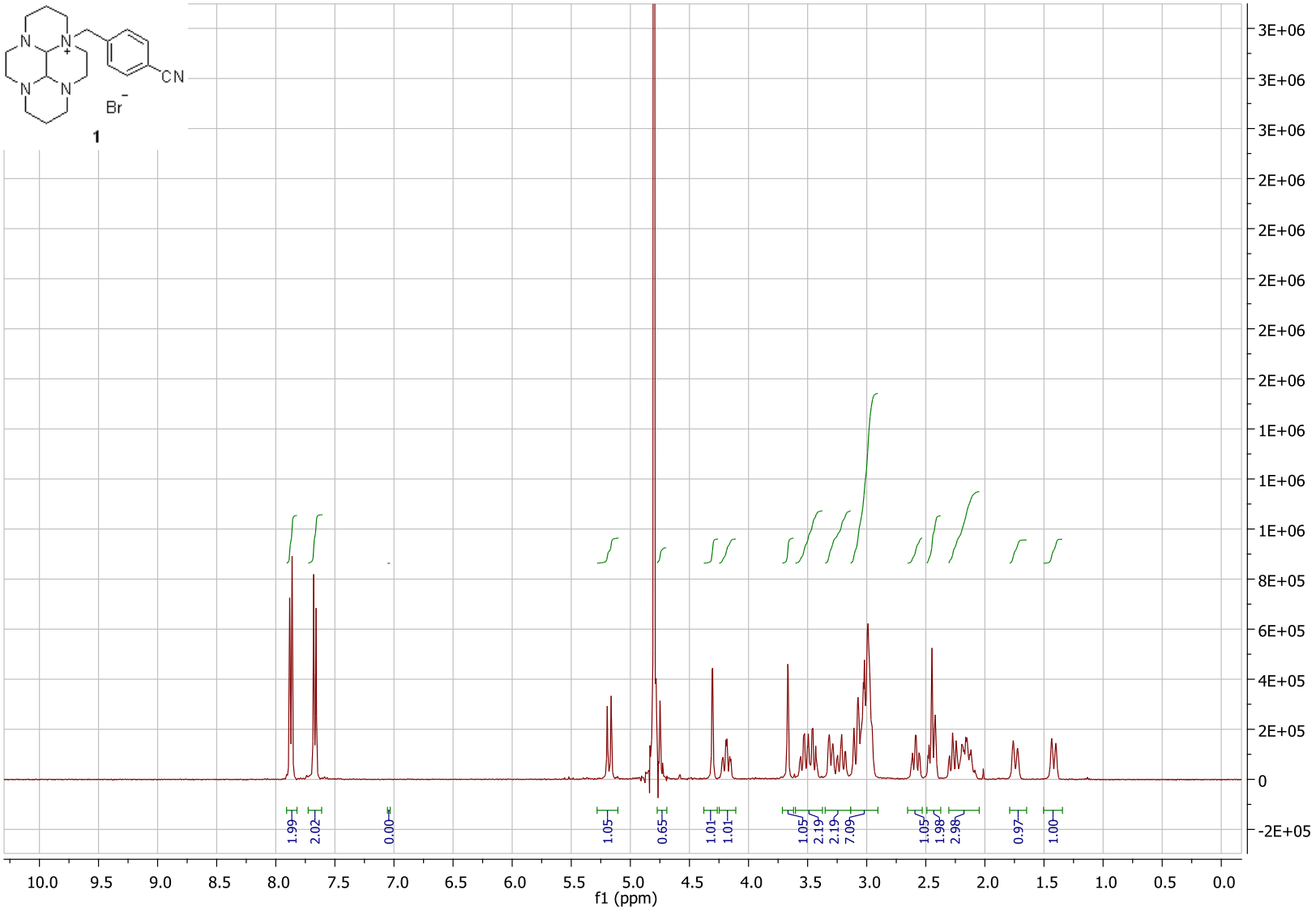
Mono- and bis-alkylation of glyoxal-bridged tetraazamacrocycles using mechanochemistry

Bassim H. Abdulwahaab, Benjamin P. Burke, Juozas Domarkas, Jon D. Silversides, Timothy J. Prior and Stephen J. Archibald[†]*

Electronic Supplementary Information

NMR


CN
Br
1
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3E+06
3E+06
2E+06
2E+06
2E+06
2E+06
2E+06
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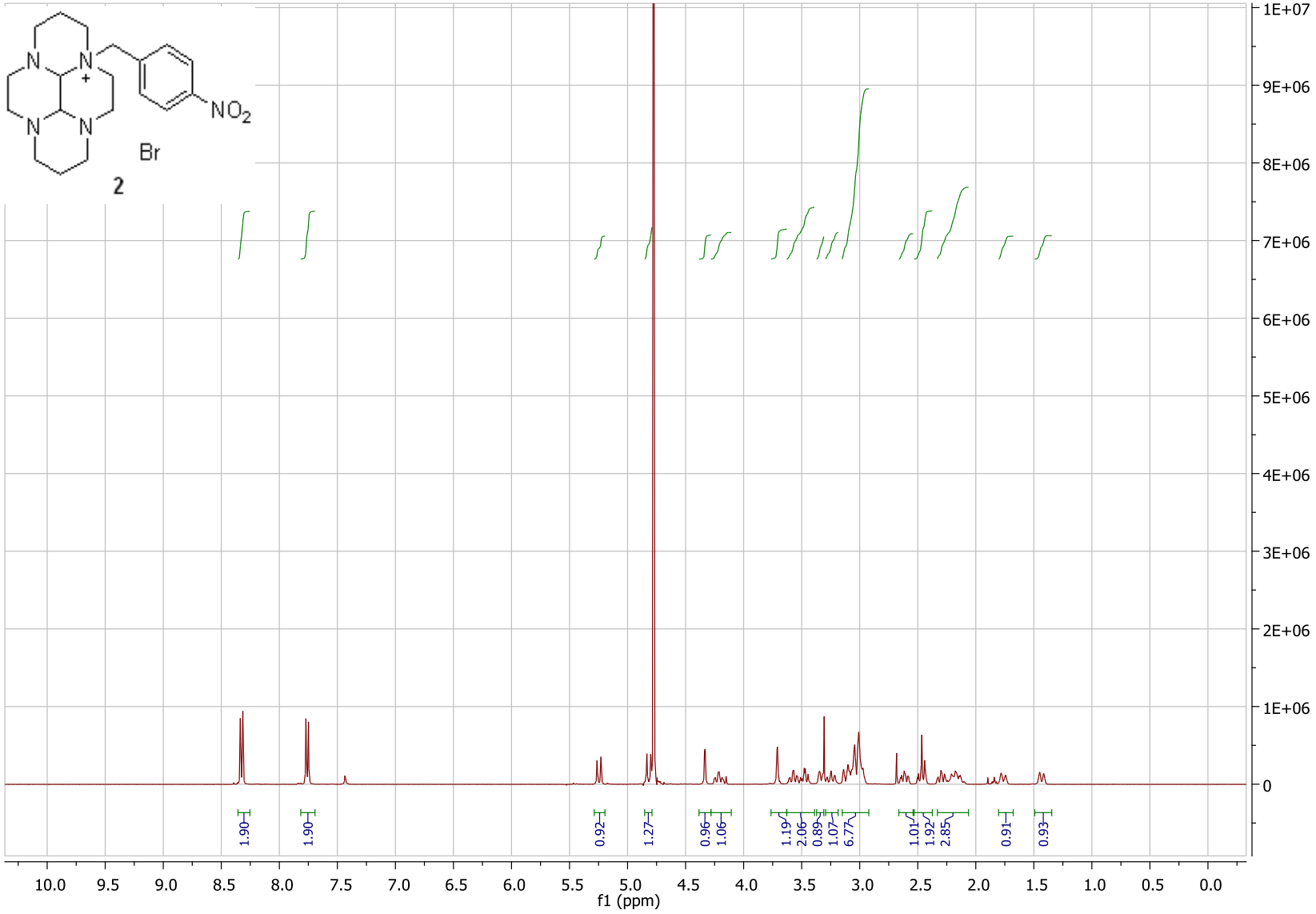
1E+06
1E+06
8E+05
6E+05
4E+05
2E+05
0
-2E+05
1.99
2.02
0.00
1.05
0.65
1.01
1.01
1.05
2.19
2.19
7.09
1.05
1.98
2.98
0.97
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


