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Continuous Flow Synthesis of Carbon-Based Molecular Cage Macrocycles *via* a Three-Fold Homocoupling Reaction

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Contents

1. General Experimental

^{1}H and ^{13}C NMR spectra were recorded on Brüker AV400 400 MHz spectrometers using a 5 mm probe with the samples regulated to 25 ^{o}C. Spectra were referenced by calibrating the residual protonated signal of $CDCl_3$ to 7.26 ppm and the $CDCl_3$ to 77.23 ppm for ^{1}H and ^{13}C spectra, respectively.

Positive ion EI mass spectra were run on a ThermoQuest MAT95XL mass spectrometer using anionisation energy of 70 eV. Accurate mass measurements were obtained with a resolution of 5000-10000 using PFK (perfluorokerosene) as the reference compound.

APCI Mass spectrometric analyses were performed on a Thermo Scientific Q Exactive mass spectrometer fitted with an APCI ion source. Positive and negative ions were recorded in an appropriate mass range at 70,000 mass resolution. The probe was used without flow of solvent, although a solution of Reserpine was introduced through the APCI probe during the experiments to serve as a lock mass in both positive and negative ion modes. The nitrogen nebulizing/desolvation gas used for vaporization was heated to 450°C in these experiments. The sheath gas flow rate was set to 25 and the auxiliary gas flow rate to 10 (both arbitrary units). The spray current was 5 µA and the capillary temperature was 320°C.

MALDI Spectra were run on a Bruker autoflex III MALDI TOF/TOF mass spectrometer with a dithranol background using a negative ion mode.

Unless otherwise stated, all compounds were obtained from commercial sources and used as received. Triethylamine (NEt_3) and pyridine were dried over KOH. Para-aminotetraphenylmethane[i], Para-Bromotetraphenylmethane[ii] and 1-ethynyl-3-isopropylsilylethynylbenzene[iii] were prepared according to literature procedures.

1.1 Flow Chemistry

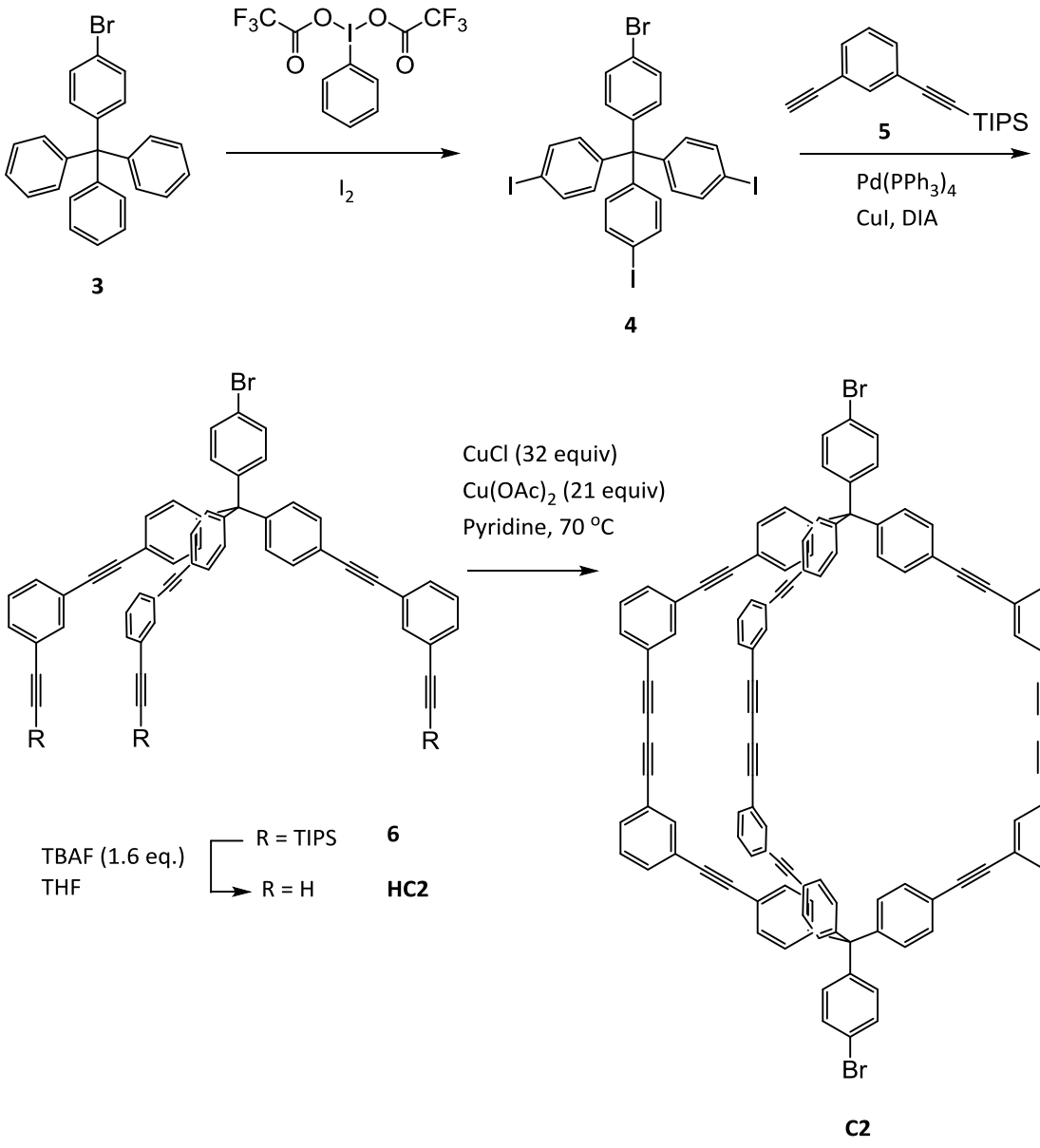
All experiments were carried out on a Vapourtec R4/R2+ continuous flow reactor. The reactor configuration comprised two flow streams driven by the Vapourtec R2+ HPLC pumps. Runs were carried out on 20-100 mg amounts of half cage HC2, with catalyst and solvent amounts scaled accordingly. The procedure for a 100 mg scale is described below.

