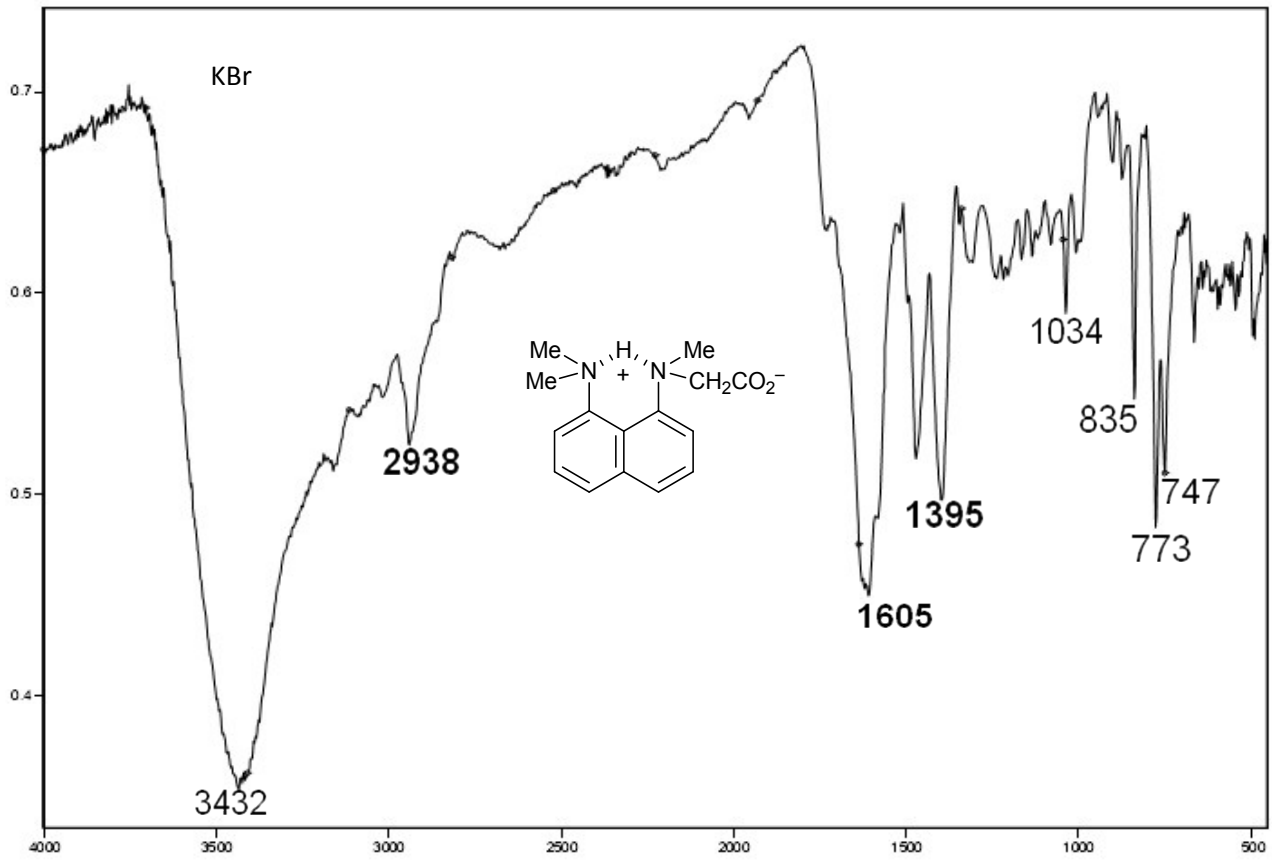
Me
N
H
N
Me
CH2CO2−
(ppm)
(ppm)
(ppm)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773
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Me
Me
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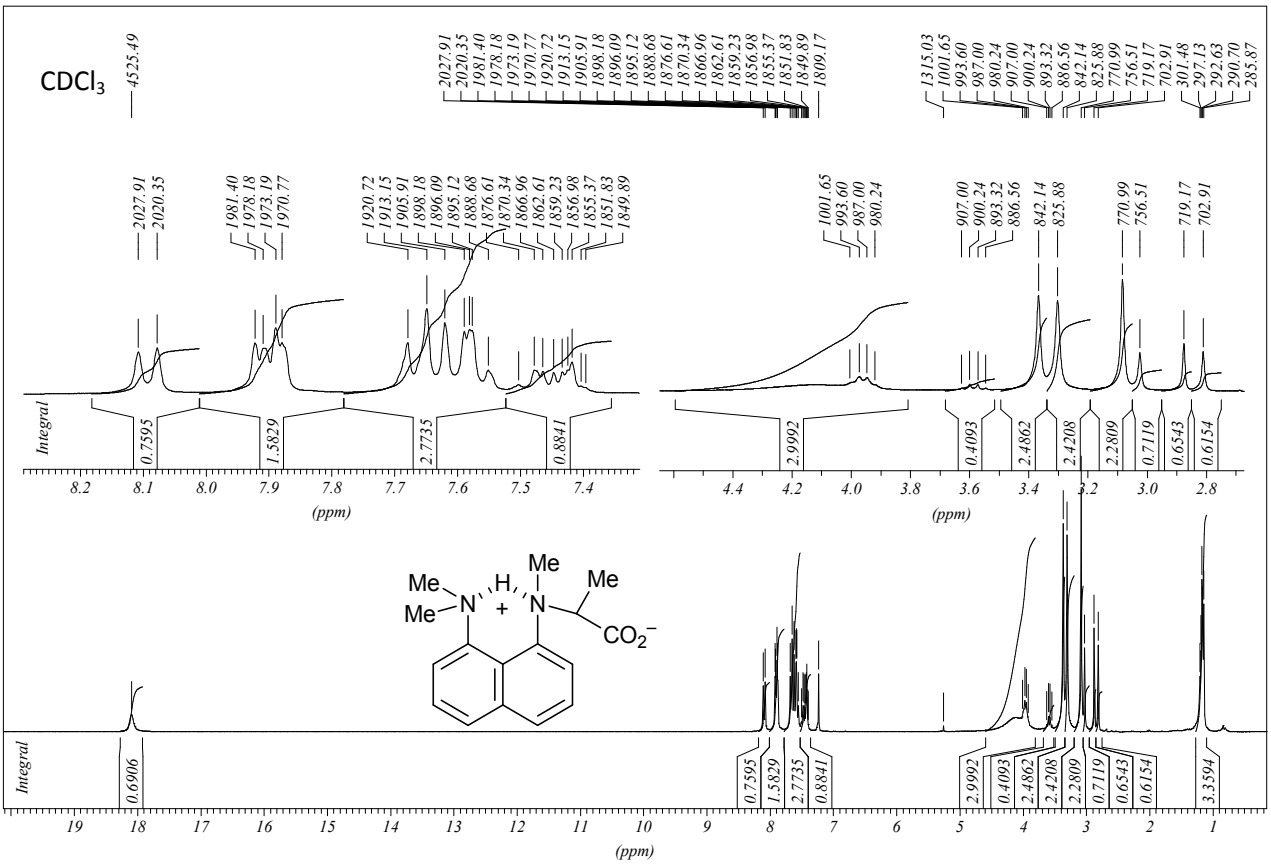