N
N
+
N
N
NO2
Br
2
1E+07
9E+06
8E+06
7E+06
6E+06
5E+06
4E+06
3E+06
2E+06
1E+06
0
1.90
1.90
0.92
1.27
0.96
1.06
1.19
2.06
0.89
1.07
6.77
1.01
1.92
2.85
0.91
0.93
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
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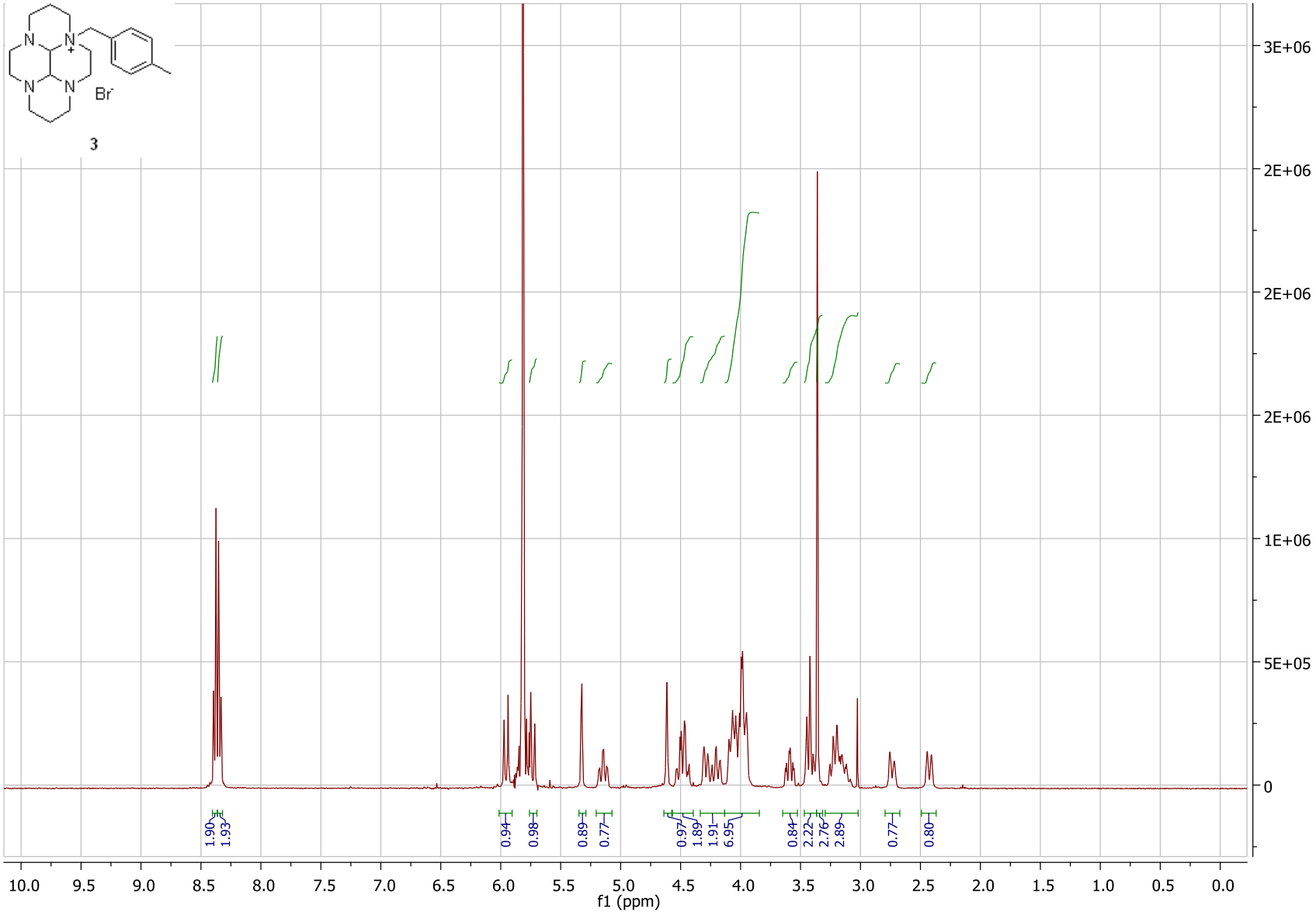
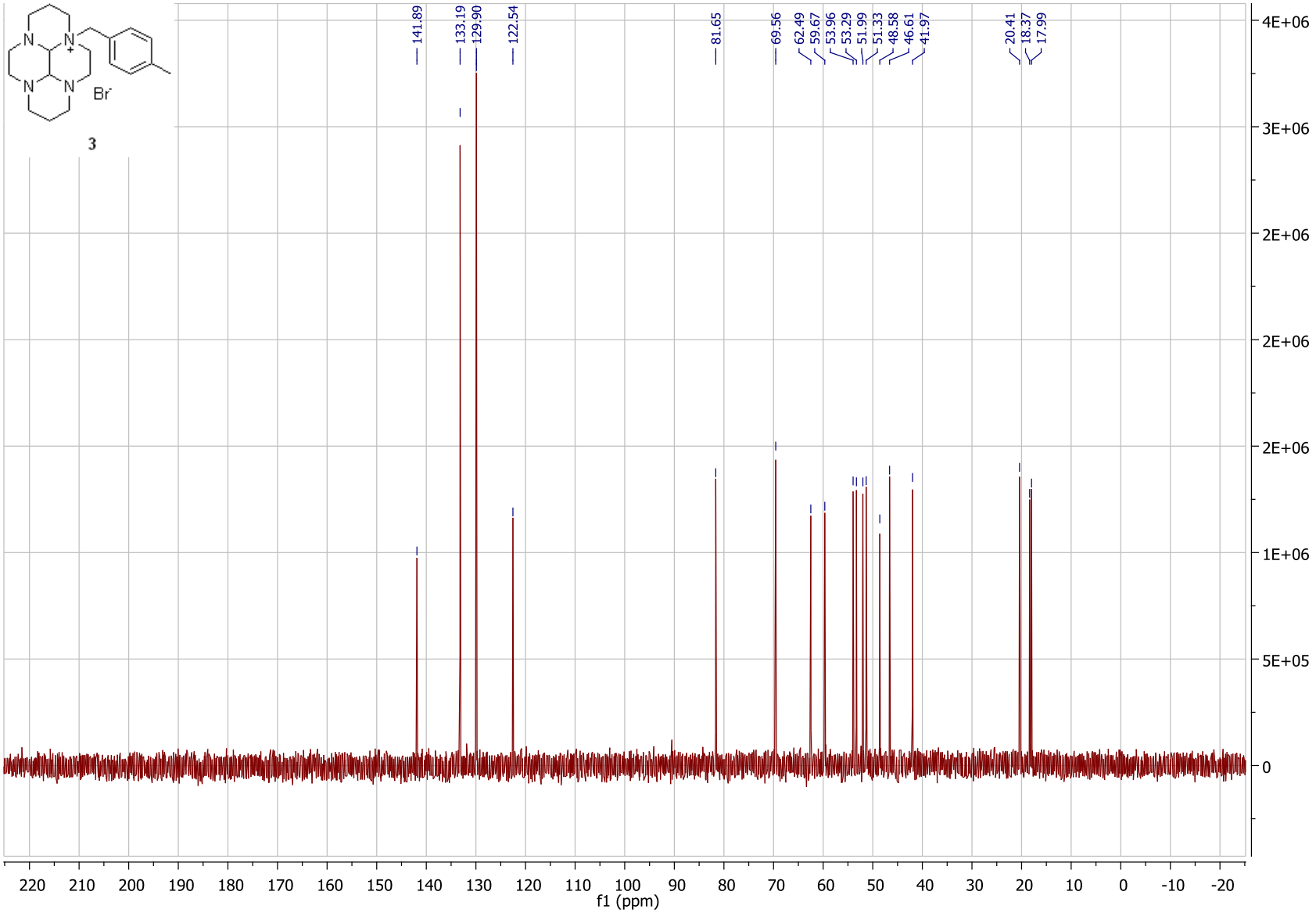
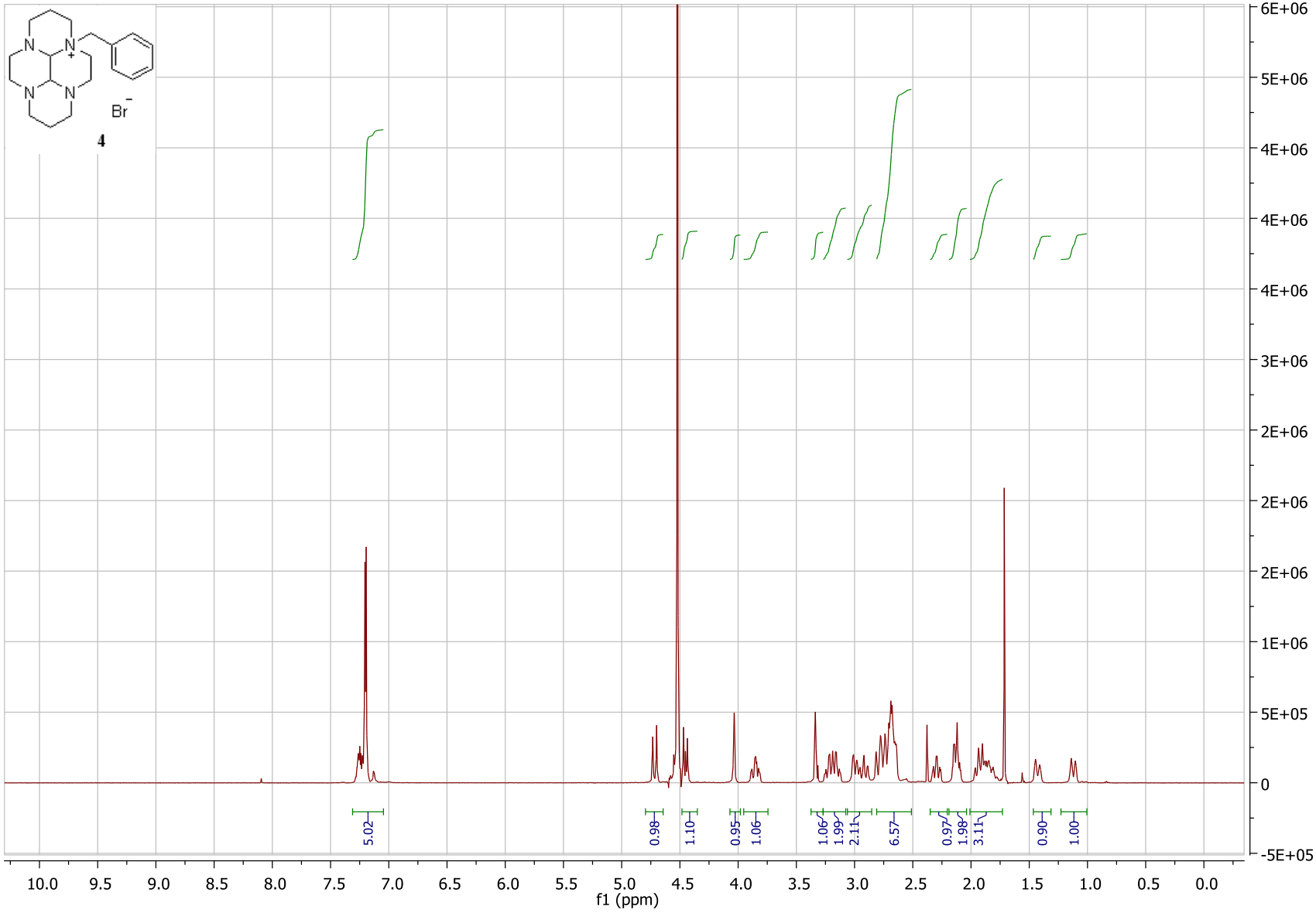
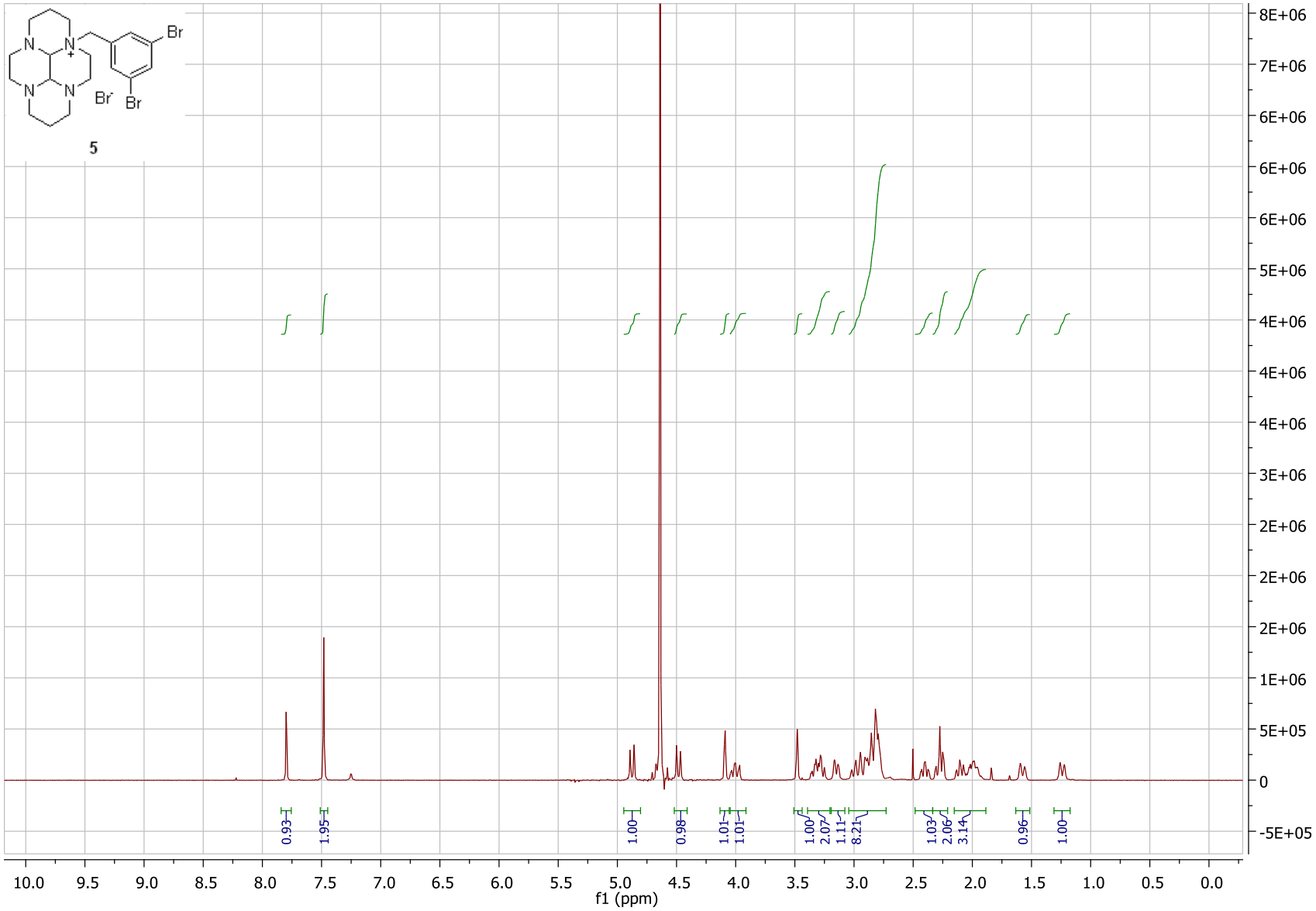
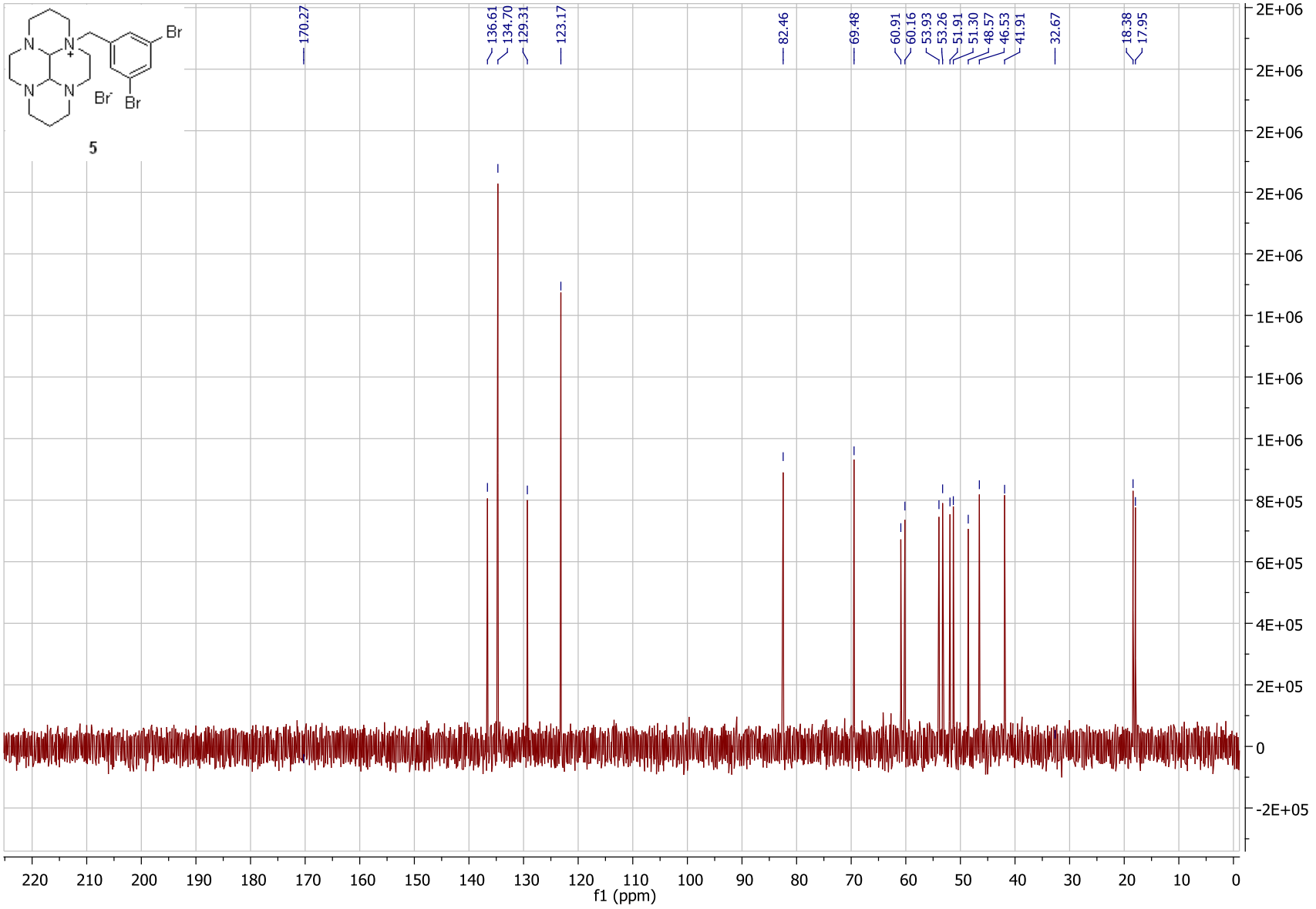
1.0
0.5
0.0
f1 (ppm)