The first stream contained a solution of the Cu catalysts ($Cu(OAc)_2 \cdot 2H_2O$, 21 equiv and CuCl, 32 equiv) in dry pyridine (100 mL) and the second stream containing the alkynyl precursor **HC2** (100 mg, dissolved in 100 mL dry pyridine). These were mixed at a T-piece (PEEK, 1.0 mm ID) before entering coiled flow reactor on the Vapourtec R4 heating module (10mm*1.0mm ID perfluoroalkoxypolymer (PFA) microreactor coils). A backpressure regulator (75 psi) was placed immediately after the flow reactor coil to pressurize the flow stream and ensure an accurate flow. The combined reagent streams were heated for a

predetermined residence time (t_r) and the product stream was collected in a flask. Following the complete delivery of each reagent stream into the microreactor coils, the reagent reservoirs were flushed with acetonitrile to remove any residual starting materials. The collected products were cooled to room temperature and processed as described below.

2. Synthetic Procedures

2.1 Cage C2



4-Bromophenyl[tris(4-iodophenyl)]methane (4)

p-Bromo-4-tritylbenzene (1.96 g, 4.91 mmol) was added, in one portion, to a solution of bis-[(trifluoroacetoxy)iodo]benzene (4.2 g, 9.82 mmol) and iodine (1.9 g, 7.37 mmol) in chloroform (60 mL), and the reaction mixture was stirred at room temperature, under nitrogen, for 12 hours. It was cooled in an ice-bath to give a pink precipitate, which was collected by vacuum filtration and washed with ice-cold chloroform. Recrystallisation from THF gave **4** as a white powder (1.93 g, 51 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.87-6.89 (d, J_{HH} = 9 Hz, 6H, aryl CH), 7.00-7.02 (d, J_{HH} = 8.7 Hz, 2H, aryl CH), 7.37-7.39 (d, J_{HH} = 8.7 Hz, 2H, aryl CH), 7.57-7.59 (d,

J_{HH} = 9 Hz, 6H, aryl CH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 63.92, 92.45, 120.78, 132.34, 132.52, 132.61, 132.81, 137.08, 145.10. ($C_{25}H_{16}BrI_3$) EI-MS (+ve mode) *m/z* 775.7.

4-(Tris{4-[triisopropylsilyl)ethynyl]phenyl}methyl)bromobenzene (6)

Copper (I) iodide (0.047 g, 0.25 mmol), $Pd(PPh_3)_2Cl_2$ (0.17 g, 0.25 mmol) and **4** (1.9 g, 2.45 mmol) were placed in a dry schlenk, evacuated and backfilled with N_2 (3×). A solution of (3-ethynyl-phenylethynyl)-triisopropylsilane (2.3 g, 8.07 mmol) in dry triethylamine (50 mL) was sparged with nitrogen and transferred, *via* a cannula, to the above mixture. The resultant yellow suspension was heated at 85 ˚C for 18 hours. After cooling to r.t., the solution was filtered through a plug of Celite with dichloromethane, and the solvents were removed under reduced pressure to give a brown solid. Purification by flash chromatography on silica, eluting with 10 % dichloromethane/petroleum ether, gave **6** as a pale yellow solid (1.85 g, 61 % yield). M.p.: 122 – 124 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.13 (s, 54H, TIPS), 1.54 (s, 9H, TIPS), 7.07-7.09 (d, J_{HH} = 8.4 Hz, 2H, aryl CH), 7.17-7.18 (d, J_{HH} = 8.4 Hz, 6H, aryl CH), 7.27-7.29 (t, 3H, aryl CH), 7.41-7.45 (m, 14H, aryl CH), 7.63 (s, 3H, aryl CH). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 11.29, 18.65, δ 62.70, 89.04, δ 89.49, 91.46, 106.10, 120.66, 120.99, 123.34, 123.89, 128.31, 130.86, 130.91, 131.04, 131.35, 132. 69, 135.00, 145.90. FT-IR (ATR, cm^{-1}) 2942, 2890, 2864, 2162, 1996, 1965. ($C_{82}H_{91}BrSi_3$)

4-[Tris(4-ethynylphenyl)methyl]bromobenzene (Half Cage HC2)

A solution of TBAF in THF (C = 1 M, 3 mL, 3.0 mmol) was added dropwise, at room temperature, to a solution of **6** (0.42 g, 0.34 mmol) in dry THF (45 mL). The orange reaction mixture was stirred at room temperature for 18 hours. THF was removed under reduced pressure, and the residue was dissolved in ethyl acetate (100 mL), washed with brine (5 × 100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give an orange solid. Purification by flash chromatography, eluting with 1:4 dichloromethane:petroleum ether, gave the half cage **2b** as a colourless solid (0.24 g, 91% yield). M.p. 109 – 111 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.09 (s, 3H, alkyne), 7.08-7.09 (d, J_{HH} = 8.4 Hz, 2H, aryl CH), 7.17-7.19 (d, J_{HH} = 8.4 HZ, 6H, aryl CH), 7.29-7.31 (t, J_{HH} = 8.4 Hz, 3H, aryl CH), 7.41-7.45 (m, 12H, aryl CH), 7.48-7.50 (d, J_{HH} = 8.4 Hz, 2H, aryl CH), 7.65 (d, J_{HH} = 8.4 Hz, 3H, aryl CH). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 64.59, 77.82, 82.74, 88.82, 89.69, 120.69, 121.15, 122.50, 123.52, 128.45, 130.88, 131.18, 131.86, 132.57, 135.11, 144.69, 145.95. FT-IR (ATR, cm^{-1}) 3290, 3065, 3032, 2211, 2106. ($C_{55}H_{31}Br$)