H
N
Me
CH2CO2−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CO2−
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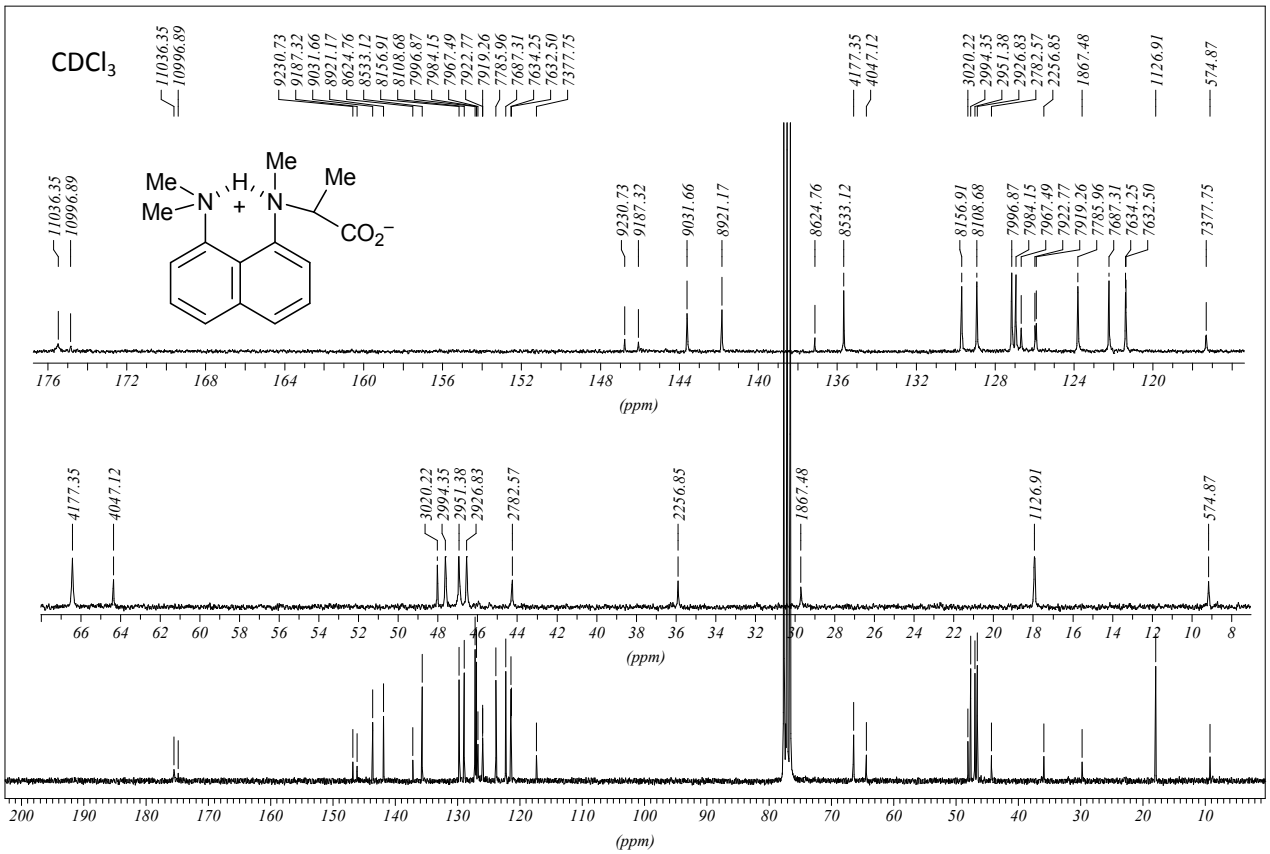
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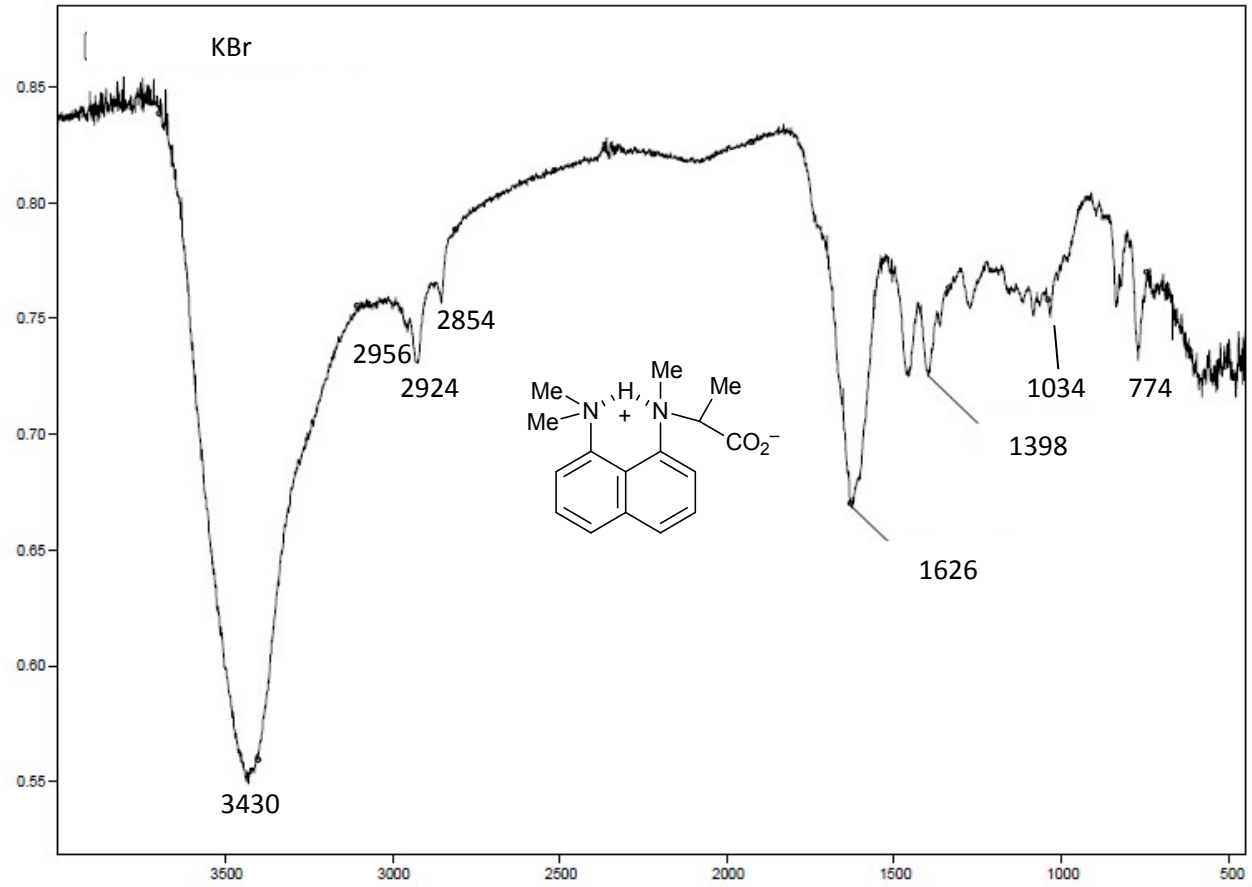