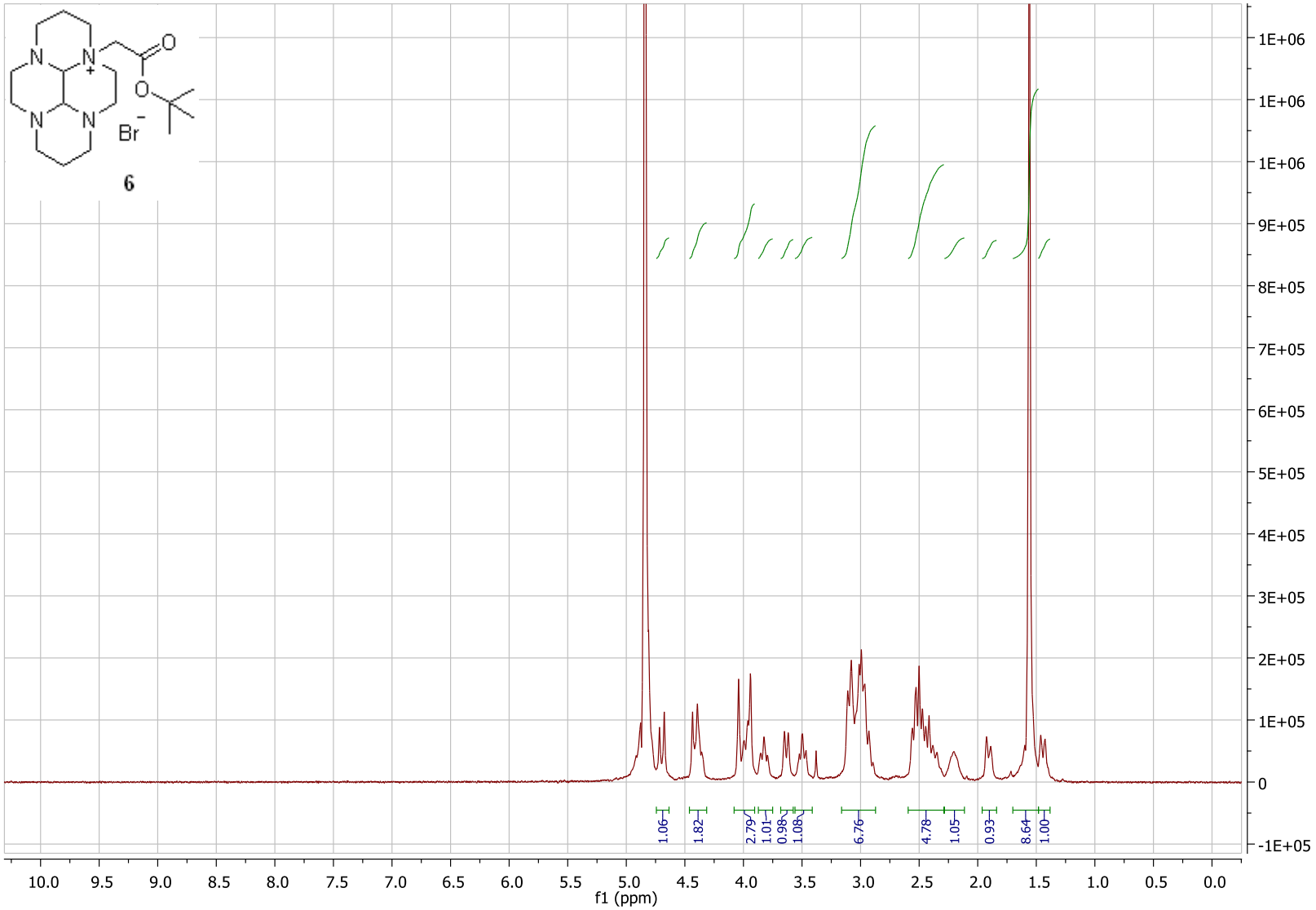

Br
3
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
1.90
1.93
0.94
0.98
0.89
0.77
0.97
1.89
1.91
6.95
0.84
2.22
2.76
2.89
0.77
0.80
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

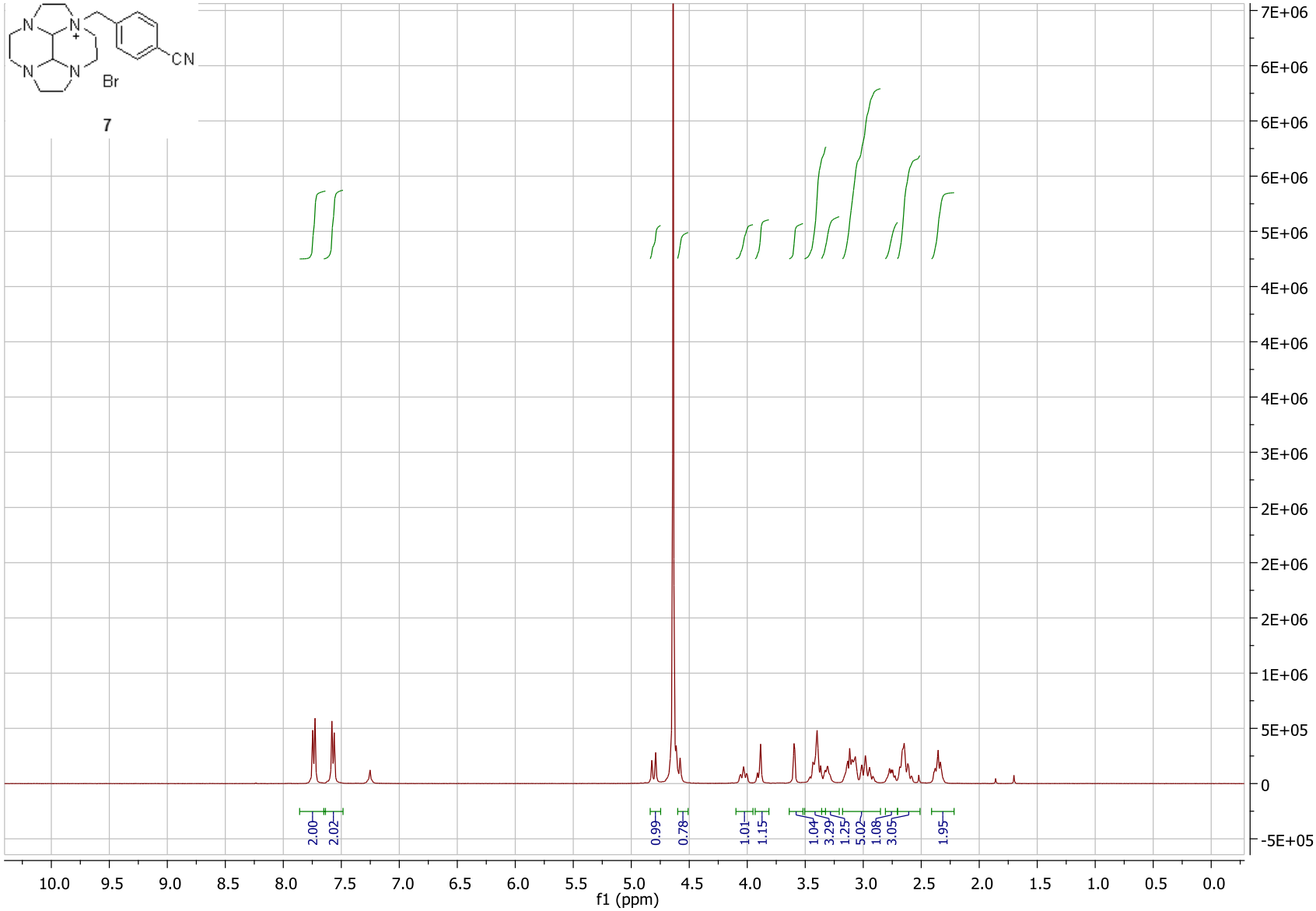

141.89
133.19
129.90
122.54
81.65
69.56
62.49
59.67
53.96
53.29
51.99
51.33
48.58
46.61
41.97
20.41
18.37
17.99
Br
3
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

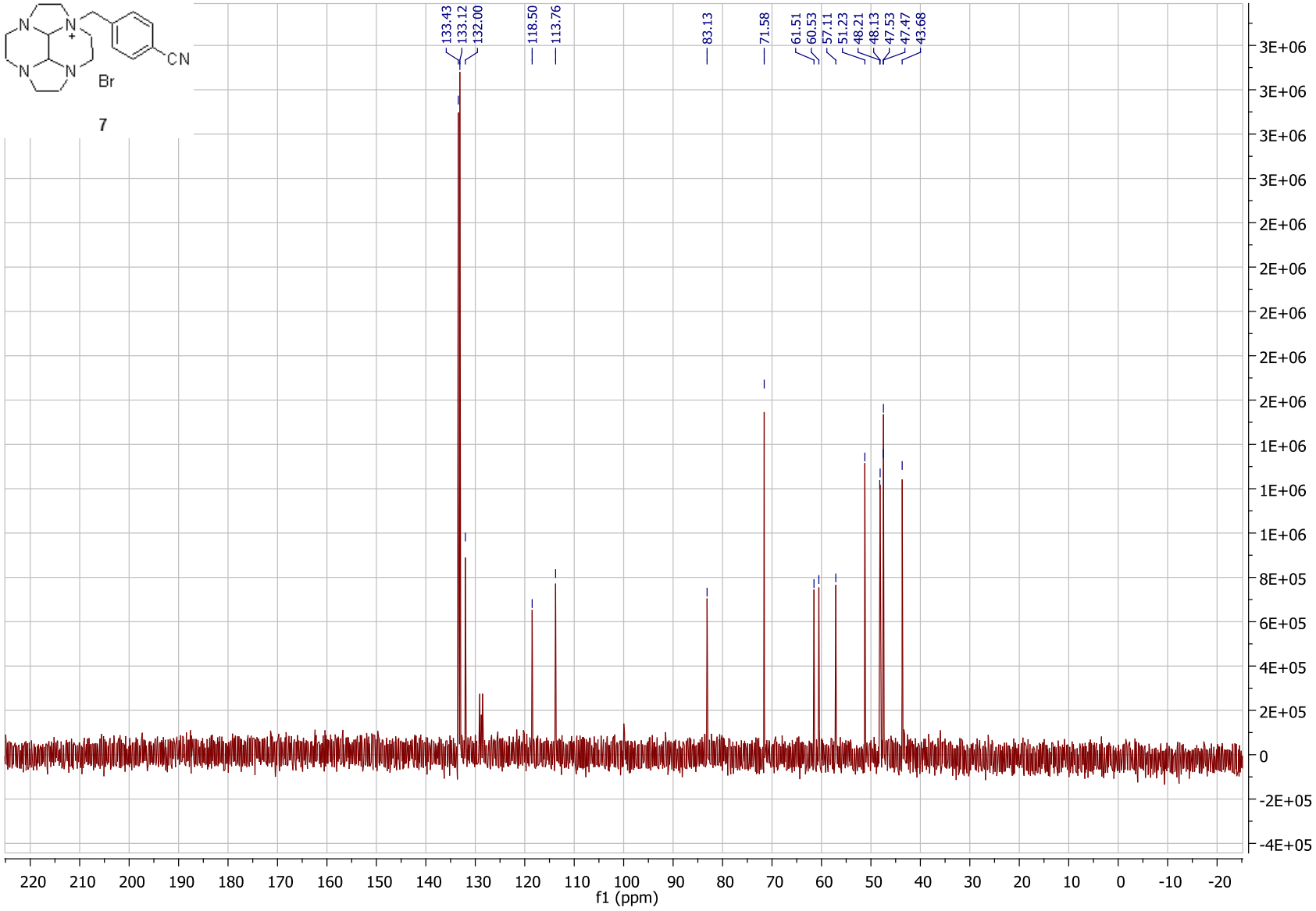

Br
4
6E+06
5E+06
4E+06
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
-5E+05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
5.02
0.98
1.10
0.95
1.06
1.06
1.99
2.11
6.57
0.97
1.98
3.11
0.90
1.00