Cage C2 – Batch Synthesis

$Cu(OAc)_2 \bullet 2H_2O$ (3.12 g, 14.34 mmol, 65 eq) was placed in a Schlenk and dehydrated at 70 °C under vacuum for 1 hour. The reaction vessel was backfilled with Ar and CuCl (0.98 g, 9.93 mmol, 45 eq) was added, followed by dry pyridine (50 mL). The resultant suspension was heated to 70 °C. A solution of tris(4-(2-(3-ethynyl)phenyl)ethynyl)phenyl)methyl-4-bromobenzene (HC2) (170 mg, 0.2 mmol) in dry pyridine (40 mL) was slowly added, *via* cannula, over a period of 6 hours. After the addition was complete, the reaction mixture was stirred at 70 °C for 2 hours. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was taken up in dichloromethane (200 mL) and washed with 1 M HCl (3 × 120 mL). The acidic washings were re-extracted with dichloromethane (2 × 60

mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (2 × 100 mL), brine (2 × 100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography, eluting with 30 % dichloromethane/petroleum ether to give **Cage C2** as a yellow solid (31 mg, 20 %). ^{1}H NMR (CDCl3, 600 MHz) δ 7.15 – 7.19 (m, 16H, aryl CH), 7.30-7.34 (t, 6H, aryl CH), 7.43 – 7.50 (m, 28H, aryl CH), 7.75 (s, 6H, aryl CH). 13C NMR (CDCl3, 150 MHz) δ 64.56, 74.45, 81.03, 88.61, 89.87, 121.09, 122.11, 123.78, 128.63, 130.84, 131.06, 131.26, 131.65, 132.70, 136.85, 146.16, 146.23. FT-IR (ATR, cm-1) 2959, 2107, 2009, 1997. ($C_{110}H_{56}Br_2$) FTMS APCI (+ve mode) *m/z* 1537.3.

Cage C2 – Flow Synthesis

NB: A 50 mg scale experiment is described. $Cu(OAc)_2 \bullet 2H_2O$ (297 mg, 1.36 mmol, 21 eq) was added to a schlenk and dehydrated at 70°C under vacuum for 1 hour. The reaction vessel was then backfilled with Ar and CuCl (205 mg, 2.07 mmol, 32 eq.) was added followed by dry pyridine (50 mL). The suspension was stirred at 70 °C for one hour before being cooled to room temperature and filtered through a sintered glass funnel into a 100 mL Erlenmeyer flask. In a second 100 mL Erlenmeyer flask, 50 mg of **HC2** was dissolved in 50 mL dry pyridine. Both flasks were placed on a Vapourtec R4 continuous flow reactor and pumped through separate feed streams each set at a predetermined flow rate. The reactor coils were set at 70 ^{o}C and the back-pressure regulator set at a maximum of 35 bar. After passing through two 10 mL reactor coils the product was collected in an Erlenmeyer flask, with acetonitrile used as the carrier solvent. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was extracted with dichloromethane (200 mL) and washed with 1 M HCl (3 × 120 mL), the acidic washings were re-extracted with dichloromethane (2 × 60 mL) and were combined with the previous organic extracts. The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2 × 100 mL), brine (2 × 100 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography, eluting with 30 % dichloromethane/petroleum ether to give **Cage C2** as a yellow solid (21% yield). ^{1}H NMR (CDCl3, 600 MHz) δ 7.15 – 7.19 (m, 16H, aryl CH), 7.30-7.34 (t, 6H, aryl CH), 7.43 – 7.50 (m, 28H, aryl CH), 7.75 (s, 6H, aryl CH). 13C NMR (CDCl3, 150 MHz) δ 64.56, 74.45, 81.03, 88.61, 89.87, 121.09, 122.11, 123.78, 128.63, 130.84, 131.06, 131.26, 131.65, 132.70, 136.85, 146.16, 146.23. FT-IR (ATR, cm-1) 2959, 2107, 2009, 1997. ($C_{110}H_{56}Br_2$) FTMS APCI (+ve mode) *m/z* 1537.3.

Table S1. Comparison of Synthetic Conditions; Batch *vs.* Flow Chemistry.

	CuCl (eq)	**$Cu(OAc)_2$ (eq)**	**Reaction time (mins)**	**Conversion (%)**
Batch Chemistry	45	65	360	20
Flow Chemistry	32	21	33.3	21

3. Structural Characterisation

3.1 Single Crystal Structure Determination

Single crystals were mounted in paratone-N oil on a nylon loop. X-ray diffraction data were collected at 100(2) K on the MX1 beamline of the Australian Synchrotron (λ = 0.7107 Å)[v]. Data sets were corrected for absorption using a multi-scan method, and structures were solved by direct methods using SHELXS-97[iv] and refined by full-matrix least squares on F^2 by SHELXL-2013,[v] interfaced through the program X-Seed.[vi] In general, all non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as invariants at geometrically estimated positions, unless specified otherwise in additional details below. CCDC 1004030 contains the supplementary crystallographic data for these structures. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Crystals of **C2** are inherently weakly diffracting and synchrotron X-ray sources were required to provide diffraction that enabled structure determination by single crystal X-ray crystallography. Data collected on our home laboratory source could not be solved. Unfortunately, even using the best crystals, grown under what were deemed to be the best conditions for growing crystals, data could only be processed out to a θ value of 18.66°. To improve the data quality, (a) crystals of varying sizes were investigated without improvement in the observed diffraction; (b) data collections were undertaken at low temperature, and; (c) synchrotron radiation was employed. As a consequence the structure solution obtained has only been utilised to confirm the structure of the cage and to generally compare the packing of this entity with another example of the cage molecule (cage **C2**). Bond lengths and angles have not been compared.

