

Supporting Information

Calix[6]arene-based Brønsted acids for molecular recognition and catalysis

Gianpiero Cera,^[a] Federica Cester Bonati,^[a] Margherita Bazzoni,^[a] Andrea Secchi,^[a]
and Arturo Arduini^[a]

*[a] Università di Parma, Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Parco Area delle
Scienze 17/A, 43124 Parma, Italy.*

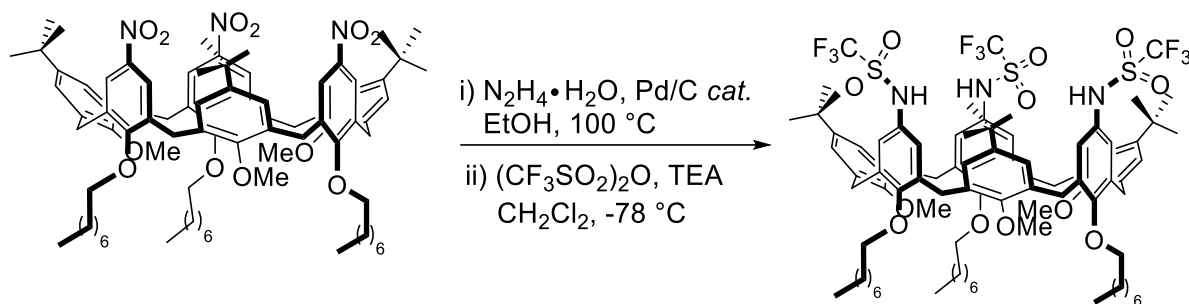
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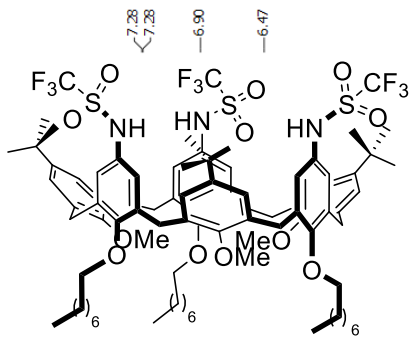
- **General Remarks and Materials**

All chemicals those syntheses are not reported hereafter were purchased from commercial sources and used as received. Solvents were dried and stored over molecular sieves previously activated in an oven (450 °C overnight). Column chromatography was performed on silica gel 60 (70-230 mesh). NMR spectra were recorded on a Bruker 400 MHz and JEOL 600 MHz using solvents as internal standards (7.26 ppm for ^1H NMR and 77.00 ppm for ^{13}C -NMR for CDCl_3). The terms m, s, d, t, q and quint represent multiplet, singlet, doublet, triplet, quadruplet and quintuplet respectively, and the term br means a broad signal. Exact masses were recorded on a LTQ ORBITRAP XL Thermo Mass Spectrometer (ESI source). Spectrophotometric titration (air-equilibrated CH_2Cl_2 , room temperature) were performed with a JASCO V-750 UV-visible spectrophotometer by adding small aliquots (typically 10 μL) of a concentrated solution of calixarene TSA **F** to a dilute solution of dioctylviologen salt. The titration curves were fitted according to a 1:1 association model by using the SPECFIT/32 software.¹ TSA calixarenes **A-G** and sulfonamide **H** were synthesized according to a known procedure.²⁻⁴ Nitroalkenes **1** were purchased from commercially available sources or synthesized following common routes.⁵

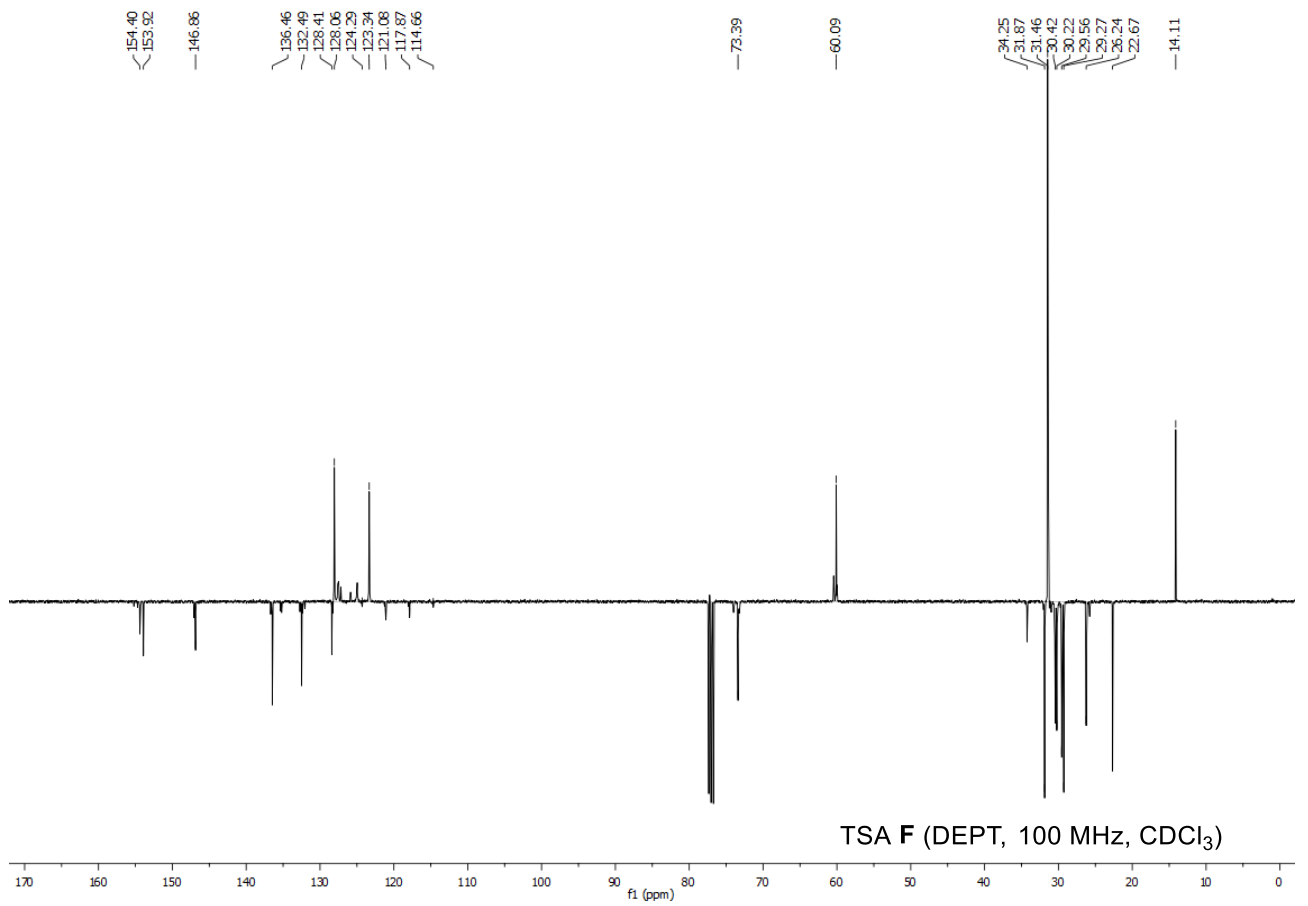
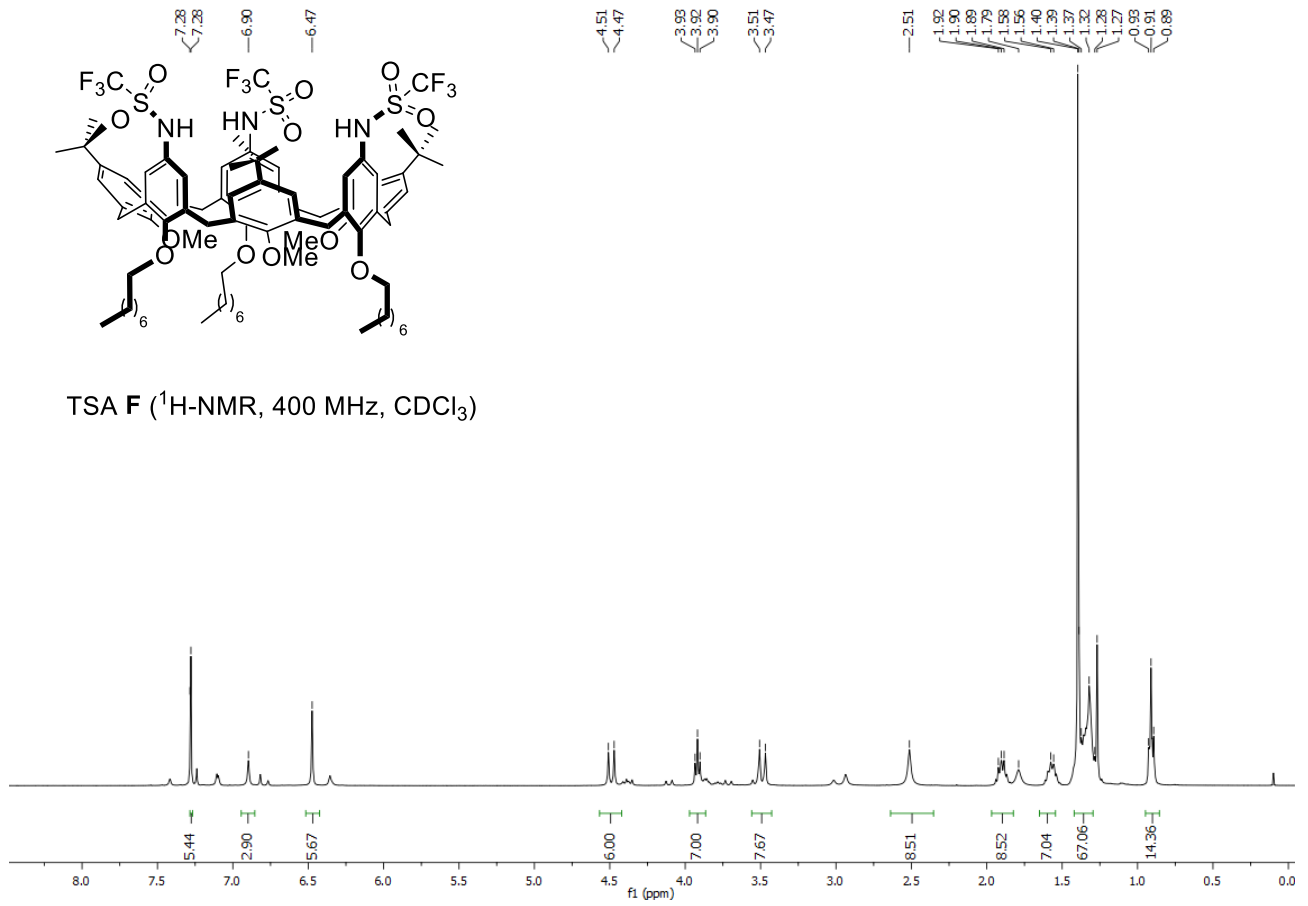
- **Synthesis and Characterisation of F**



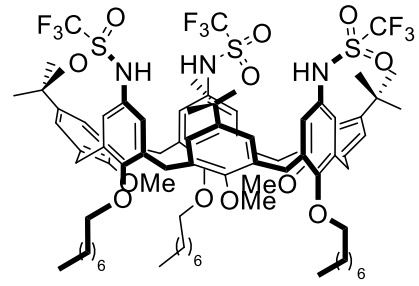
In a two-necked round bottomed flask, under N_2 atmosphere, Pd/C (10 mol %) was added to a suspension of **A** (395 mg, 0.3 mmol) in EtOH (100 ml). Subsequently, $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (6 mmol, 20 eq.) was added dropwise and the reaction placed in an oil-bath where it was refluxed at 100 °C for 24 hs. After completion determined by TLC analysis, the reaction was cooled-down to room temperature, and then filtered through a Celite pad to remove the Pd/C catalyst. The mixture was concentrated at reduced pressure and water (30 ml) was added. After extraction with CH_2Cl_2 (3 x 30 ml), organic phases were dried over Na_2SO_4 and concentrated at reduced pressure to afford a pale yellow solid. The crude was dissolved with dry CH_2Cl_2 (15 ml) under N_2 atmosphere and TEA (1.2 mmol, 4.0 eq.) was added. Subsequently, the mixture was cooled down at -78 °C and trifluoromethanesulfonic anhydride (1.0 mmol, 3.5 eq.) was added as a CH_2Cl_2 solution (5 ml) over 30 mins. The reaction was stirred for 4 hs. After completion, H_2O (20 ml) was added and the mixture extracted with CH_2Cl_2 (3 x 30 ml). The organic layers were dried over Na_2SO_4 , concentrated at reduced pressure and the crude purified by column chromatography on silica gel (*n*-Hex/AcOEt: 80:20) yielding TSA **F** (345 mg, 71%) as a white solid. **M. p.** = 100-103 °C. $^1\text{H NMR}$ *pseudo cone conformer* (400 MHz, CDCl_3) δ = 7.28 (s, 6H), 6.90 (s, 3H, NH), 6.47 (s, 6H), 4.49 (d, J = 15.3 Hz, 6H), 3.92 (t, J = 6.5 Hz, 6H), 3.49 (d, J = 15.5 Hz, 6H), 2.51 (bs, 9H), 1.95 – 1.83 (m, 6H), 1.62 – 1.51 (m, 6H), 1.38 – 1.28 (m, 24H), 1.35 (d, J = 20.9 Hz, 4H), 0.99 – 0.86 (m, 9H). $^{13}\text{C NMR}$ *pseudo cone conformer* (101 MHz, CDCl_3) δ = 154.4 (C_q), 153.9 (C_q), 146.9 (C_q), 136.5 (C_q), 132.5 (C_q), 128.4 (C_q), 128.1 (CH), 123.3 (CH), 119.5 (q, $J_{\text{C-F}}$ = 322 Hz, C_q), 73.4 (CH_2), 60.1 (CH_3), 34.2 (C_q), 31.9 (CH_2), 31.5 (CH_3), 30.4 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 26.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3). $^{19}\text{F NMR}$ (565 MHz, CDCl_3) δ = -75.20. **HR-MS** (ESI) m/z : $[\text{M}+\text{NH}_4]^+$ calcd. for $\text{C}_{84}\text{H}_{118}\text{F}_9\text{N}_4\text{O}_{12}\text{S}_3$: 1641.77647; found 1641.77625.



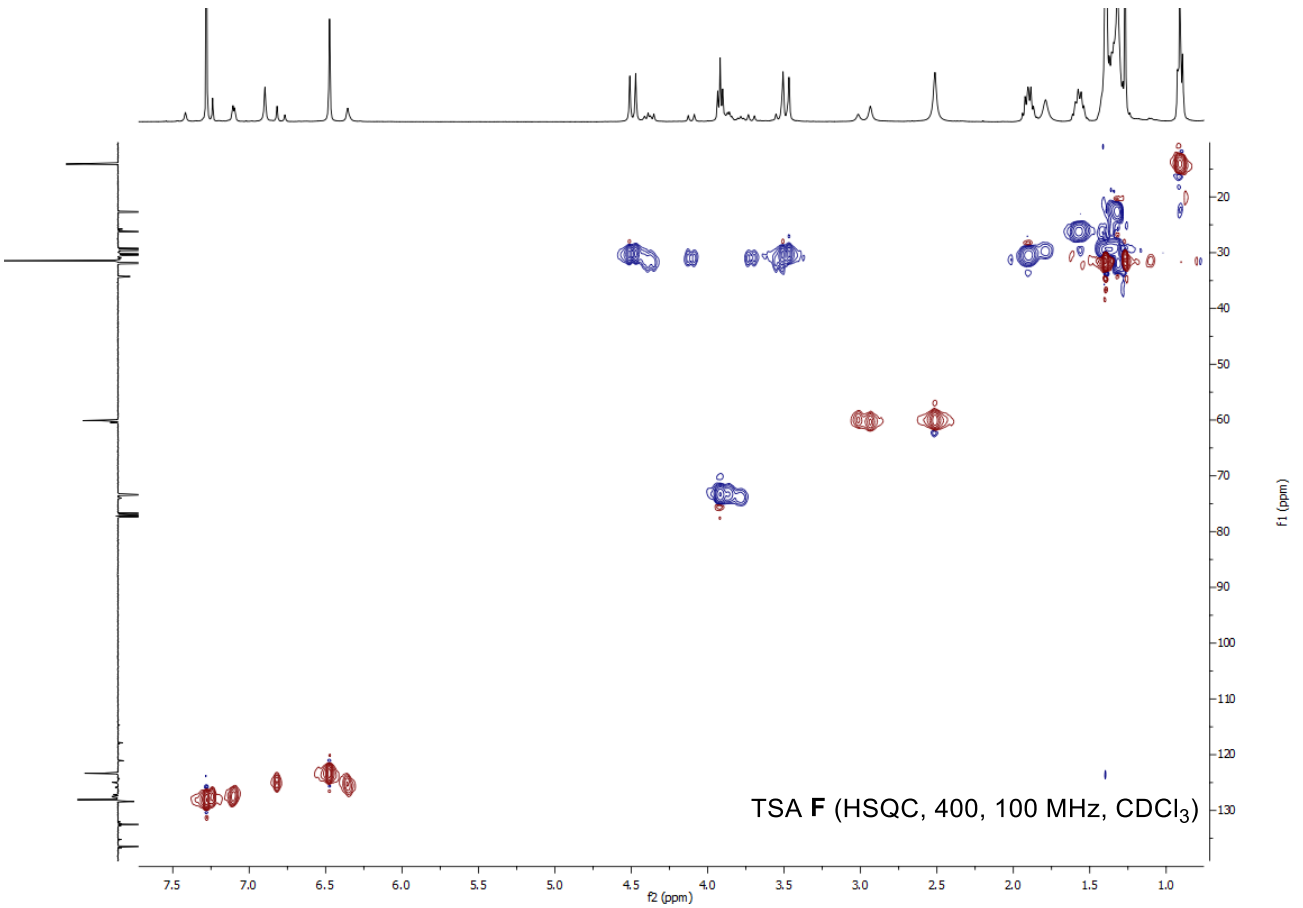
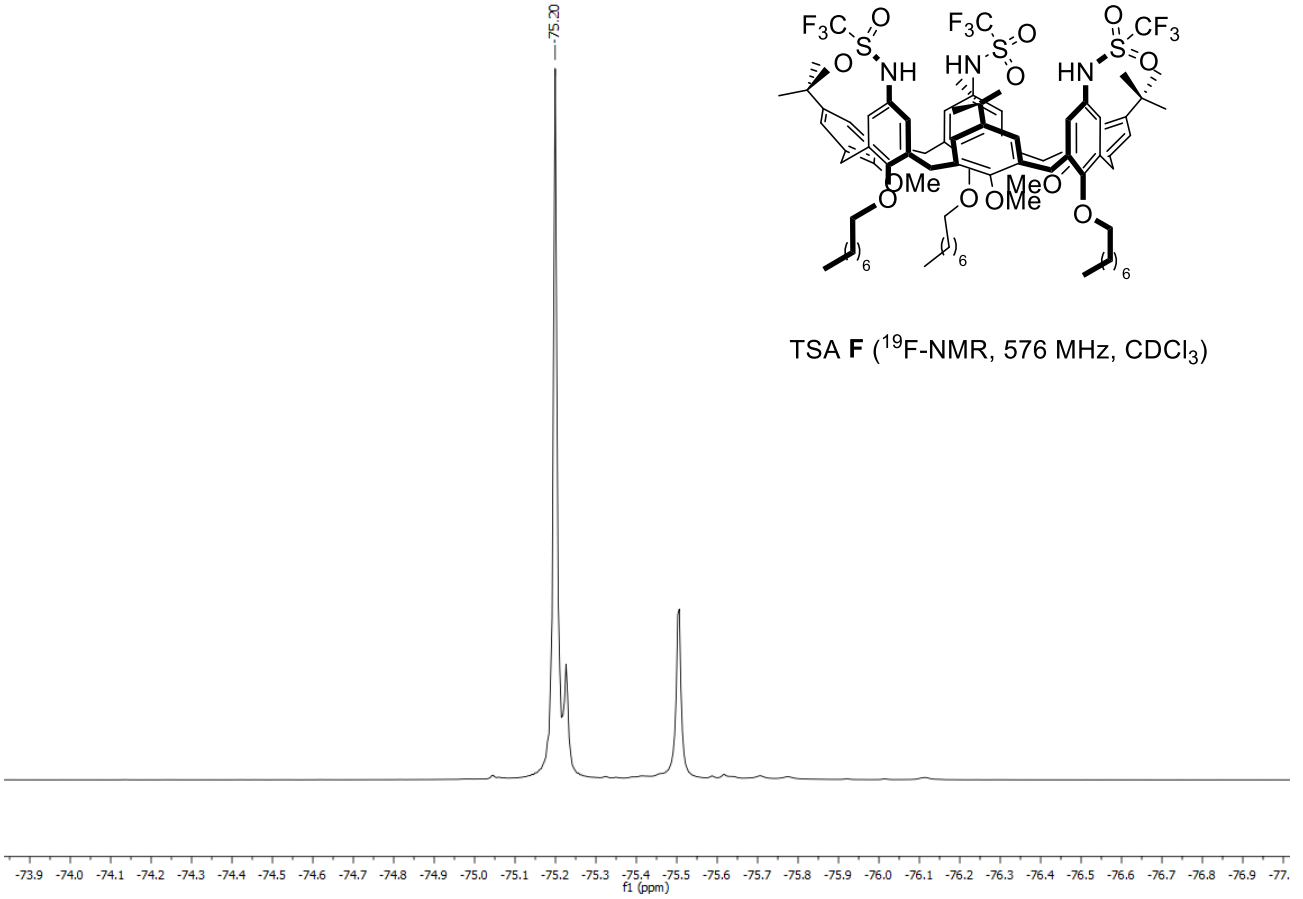
TSA F ($^1\text{H-NMR}$, 400 MHz, CDCl_3)



TSA F (DEPT, 100 MHz, CDCl_3)



TSA F (^{19}F -NMR, 576 MHz, CDCl_3)



TSA F (HSQC, 400, 100 MHz, CDCl_3)