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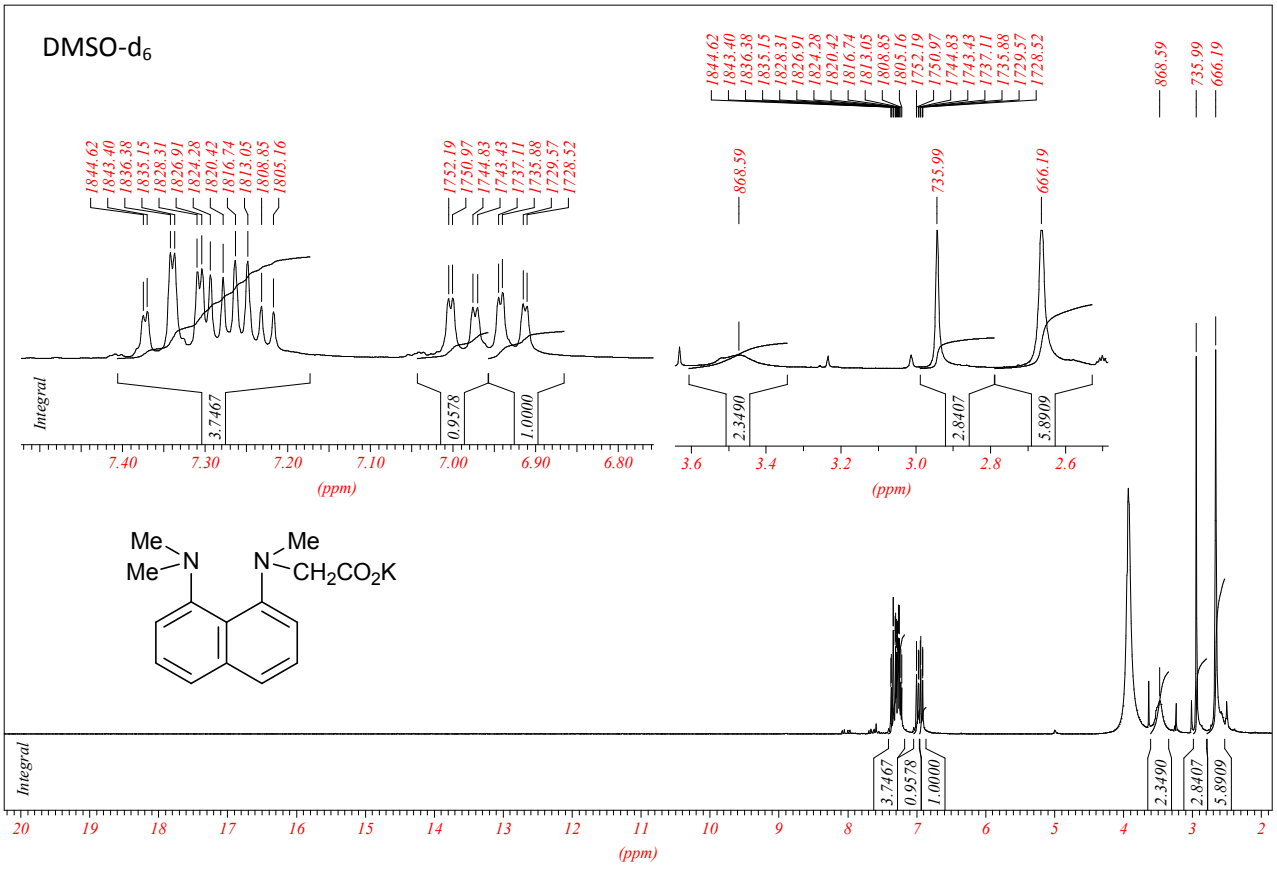
CO2−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1729.57
1728.52
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735.99
666.19
Integral