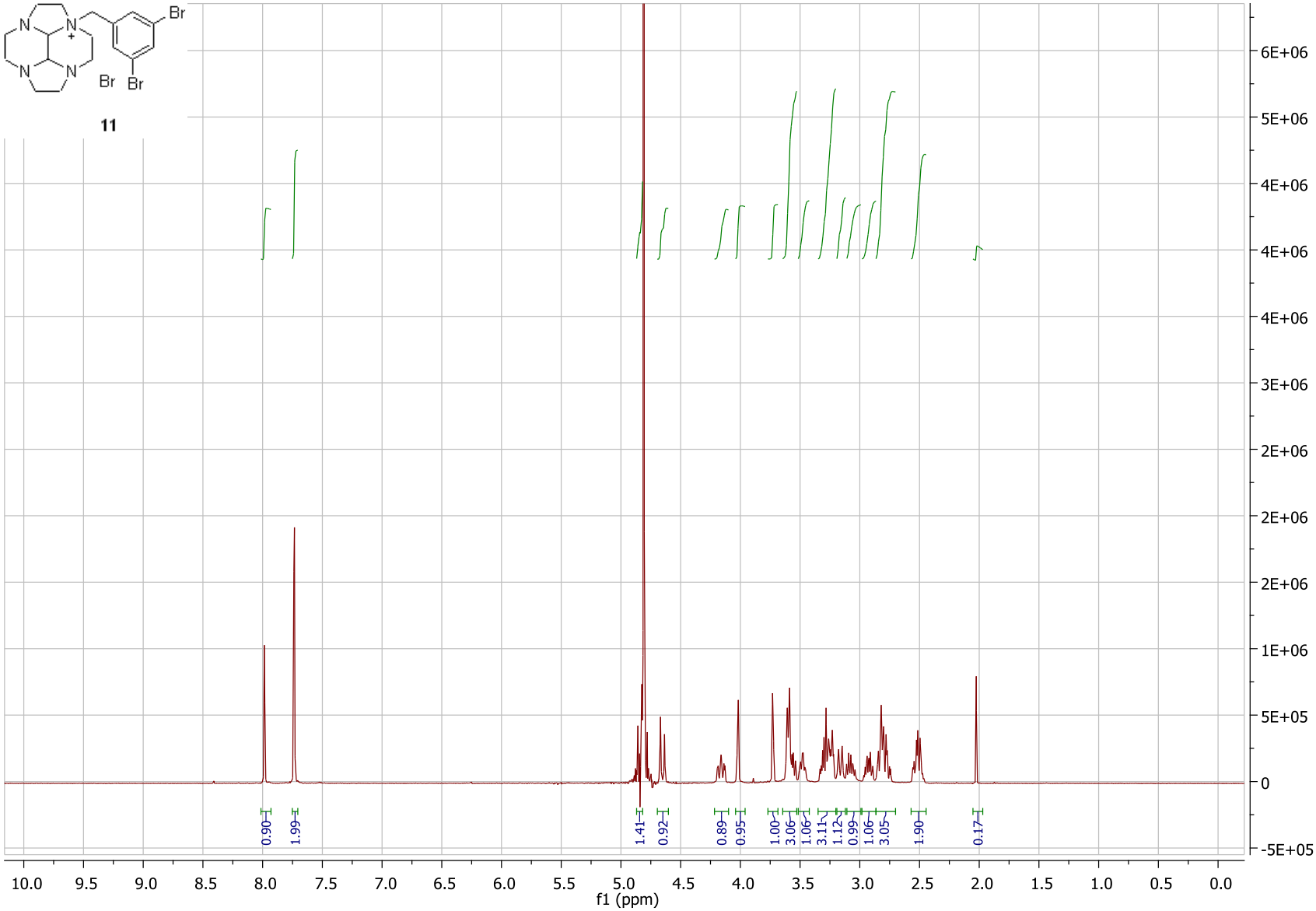

Br
Br
Br
5
8E+06
7E+06
6E+06
6E+06
6E+06
5E+06
4E+06
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
-5E+05
0.93
1.95
1.00
0.98
1.01
1.01
1.00
2.07
1.11
8.21
1.03
2.06
3.14
0.96
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

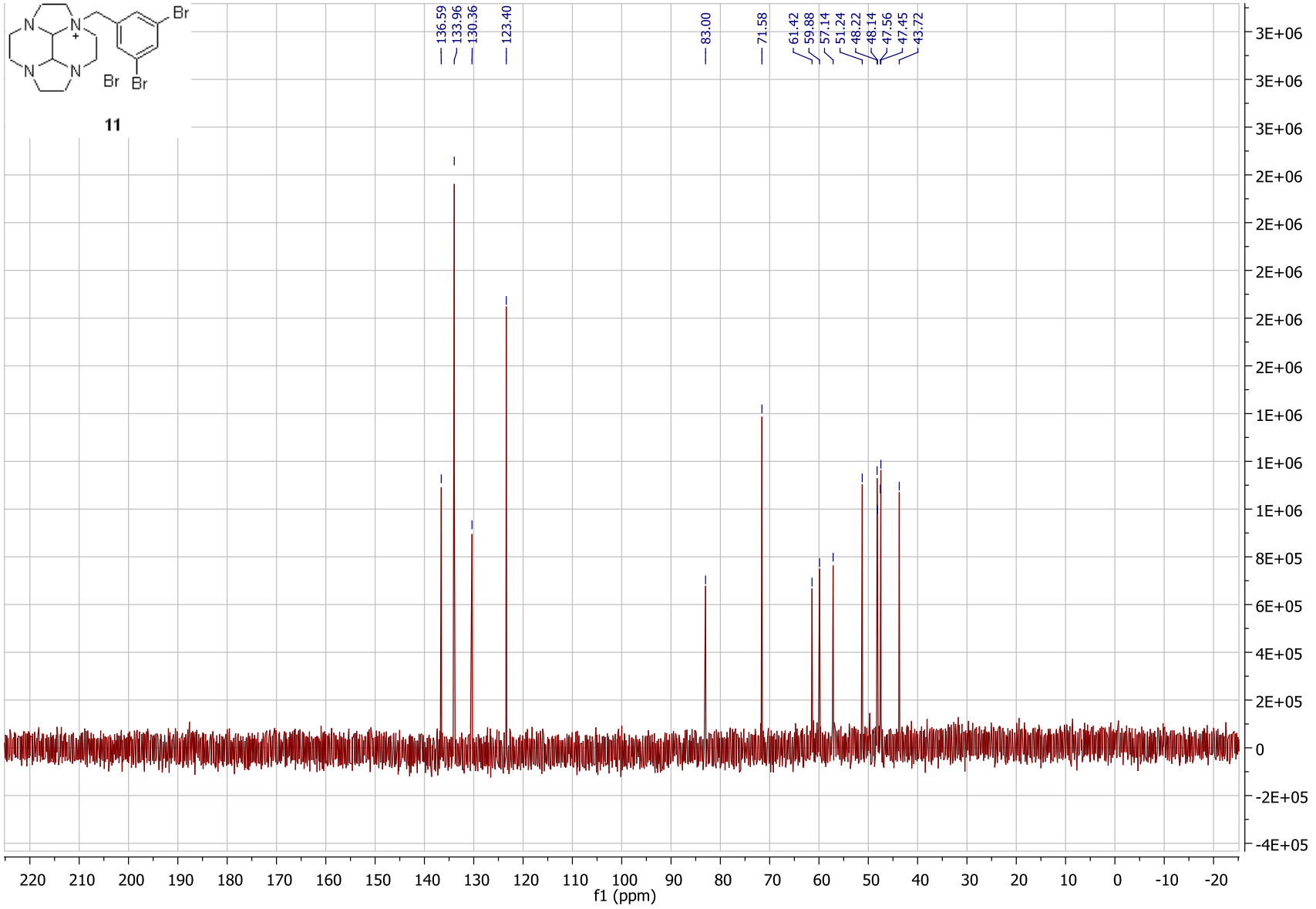

5
170.27
136.61
134.70
129.31
123.17
82.46
69.48
60.91
60.16
53.93
53.26
51.91
51.30
48.57
46.53
41.91
32.67
18.38
17.95
2E+06
1E+06
8E+05
6E+05
4E+05
2E+05
0
-2E+05
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

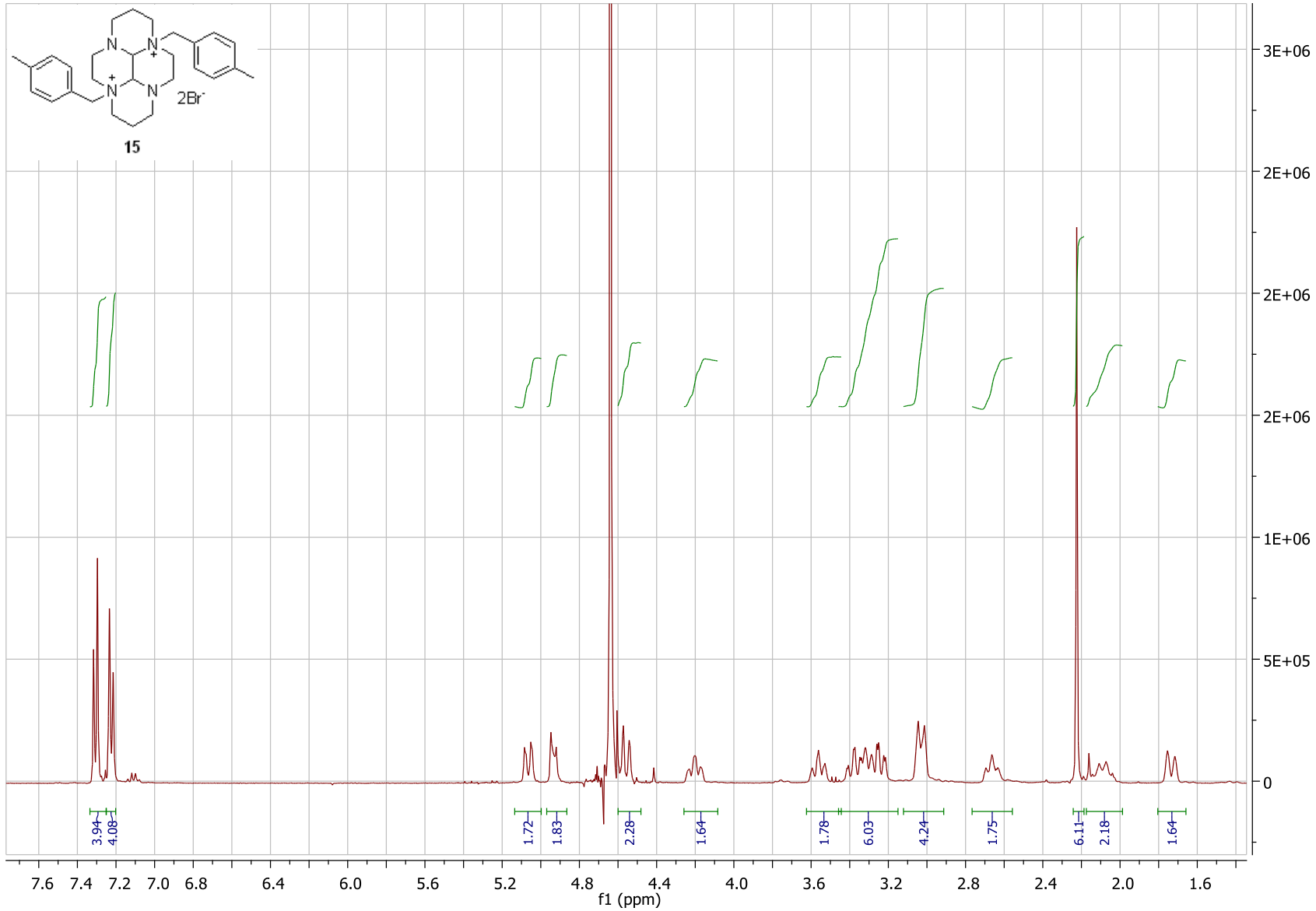

6
Br
1E+06
1E+06
1E+06
9E+05
8E+05
7E+05
6E+05
5E+05
4E+05
3E+05
2E+05
1E+05
0
-1E+05
1.06
1.82
2.79
1.01
0.98
1.08
6.76
4.78
1.05
0.93
8.64
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