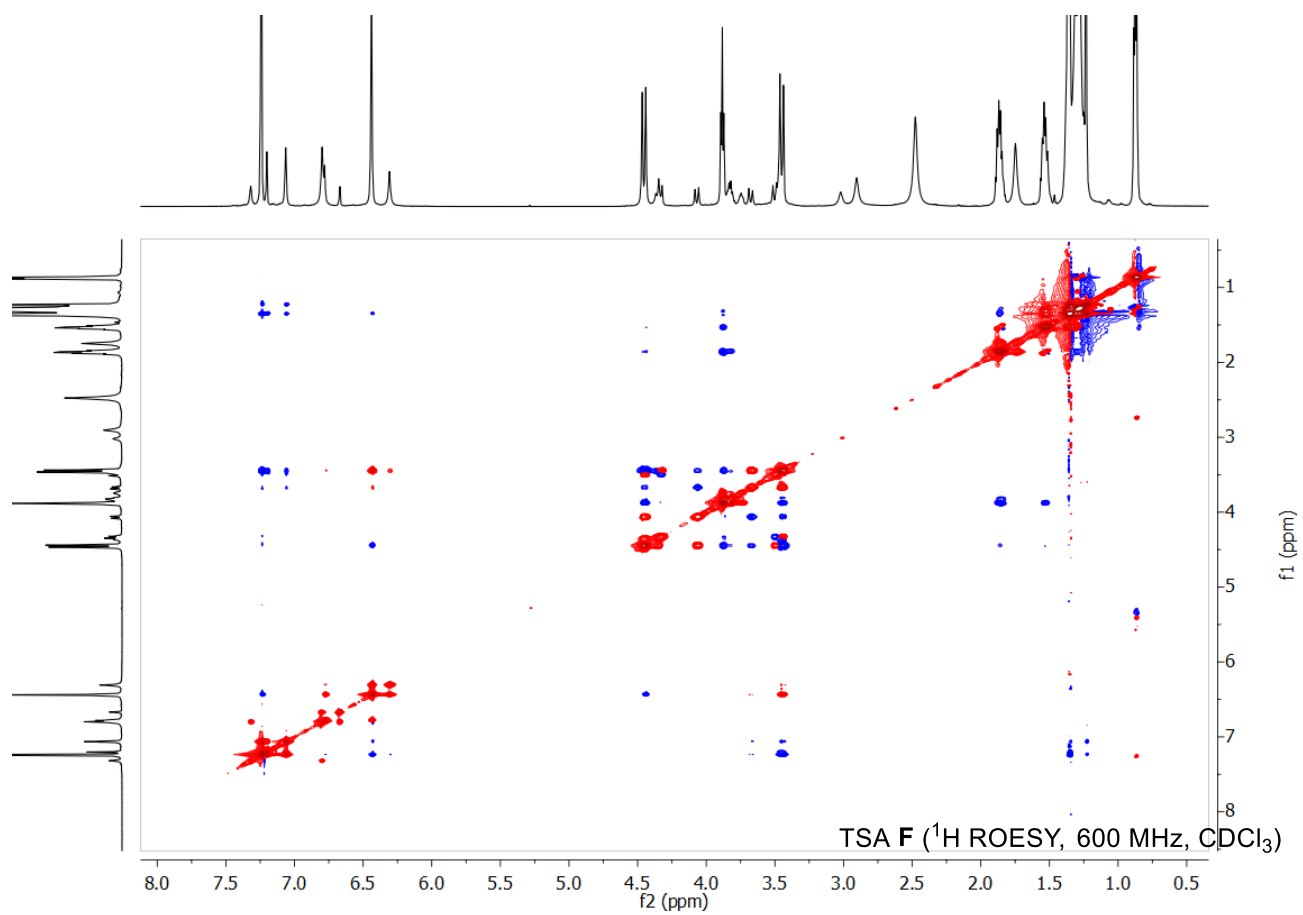
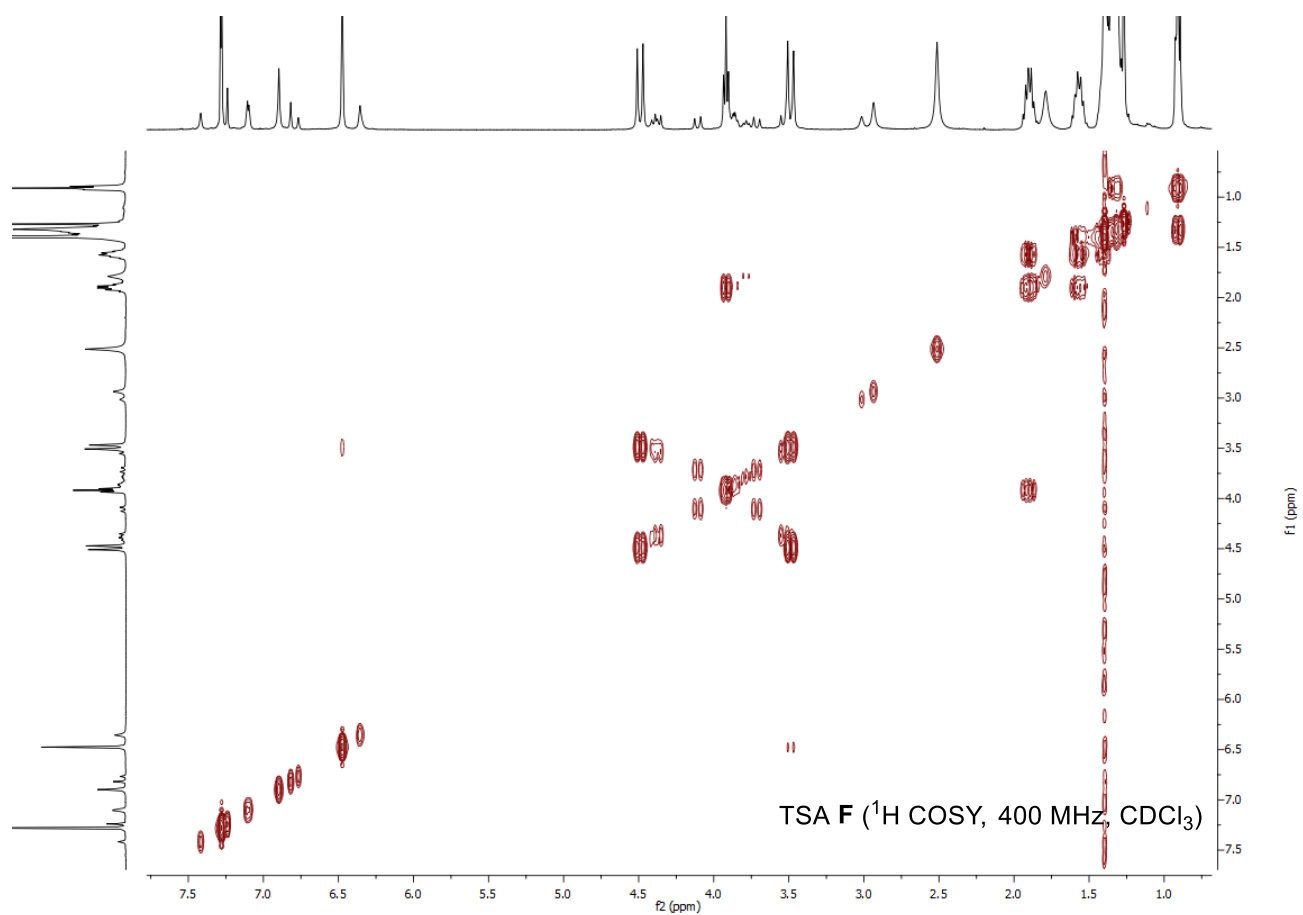


Figure S1. (Top) HR-MS (TOF) spectrum of TSA F, and (Down) expansion showing its isotopic pattern.

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T: FTMS + p ESI Full ms [100.00-2000.00]

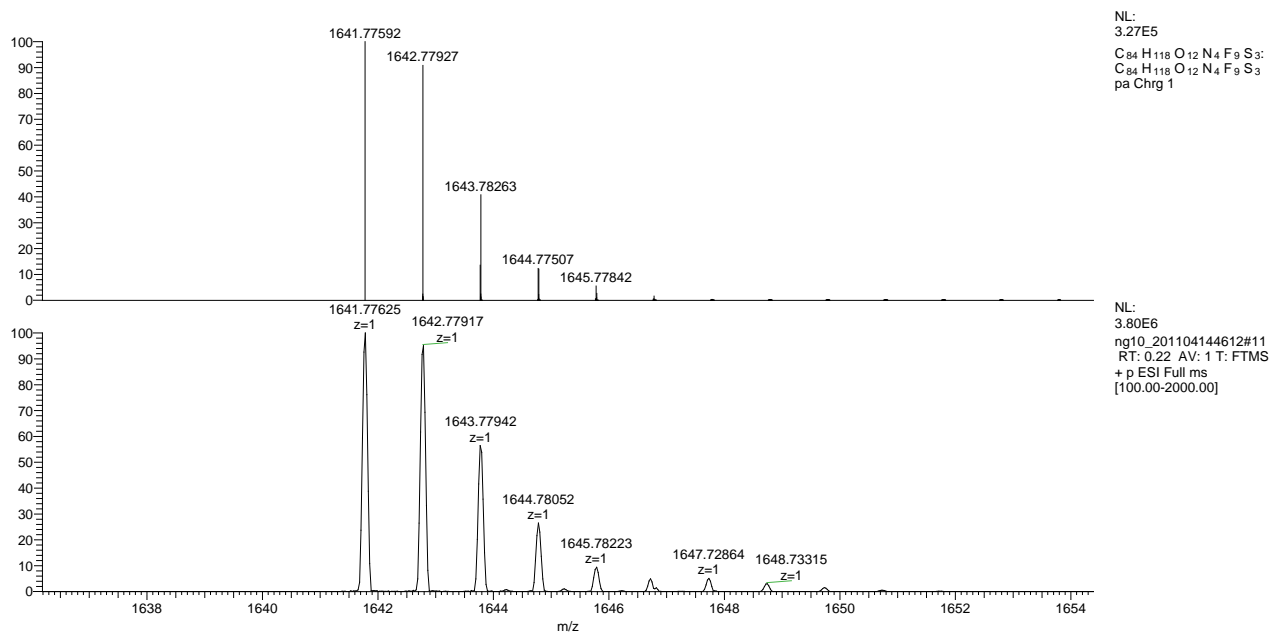
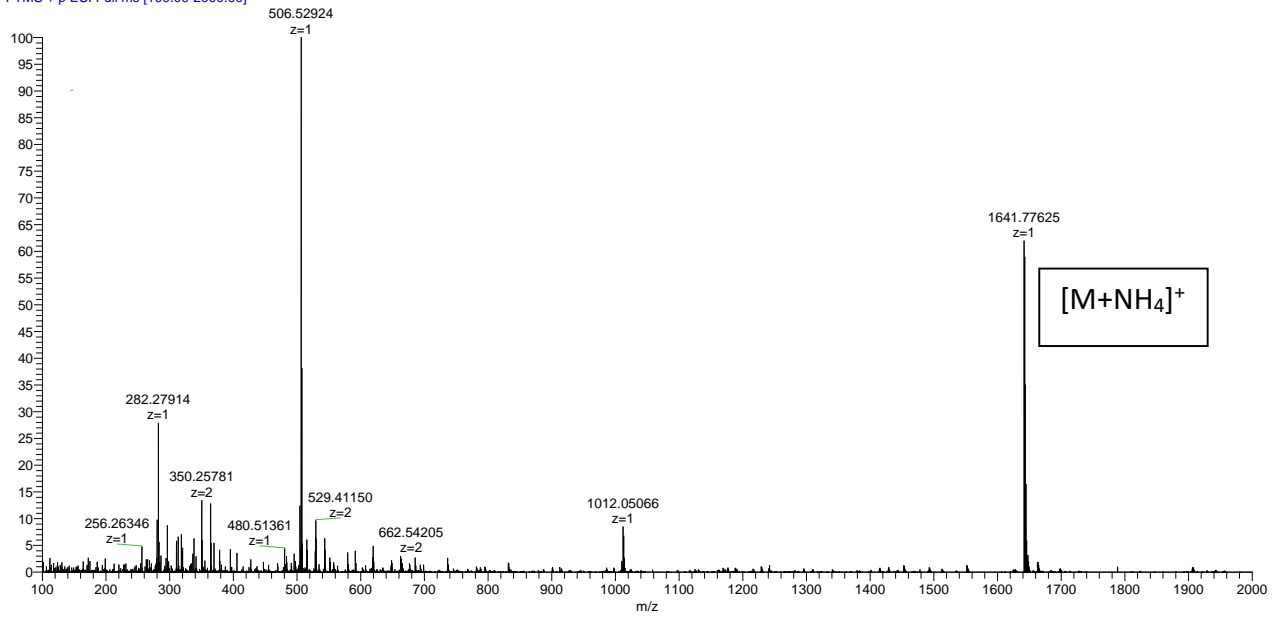


Figure S2. 1D-ROESY spectra of TSA **F** recorded with selective irradiation of axial methylene protons of “distorted” cone conformation at 4.12 (blue spectrum) and OCH₃ signal of pseudo-cone conformation at 2.51 (green spectrum) ppm. Their interchanges are highlighted with blue and green dotted line respectively, showing a slow exchange at the NMR time scale of the two conformers.

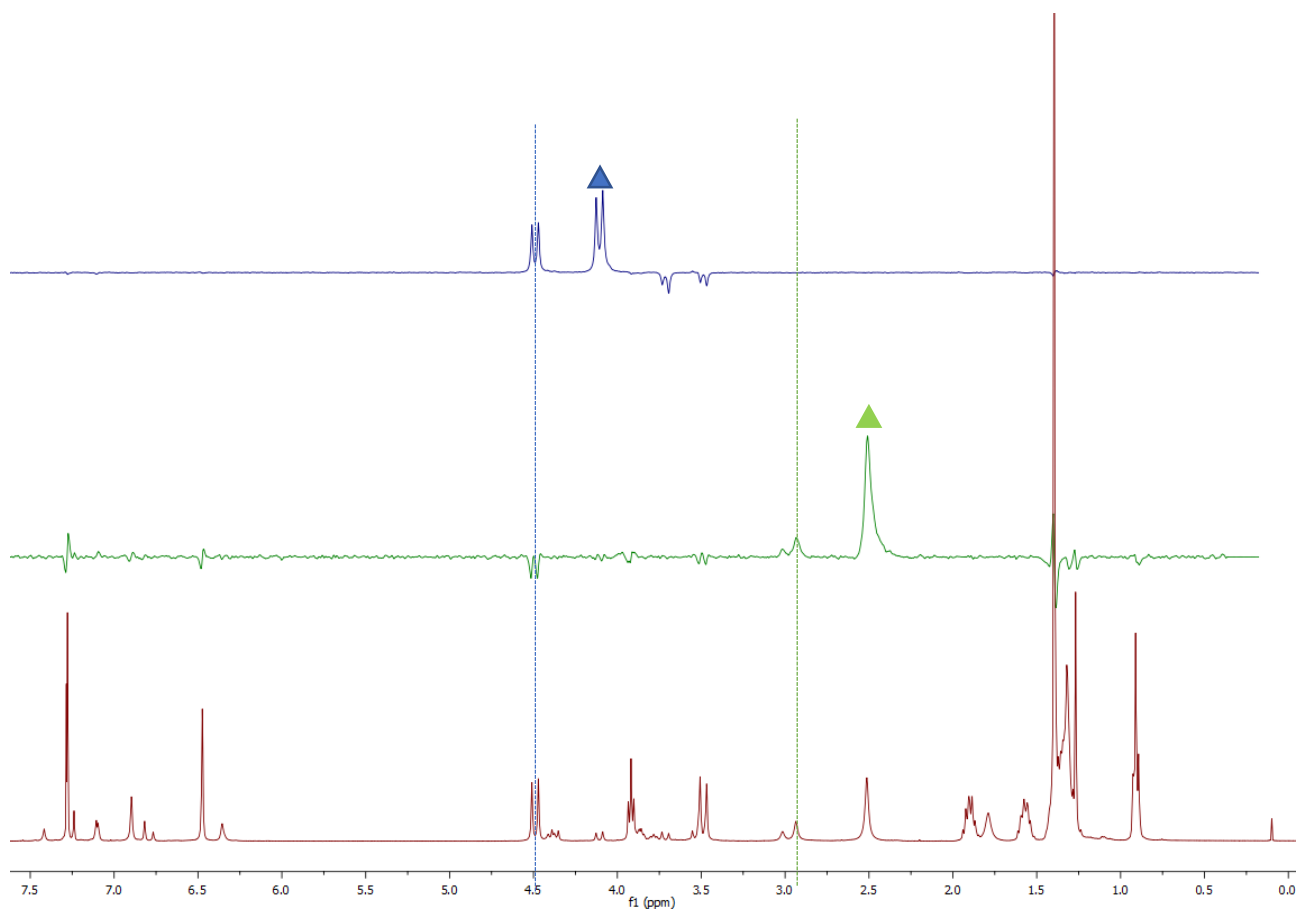
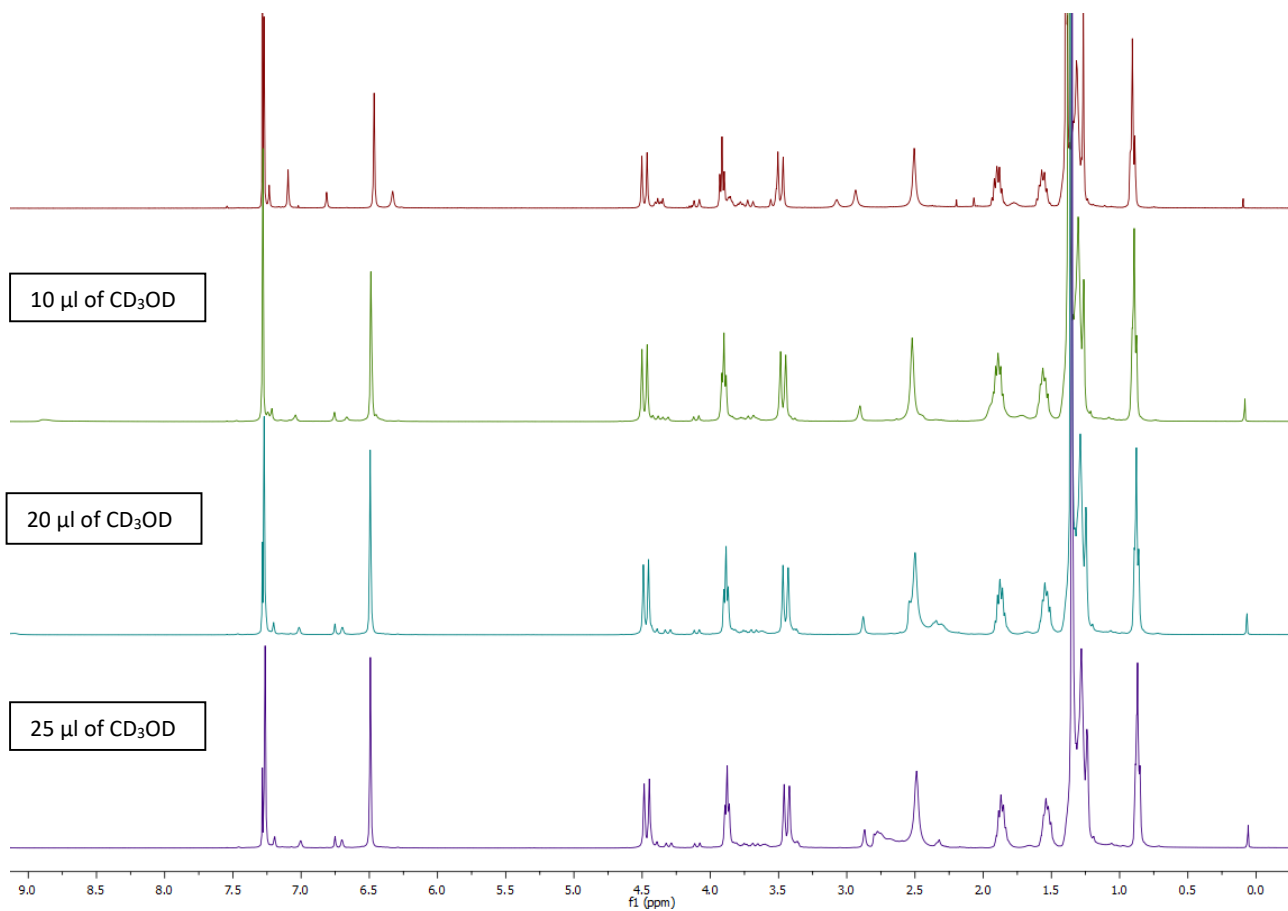
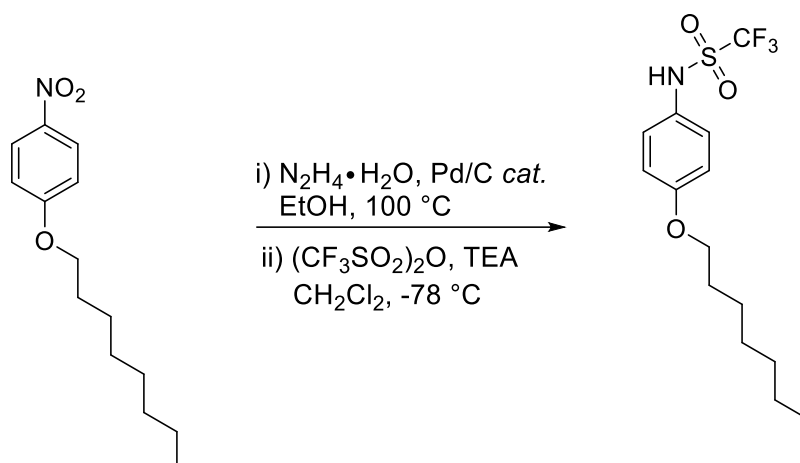


Figure S3. ^1H -NMR spectra of a 0.04 M solution of TSA F in CDCl_3 (top). To this solution sequential additions of CD_3OD were carried out to evaluate the interchange of distorted pseudo cone and pseudo cone conformers.



- **Synthesis and Characterisation of H**

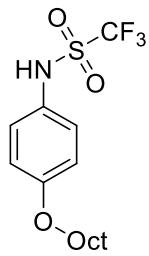


In a two-necked round bottomed flask, under N_2 atmosphere, Pd/C (10 mol %) was added to a suspension of 1-nitro-4-(octyloxy)benzene^[4] (502 mg, 2.0 mmol) in EtOH (100 ml). Subsequently, $NH_2NH_2 \cdot H_2O$ (20.0 mmol, 10 eq.) was added dropwise and the reaction placed in an oil-bath where it was refluxed at 100 °C for 4 hs. After completion determined by TLC analysis, the reaction was cooled-down to room temperature, and then filtered through a Celite pad to remove the Pd/C catalyst. The mixture was concentrated at reduced pressure and water (30 ml) was added. After extraction with CH_2Cl_2 (3 x 30 ml), organic phases were dried over Na_2SO_4 and concentrated at reduced pressure to afford a pale yellow solid. The crude was dissolved with dry CH_2Cl_2 (50 ml) under N_2 atmosphere and TEA (4.0 mmol, 2.0 eq.) was added. Subsequently, the mixture was cooled down at -78 °C and trifluoromethanesulfonic anhydride (3.0 mmol, 1.5 eq.) was added as a CH_2Cl_2 solution (15 ml) over 30 mins. The reaction was stirred for 2 hs. After completion, H_2O (50 ml) was added and the mixture extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were dried over Na_2SO_4 , concentrated at reduced pressure and the crude purified by column chromatography on silica gel (*n*-Hex/AcOEt: 80:20) yielding **H** (562 mg, 80%) as a pale yellow solid. **M. p.** = 42-45 °C. ¹**H NMR** (400 MHz, $CDCl_3$) δ = 7.28 – 7.19 (m, 2H), 6.93 – 6.89 (m, 2H), 6.88 (bs, 1H), 3.97 (t, J = 6.5 Hz, 2H), 1.80 (dt, J = 14.5, 6.6 Hz, 2H), 1.52 – 1.42 (m, 2H), 1.41 – 1.24 (m, 8H), 0.98 – 0.86 (m, 3H). ¹³**C NMR** (600MHz, $CDCl_3$) δ = 159.2 (C_q), 127.3 (CH), 125.5 (C_q), 120.0 (q, J_{C-F} = 323 Hz, C_q), 115.4 (CH), 68.5 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3). ¹⁹**F NMR** (565 MHz, $CDCl_3$) δ = -75.00. **HR-MS** (ESI) m/z : $[M+H]^+$ calcd. for $C_{15}H_{23}F_3NO_3S$: 354.1351; found 353.1348.