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7.30
7.20
7.10
7.00
6.90
6.80
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3.4
3.2
3.0
2.8
2.6
(ppm)
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Me
N
N
Me
CH2CO2K
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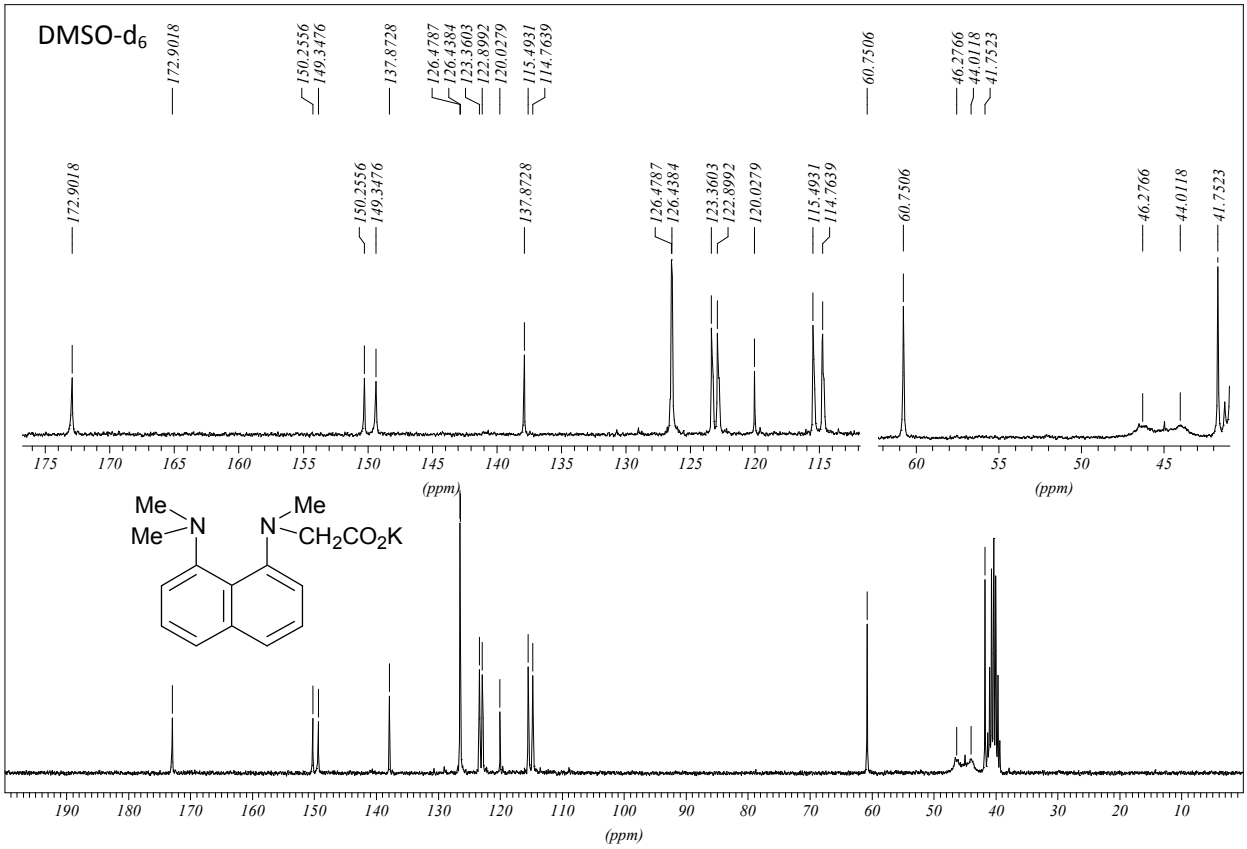
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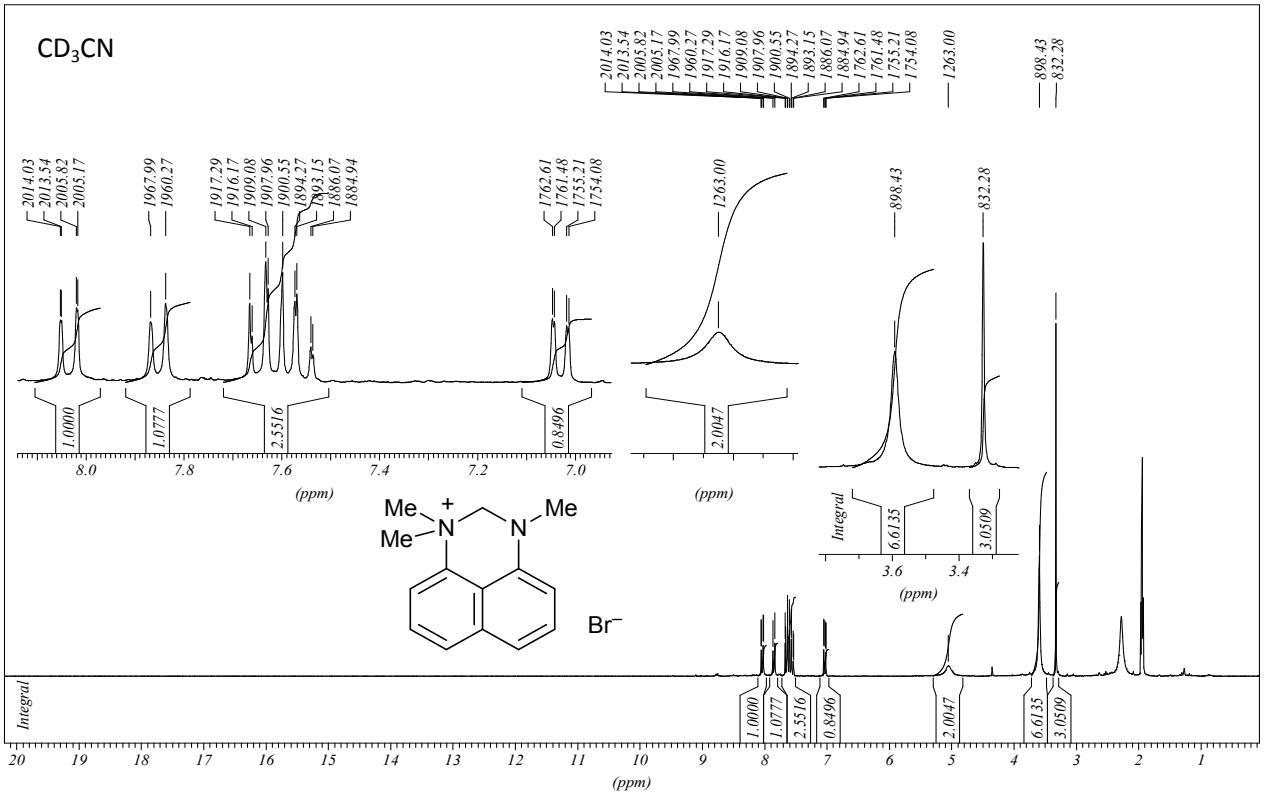
(ppm)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1762.61
1761.48
1755.21
1754.08
1263.00
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832.28