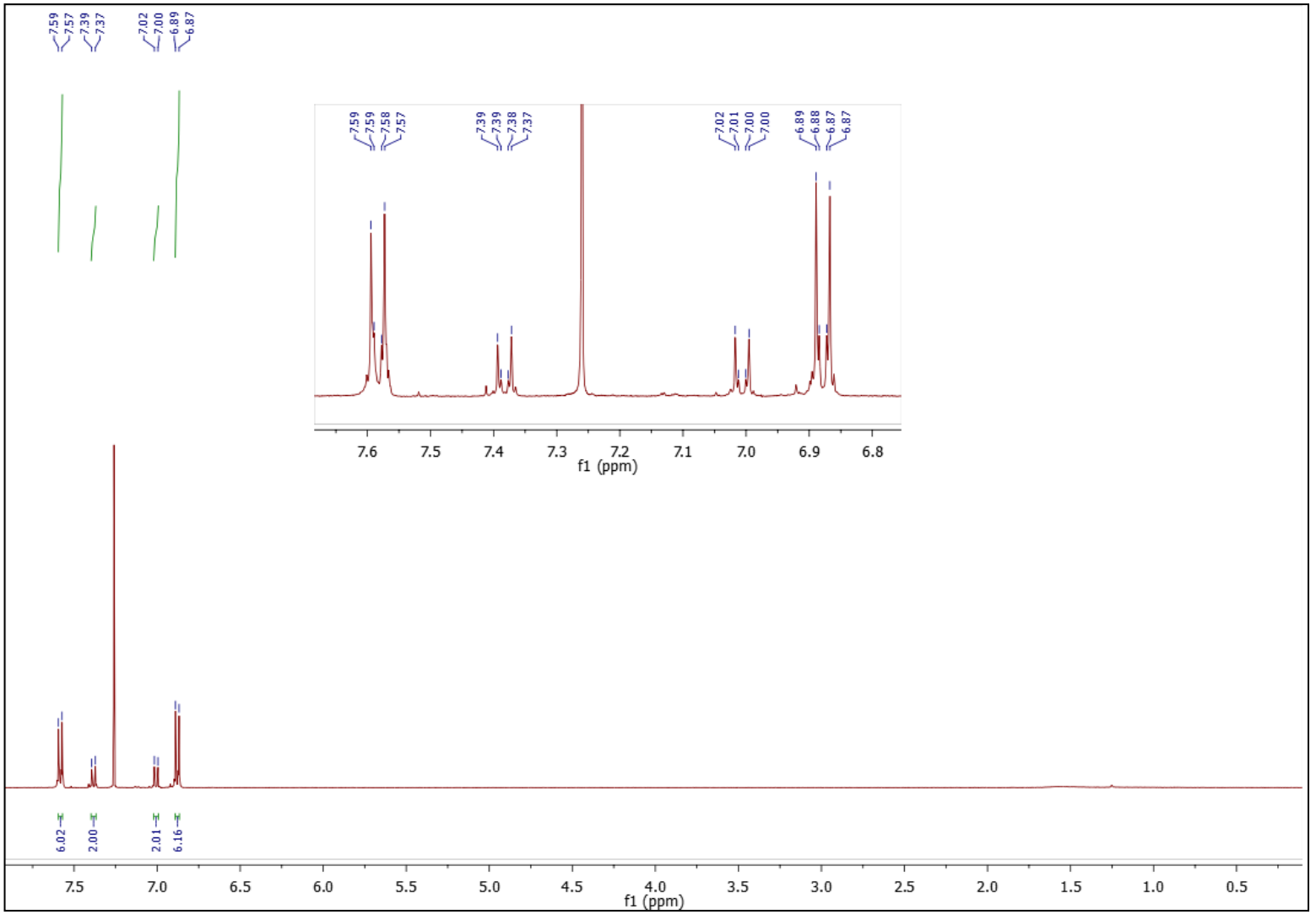
Additionally, the structure has very large solvent accessible voids which contain a number of diffuse electron density peaks that could not be adequately identified and refined as solvent. The SQUEEZE[vi] routine of PLATON was applied to the collected data, which resulted in significant reductions in R_1 and wR_2 and an improvement in the GOF.

Table S2. Crystal and X-ray experimental data for **C2**.

Compound	**C2**
Empirical formula	$C_{110}H_{56}Br_2$
Formula weight	1537.36
Crystal system	tetragonal
Space group	*I4₁/acd*
a (Å)	39.709(6)
c (Å)	39.724(8)
Volume (Å^3)	62636(22)
Z	16
D_{calc} (Mg/m^3)	0.652
Absorption coefficient (mm^{-1})	0.544
F(000)	12576
Crystal size (mm^3)	0.20 x 0.20 x 0.10
Theta range for data (°)	1.026 - 18.659
Reflections collected	170819
Independent reflections [R(int)]	5979 [0.1152]
Completeness to theta max (%)	99.7
Observed reflections [I>2σ(I)]	4972
Data / restraints / parameters	5979/0/505
Goodness-of-fit on F2	1.325
R_1 [I>2σ(I)]	0.1092
wR_2 (all data)	0.3186
Largest diff. peak and hole (e.Å^{-3})	0.275 & -1.084