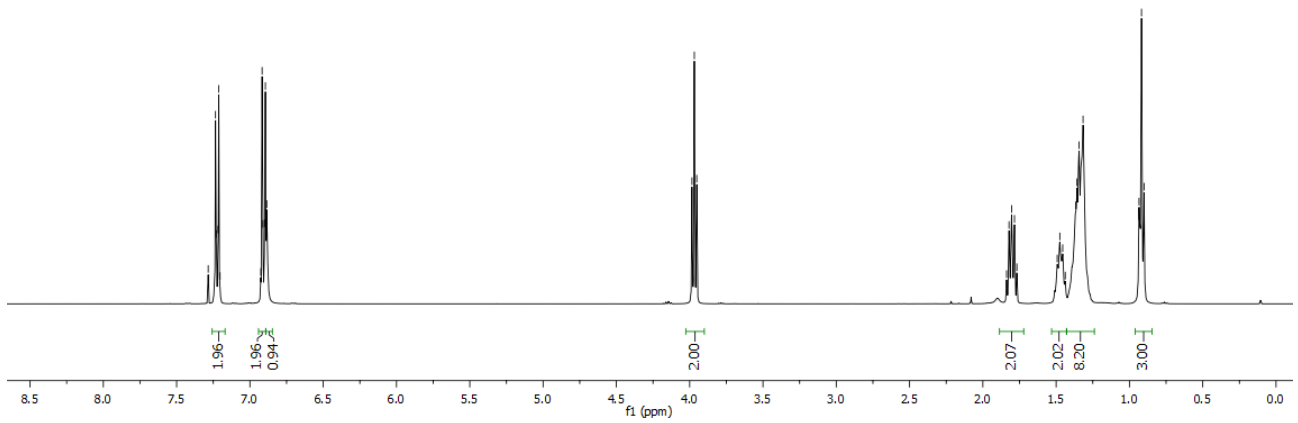
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7.22
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6.90
6.89
6.88

3.98
3.97
3.95

1.84
1.82
1.80
1.79
1.77
1.49
1.48
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1.34
1.32
1.09
1.08
0.90



(400 MHz, CDCl₃)



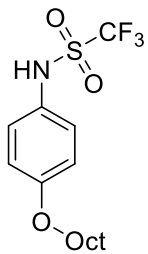
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123.11
120.98
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115.37

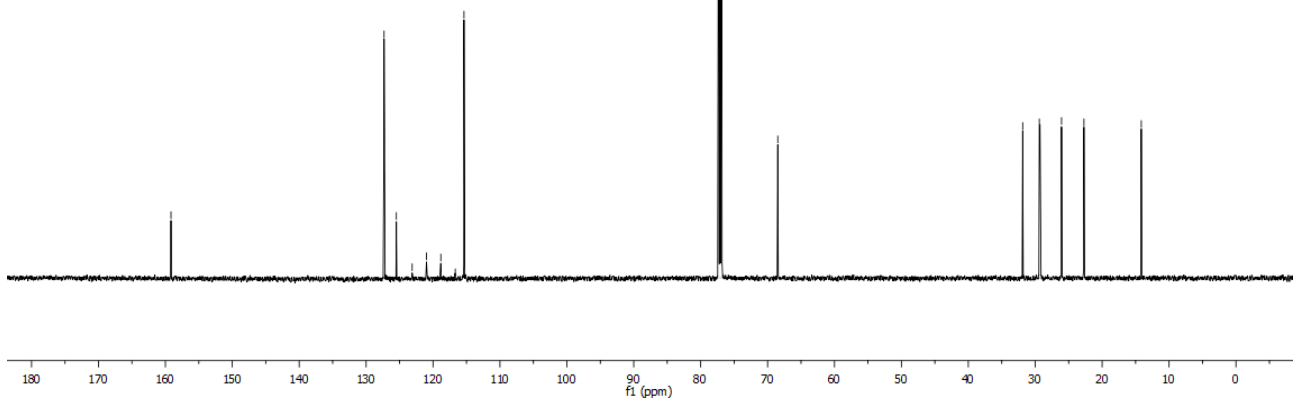
68.48

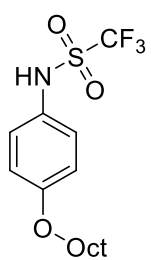
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29.39
26.07
22.72

14.15



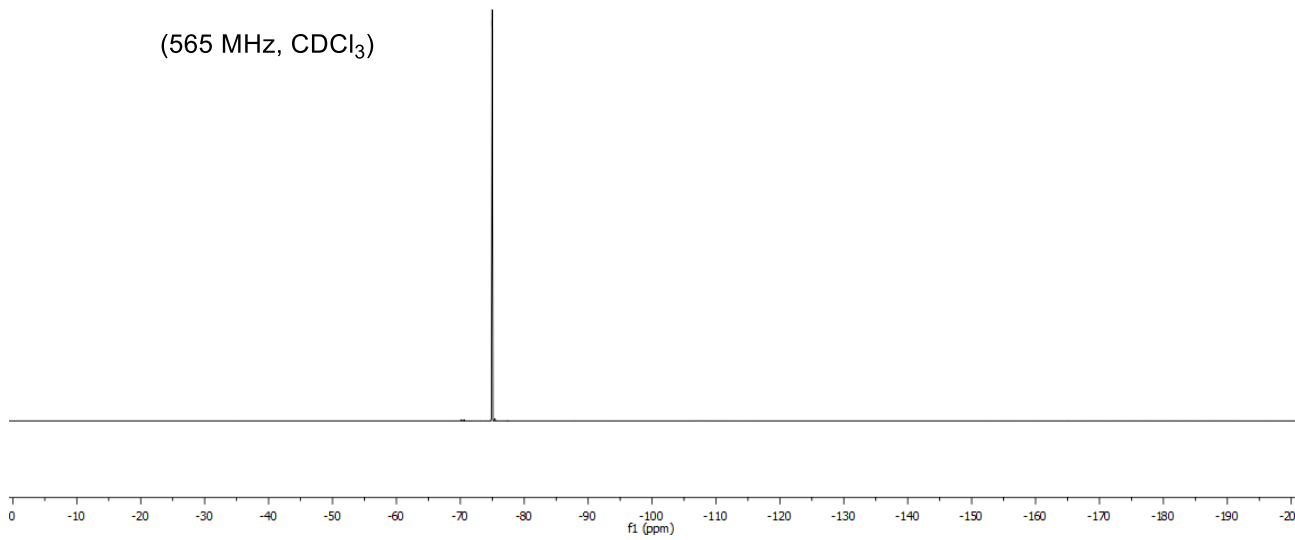
(600 MHz, CDCl₃)





(565 MHz, CDCl₃)

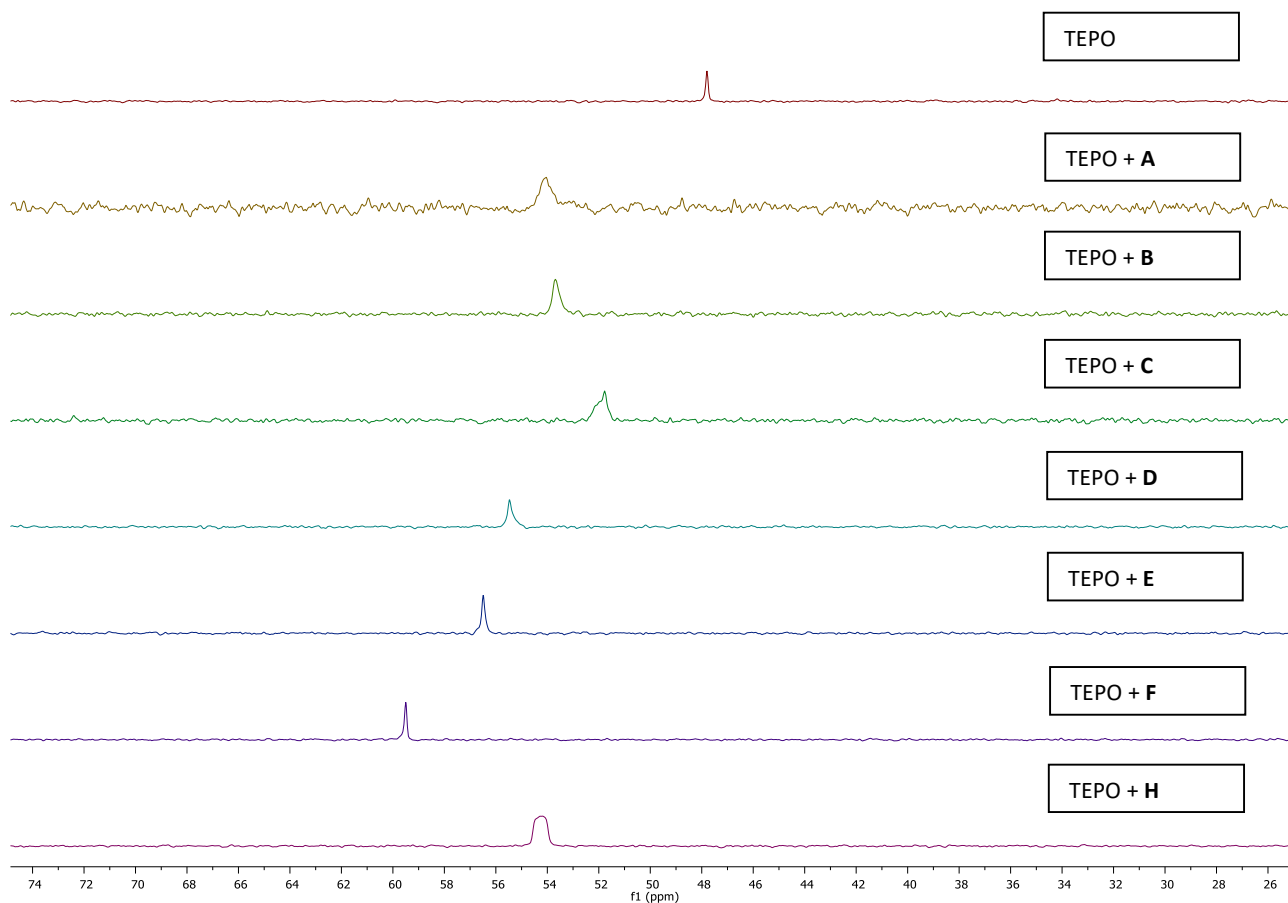
--75.00



- **Guttman-Becket Plot**

Figure S4. Titration Results for a Series of Trisulfonamides (TSA **A-F**) and monomeric trifluoromethyl-analogue **H** with Et₃PO (5mM in C₆D₆) monitored by ³¹P NMR.

From a stock solution of TEPO (5mM in C₆D₆), 400 μl were taken out and added to an NMR tube containing 0.006 mmol of the corresponding analyte (3 equiv). The tube was subsequently analyzed by ³¹P NMR.

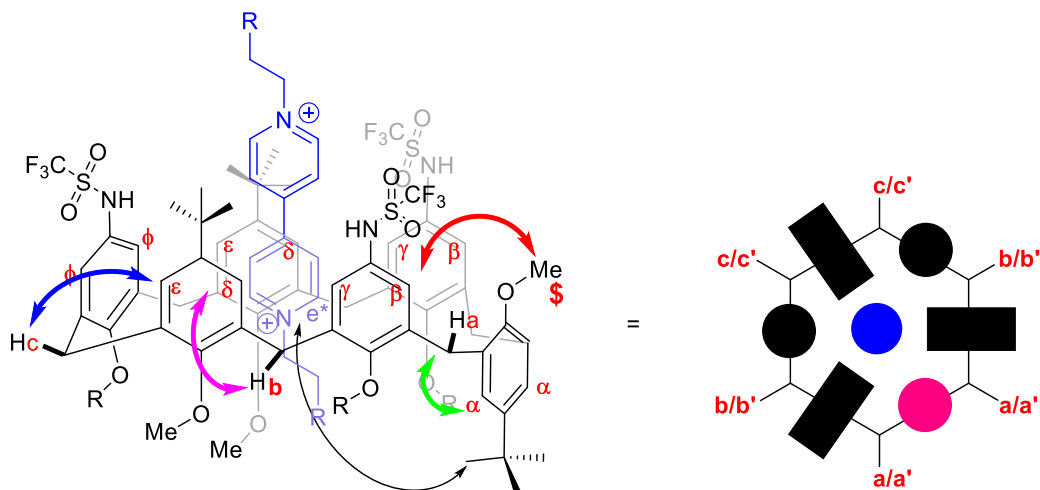
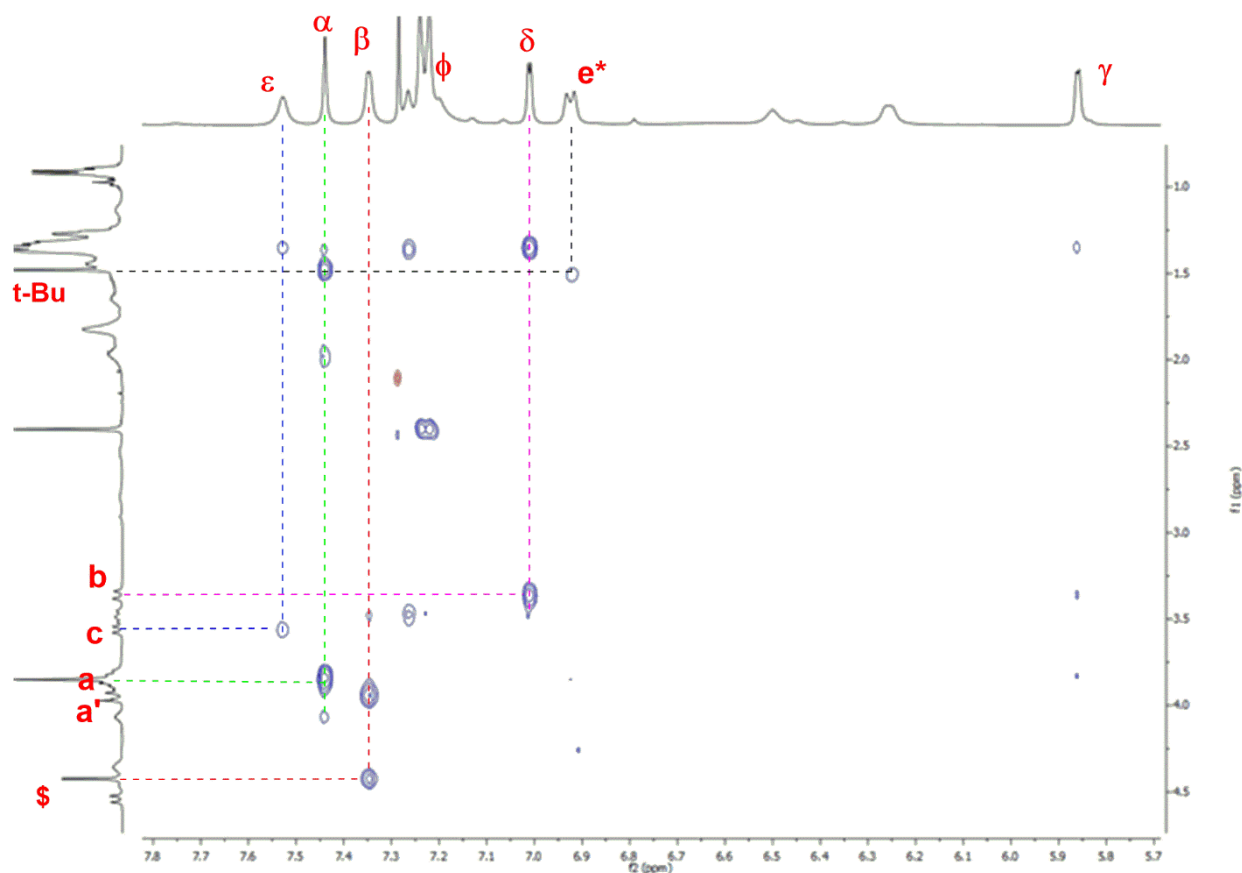


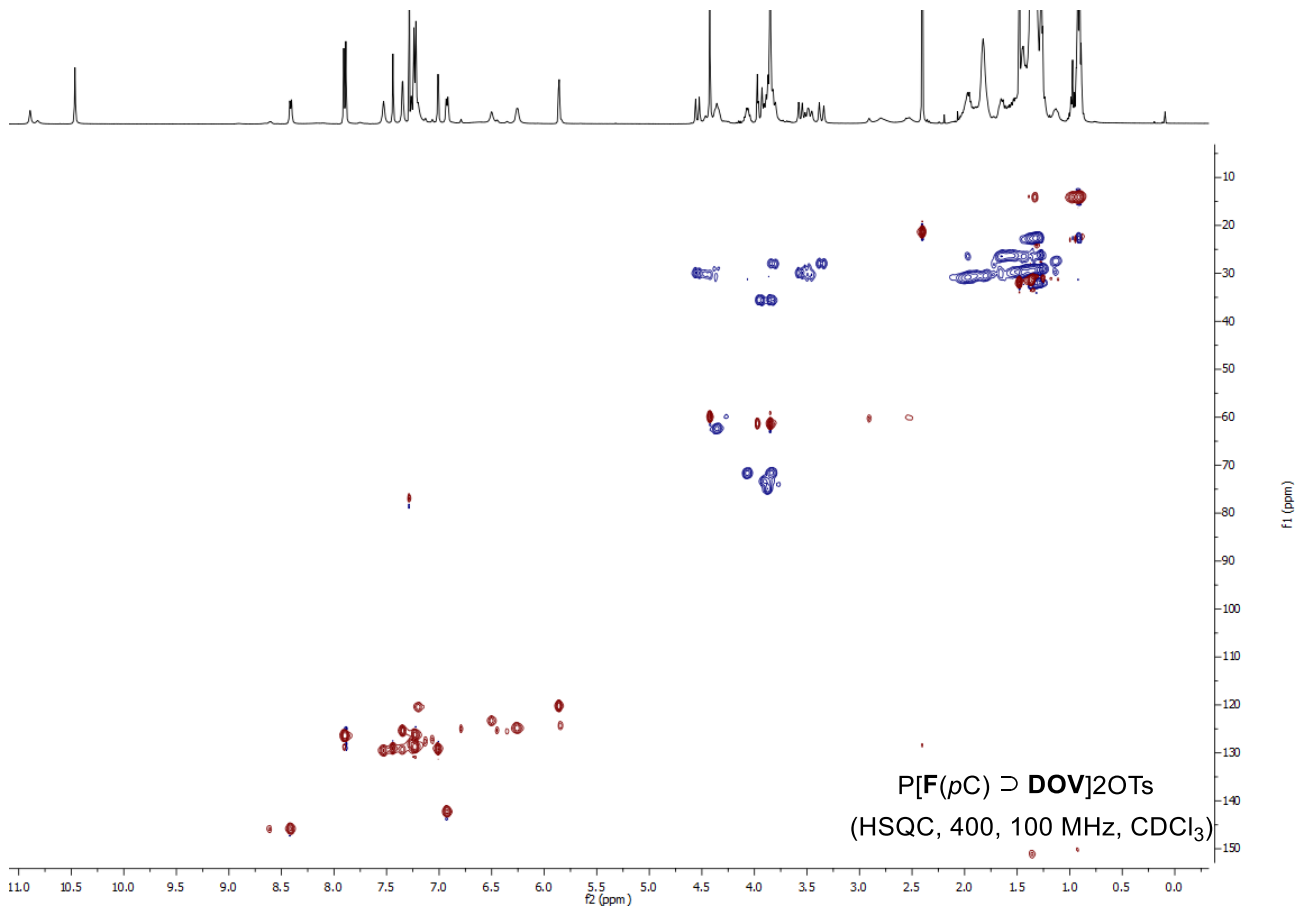
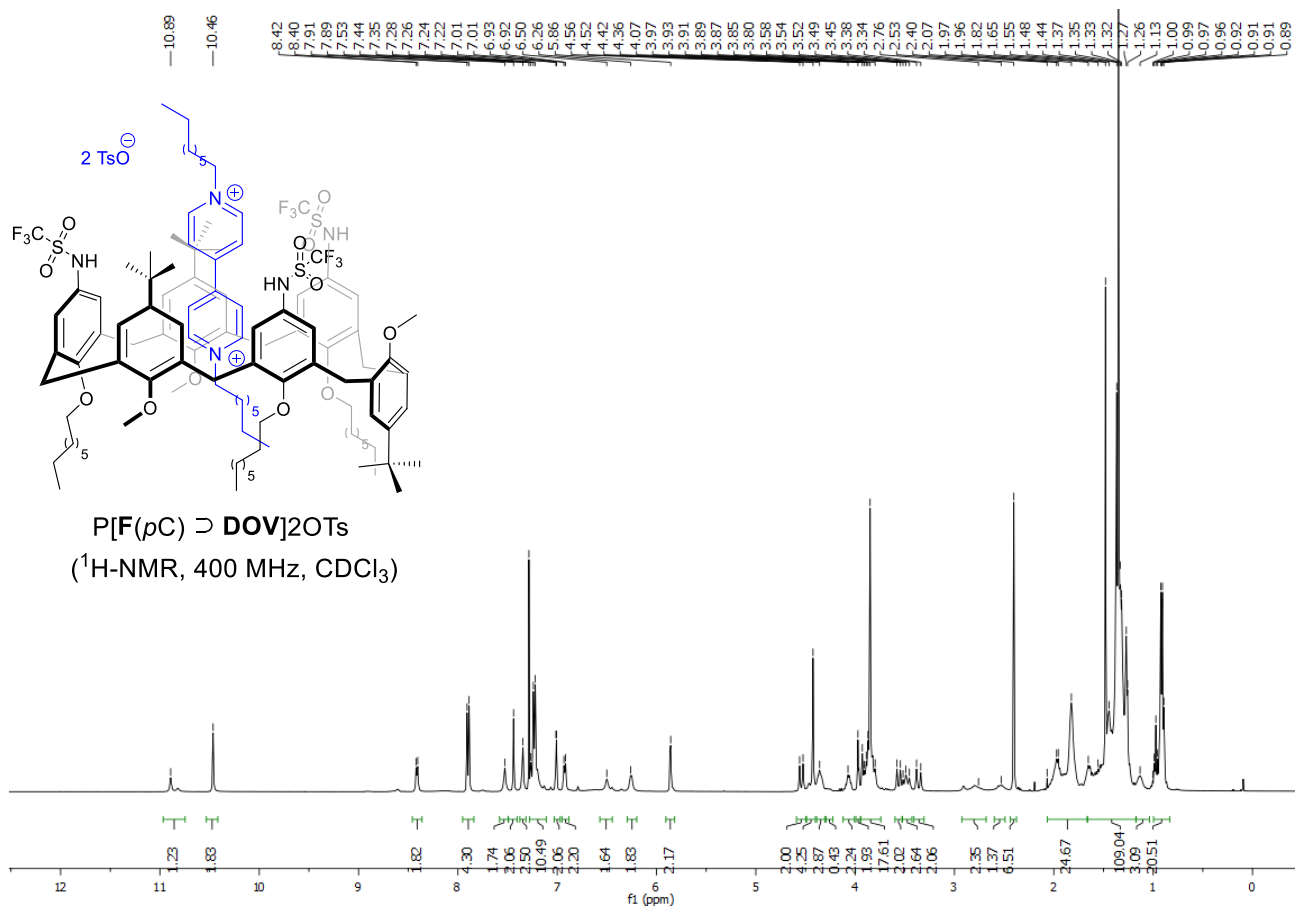
	$\delta_{3.0}$ (ppm)	$\Delta\delta$ (ppm)
TEPO	47.79	
TEPO+A	54.05	6.26
TEPO+B	53.71	5.92
TEPO+C	51.75	3.96
TEPO+D	55.51	7.72
TEPO+E	56.50	8.71
TEPO+F	59.49	11.70
TEPO+ H	54.48	7.01

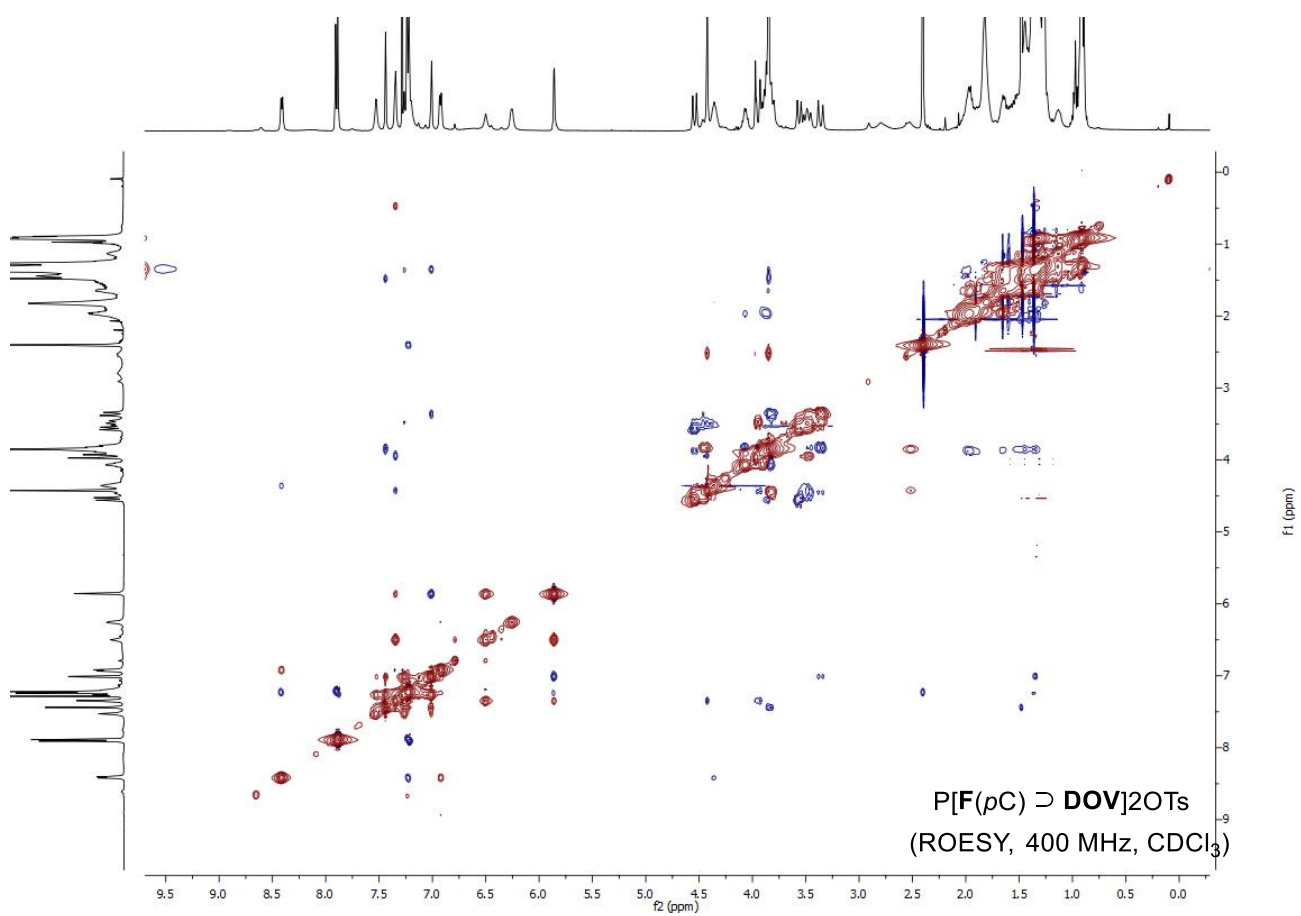
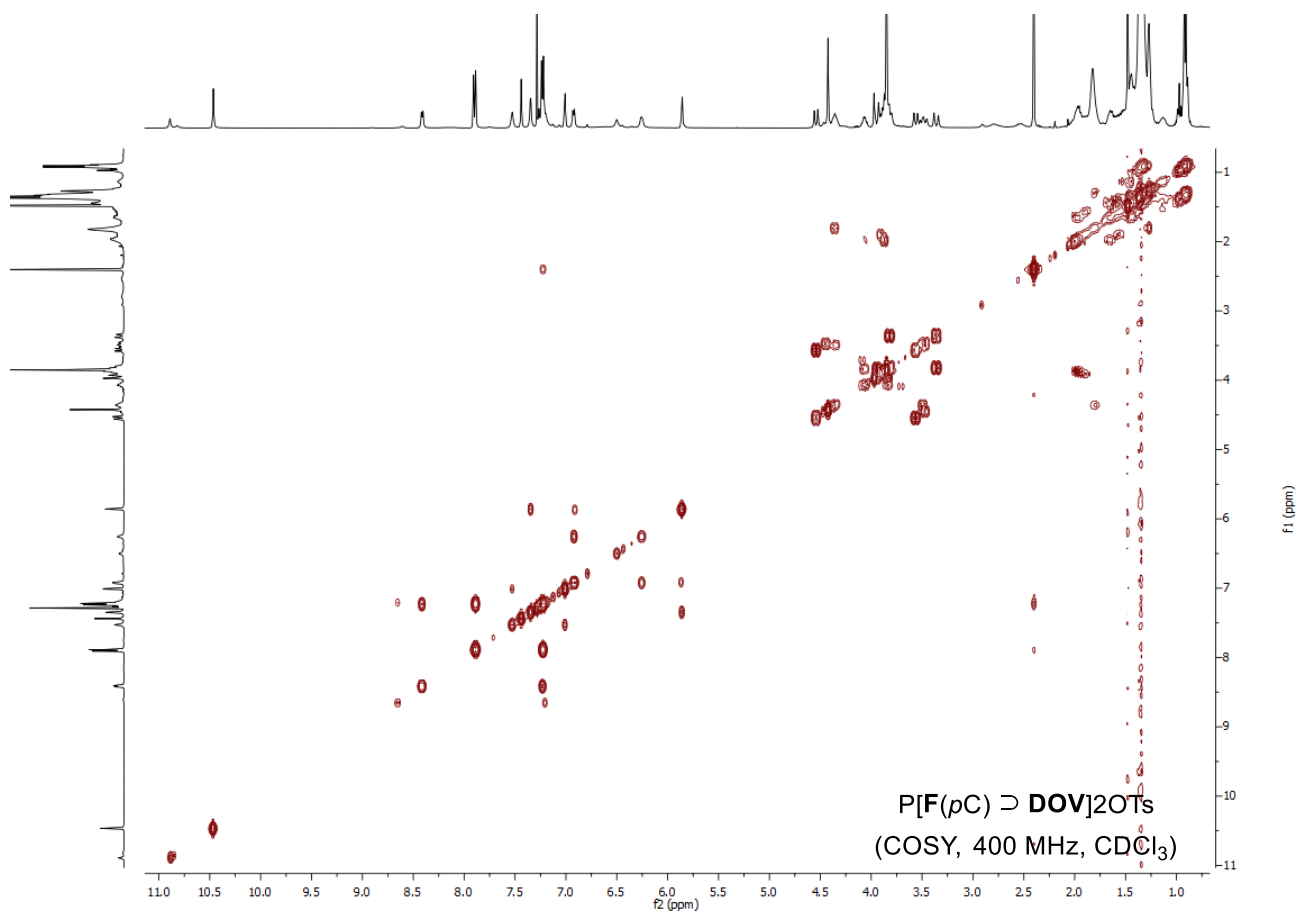
- **NMR Characterisation of P[F(*p*C)⊃DOV]2OTs**