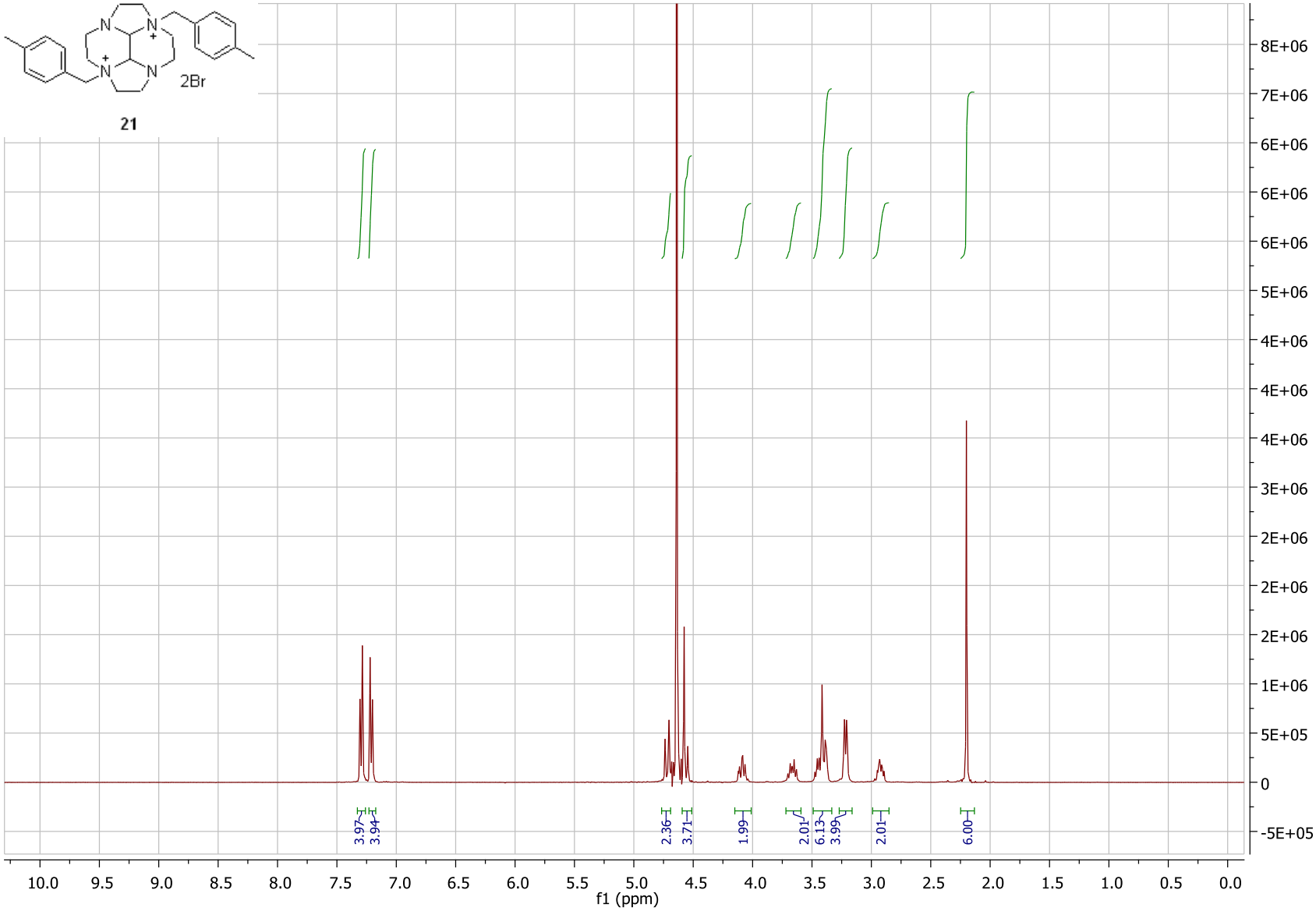

N
N
+
N
N
Br
CN
7
7E+06
6E+06
6E+06
6E+06
5E+06
4E+06
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
-5E+05
2.00
2.02
0.99
0.78
1.01
1.15
1.04
3.29
1.25
5.02
1.08
3.05
1.95
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

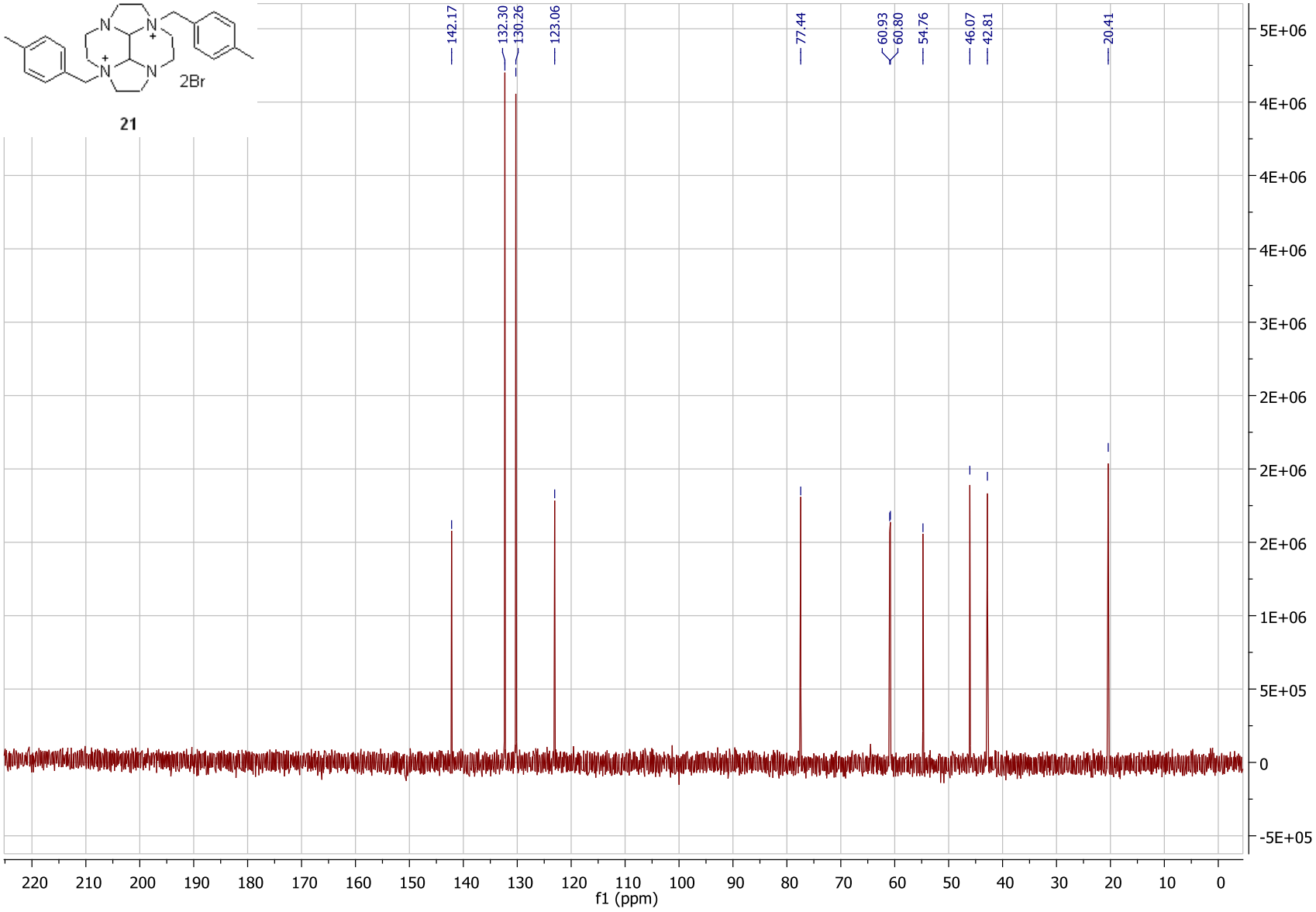

N
N
N
N
+
Br
CN
7
133.43
133.12
132.00
118.50
113.76
83.13
71.58
61.51
60.53
57.11
51.23
48.21
48.13
47.53
47.47
43.68
3E+06
3E+06
3E+06
3E+06
2E+06
2E+06
2E+06
2E+06
2E+06
2E+06
1E+06
1E+06
1E+06
8E+05
6E+05
4E+05
2E+05
0
-2E+05
-4E+05
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

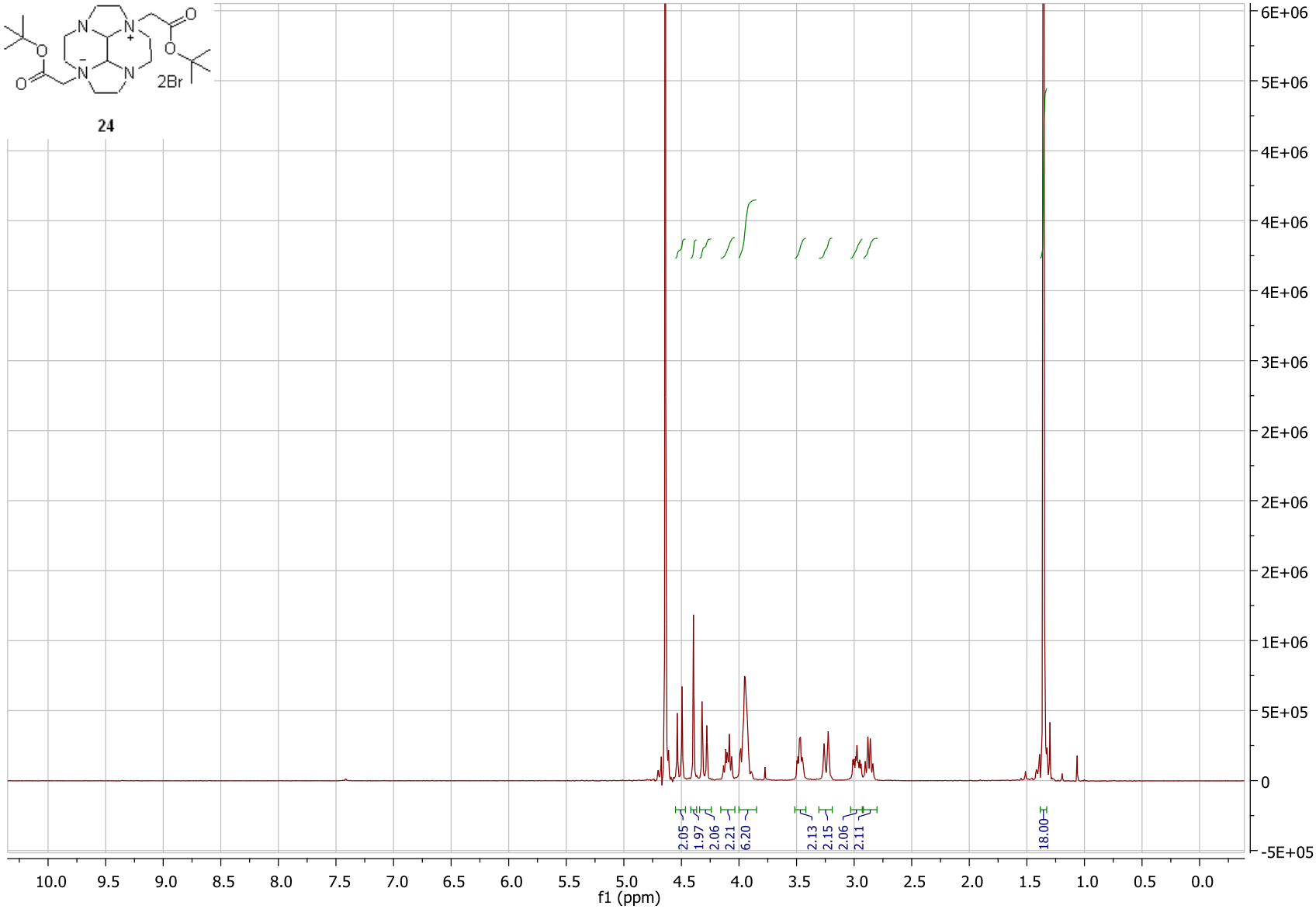

Br
Br Br
11
6E+06
5E+06
4E+06
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
-5E+05
0.90
1.99
1.41
0.92
0.89
0.95
1.00
3.06
1.06
3.11
1.12
0.99
1.06
3.05
1.90
0.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

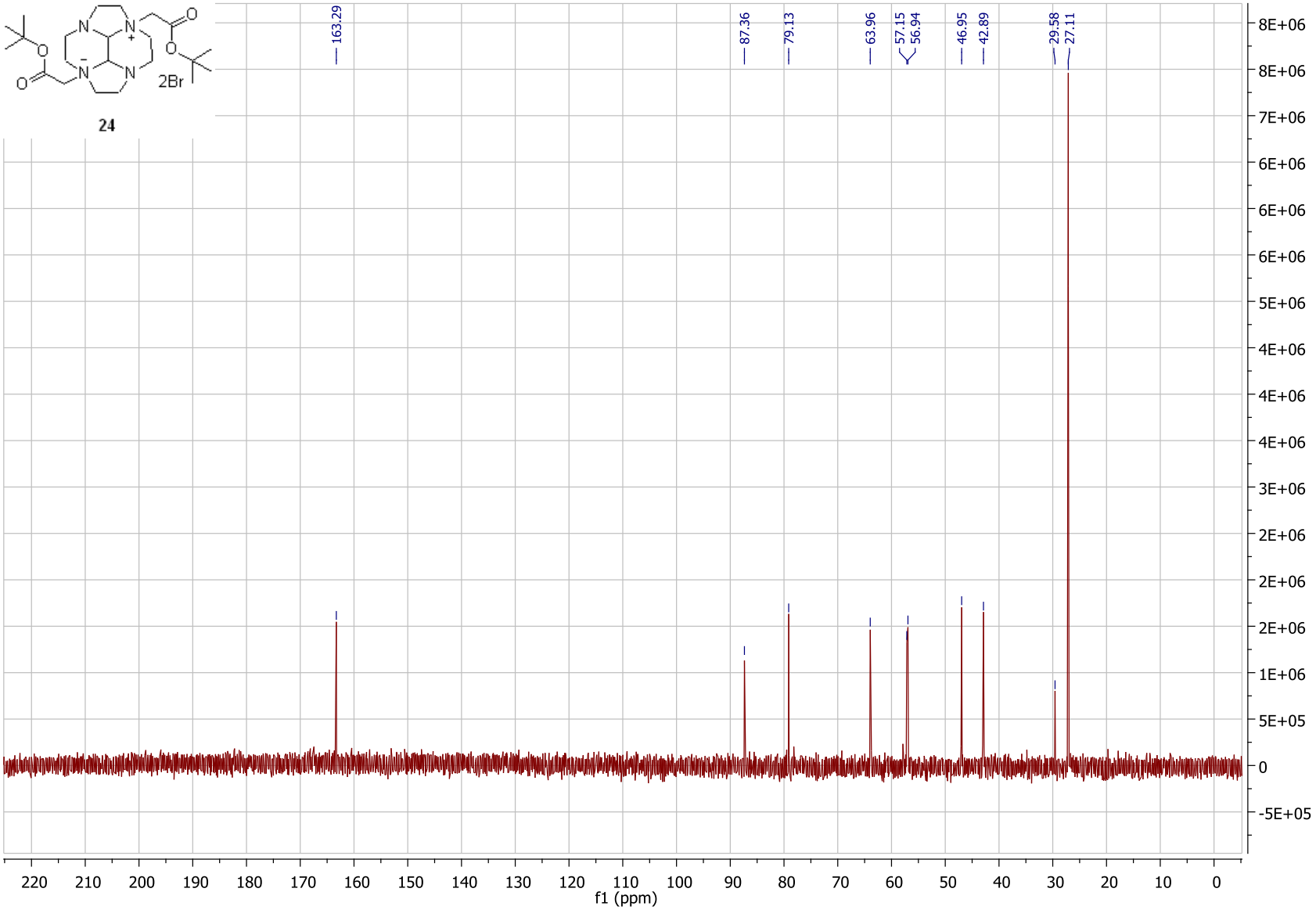

11
136.59
133.96
130.36
123.40
83.00
71.58
61.42
59.88
57.14
51.24
48.22
48.14
47.56
47.45
43.72
f1 (ppm)