3.2 NMR Spectra

Compound **4**



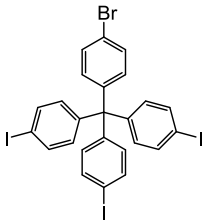


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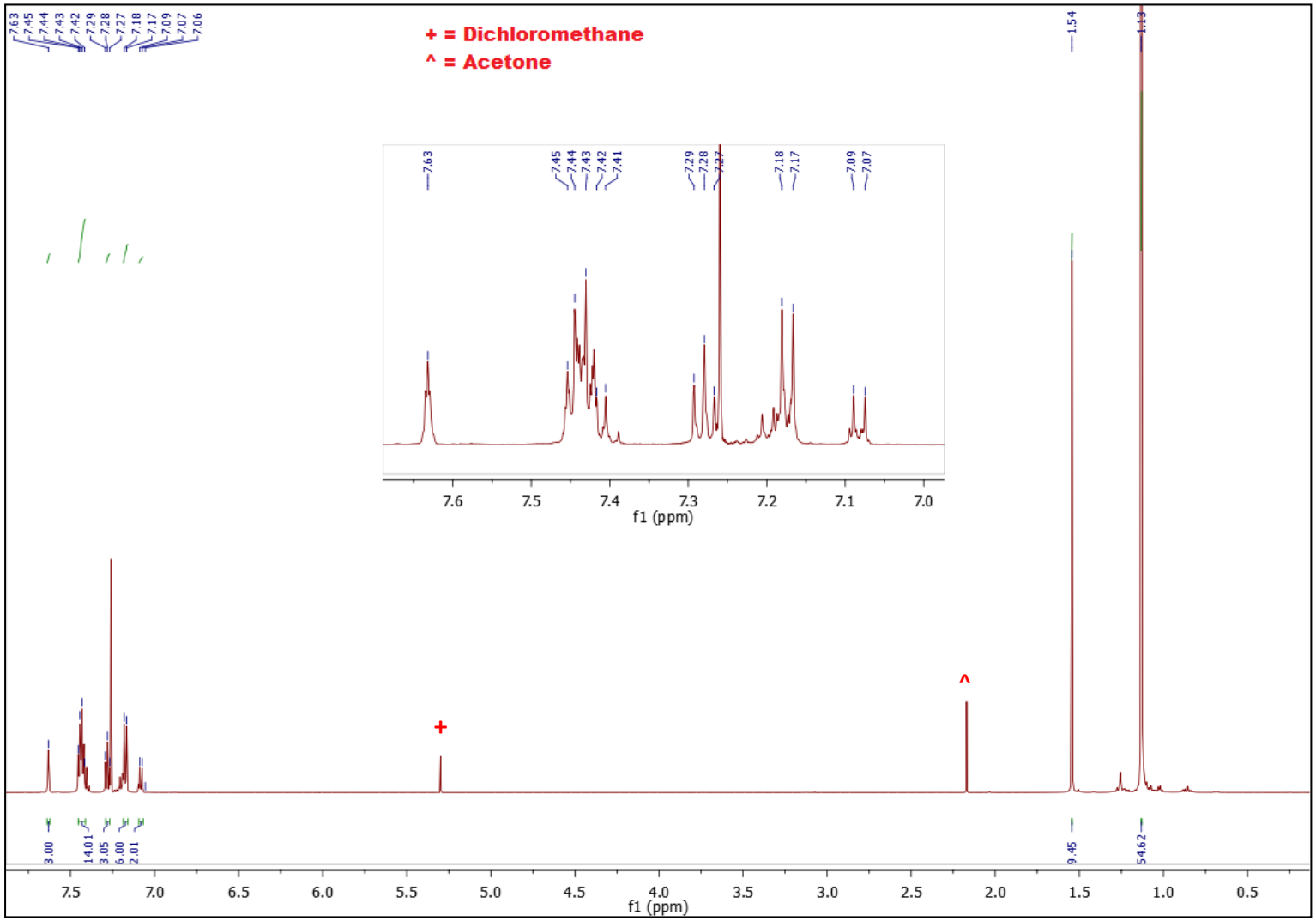
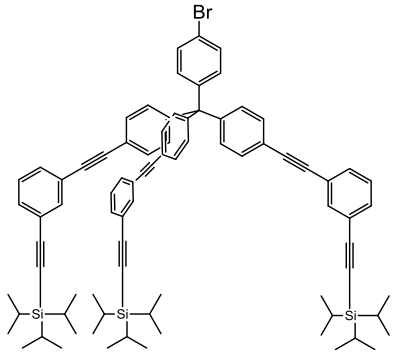
Figure S4: 1H NMR spectrum for **4** in $CDCl_3$