Figure S5. Expanded region of 2D ROESY-NMR (CDCl₃, 400 MHz, spin-lock = 200 ms) spectrum of P[F(*p*C)⊃DOV]2OTs showing key ROE contacts between:

- The aromatic CH β of TSA F and OMe δ (red)
- The aromatic CH α of TSA F and H_a (green)
- The aromatic CH δ of TSA F and H_b (purple)
- The aromatic CH ε of TSA F and H_c (blue)
- The aromatic CH e* of DOV with *t*-Bu (black)







- Spectrophotometric Titration of P[F(pC)DOV]2OTs

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Version - 3.0

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Nmeas - 18
Nwave - 551

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Time - 16:01:49
Model - 0
Index - 0
Function - 2
Species - 3
Params - 3

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0 1 0	True	True	GUEST BIANCO.FIX
1 1 0	False	False	

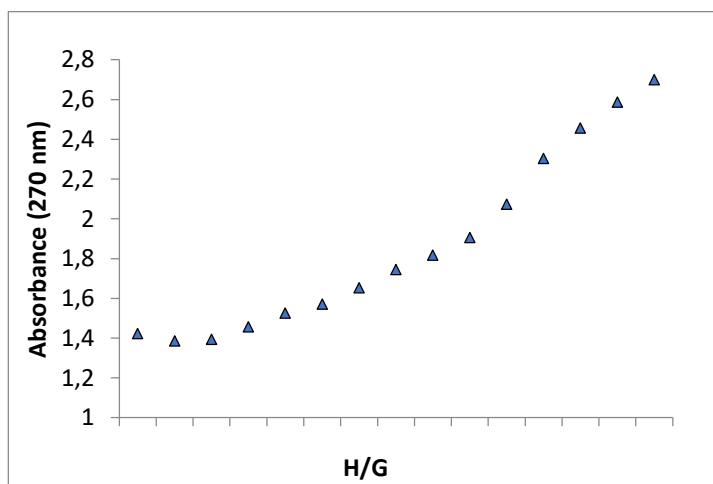
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1 1 0	False	3.48121E+00 +/-	4.84558E-01

[CONVERGENCE]
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Convergence - 1.000E-03
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SigmaY - 2.104E-01

[COVARIANCE]
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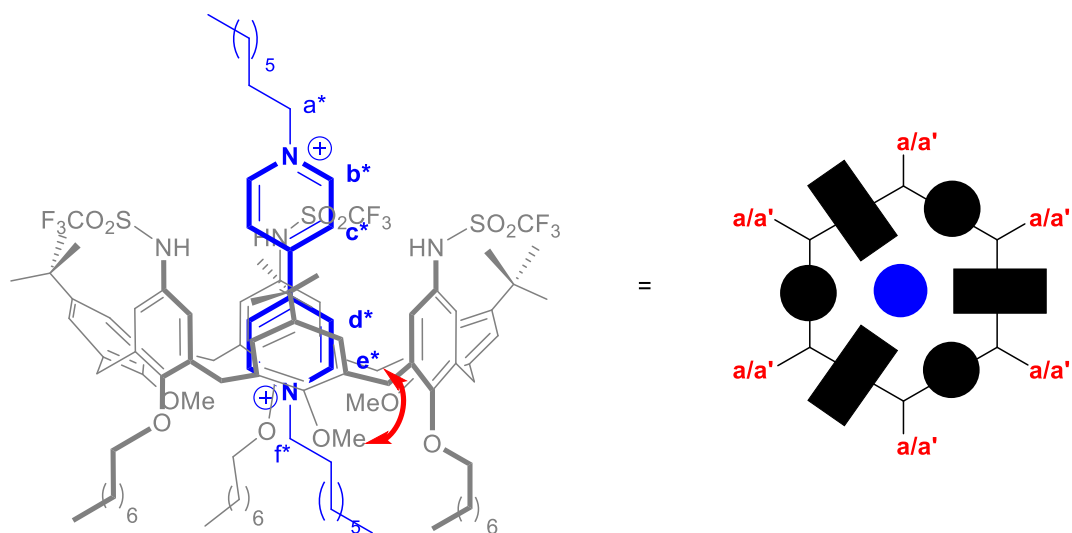
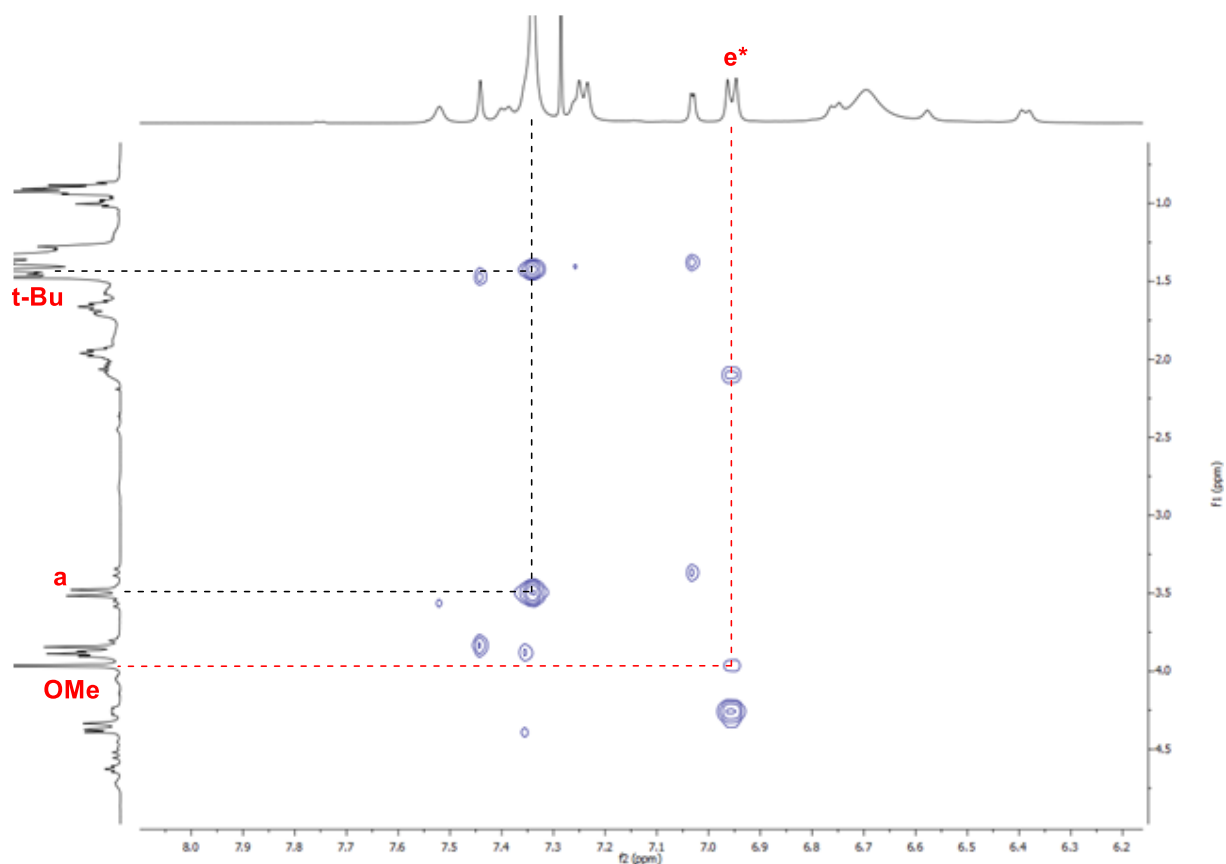
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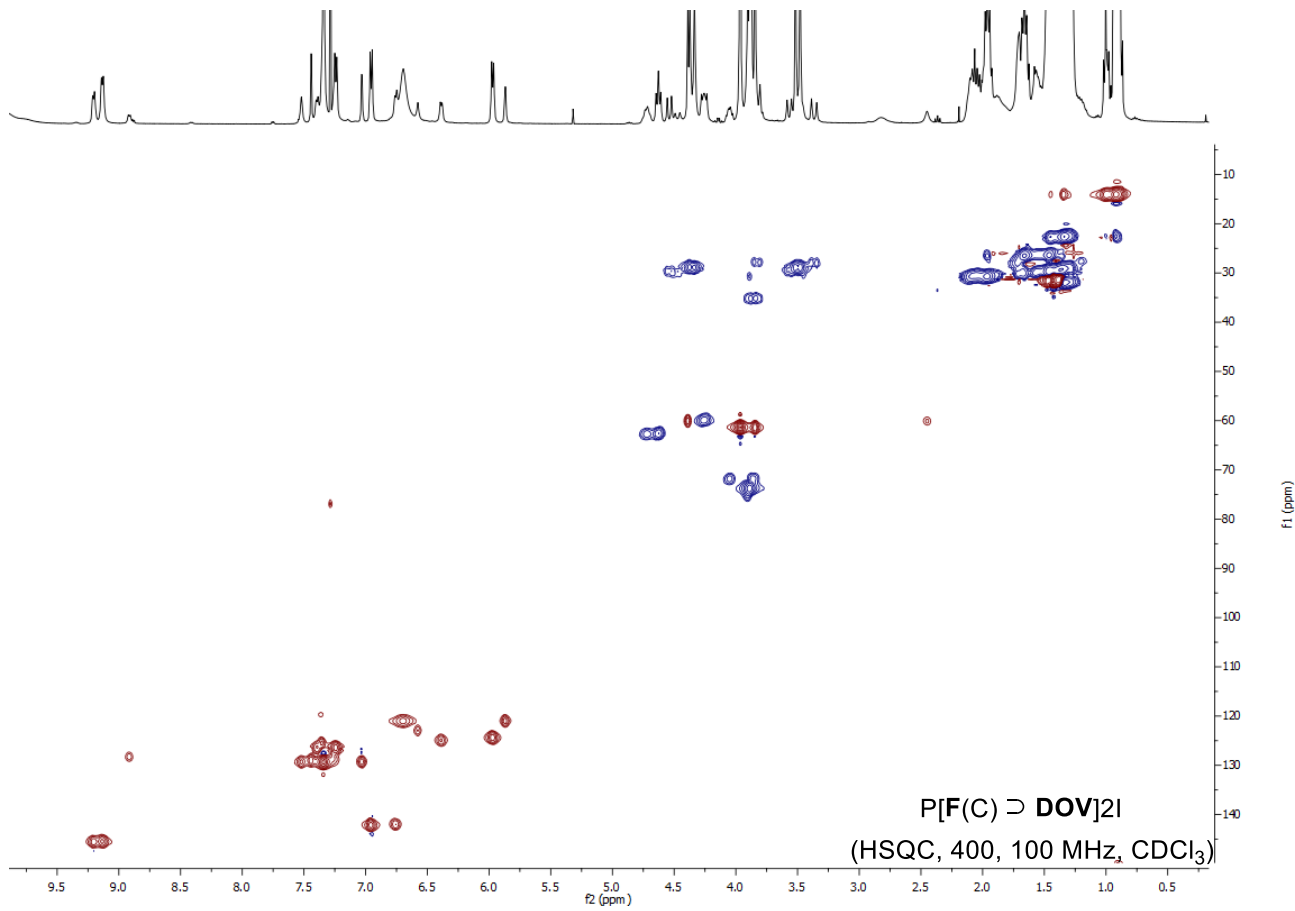
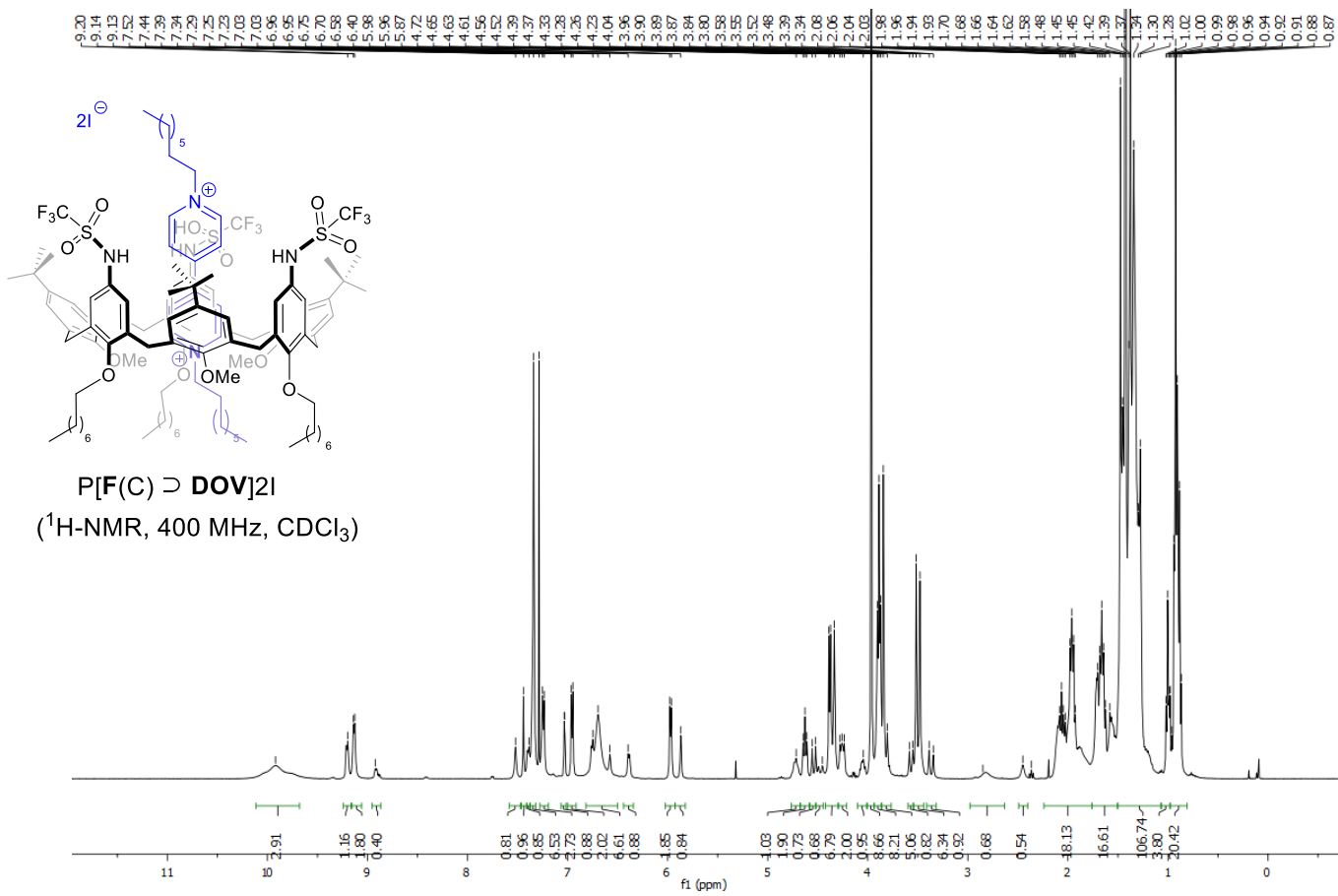
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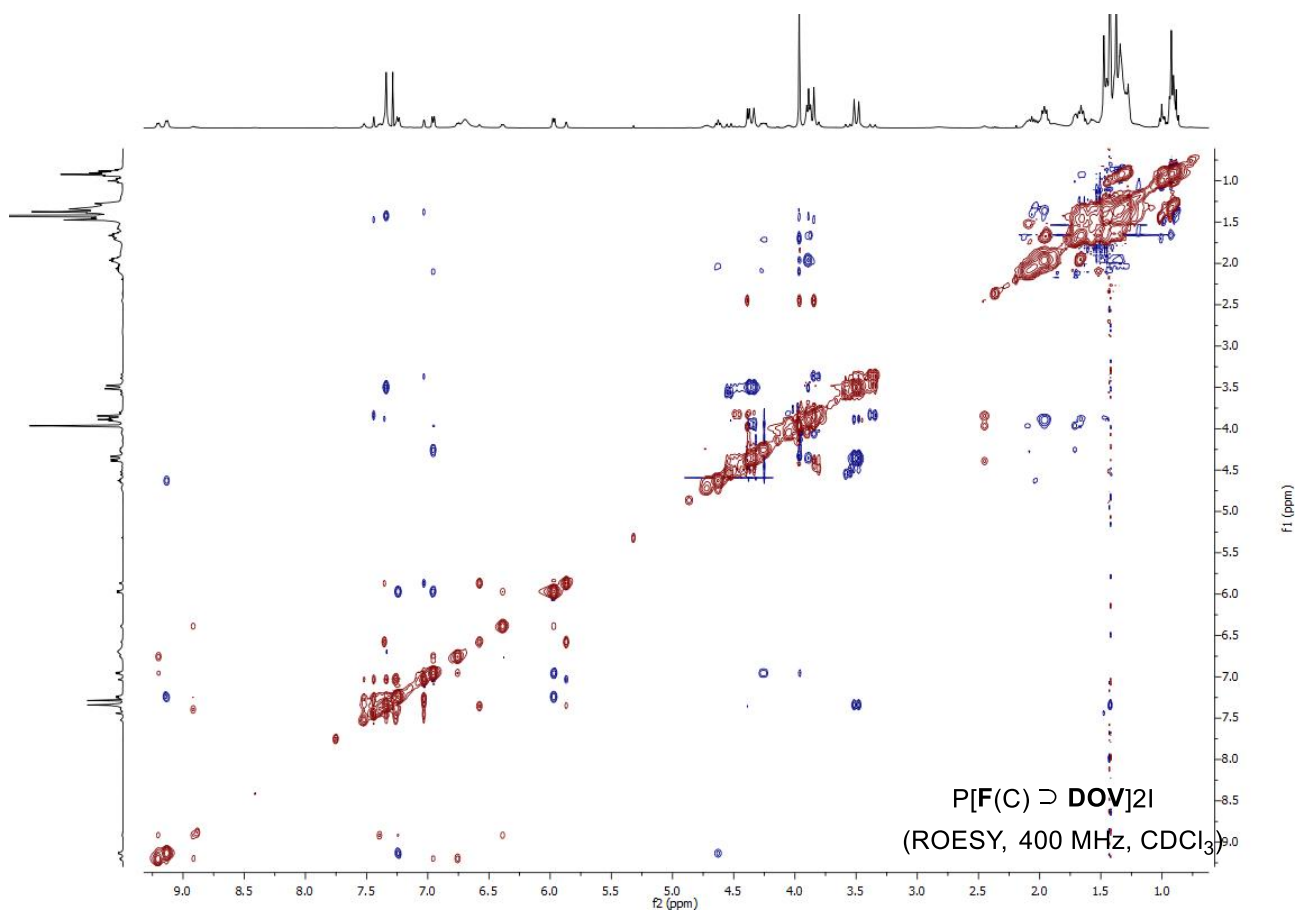
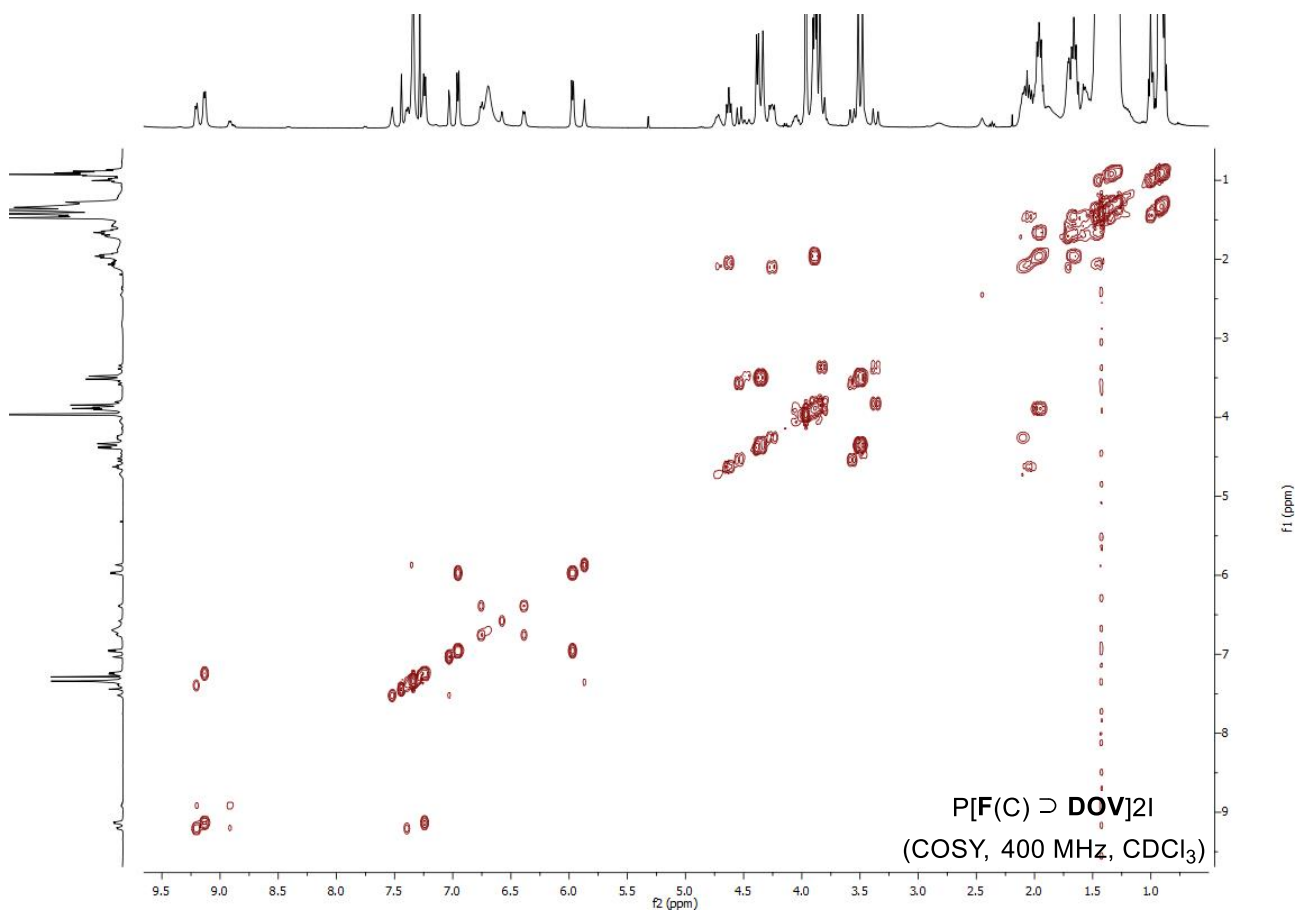


- NMR Characterisation of P[F(C)DOV]2I

Figure S6. Expanded region of 2D ROESY-NMR (CDCl₃, 400 MHz, spin-lock = 200 ms) spectrum of P[F(C)DOV]2I showing key ROE contact between the aromatic CH e* of DOV and OMe (red)







- **Competition Studies**

Figure S7. Experiment in the presence of a competitive binder (DOV•2OTs).