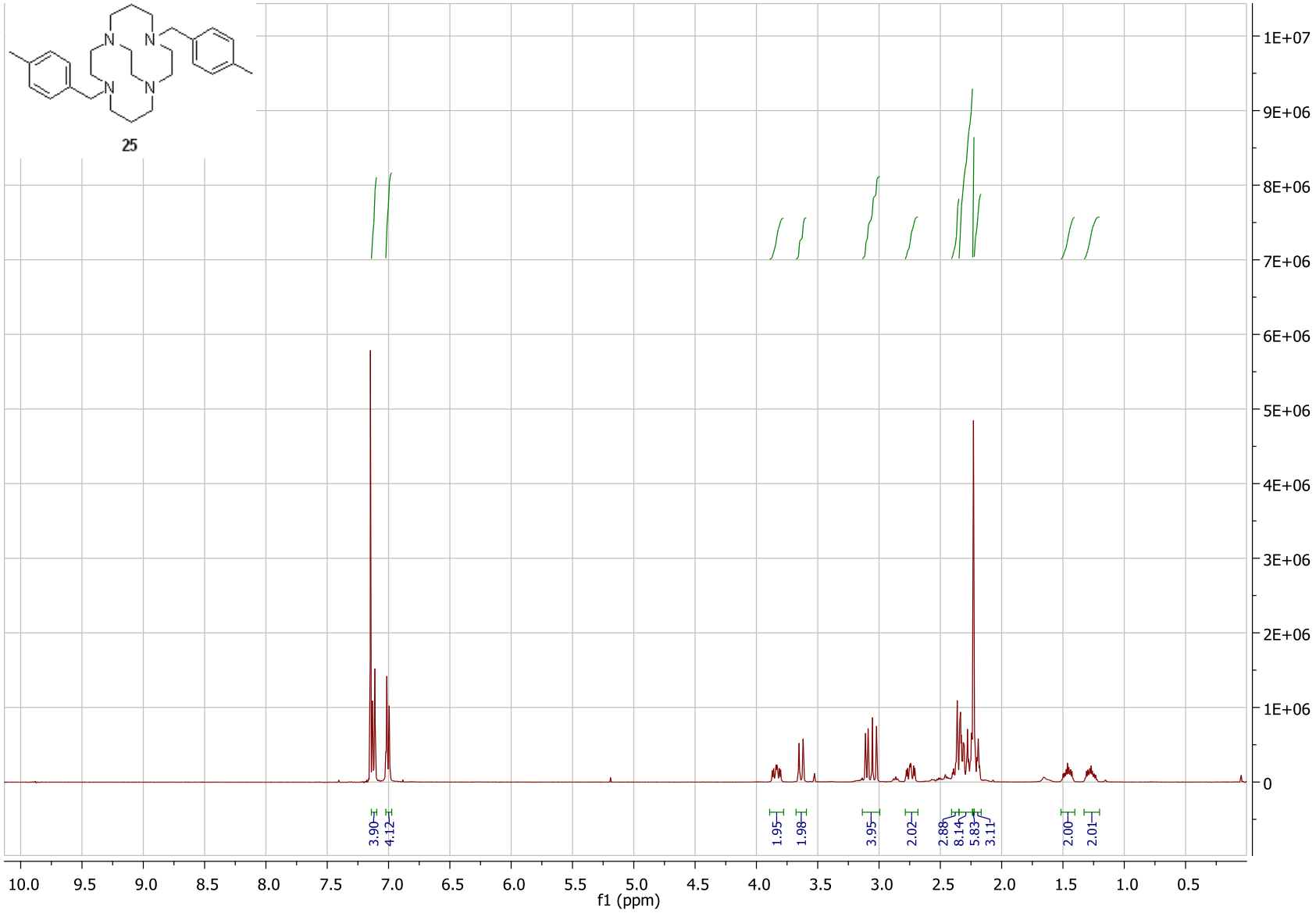

2Br-
15
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
3.94
4.08
1.72
1.83
2.28
1.64
1.78
6.03
4.24
1.75
6.11
2.18
1.64
7.6 7.4 7.2 7.0 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6
f1 (ppm)

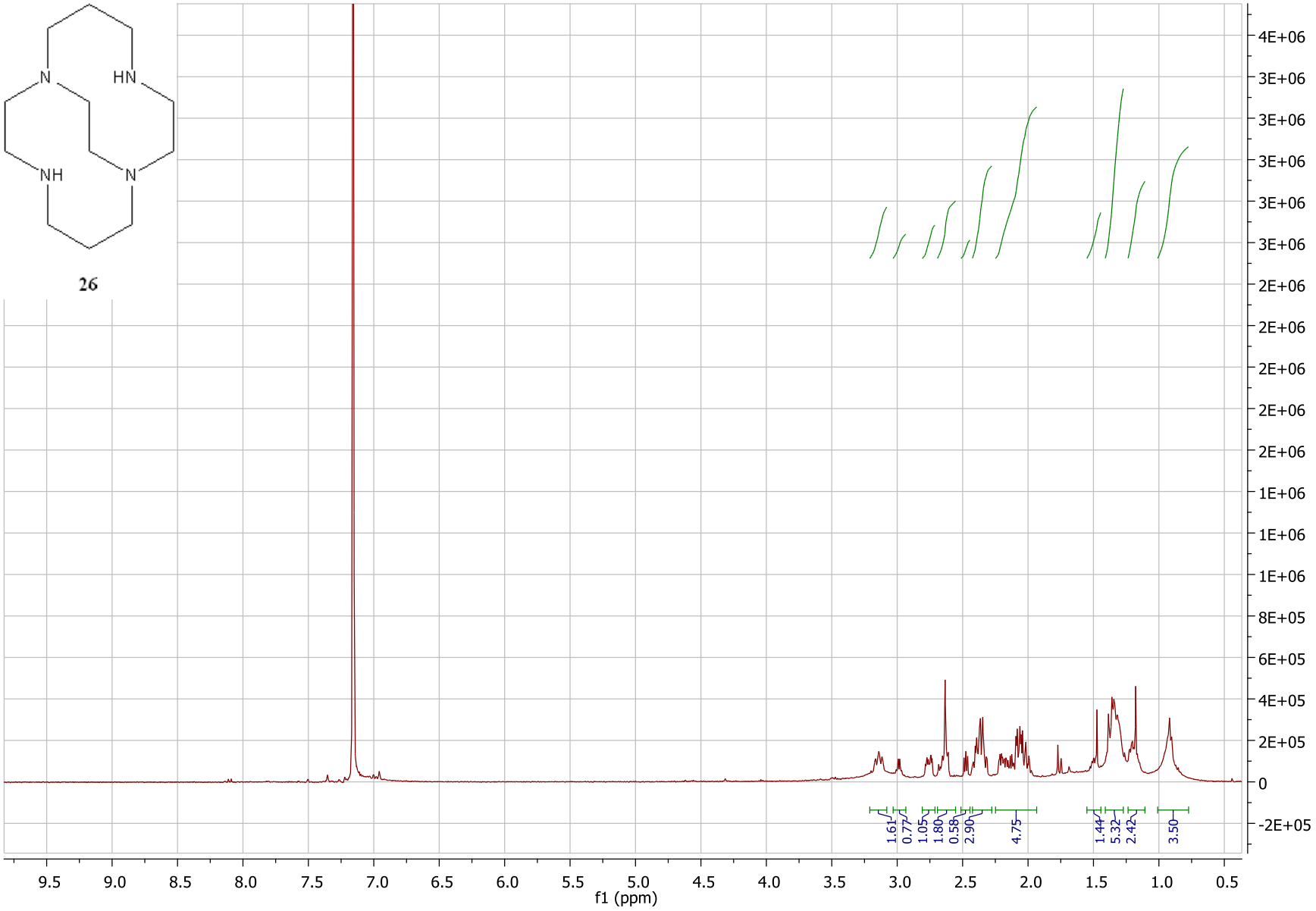

2Br
21
8E+06
7E+06
6E+06
6E+06
6E+06
5E+06
4E+06
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
-5E+05
3.97
3.94
2.36
3.71
1.99
2.01
6.13
3.99
2.01
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

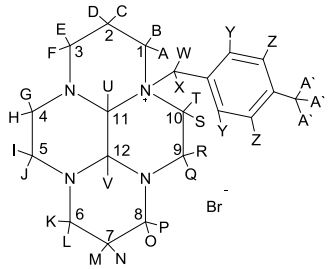

21
2Br
142.17
132.30
130.26
123.06
77.44
60.93
60.80
54.76
46.07
42.81
20.41
5E+06
4E+06
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
-5E+05
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


24
2Br
6E+06
5E+06
4E+06
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
-5E+05
2.05
1.97
2.06
2.21
6.20
2.13
2.15
2.06
2.11
18.00
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
f1 (ppm)


24
2Br
163.29
87.36
79.13
63.96
57.15
56.94
46.95
42.89
29.58
27.11
8E+06
8E+06
7E+06
6E+06
6E+06
6E+06
5E+06
4E+06
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
-5E+05
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


25
1E+07
9E+06
8E+06
7E+06
6E+06
5E+06
4E+06
3E+06
2E+06
1E+06
0
3.90
4.12
1.95
1.98
3.95
2.02
2.88
8.14
5.83
3.11
2.00
2.01
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
f1 (ppm)

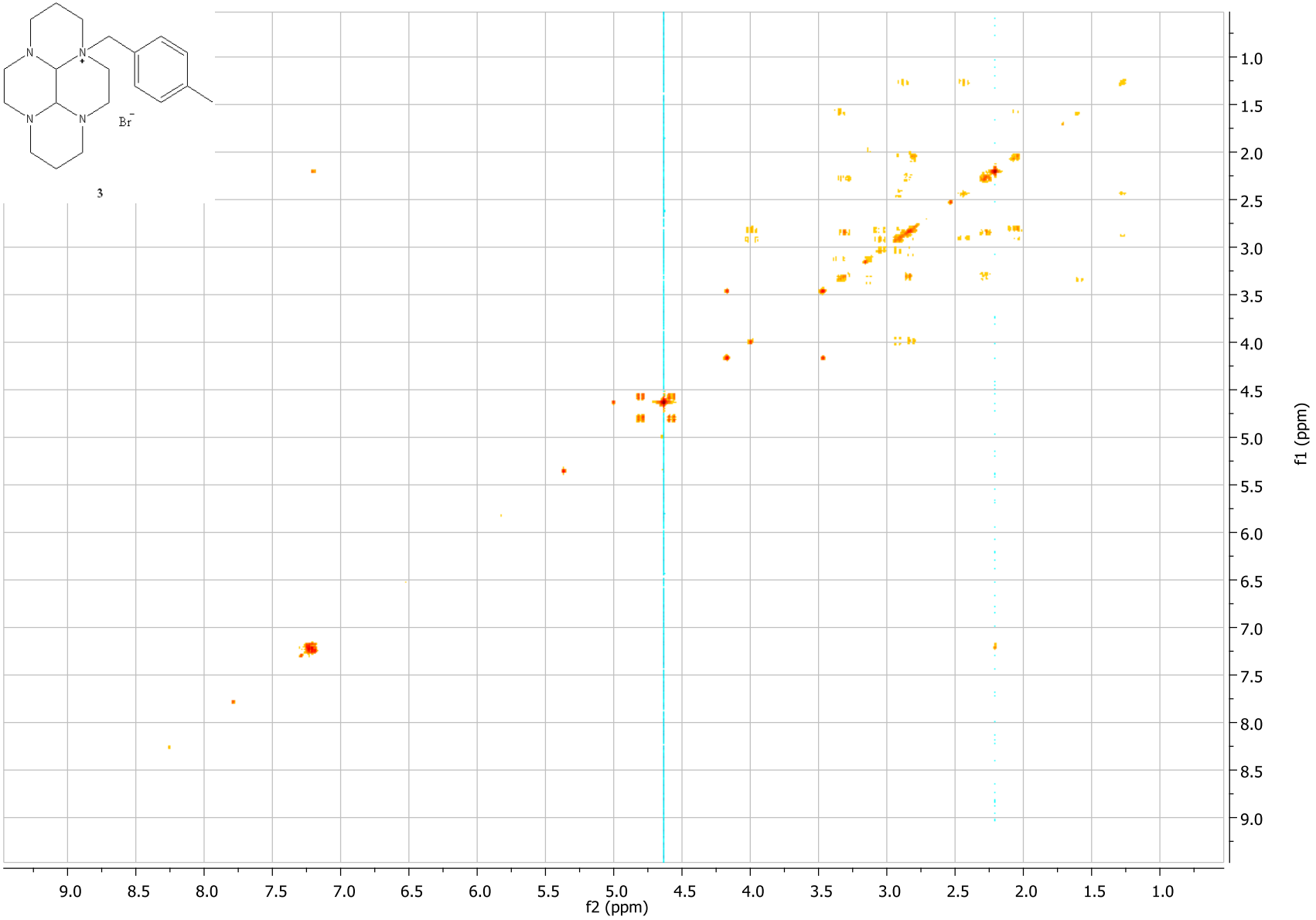

N
HN
NH
N
26
4E+06
3E+06
3E+06
3E+06
3E+06
3E+06
2E+06
2E+06
2E+06
2E+06
2E+06
1E+06
1E+06
1E+06
8E+05
6E+05
4E+05
2E+05
0
-2E+05
1.61
0.77
1.05
1.80
0.58
2.90
4.75
1.44
5.32
2.42
3.50
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