1.0000
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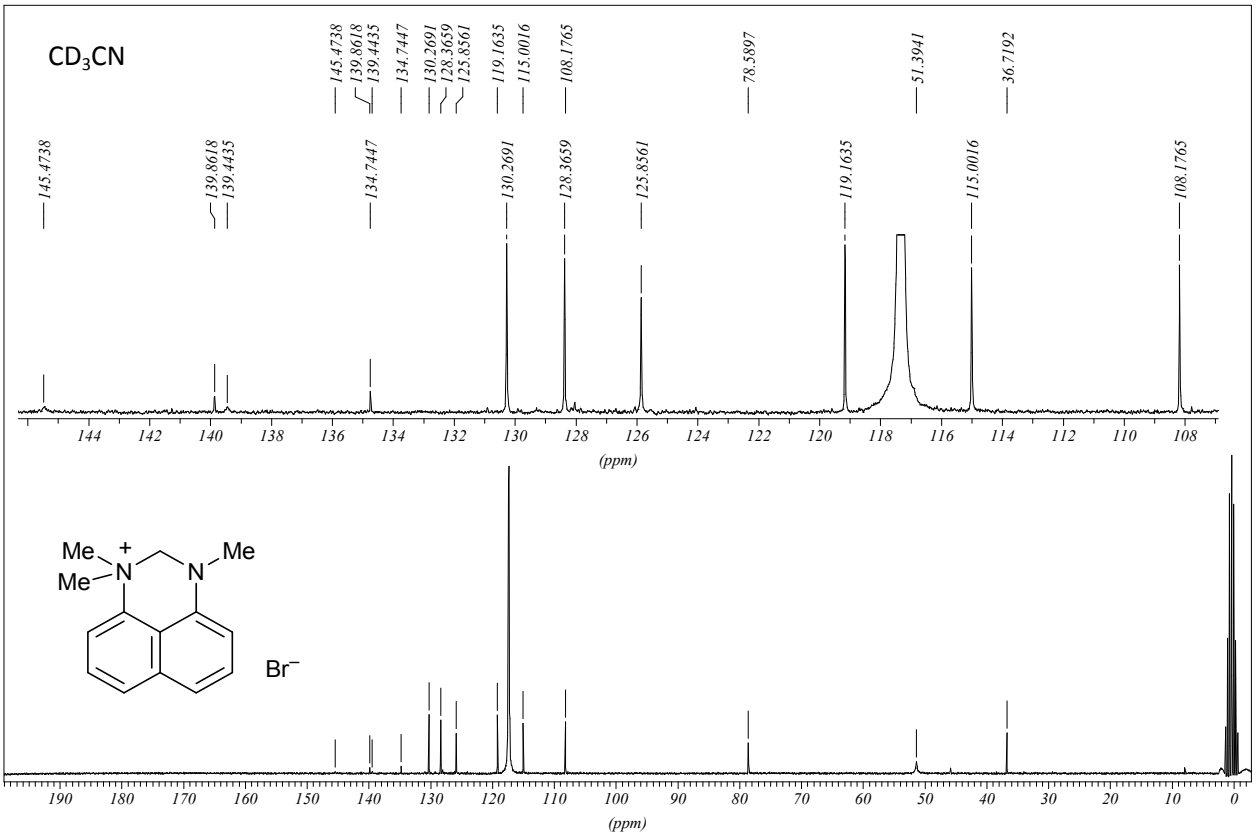
N
N
Me
Br⁻
(ppm)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Me
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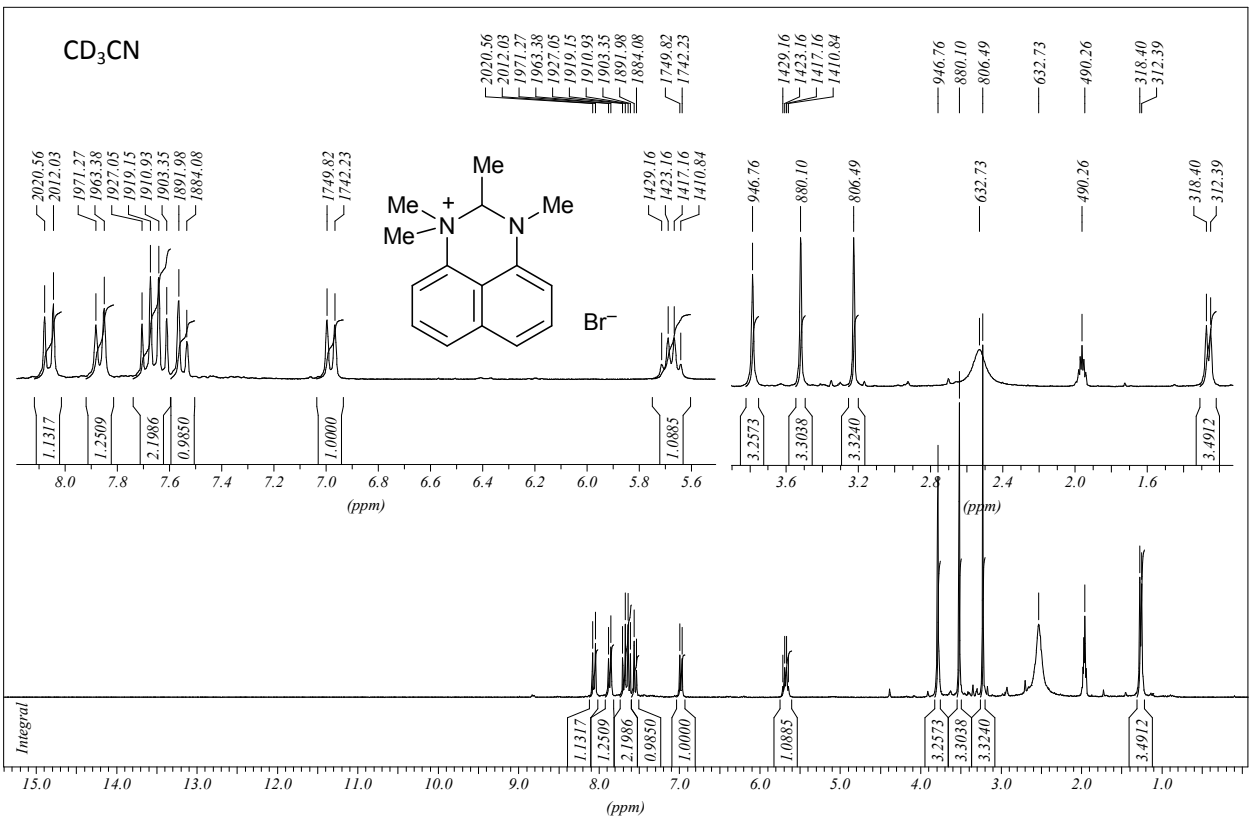