In a glass tube, **1a** (17.9 mg, 0.1 mmol), **2a** (35.1 mg, 0.3 mmol), **F** (8.2 mg, 5 mol %) and DOV•2OTs (6.5 mg, 10 mol %) were subsequently added. Distilled H₂O (0.25 ml, 0.4 M) was added and the reaction placed in a pre-heated oil bath at 37°C. After 16 hs CH₂Cl₂ (10 ml) was added and the mixture passed through a short pad of silica. The mixture was concentrated under reduced pressure and the crude analysed by ¹H-NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (13.2 mg).

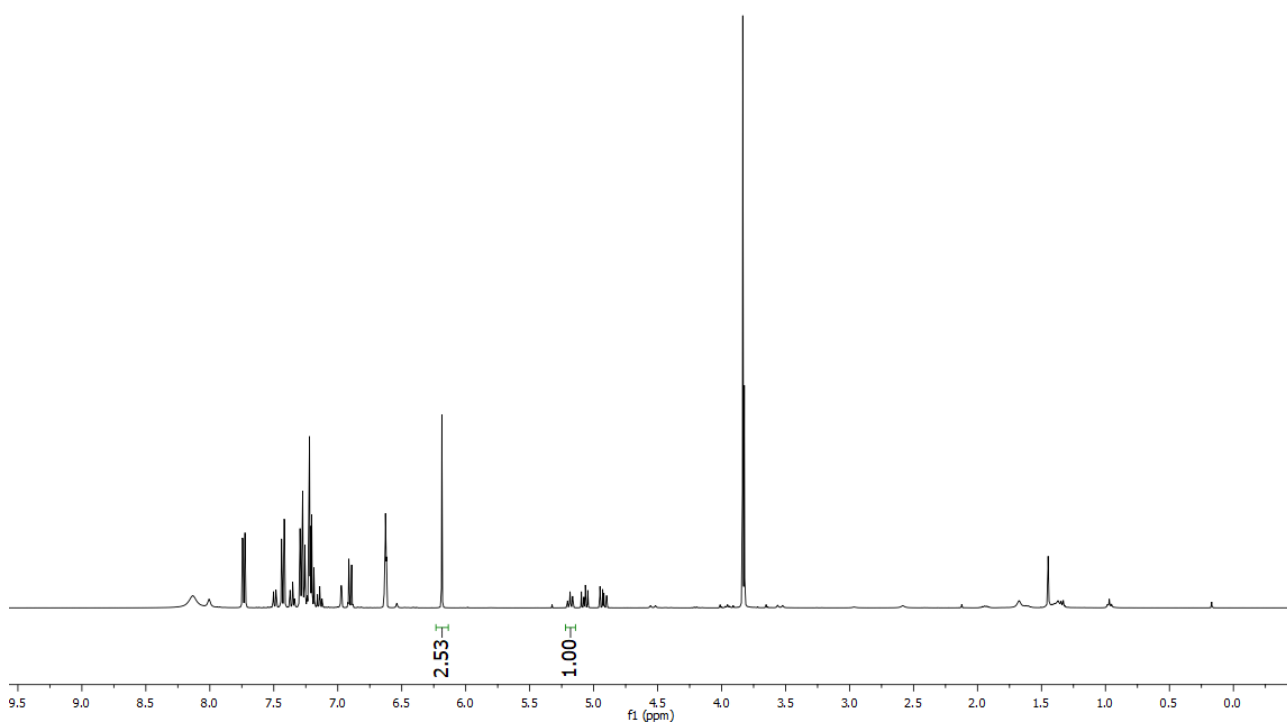
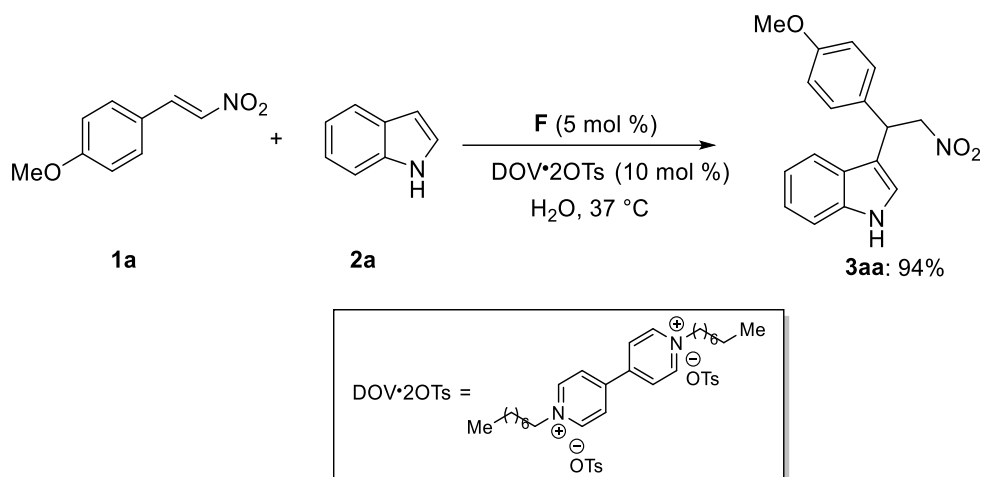
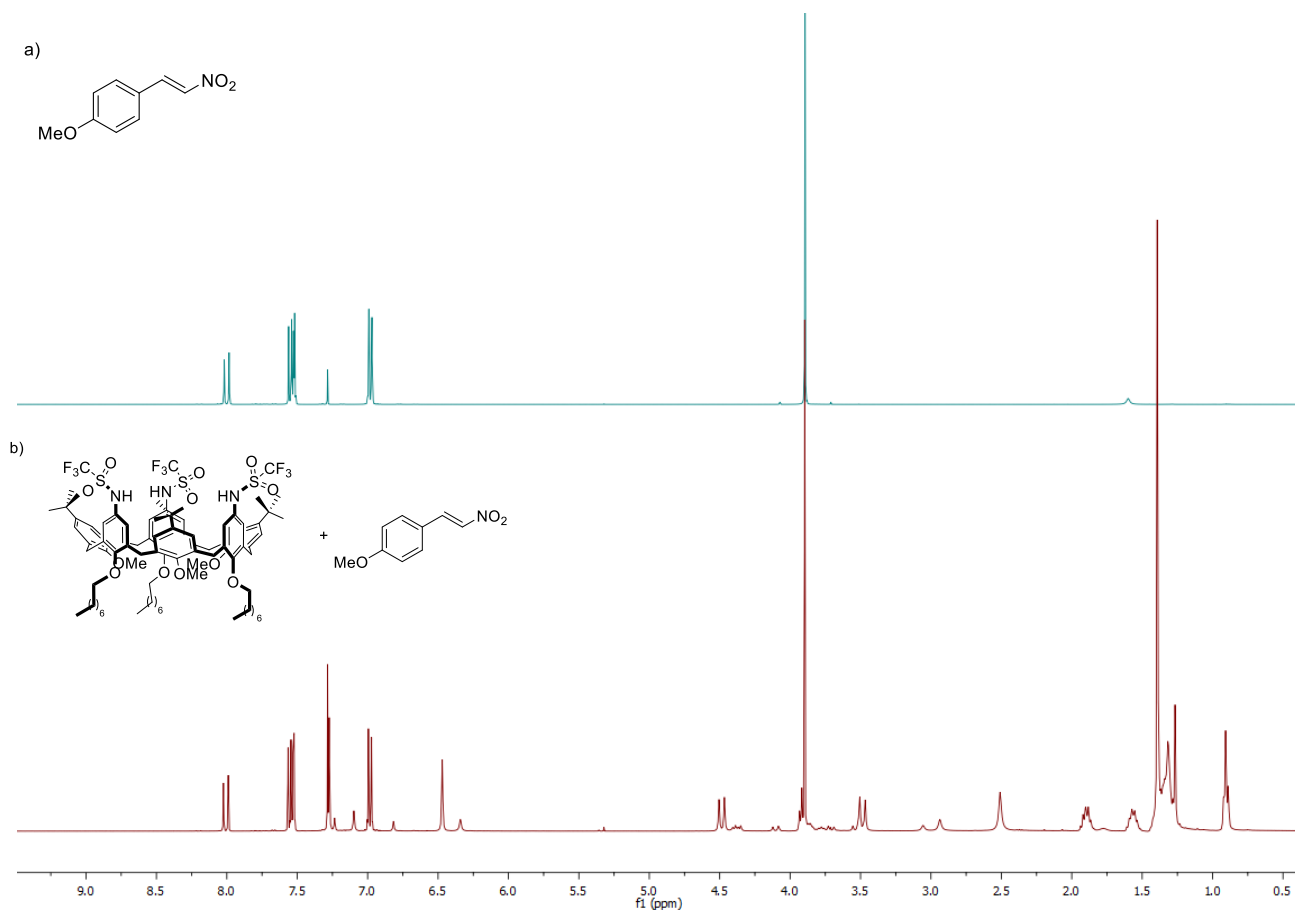
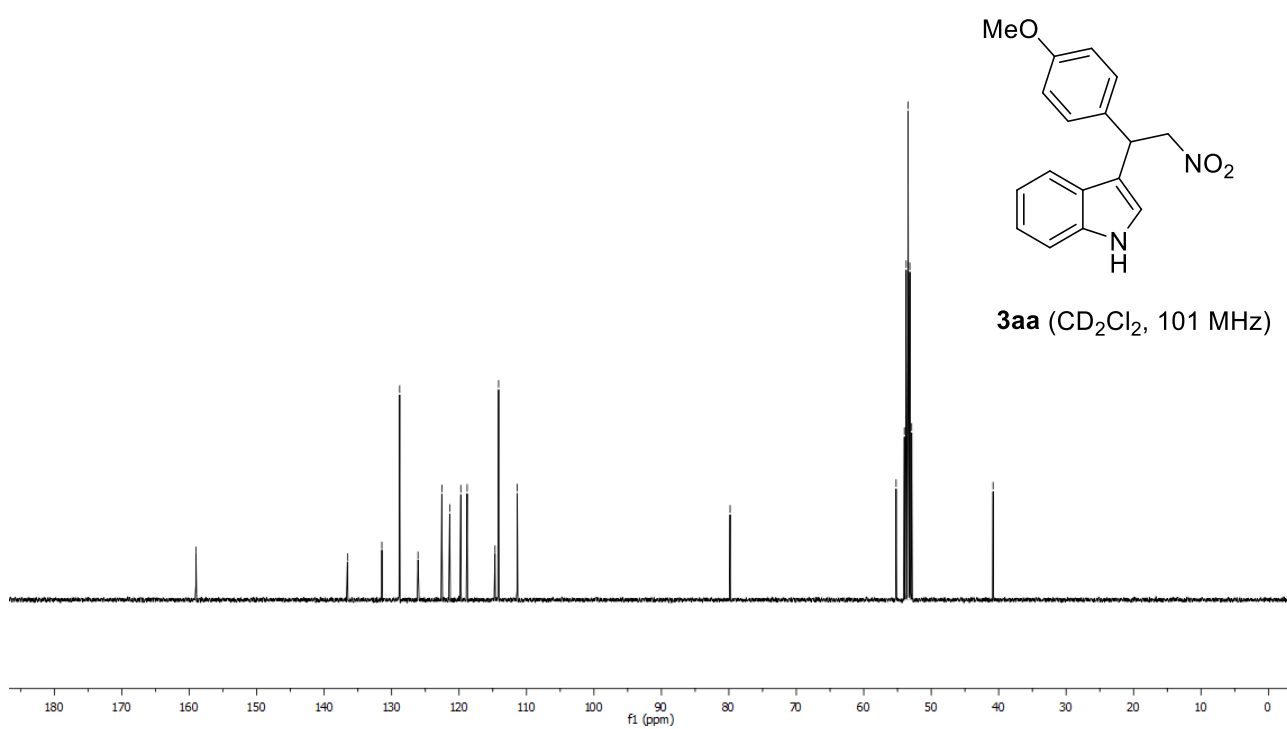
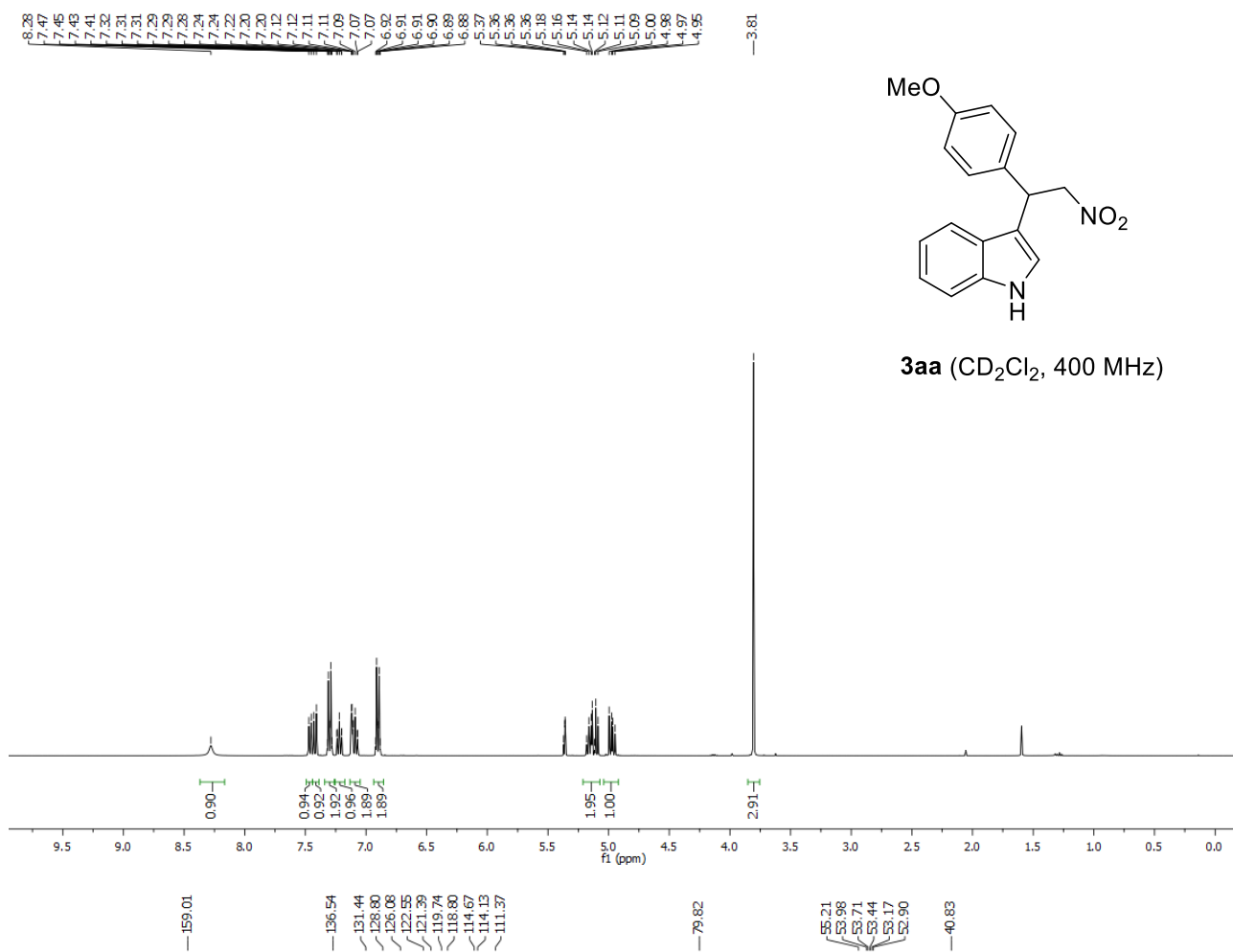


Figure S8. Tentative complexation of nitrostyrene **1a** with TSA **F**

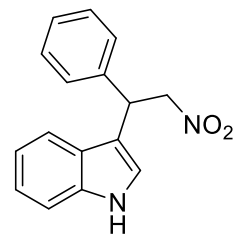
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) of a) nitrostyrene **1a**; b) 1:1.5 mixture of TSA **F** and nitrostyrene **1a**.



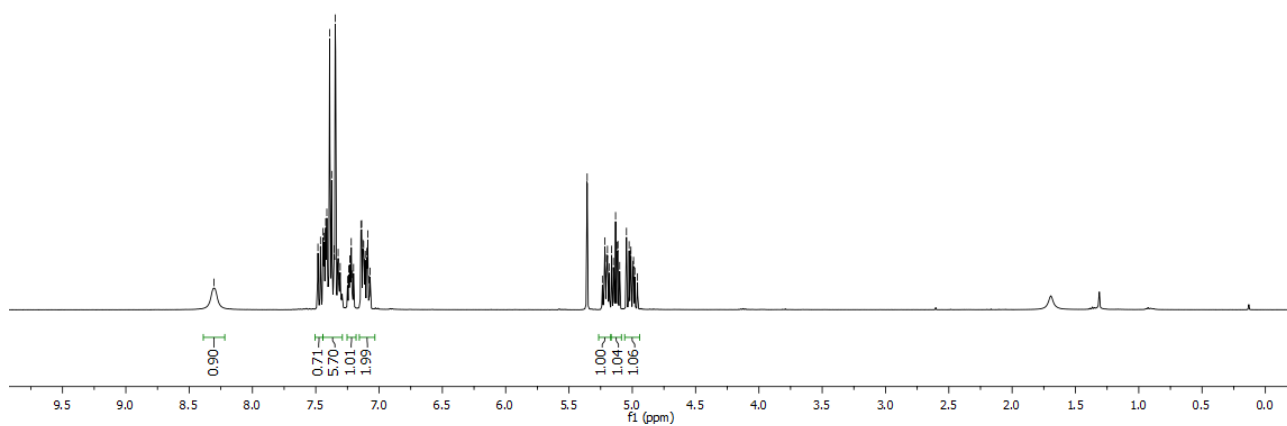
• NMR Spectra of H and Compounds 3



8.30
7.46
7.44
7.43
7.42
7.41
7.39
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7.33
7.32
7.31
7.25
7.24
7.23
7.22
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7.14
7.13
7.12
7.11
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7.09
7.07
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5.94
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5.16
5.15
5.14
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5.02
5.01
4.99
4.98



3ba (CD₂Cl₂, 400 MHz)

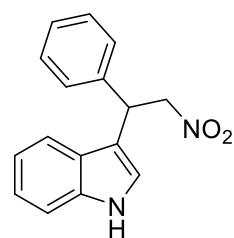


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118.73
114.32
111.40

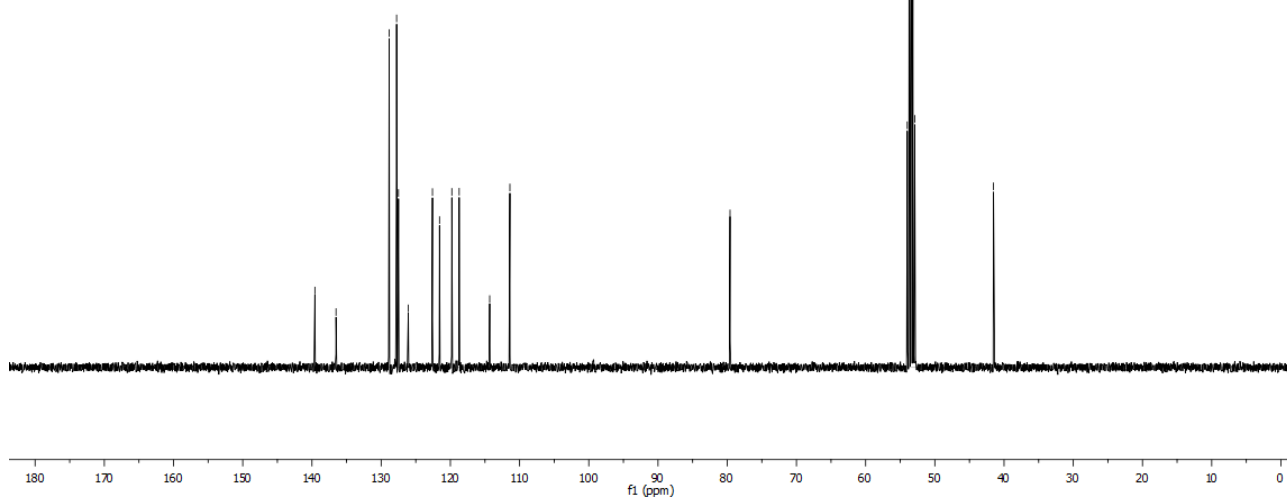
79.59

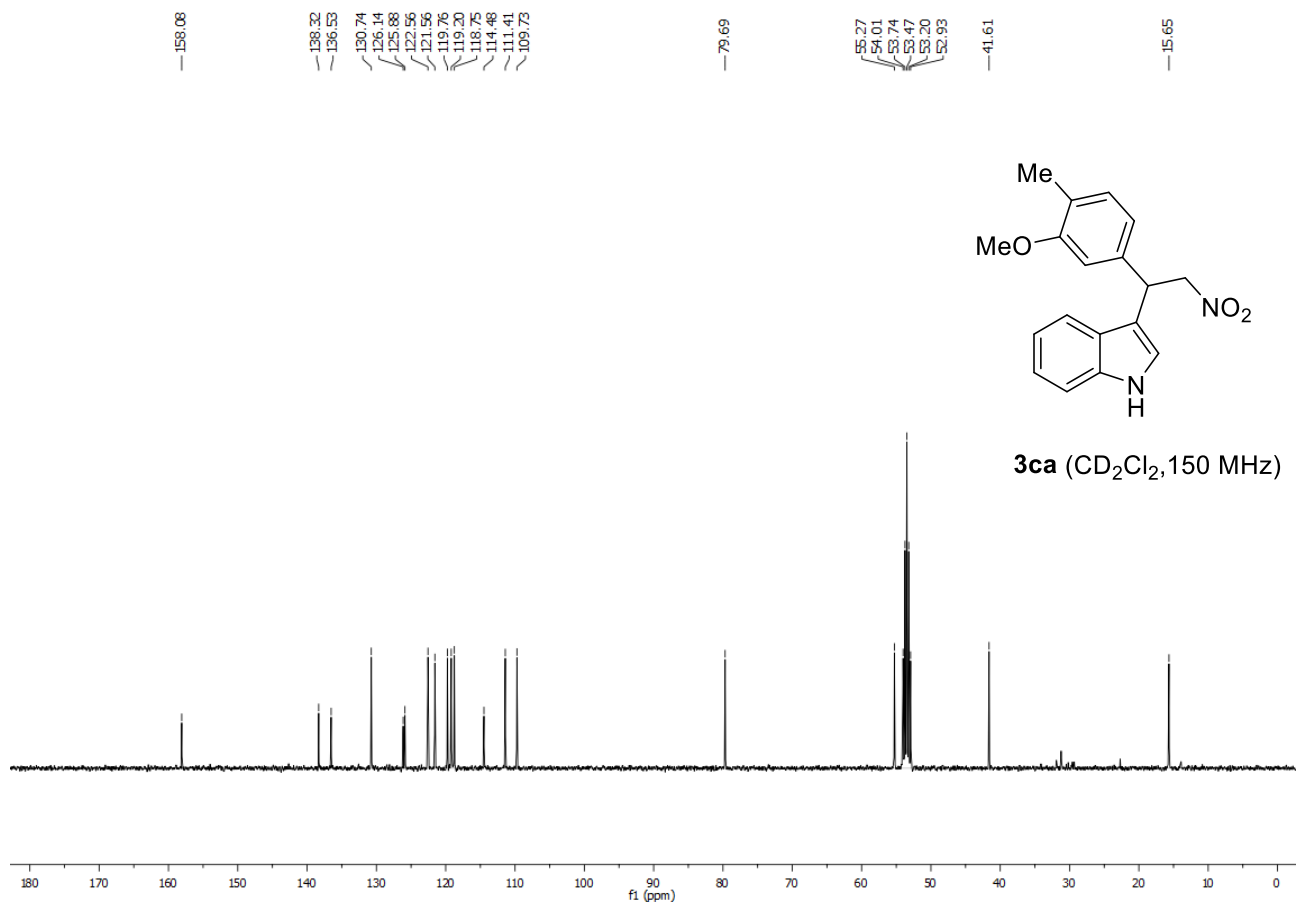
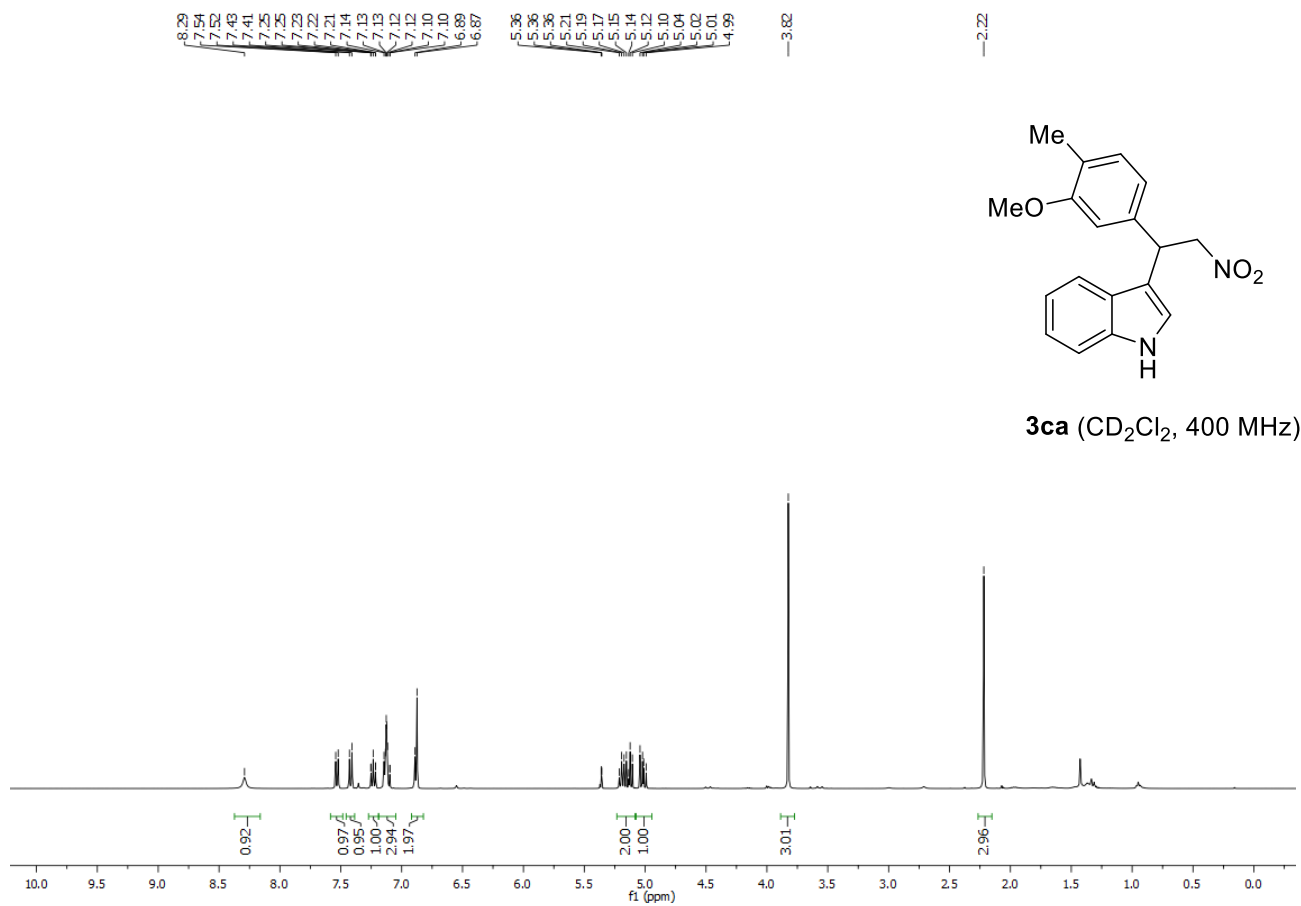
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53.72
53.45
53.18
52.91