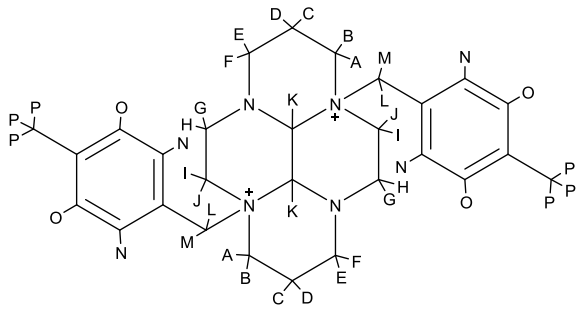


3

Atom	^{1}H	Mult	J, Hz	COSY
C	1.46	md	14.2	A,D,E or F
N	1.77	md	14.2	L,M,P
D,M,O	2.09-2.33	m		A,B,C,E F,K,L,N,P
A`	2.39	s		Z
H,J	2.43-2.51	m		I,G
A	2.62	td	3.3; 12.5	B,C,D
B,E,F,G, Q,P,T	2.95-3.15	m		A,C,D,H,I,J,M ,N,O,R,S
R	3.17-3.29	m		Q,S,T
K	3.29-3.36	md	12.9	L,M,N
I,L	3.44-3.59	m		G,H,J,K,M,N,
V	3.65	s		U
S	4.18	td	3.7; 13.0	Q,R,T
U	4.35	d	1.8	V
W	4.76	d	13.4	X
X	4.99	d	13.4	W
Y	7.17	d	8.4	Z
Z	7.21	d	8.4	Y, `

δ, ppm	Atom, ^{13}C, HMQC
18.58	C_{CD} or C_{NM}
18.96	C_{CD} or C_{NM}
20.99	$C_{A'}$
42.56	C_{IJ}
47.20	C_{RQ}
49.18	C_{ST}
51.92	C_{EF}
52.58	C_{OP}
53.88	C_{HG}
54.55	C_{AB}
60.26	C_{KL}
63.08	C_{XW}
70.15	C_{U}
82.24	Cv
123.12	C_{Y}-C-C_{Y}
130.48	C_{Y}
133.77	C_{Z}
142.49	Cz-C-Cz

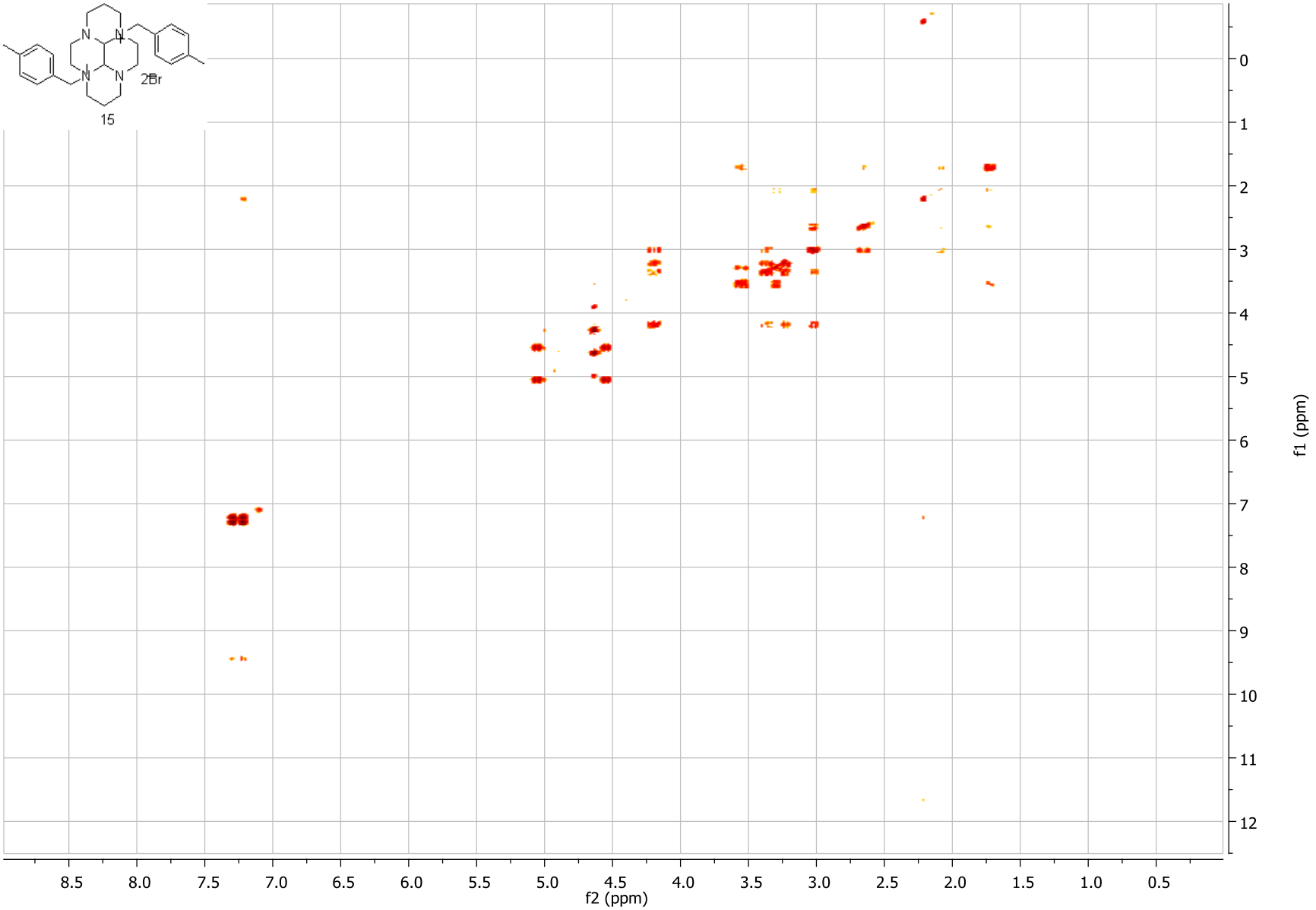

N
N
N
N
Br⁻
3
f2 (ppm)
f1 (ppm)



15

Atom, ^{1}H	δ, ppm	Mult	J, Hz	FDQ-COSY
C	1.88	d	15.2	A,D,E
D	2.31-2.17	m		B,C,F
P	2.37	s		O
E	2.81	d	12.5	C,D,F
F	3.18	d	12.5	E,D
G	3.18	d	12.5	H,I
J	3.59-3.33	m		G,H,I
B	3.59-3.33	m		A,D
H	3.59-3.33	m		G,I,J
A	3.71	t	12.3	B,C
I	4.35	t	11.5	G,H,J
L	4.71	d	13.0	M
K	5.08	d	8.1	
M	5.21	d	13.0	L
O	7.37	d	7.9	N,P
N	7.45	d	7.9	N

δ, ppm	Atom,^{13}C, HMQC
18.53	C_{CD}
20.98	C_{p}
46.53	C_{IJ}
47.34	C_{EF}
51.81	C_{AB}
60.91	C_{HG}
62.88	C_{LM}
77.22	C_{K}
122.08	C-C_{P}
130.60	C_{O}
133.67	C-C_{LM}
142.88	C_{N}


N
N
N
N
2Br
15
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
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
f2 (ppm)

Crystallographic data

Crystallographic data for compound 15

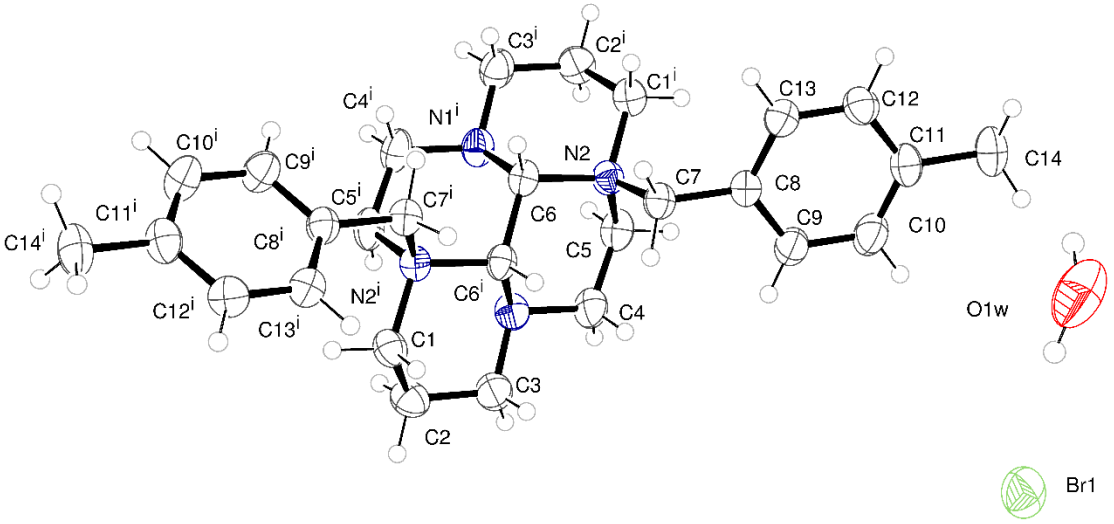


Figure 1: ORTEP plot with atoms drawn as 50% probability ellipsoids. The full macrocycle is represented. Symmetry equivalent atoms are generated by the operator *i* = −*x*, *y*, 1.5−*z*.

The macrocycle resides on a twofold screw axis within the crystal and the second half is generated from the first by application of this symmetry operation. There is limited hydrogen bonding within the structure between the water and the bromide anions.

Table 1. Crystal data and structure refinement for compound 15.

Identification code	**compound 15** (sja16_14)	
Empirical formula	C28 H42 Br2 N4 O	
Structural formula	$(C_{28}H_{40}N_4)$ 2(Br). H_2O	
Formula weight	610.47	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	C 2 2 21	
Unit cell dimensions	a = 10.7048(7) Å	α= 90°.
	b = 13.9924(8) Å	β= 90°.
	c = 18.8717(13) Å	γ = 90°.
Volume	2826.7(3) $Å^3$	
Z	4	
Density (calculated)	1.434 Mg/m^3	
Absorption coefficient	2.895 mm^{-1}	
F(000)	1264	
Crystal size	0.400 × 0.400 × 0.100 mm^3	
Theta range for data collection	2.396 to 29.282°.	
Index ranges	$-14 \leq h \leq 14$, $-19 \leq k \leq 19$, $-25 \leq l \leq 25$	
Reflections collected	10839	
Independent reflections	3821 [R(int) = 0.1380]	
Completeness to theta = 25.242°	99.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3821 / 2 / 164	
Goodness-of-fit on F^2	0.914	
Final R indices [I>2sigma(I)]	R1 = 0.0626, wR2 = 0.1441	
R indices (all data)	R1 = 0.0842, wR2 = 0.1532	
Absolute structure parameter	0.20(2)	
Largest diff. peak and hole	1.827 and -0.914 $e.Å^{-3}$	

Crystallographic data for Compound 21 (Form I)

Compound **21** was found to crystallise in two different forms that differed in the level of solvation. Form I was produced by diffusion of methanol into an ether solution of **21**. During the analysis of form I, some of the solvent present (ether/methanol) evaporated and a second solvate, Form II, was obtained. Each form contains the same macrocycle.

Form I has composition $(C_{26}H_{36}N_4)$. 2(Br). H_2O

Form II has composition $(C_{26}H_{36}N_4)$ 2(Br). CH_3OH. $1.5H_2O$

21 (Form 1) displays beautiful crystallographic disorder of the macrocycle. Within the solid state there is disorder in the orientation of the cylen core. Standard techniques were used to model this disorder (see CIF file). The structure and disorder are exemplified in the ORTEP plots below.