Br⁻
(ppm)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1963.38
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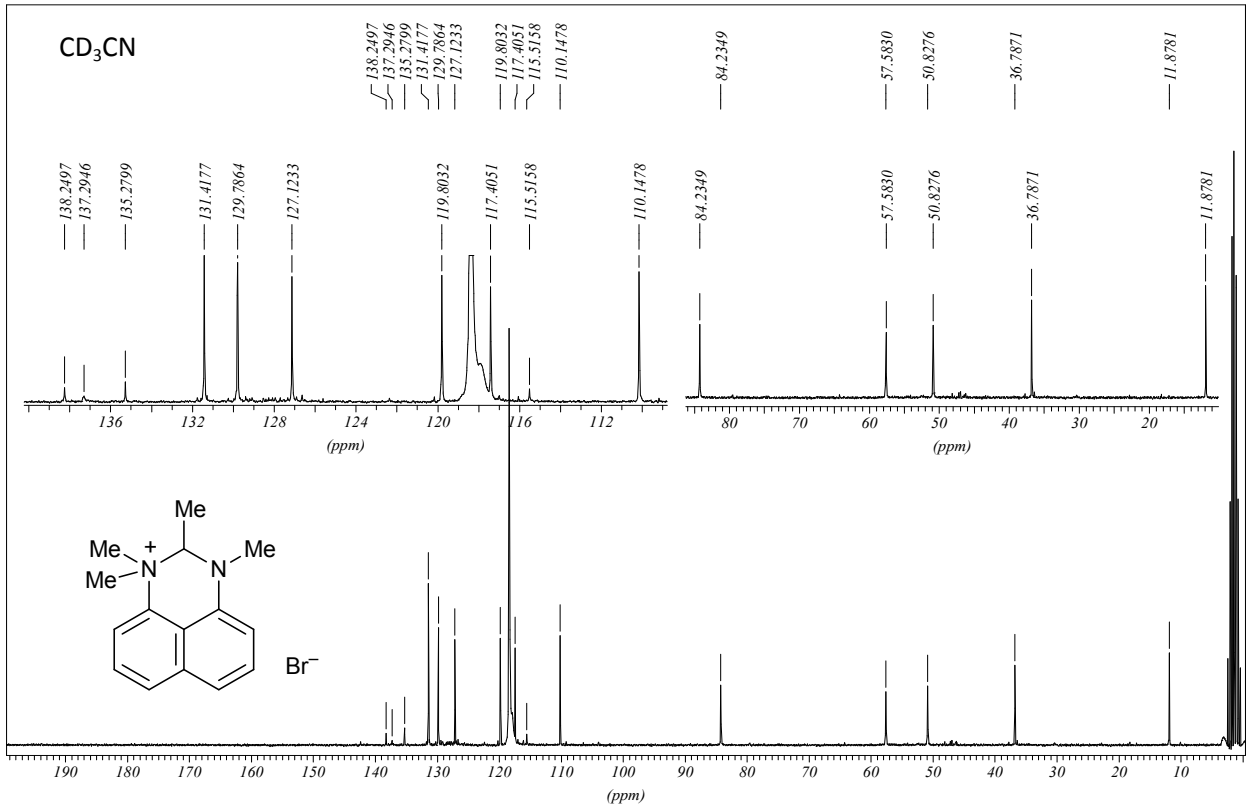
1742.23
1429.16
1423.16
1417.16
1410.84
946.76
880.10
806.49
632.73
490.26
318.40
312.39
Me
Me
N
N
Me
Me
Br⁻
1.1317
1.2509
2.1986
0.9850
1.0000
1.0885
3.2573
3.3038
3.3240
3.4912
Integral
(ppm)


CD3CN
138.2497
137.2946
135.2799
131.4177
129.7864
127.1233
119.8032
117.4051
115.5158
110.1478
84.2349
57.5830
50.8276
36.7871
11.8781
(ppm)
Me
Me
Me
N
N
Br⁻