41.53

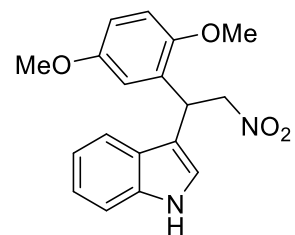


3ba (CD₂Cl₂, 101 MHz)

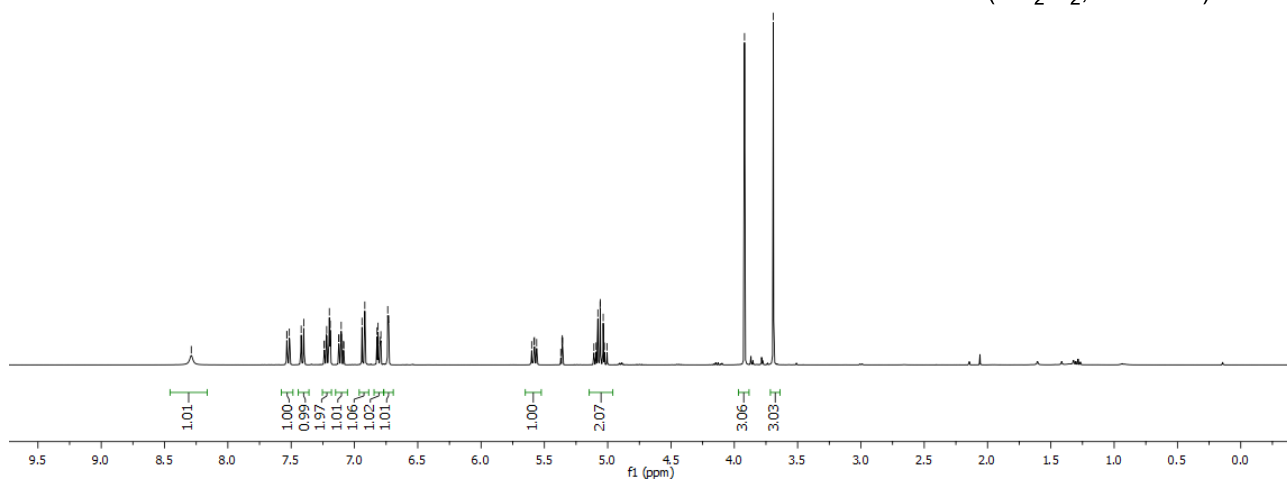




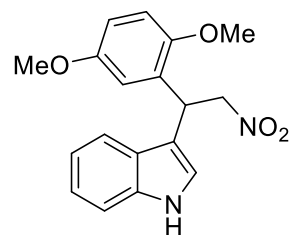
8.29
7.53
7.51
7.42
7.40
7.24
7.24
7.22
7.20
7.19
7.12
7.12
7.11
7.10
7.09
7.08
6.94
6.92
6.81
6.80
6.79
6.74
6.73
5.60
5.58
5.55
5.55
5.37
5.36
5.36
5.11
5.09
5.08
5.06
5.06
5.04
5.03
5.00
—3.92
—3.69



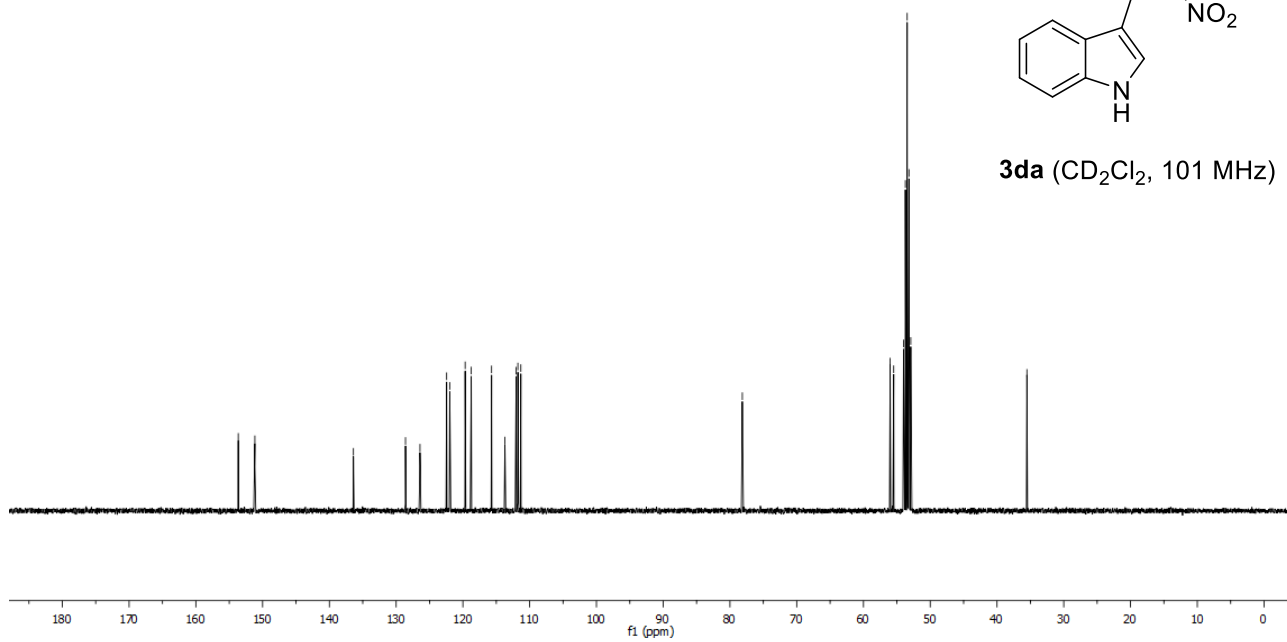
3da (CD₂Cl₂, 400 MHz)

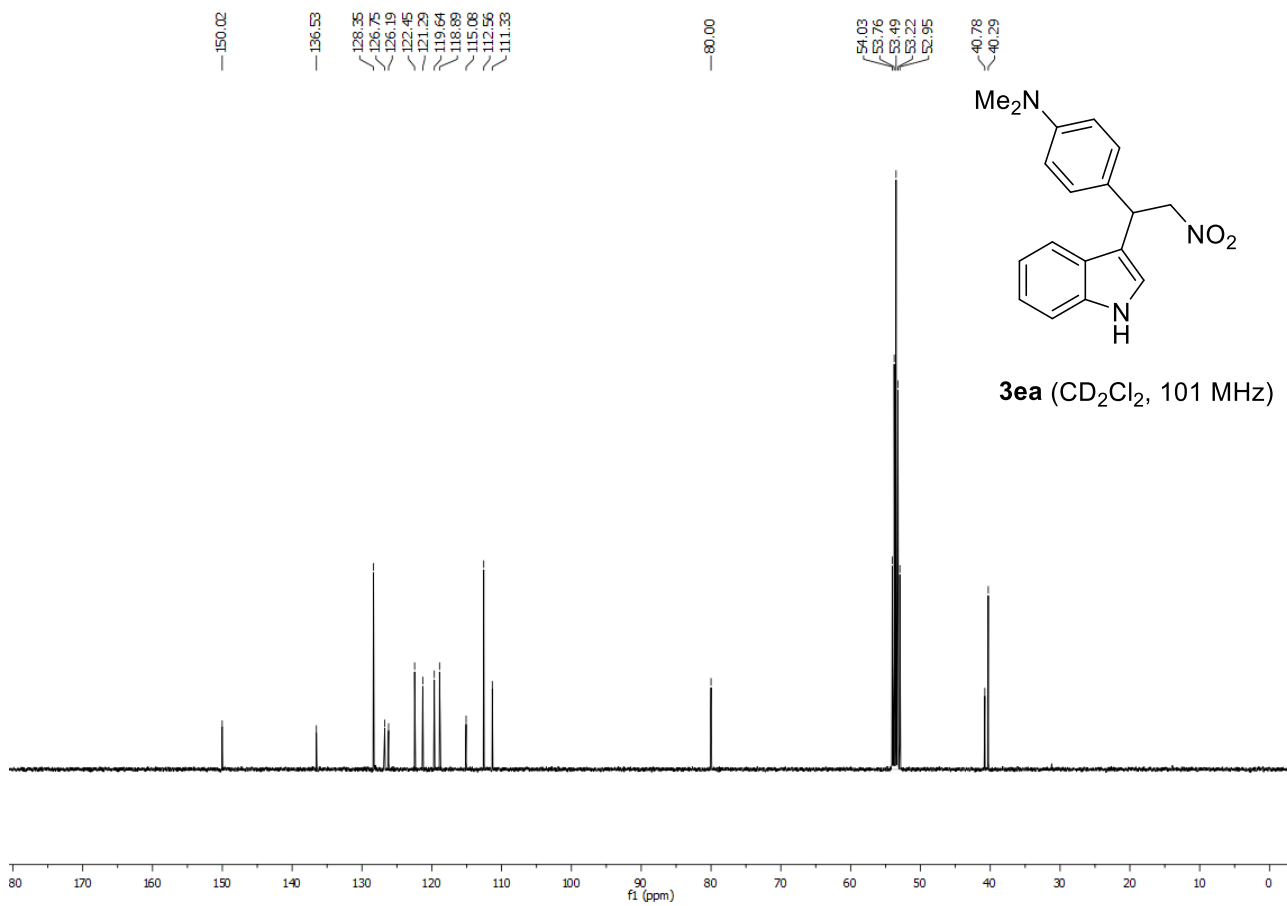
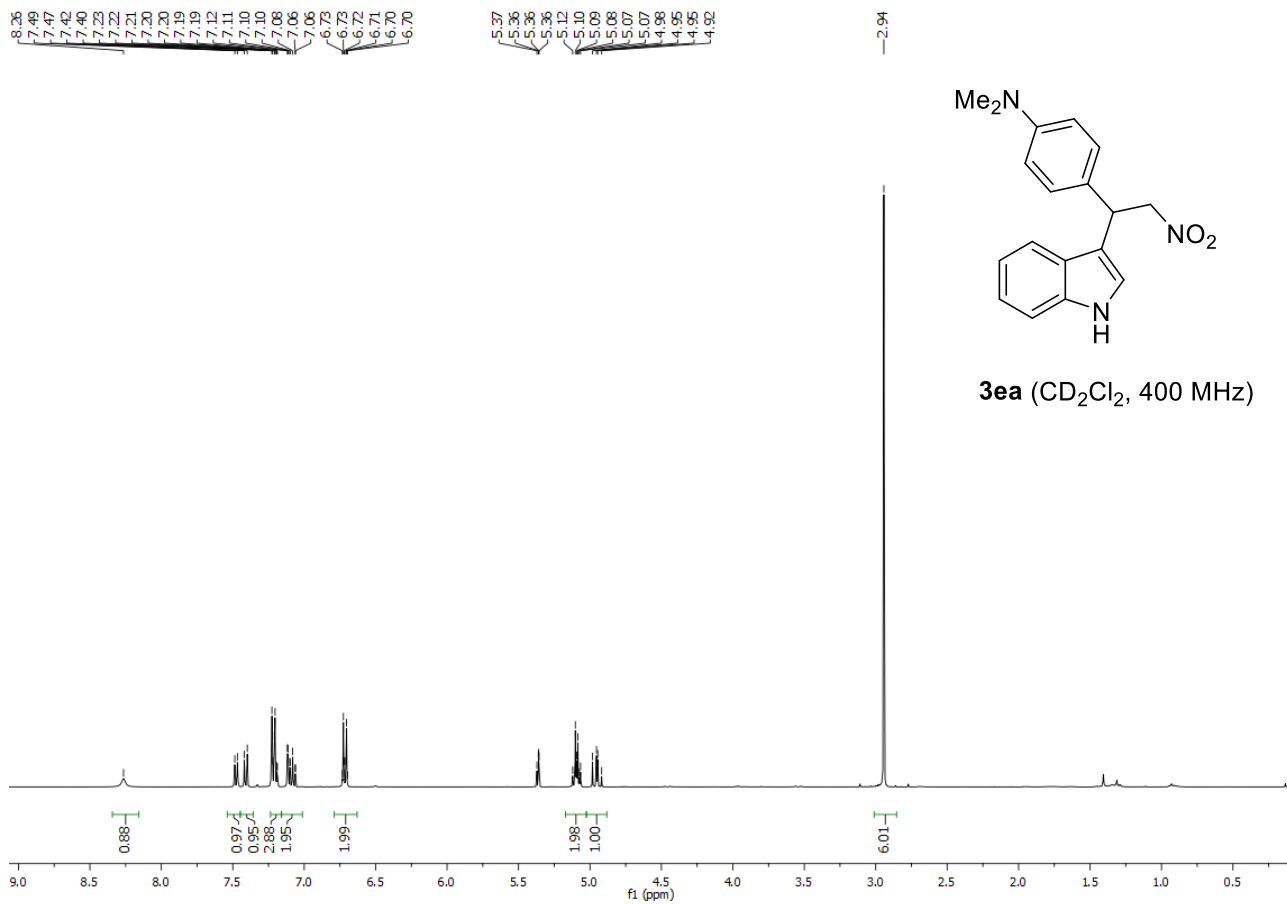


—153.65
—151.16
—136.40
128.60
126.43
122.44
121.97
119.66
118.75
115.70
113.71
112.02
111.76
111.32
—78.15
56.00
55.47
54.00
53.73
53.46
53.19
52.92
—36.52

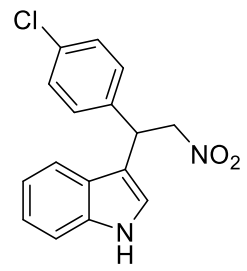


3da (CD₂Cl₂, 101 MHz)

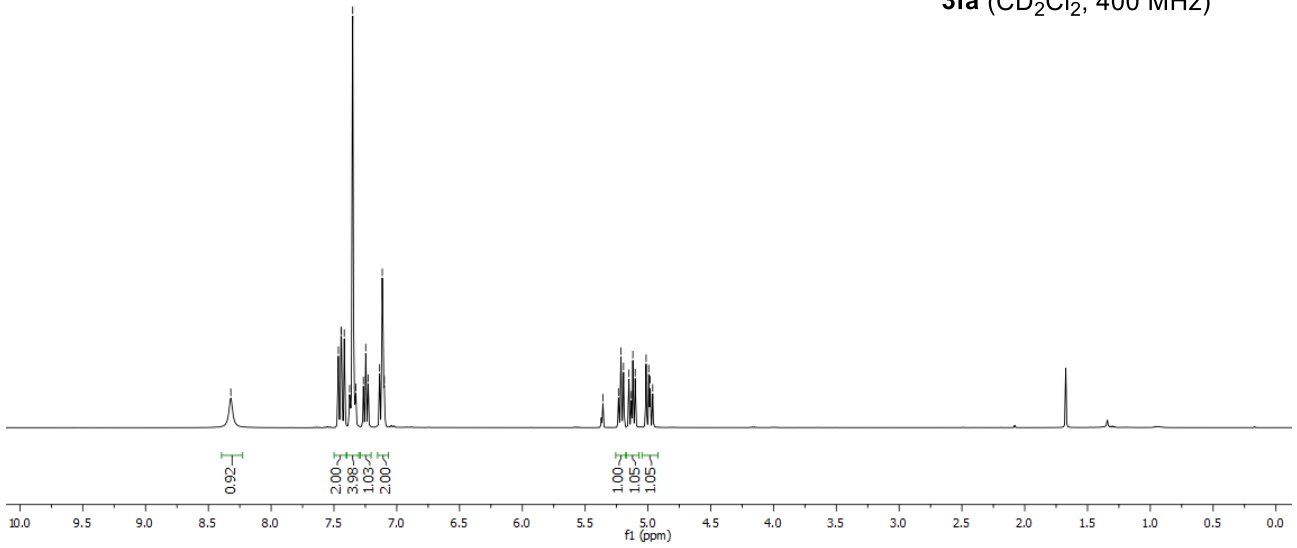




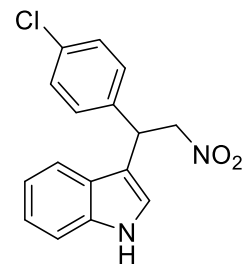
8.32
7.47
7.44
7.44
7.42
7.38
7.36
7.33
7.27
7.25
7.23
7.14
7.12
7.10
5.36
5.22
5.21
5.19
5.15
5.13
5.12
5.01
4.99
4.98
4.96



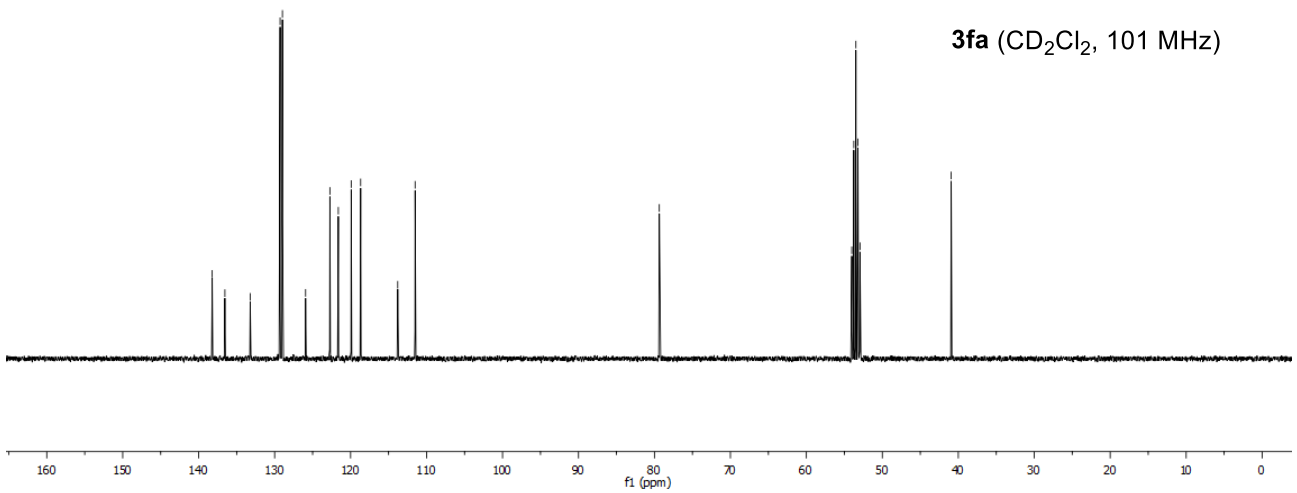
3fa (CD₂Cl₂, 400 MHz)



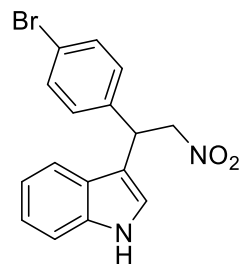
138.22
136.55
133.22
129.28
128.98
125.92
122.73
121.62
119.92
118.68
113.80
111.51
79.36
54.02
53.75
53.48
53.21
52.94
40.93



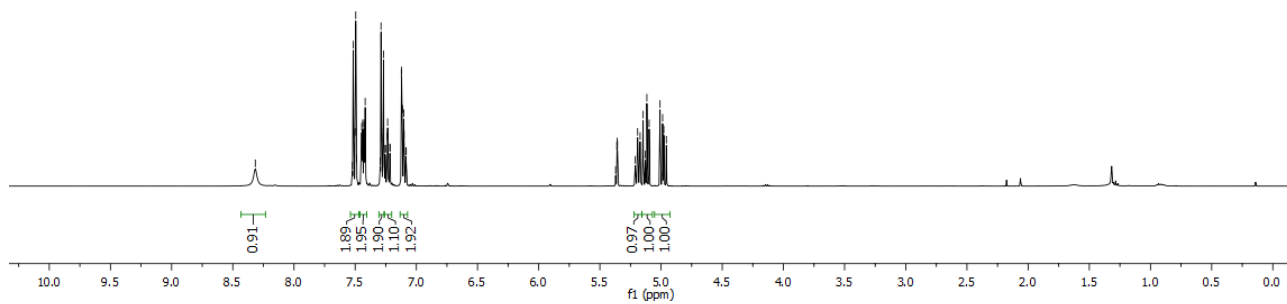
3fa (CD₂Cl₂, 101 MHz)



8.32
7.62
7.51
7.50
7.49
7.45
7.44
7.44
7.43
7.42
7.42
7.30
7.29
7.28
7.27
7.27
7.26
7.25
7.25
7.24
7.23
7.22
7.21
7.12
7.12
7.11
7.11
7.10
7.10
7.09
7.08
5.37
5.36
5.36
5.36
5.21
5.19
5.15
5.13
5.12
5.10
5.01
4.98
4.96



3ga (CD₂Cl₂, 400 MHz)

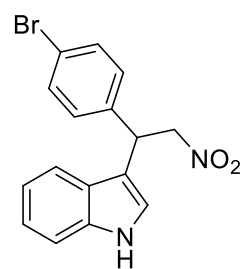


138.70
136.51
131.94
129.62
125.88
122.73
121.98
121.32
119.91
118.65
113.70
111.49