Compound **6**

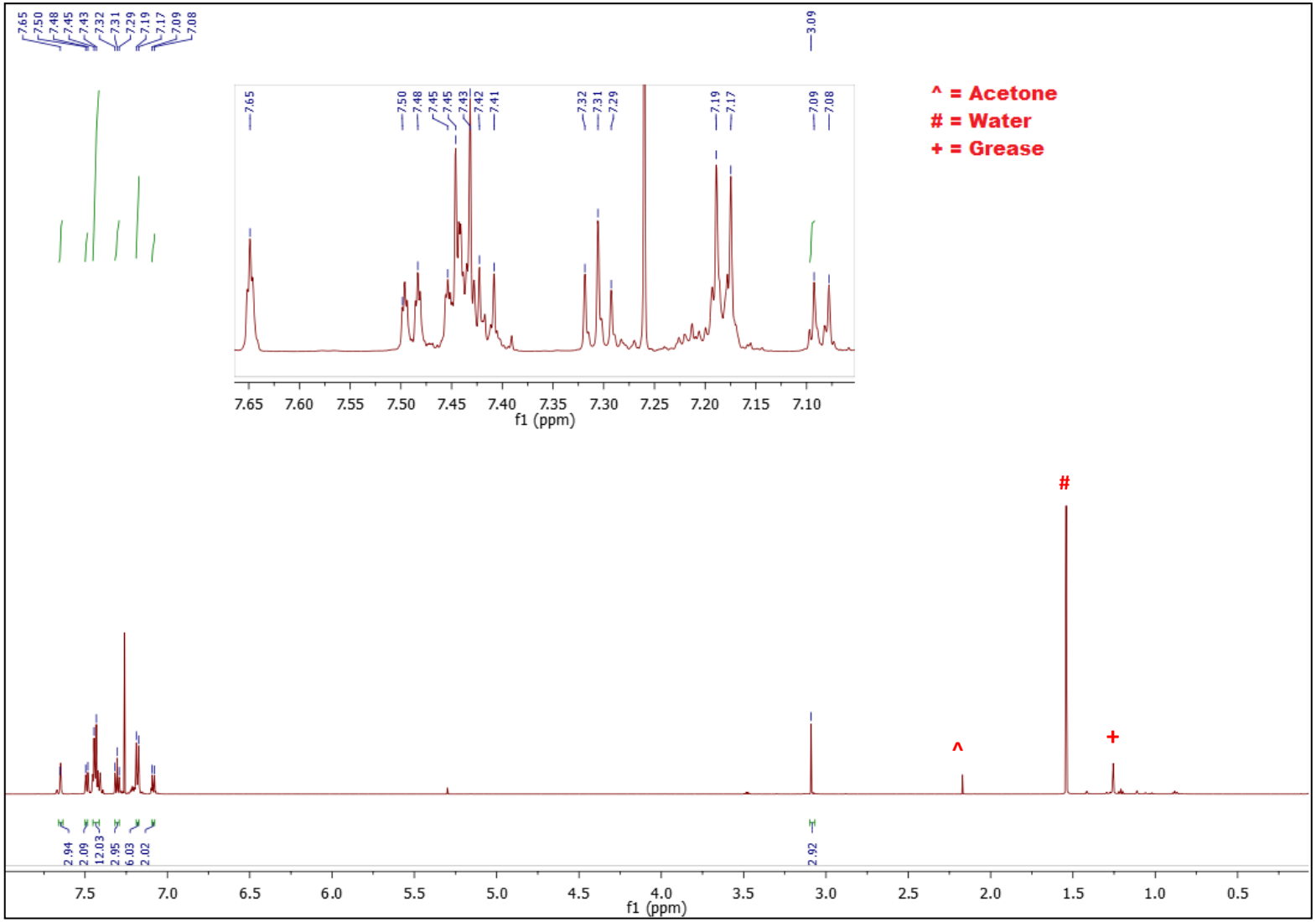


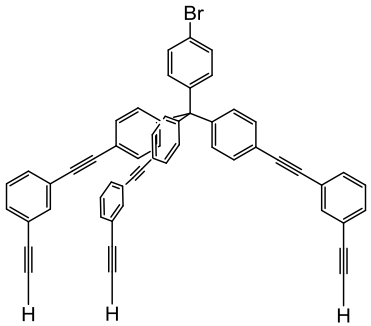


6

Figure S5: 1H NMR spectrum for **6** in $CDCl_3$

Compound **HC2**





HC2

Figure S6: 1H NMR spectrum for **HC2** in $CDCl_3$

Compound **C2**

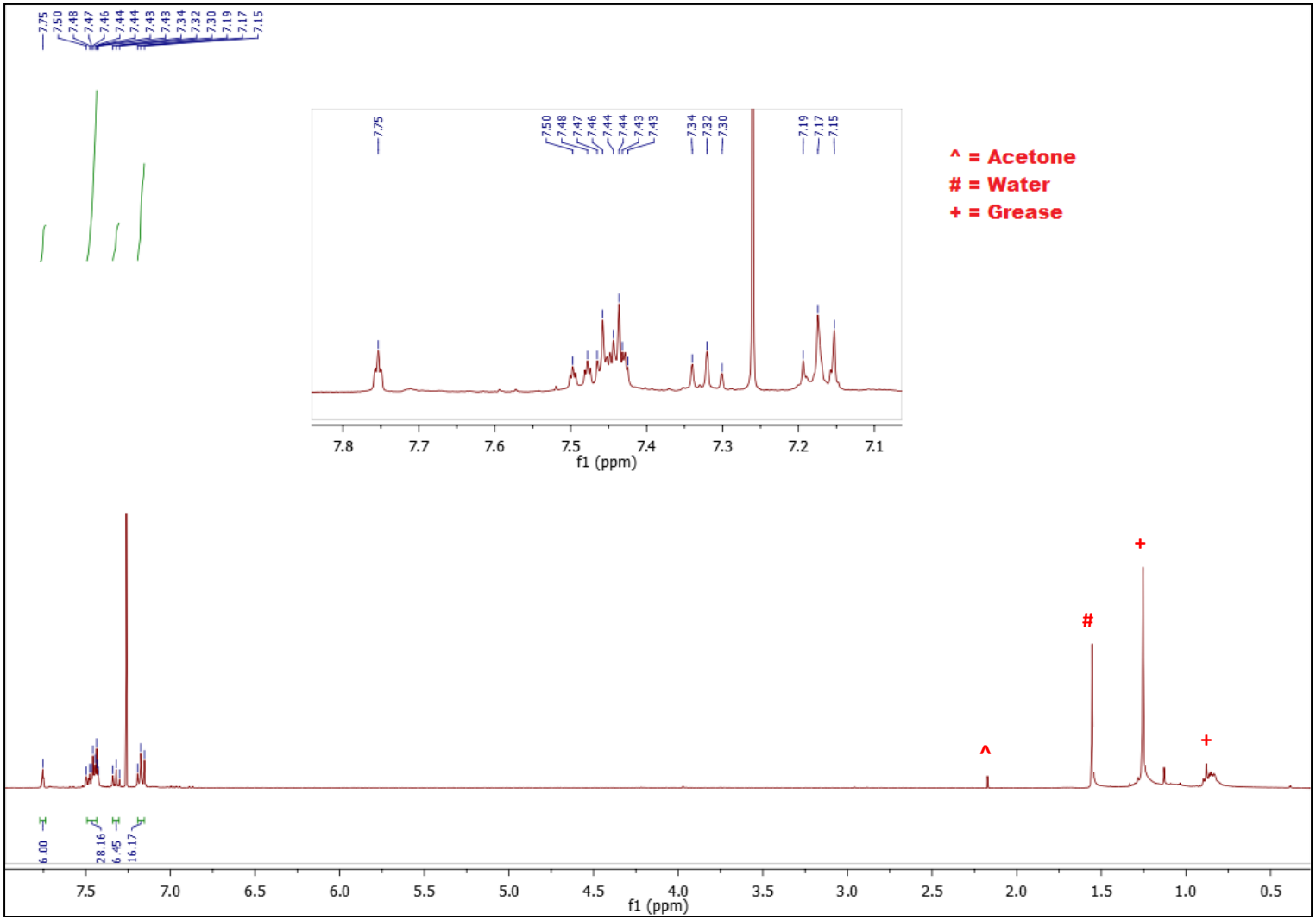
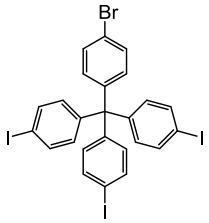