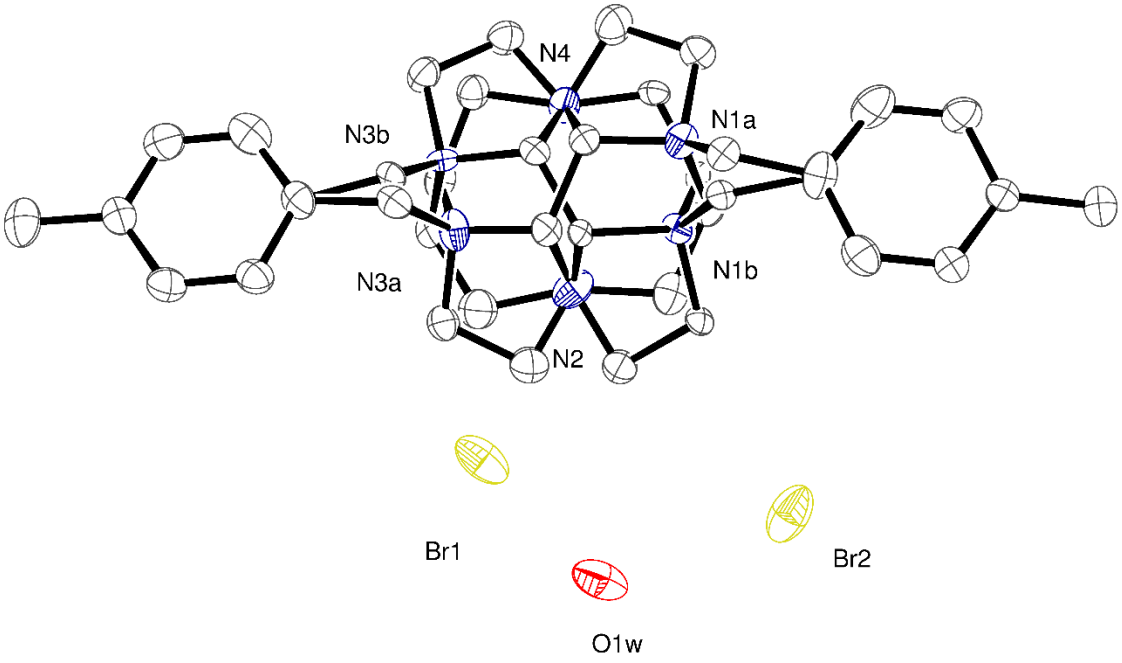


Figure 2: ORTEP plot of 21 (Form I) with atoms drawn as 50% probability ellipsoids. The full macrocycle is represented. For clarity only selected atoms are labelled and hydrogen atoms are omitted.

The molecule present is much clearer if the two different orientations of the cyclen are coloured differently as shown below. The major orientation (60.1(7)%) of the ring is coloured black and the minor orientation (39.9(7)%) is coloured red.

A diagram to confirm the correct product is shown in Figure 4.

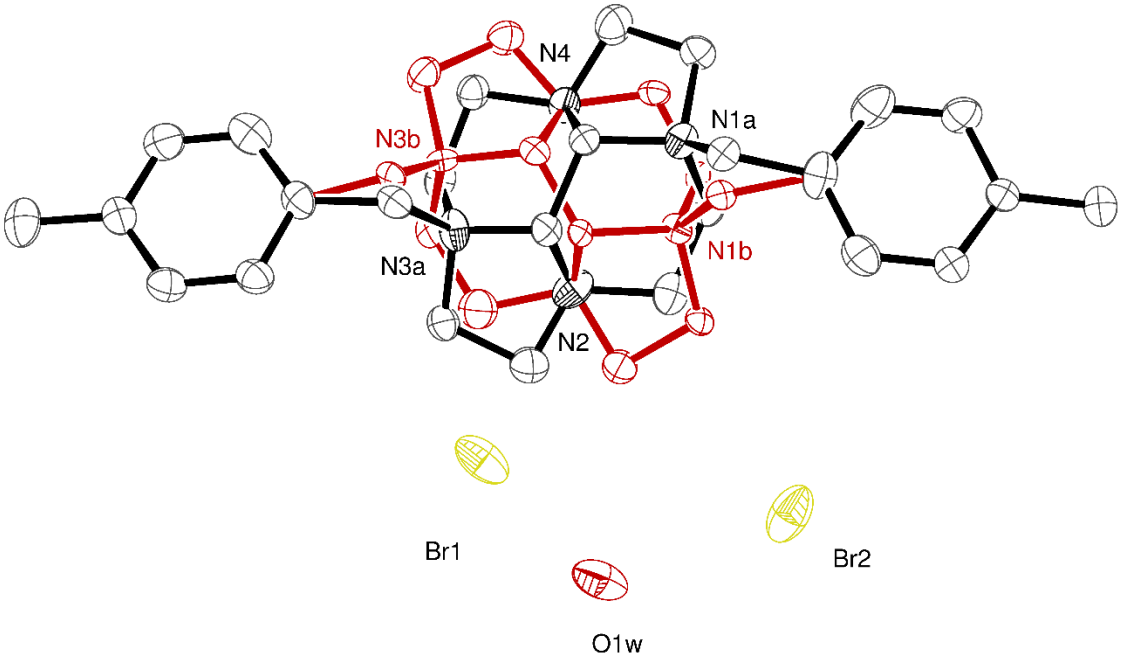


Figure 3: ORTEP plot of Form I with atoms drawn as 50% probability ellipsoids. The two different orientations of the full macrocycle are coloured differently. For clarity only selected atoms are labelled and hydrogen atoms are omitted. The atoms labelled N2 and N4 are common to both orientations.

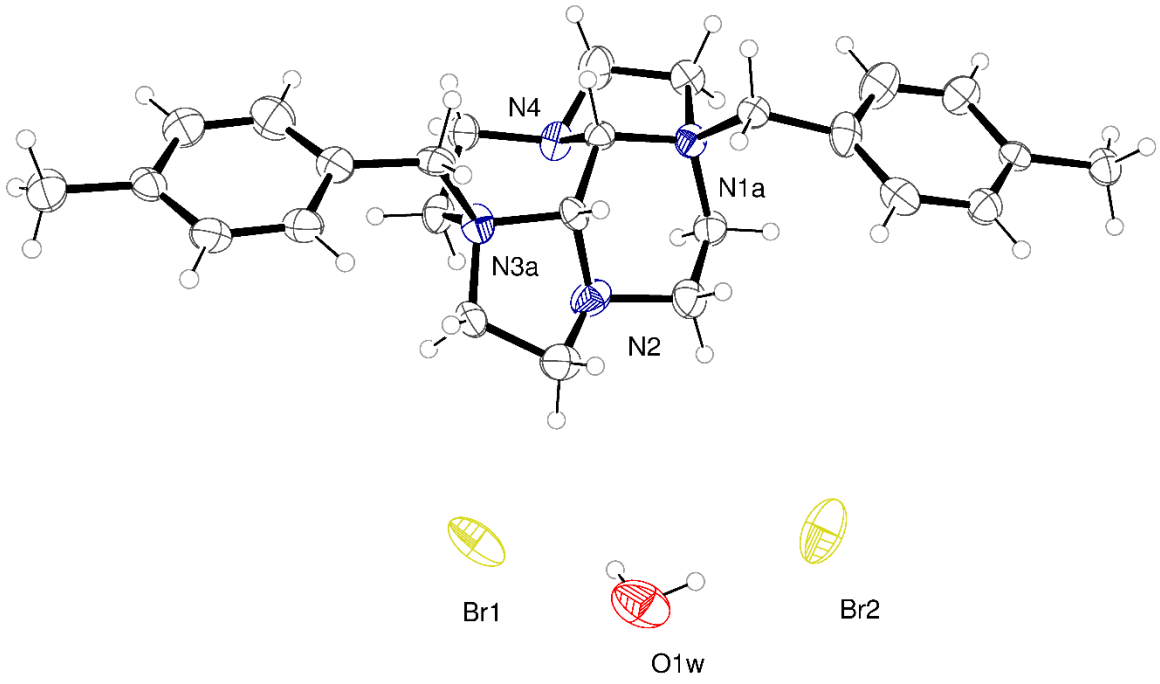


Figure 4: ORTEP plot with atoms of major component of Form I drawn as 50% probability ellipsoids.

Table 2. Crystal data and structure refinement for compound 21 (Form I).

Identification code	**compound 21 (Form I)**	
Empirical formula	C26 H38 Br2 N4 O	
Structural formula	$(C_{26}H_{36}N_4)$ 2(Br). H_2O	
Formula weight	582.42	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P $2_1/n$	
Unit cell dimensions	a = 14.5400(9) Å	α= 90°.
	b = 10.1743(8) Å	β= 102.778(5)°.
	c = 18.1427(11) Å	γ = 90°.
Volume	2617.5(3) $Å^3$	
Z	4	
Density (calculated)	1.478 Mg/m^3	
Absorption coefficient	3.123 mm^{-1}	
F(000)	1200	
Crystal size	0.260 × 0.260 × 0.220 mm^3	
Theta range for data collection	1.630 to 26.149°.	
Index ranges	$-18 \leq h \leq 18$, $-11 \leq k \leq 12$, $-22 \leq l \leq 22$	
Reflections collected	13153	
Independent reflections	5127 [R(int) = 0.0711]	
Completeness to theta = 25.242°	98.1 %	
Absorption correction	Analytical	
Max. and min. transmission	0.5509 and 0.4948	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5127 / 274 / 435	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0998, wR2 = 0.2221	
R indices (all data)	R1 = 0.1519, wR2 = 0.2426	
Largest diff. peak and hole	1.284 and -1.458 $e.Å^{-3}$	

Crystallographic data for Compound 21 (Form II)

The second crystal form of compound 21 does not contain disorder. Its composition differs from Form I only in the solvent present.

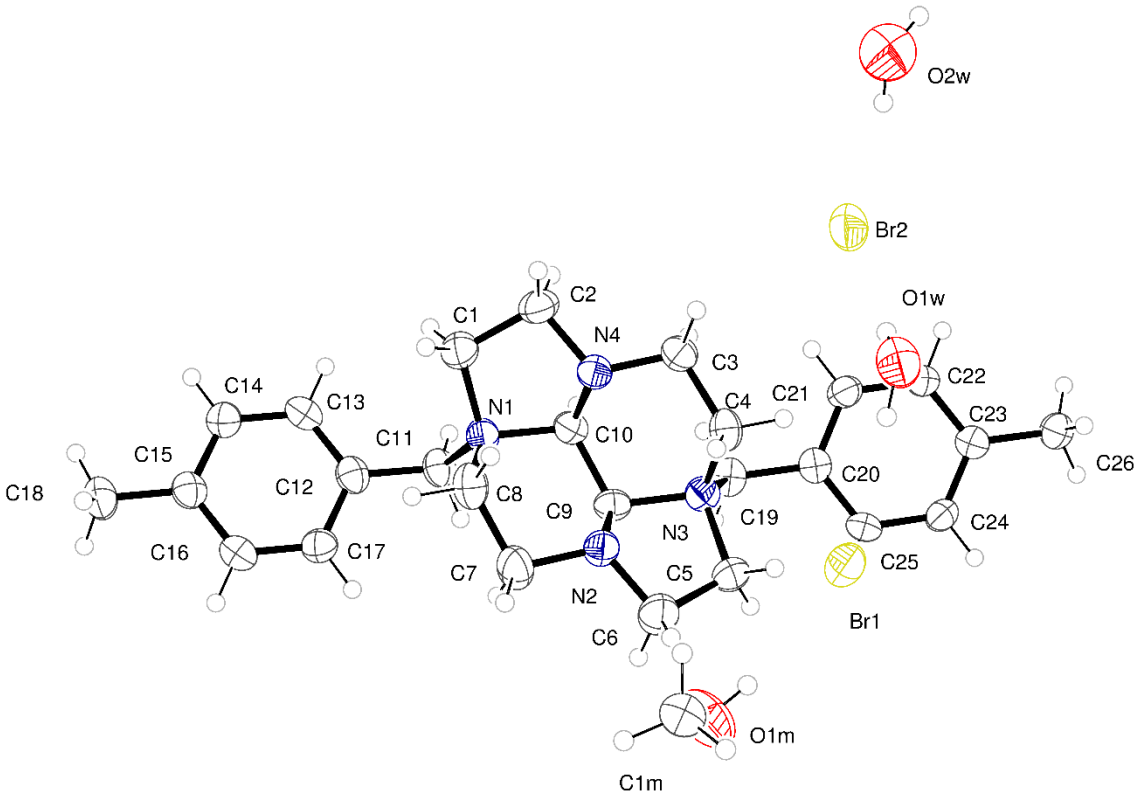


Figure 5: ORTEP plot for Form II with atoms drawn as 50% probability ellipsoids. The full macrocycle is represented. For clarity only selected atoms are labelled and hydrogen atoms are omitted.

Table 3. Crystal data and structure refinement for compound 21 (Form I).

Identification code	**compound 21 (Form II)**	
Empirical formula	C27 H43 Br2 N4 O2.50	
Structural formula	$(C_{26}H_{36}N_4)$ 2(Br). CH_3OH. 1.5H_2O	
Formula weight	623.47	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P $2_1/n$	
Unit cell dimensions	a = 9.7180(5) Å	α= 90°.
	b = 22.6793(13) Å	β= 102.826(4)°.
	c = 13.0099(7) Å	γ = 90°.
Volume	2795.8(3) $Å^3$	
Z	4	
Density (calculated)	1.481 Mg/m^3	
Absorption coefficient	2.933 mm^{-1}	
F(000)	1292	
Crystal size	0.420 × 0.160 × 0.120 mm^3	
Theta range for data collection	1.796 to 25.641°.	
Index ranges	$-11 \le h \le 8$, $-24 \le k \le 27$, $-15 \le l \le 15$	
Reflections collected	14043	
Independent reflections	5246 [R(int) = 0.0771]	
Completeness to theta = 25.242°	99.7 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5246 / 8 / 336	
Goodness-of-fit on F^2	1.013	
Final R indices [I>2sigma(I)]	R1 = 0.0534, wR2 = 0.1430	
R indices (all data)	R1 = 0.0819, wR2 = 0.1558	
Largest diff. peak and hole	1.139 and -1.819 e.$Å^{-3}$	