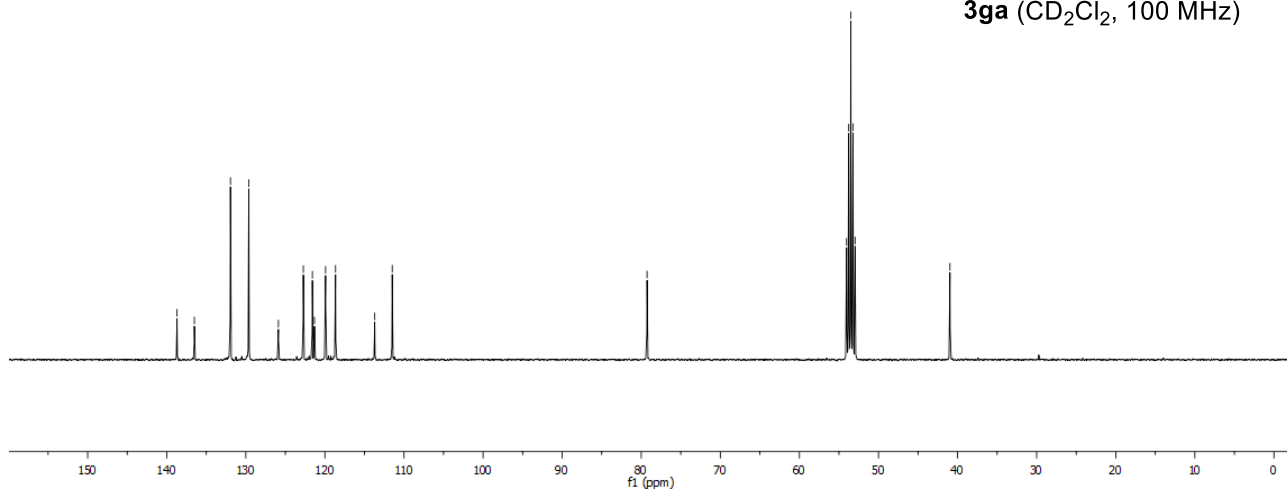
79.26

54.04
53.77
53.50
53.23
52.96

40.97



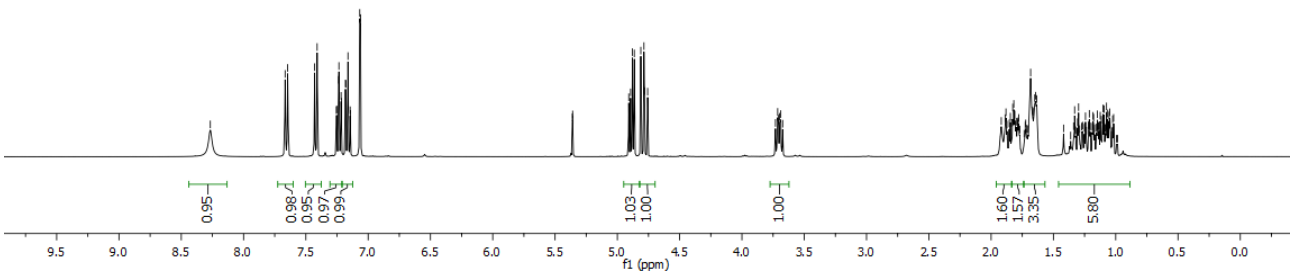
3ga (CD₂Cl₂, 100 MHz)



8.37
7.67
7.66
7.45
7.41
7.25
7.24
7.23
7.22
7.21
7.18
7.18
7.16
7.16
7.14
7.14
7.07
7.06
5.36
5.36
5.36
4.91
4.89
4.88
4.88
4.81
4.79
4.78
4.78
3.73
3.71
3.70
3.69
3.67
1.92
1.89
1.87
1.85
1.85
1.84
1.83
1.82
1.81
1.80
1.79
1.78
1.78
1.72
1.72
1.68
1.67
1.66
1.65
1.64
1.63
1.33
1.31
1.30
1.24
1.24
1.22
1.21
1.18
1.18
1.15
1.13
1.12
1.12
1.10
1.09
1.07
1.06
1.05
1.02
1.02



3ha (CD₂Cl₂, 400 MHz)



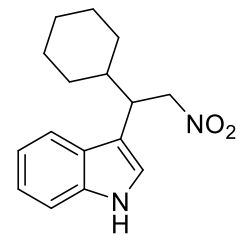
136.27
126.89
122.44
122.13
119.52
118.98
113.22
111.39

78.75

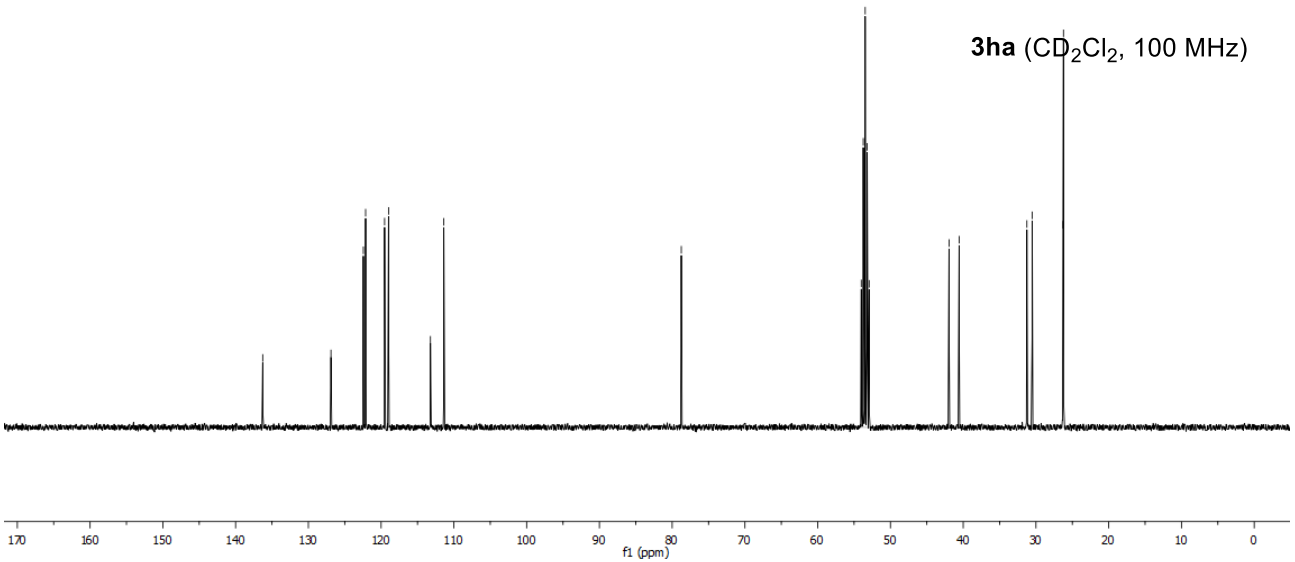
54.01
53.74
53.47
53.19
52.92

41.95
40.56

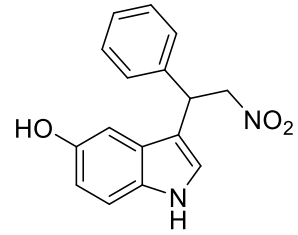
31.25
30.51
28.29
26.22



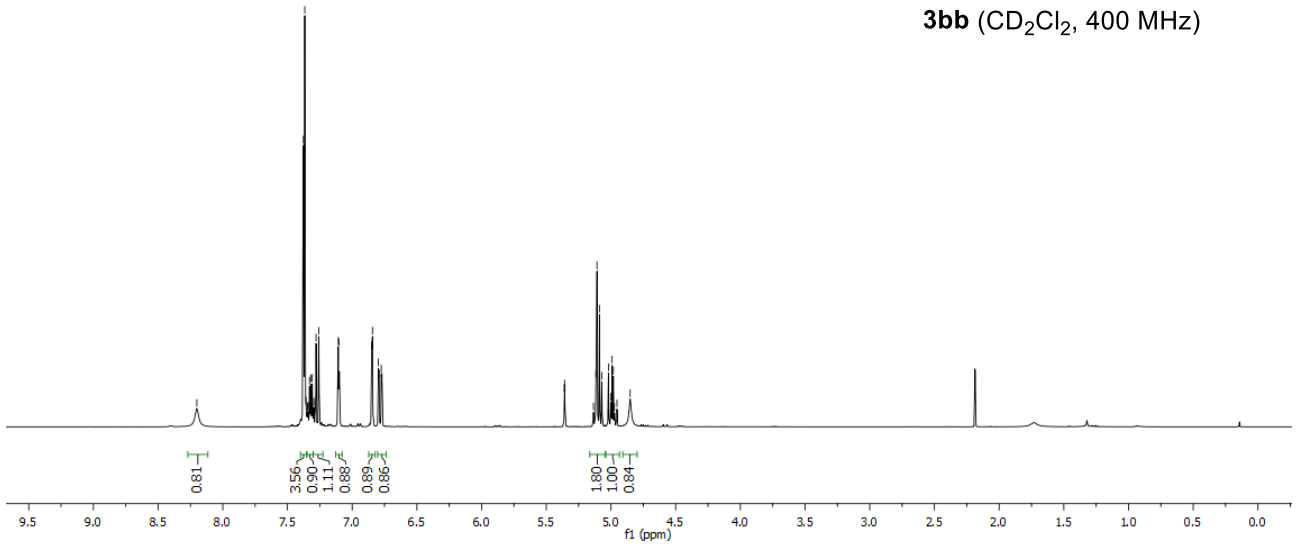
3ha (CD₂Cl₂, 100 MHz)



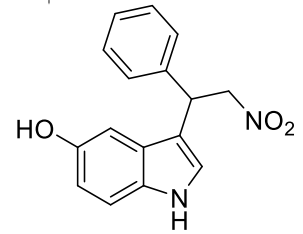
8.20
7.38
7.37
7.36
7.35
7.24
7.24
7.23
7.32
7.31
7.30
7.29
7.28
7.26
7.11
7.10
6.85
6.84
6.80
6.79
6.78
6.77
5.36
5.36
5.36
5.14
5.12
5.11
5.09
5.07
5.02
5.00
4.99
4.98
4.97
4.95
4.85



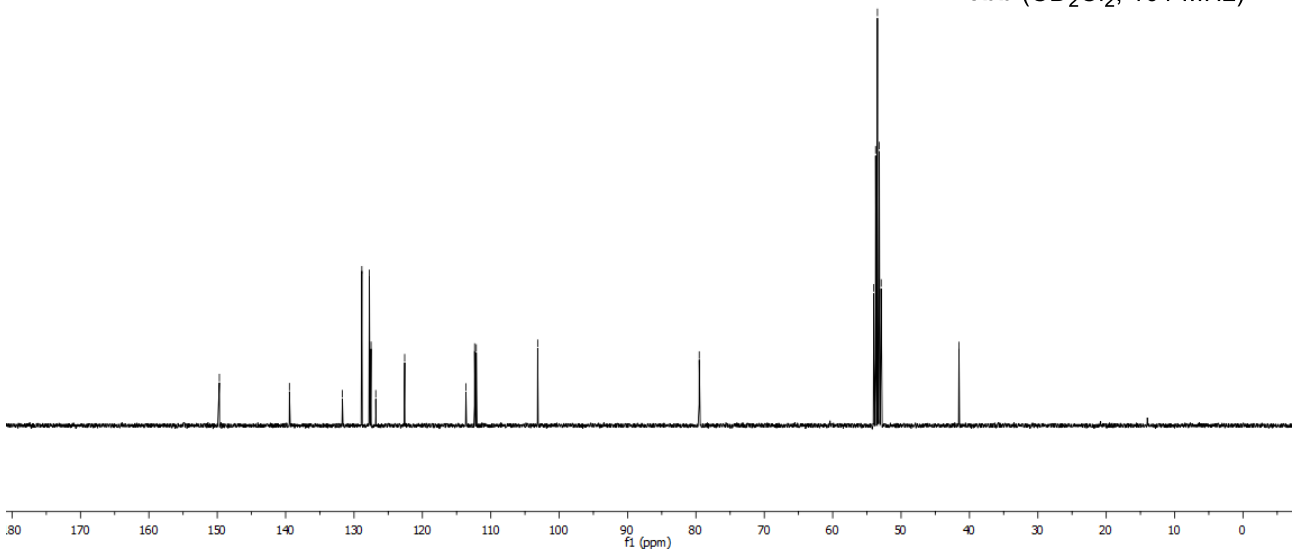
3b (CD₂Cl₂, 400 MHz)

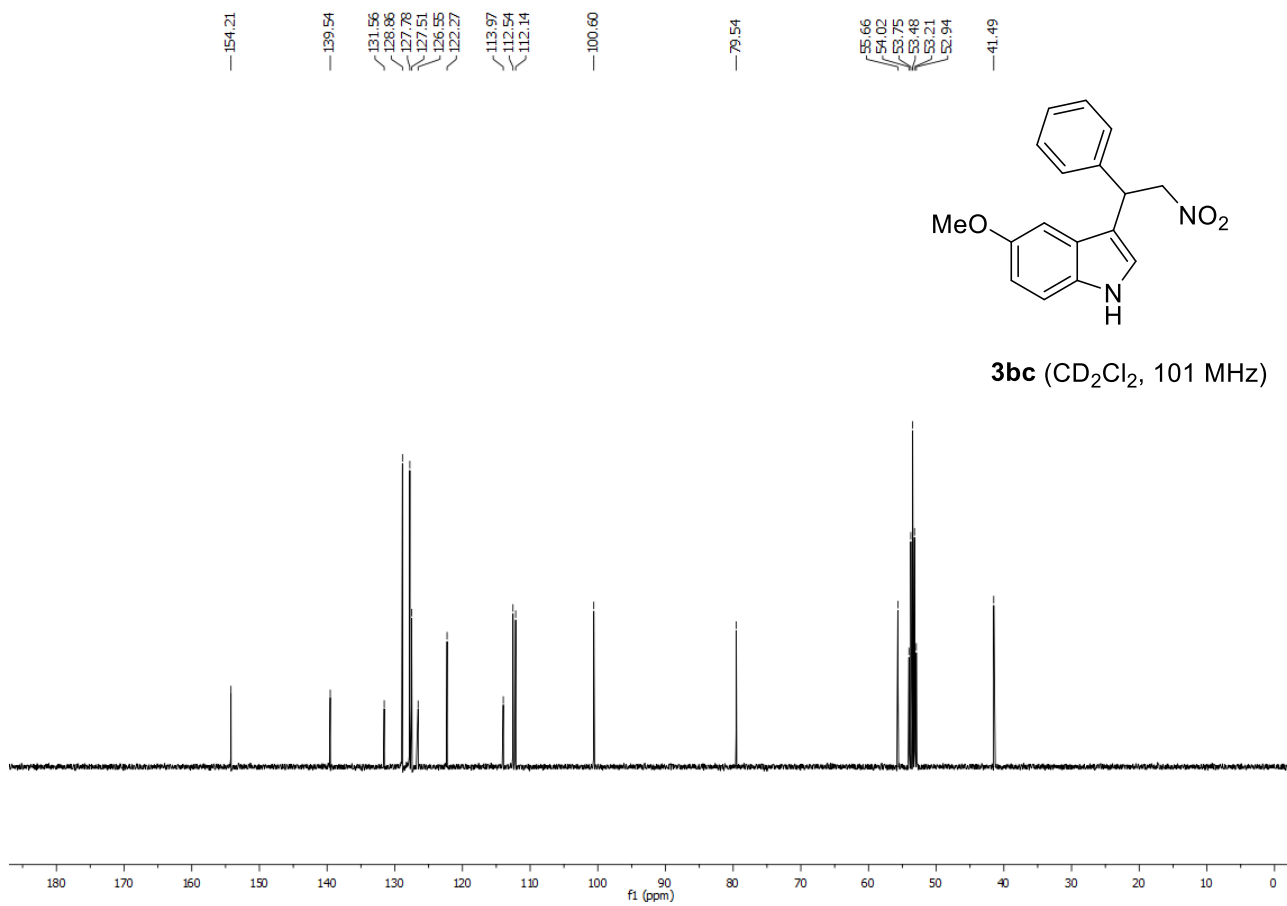
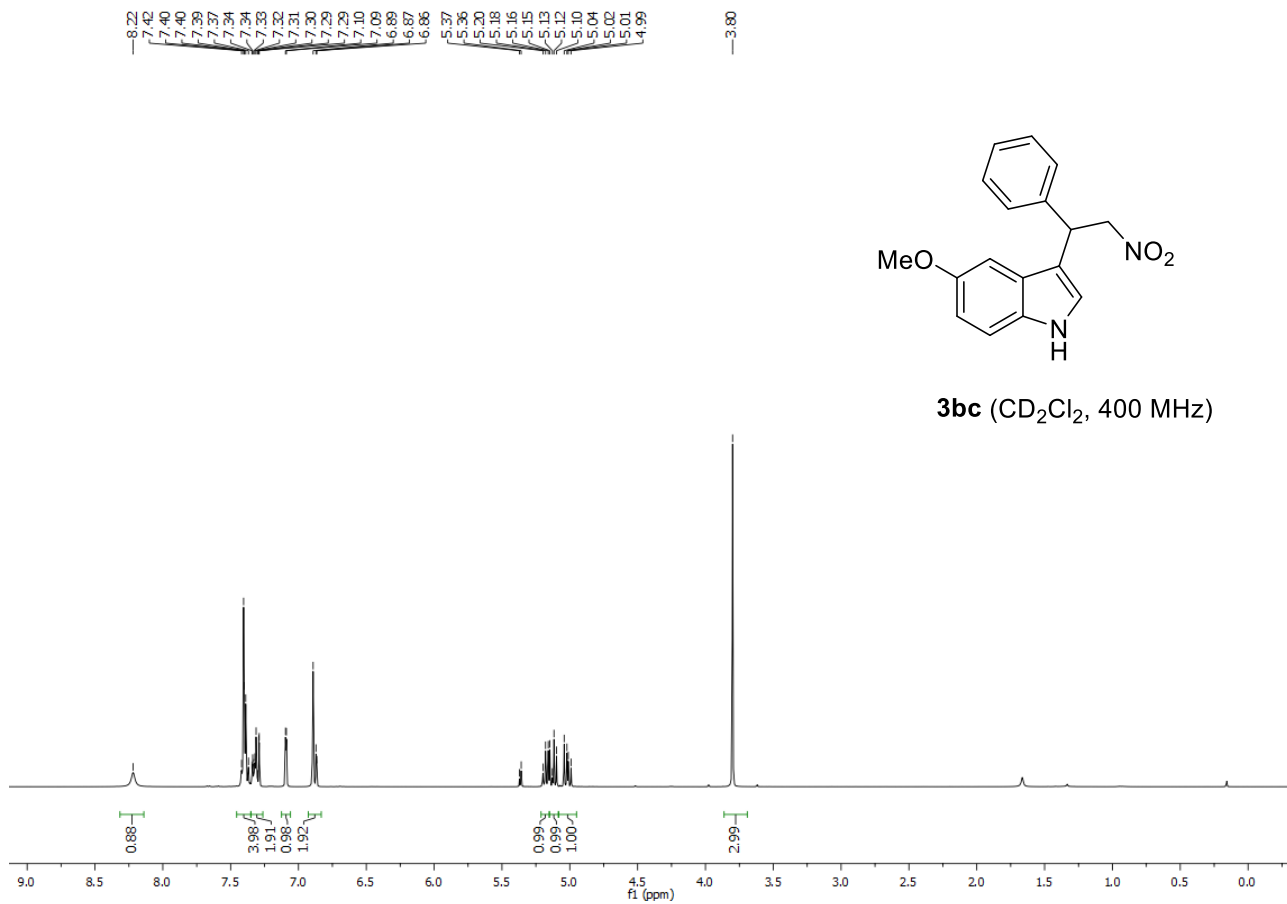


149.69
139.45
131.70
128.95
127.75
127.51
126.82
122.99
113.64
112.36
112.12
103.14
79.52
54.00
53.73
53.46
53.19
52.92
41.53

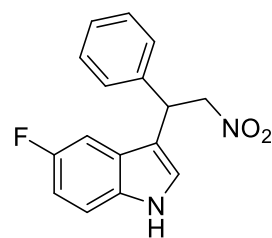


3b (CD₂Cl₂, 101 MHz)

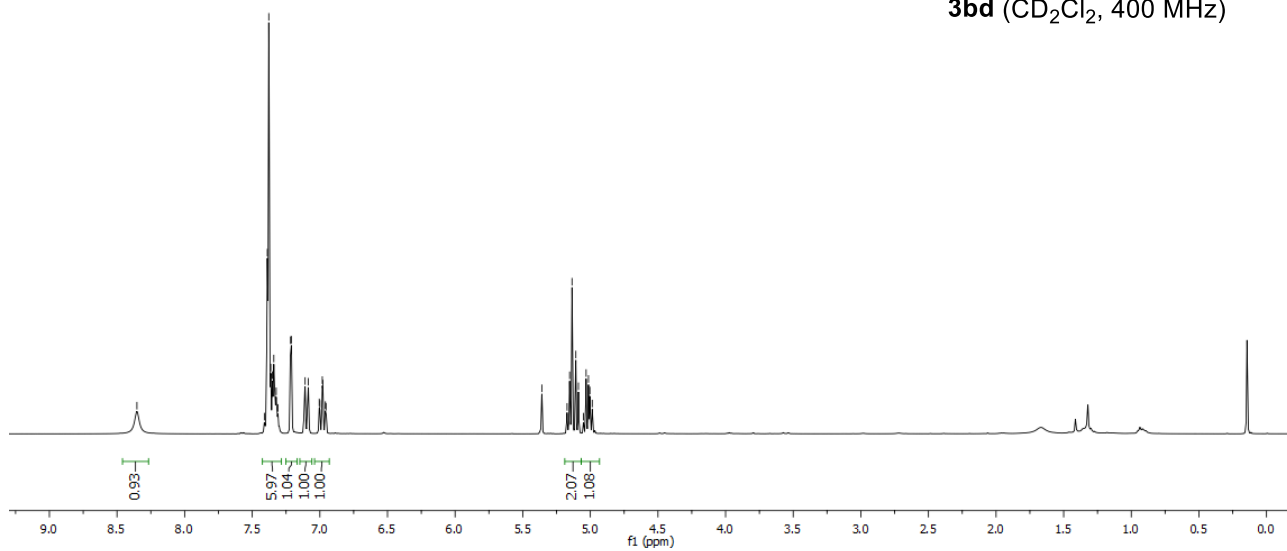




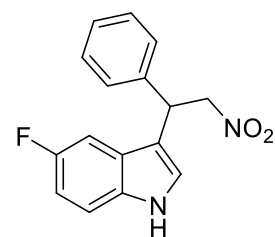
8.35
7.41
7.39
7.38
7.36
7.34
7.32
7.22
7.21
7.11
7.08
7.00
6.98
6.96
5.36
5.17
5.15
5.14
5.11
5.09
5.05
5.03
5.01
5.00
4.99



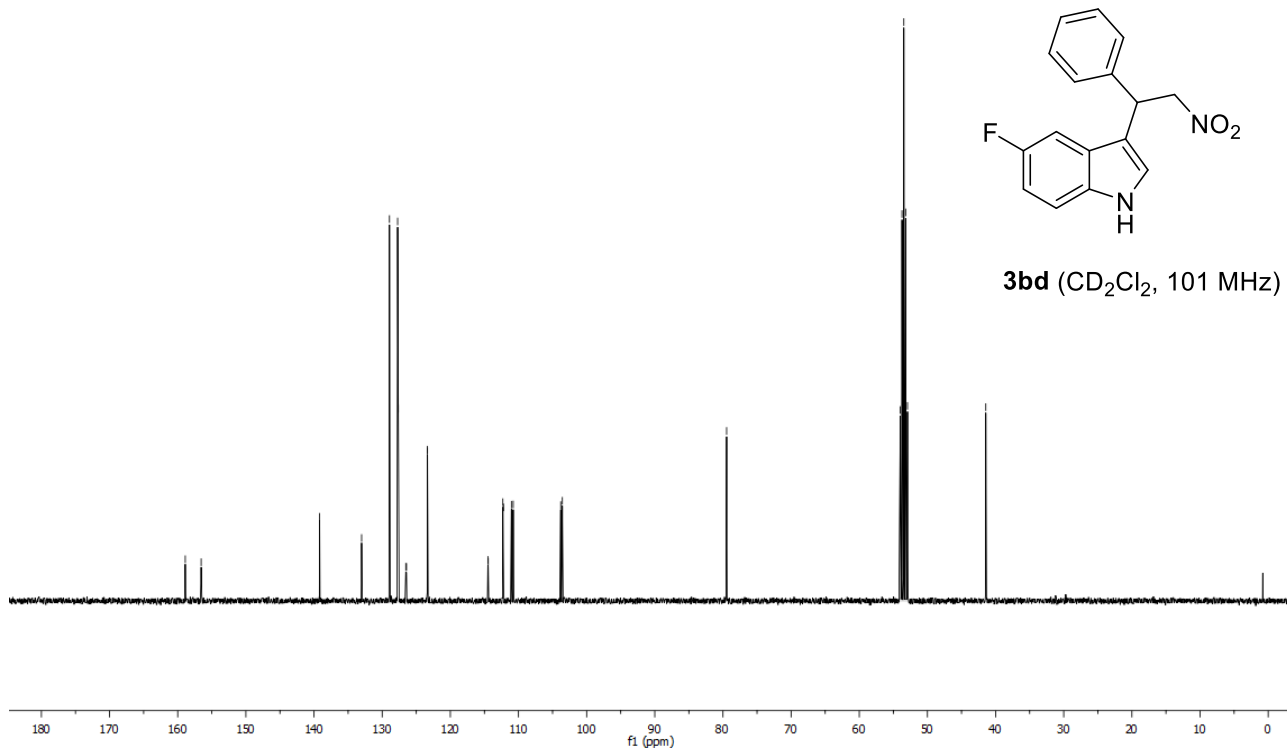
3bd (CD₂Cl₂, 400 MHz)



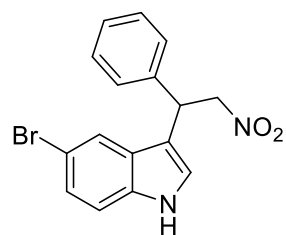
158.90
156.55
139.18
133.02
128.95
127.73
127.63
126.53
126.44
123.35
123.35
114.49
114.44
112.30
112.20
111.04
110.78
103.80
103.57
79.46
54.00
53.73
53.46
53.19
52.92
41.44