Figure S7: 1H NMR spectrum for Cage **C2** in $CDCl_3$

3.3 Mass Spectra

Compound **4**



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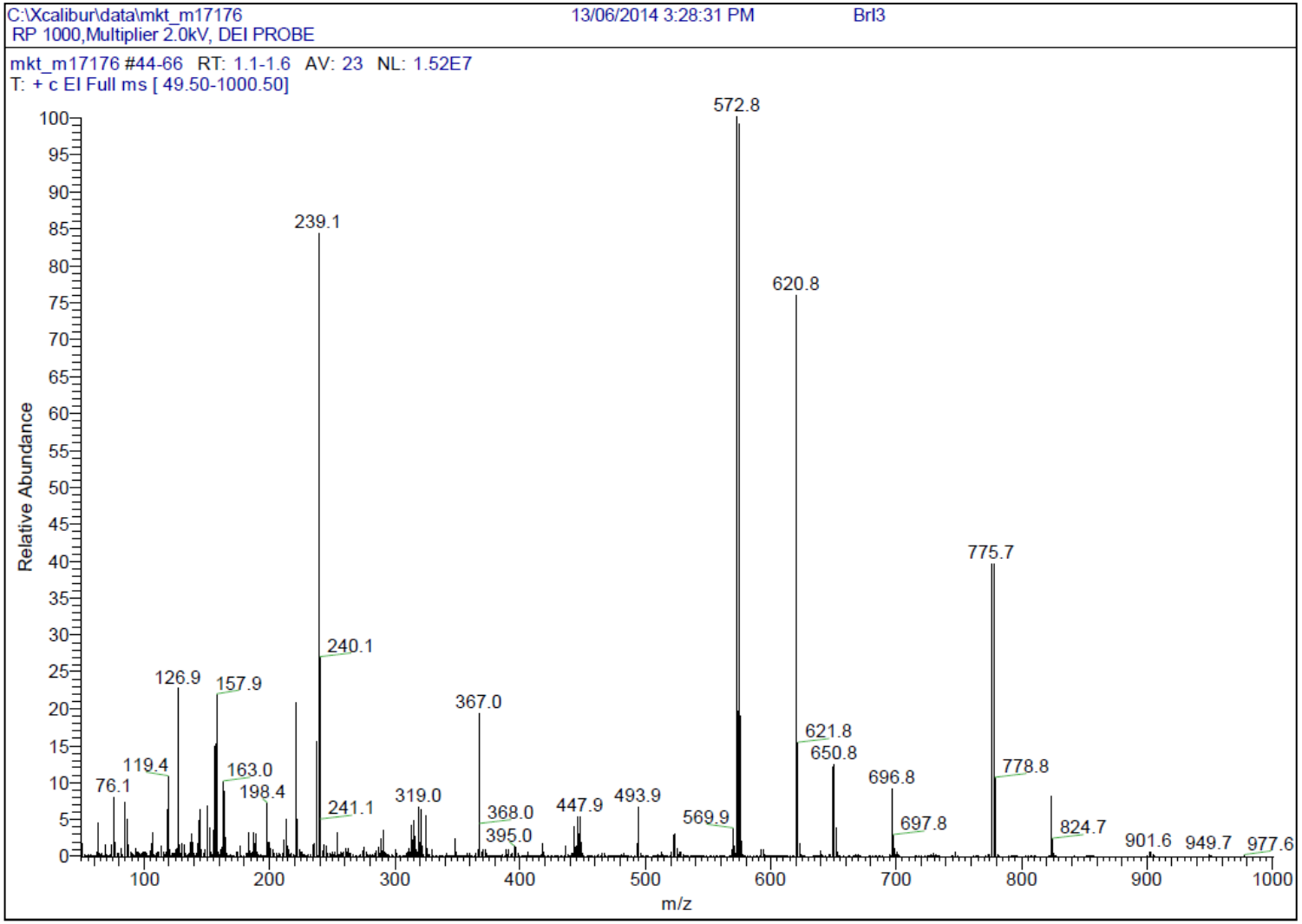