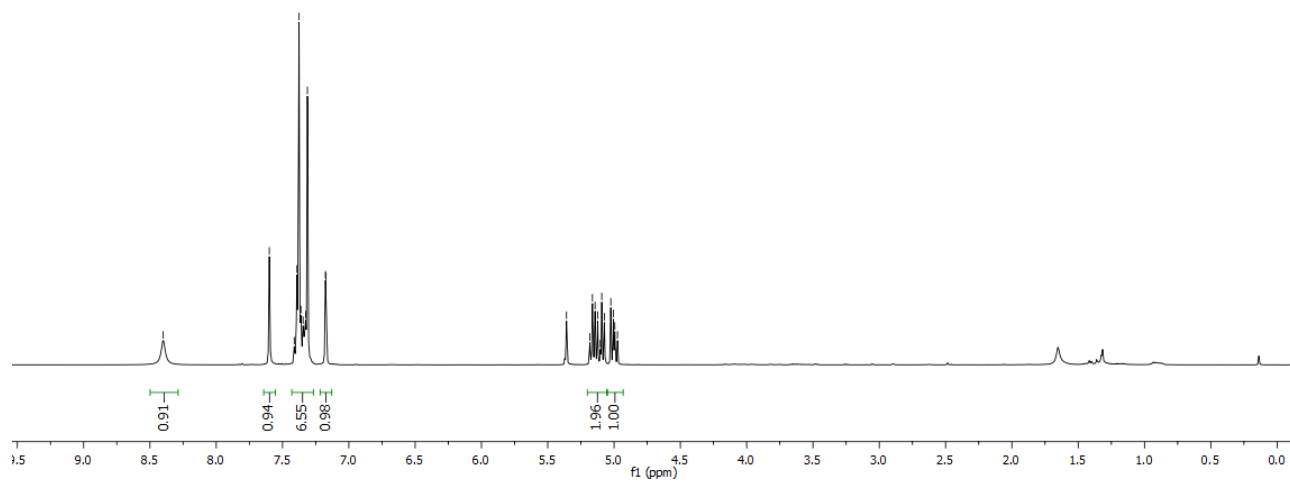
3bd (CD₂Cl₂, 101 MHz)



8.40
7.60
7.41
7.39
7.38
7.36
7.35
7.33
7.31
7.18
7.17
5.36
5.18
5.16
5.14
5.12
5.10
5.09
5.07
5.00
4.99



3be (CD₂Cl₂, 400 MHz)

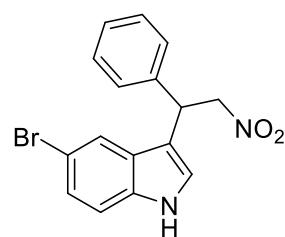


139.06
135.13
128.96
127.88
127.71
127.68
125.44
122.92
121.28
113.99
113.01
112.96

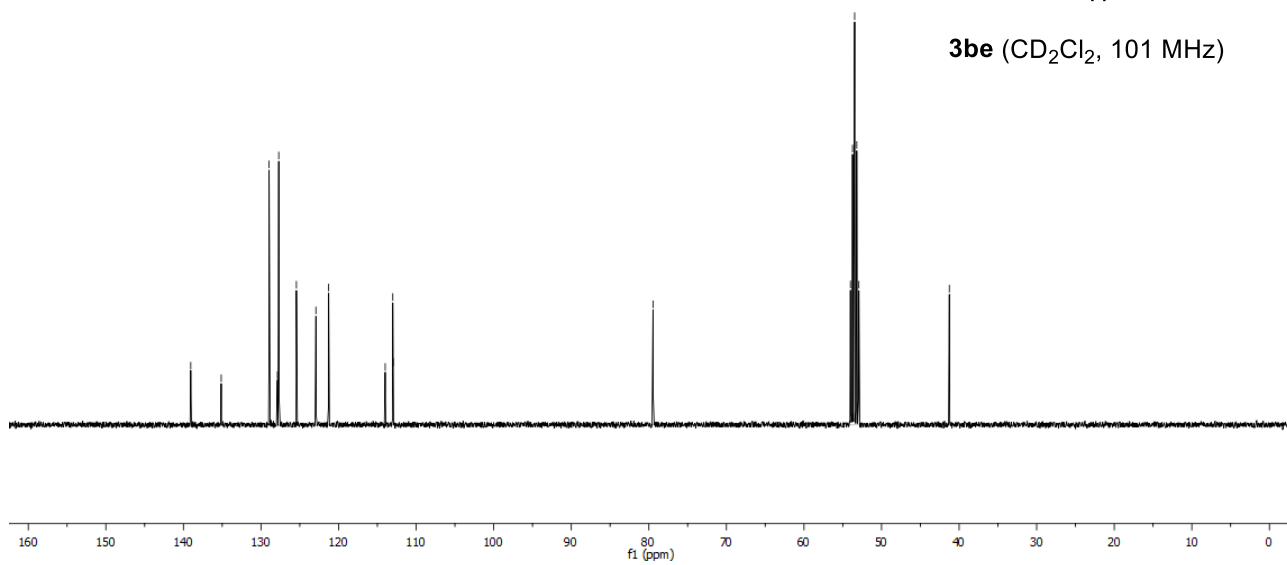
79.46

54.01
53.74
53.47
53.20
52.93

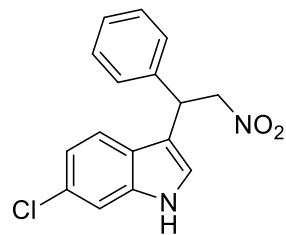
41.26



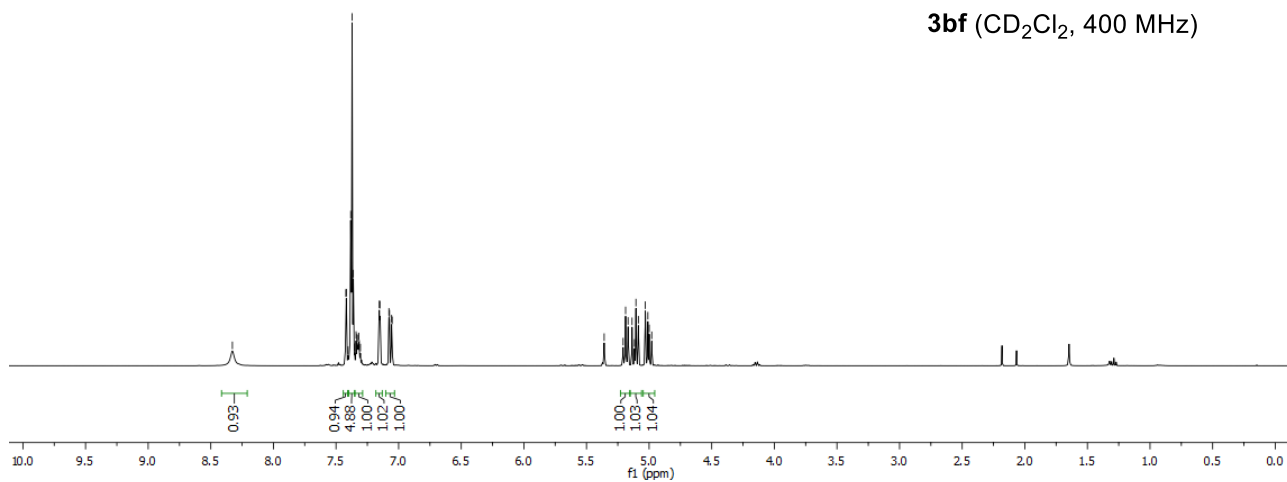
3be (CD₂Cl₂, 101 MHz)



8.33
7.42
7.40
7.38
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.30
7.15
7.15
7.08
7.07
7.06
7.05
5.36
5.21
5.19
5.17
5.14
5.12
5.11
5.09
5.01
5.00
4.98



3b (CD₂Cl₂, 400 MHz)

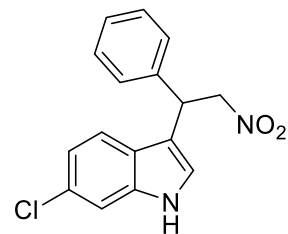


139.24
136.85
128.94
128.41
127.75
127.66
124.81
122.30
120.45
119.80
114.59
111.32

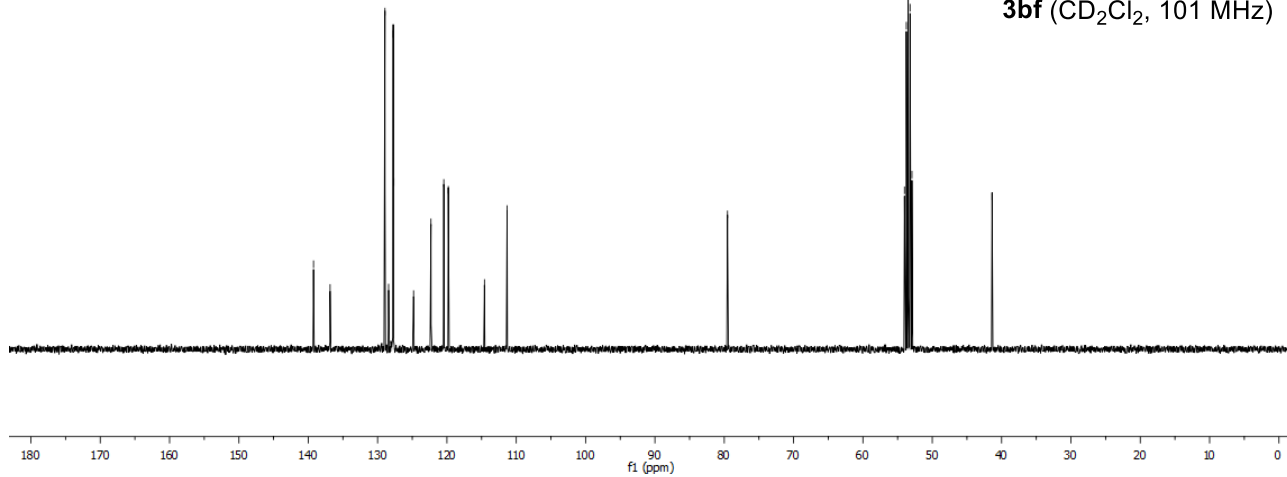
79.53

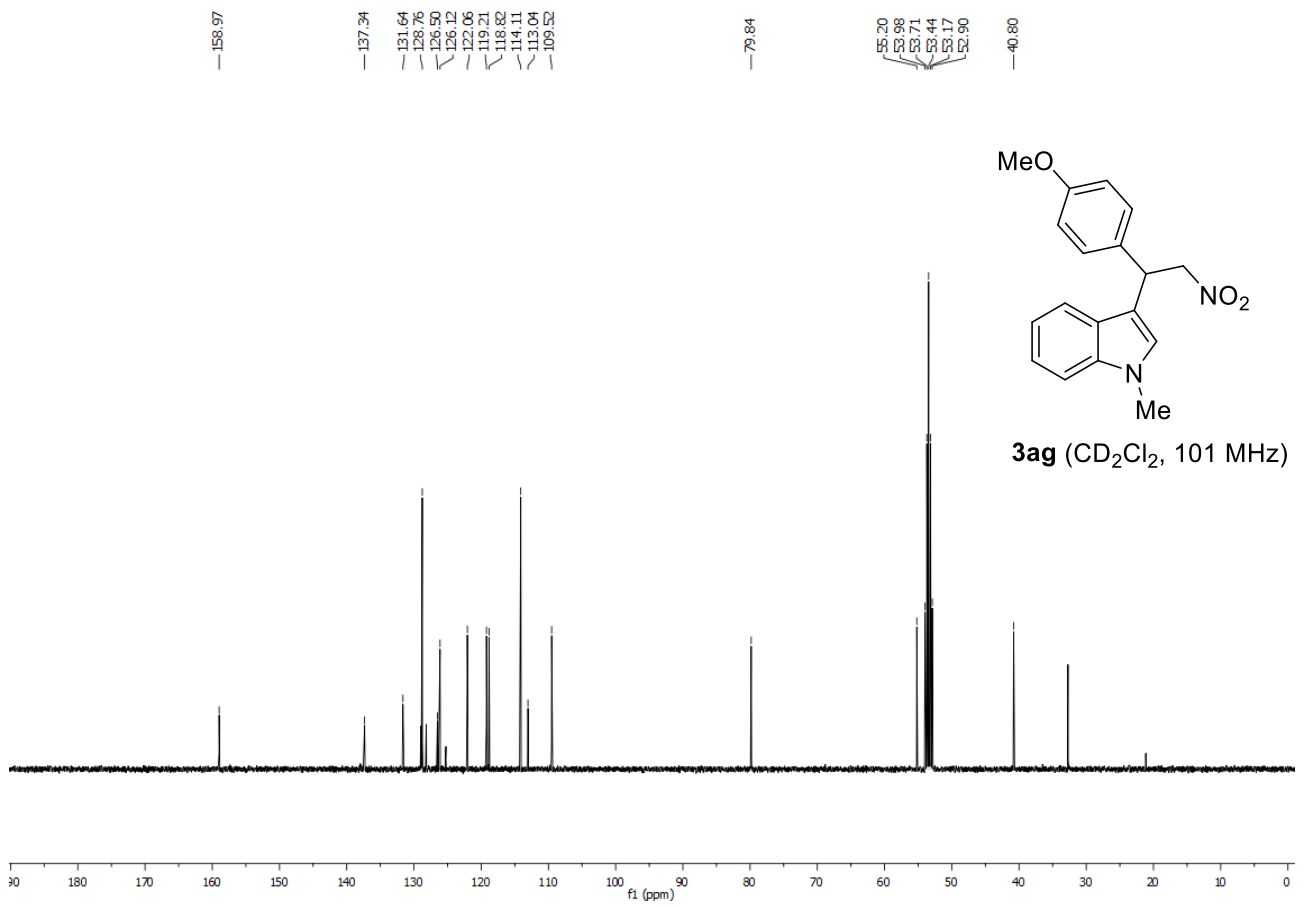
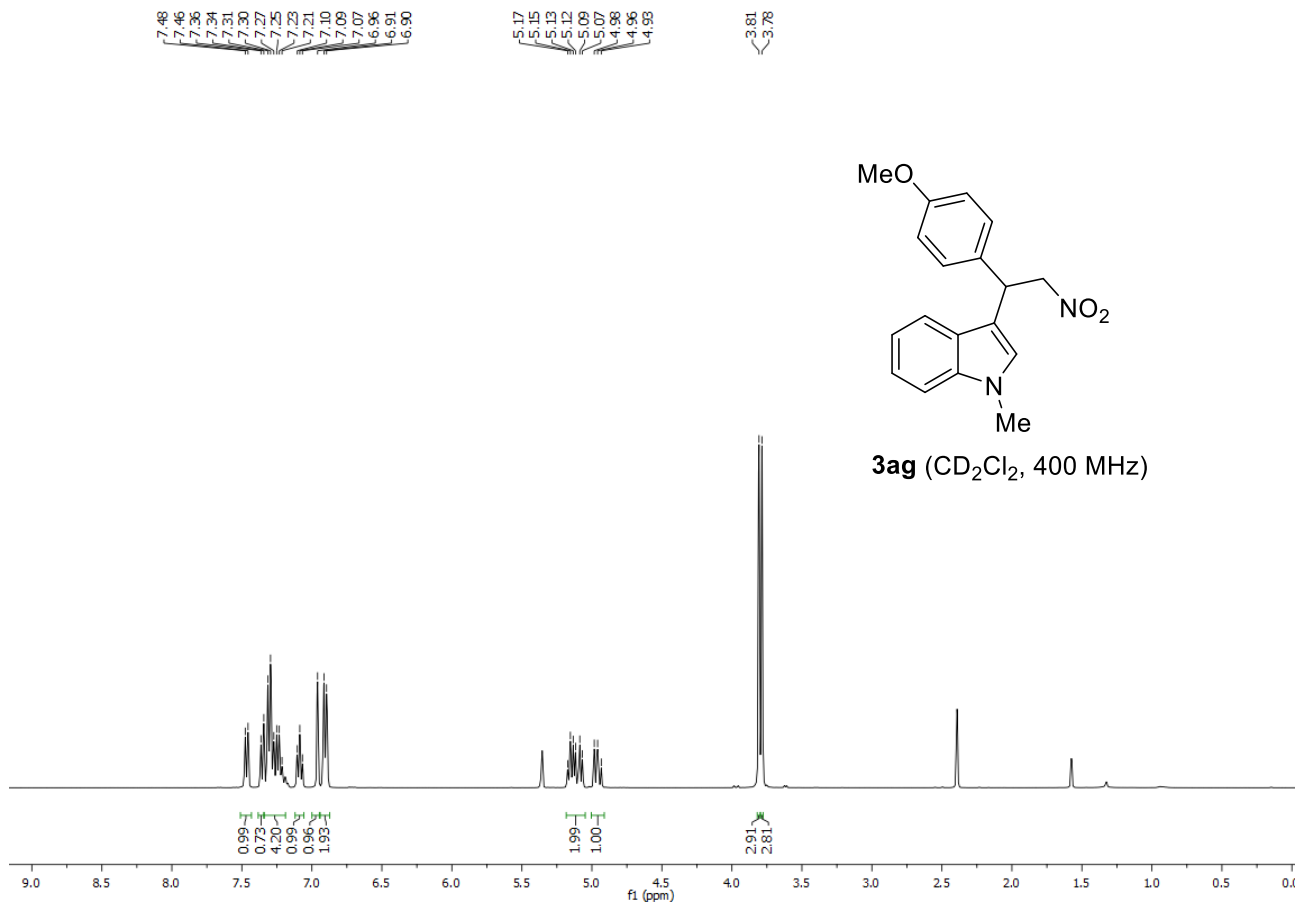
54.01
53.74
53.47
53.20
52.93

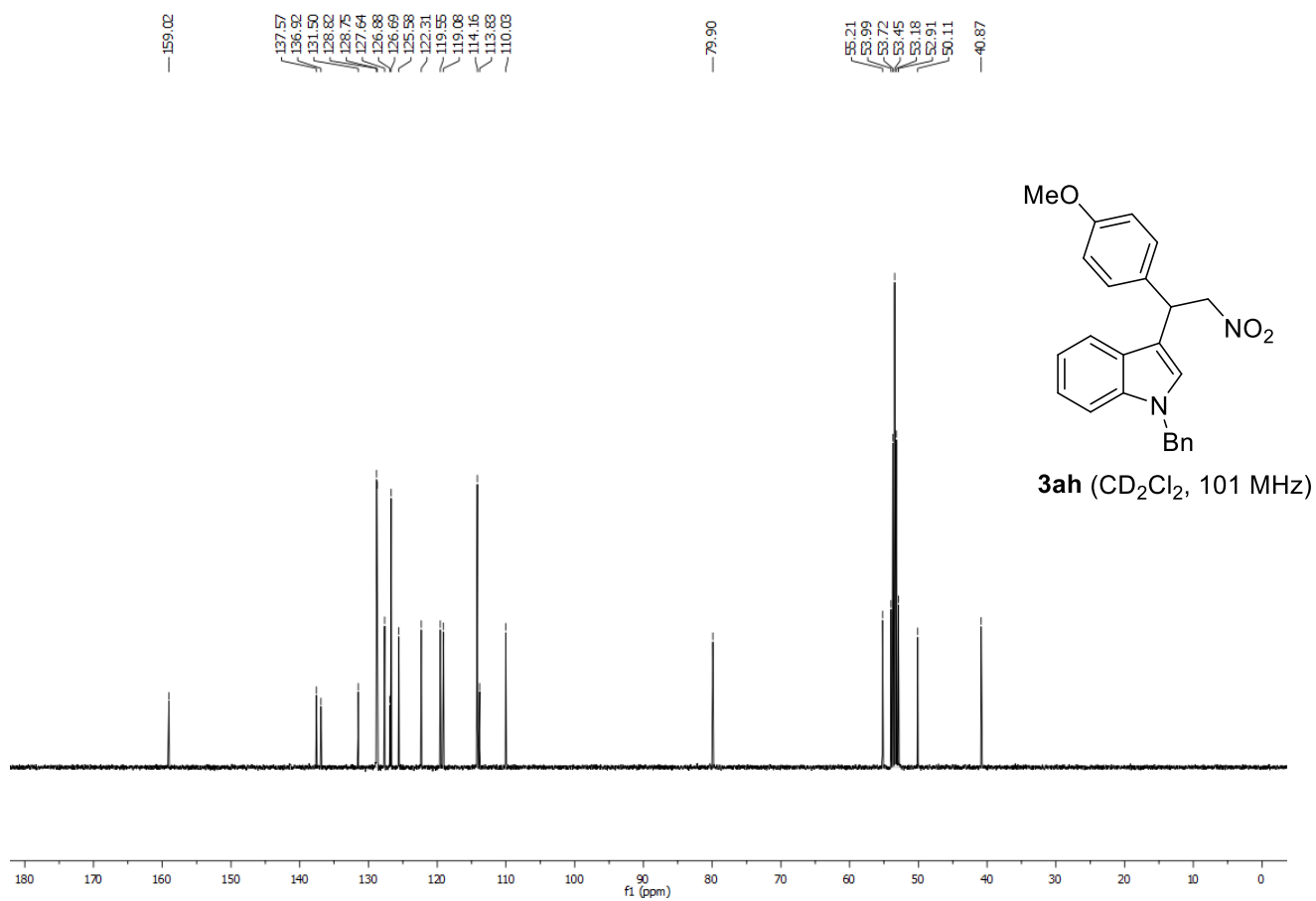
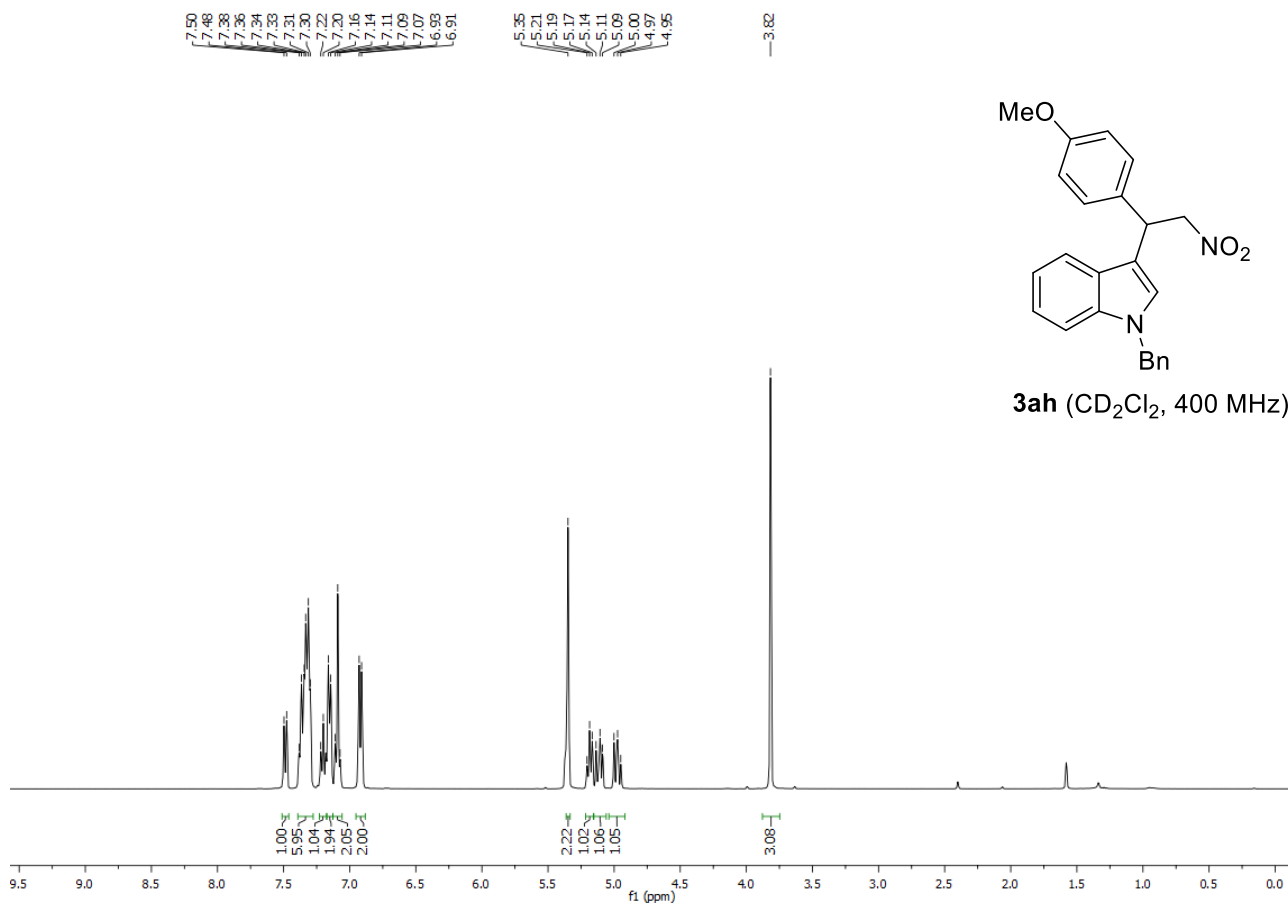
41.37



3b (CD₂Cl₂, 101 MHz)







- **References**

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5. R.-J. Tang, T. Milcent and B. Crousse, *RSC Adv.*, 2018, **8**, 10314.