Figure S8: Mass spectrum (EI) for **4**

Compound **C2**

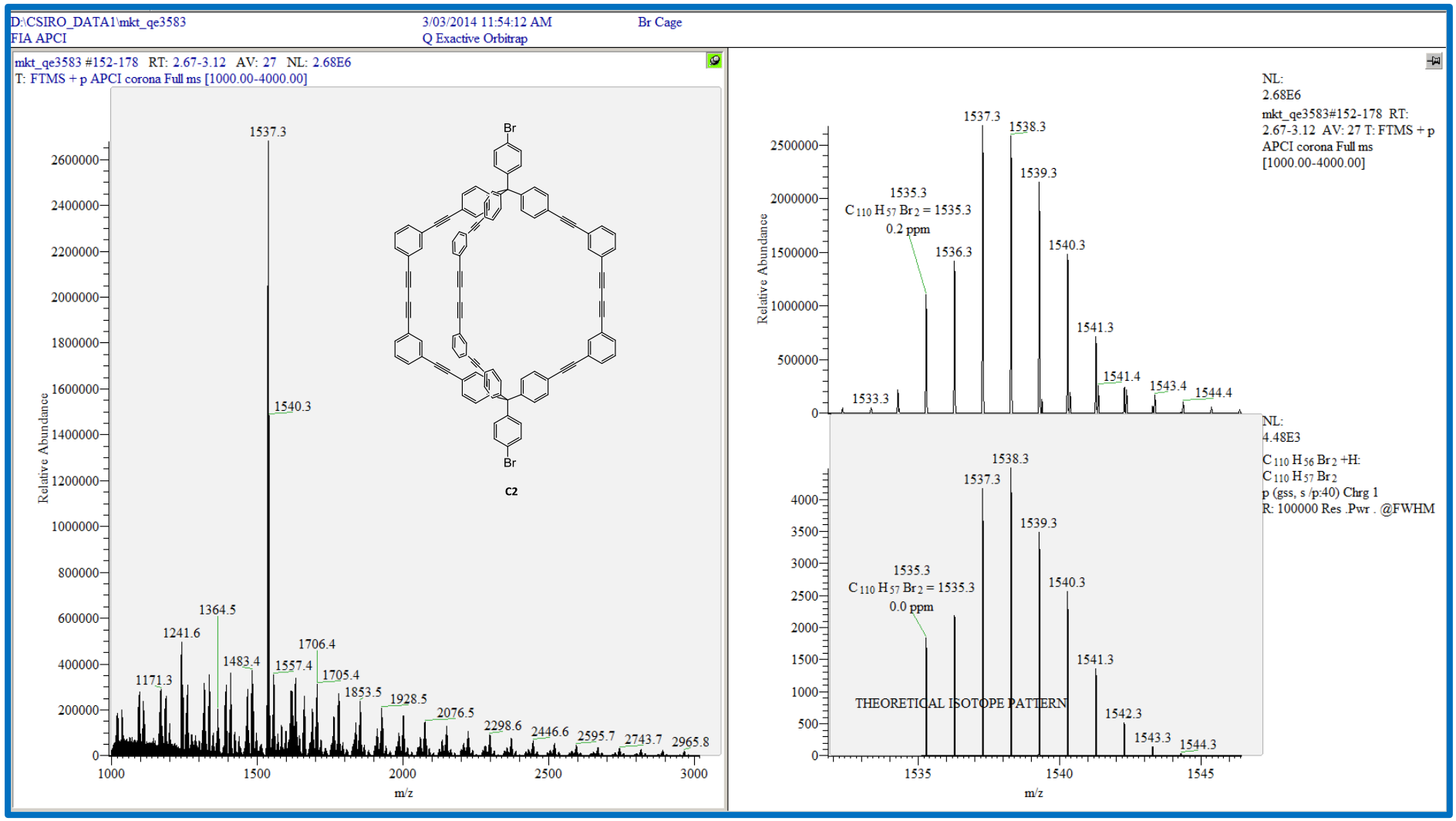

Figure S9: Mass spectrum (APCI) for **C2**

Compound **C2**

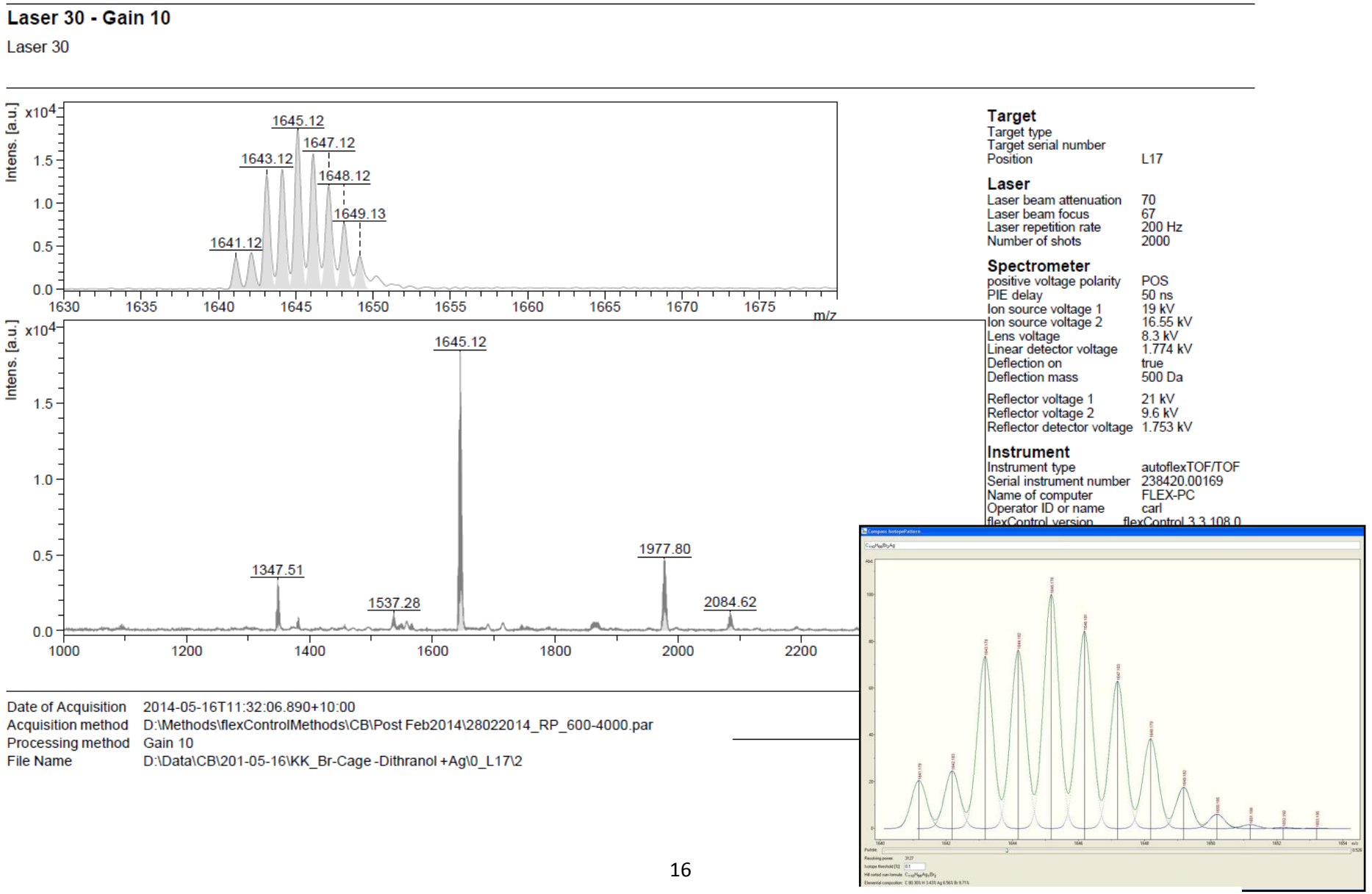

Figure S10: Mass spectrum (MALDI, Dithranol matrix with AgTFA calibration) for **C2**

Inset: Theoretical isotope pattern for **C2**; M+Ag ion.

3.4 Space-Time Yield Calculations

Space-Time yield = Mass produced per unit volume per day

$$\frac{\boldsymbol{mass\ product\ (g)}}{\boldsymbol{unit\ volume\ (m^3)}} \Big/ \boldsymbol{day}$$

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Subst.	Flow rate (mL/min) (feed tank)	Flow rate (mL/min) (reactor coil)	Grams Mol X1 10 mL feed tank	Grams Mol X1 10 mL reactor coil	N(Mol X1) 10 mL feed tank	n(Mol X1) 10 mL reactor coil	Conv %	Molar ratio	N(Mol X2) 10 mL product	Mass Mol X2 (10 mL) product	Grams Mol X2 prod in 1 min	Grams X2 prod/day	Vol/day (mL)	m^3/day	STY g/m^3/day
	[X]	X	0.01	D2/2	0.01/770.26	F2/2	[X]	H2/2	G2*I2	1534.47*J2	K2*C2/10	L2*60*24	C2*60*24	N2*E-6	M3/O3
Br	0.3	0.6	0.01	0.005	1.29843E-05	6.49216E-06	21%	11%	6.81677E-07	0.00104584	6.2751E-05	0.090360729	864	0.000864	104.584177

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