

## Supplementary Information

### High-Efficiency Non-Thermal Plasma Synthesis of Imine Macrocycles

Patrycja Roszkowska,<sup>†a</sup> Abbie Scholes,<sup>†a</sup> James L. Walsh,<sup>b</sup> Timothy L. Easun,<sup>c</sup> Anna G. Slater<sup>\*a</sup>

a. Department of Chemistry and Materials Innovation Factory, University of Liverpool, Crown Street, Liverpool L69 7ZD, United Kingdom

b. Engineering and Technology, School of Physics, University of York, York YO10 5DD, UK

c. School of Chemistry, Haworth Building, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

<sup>†</sup> These authors contributed equally to this work.

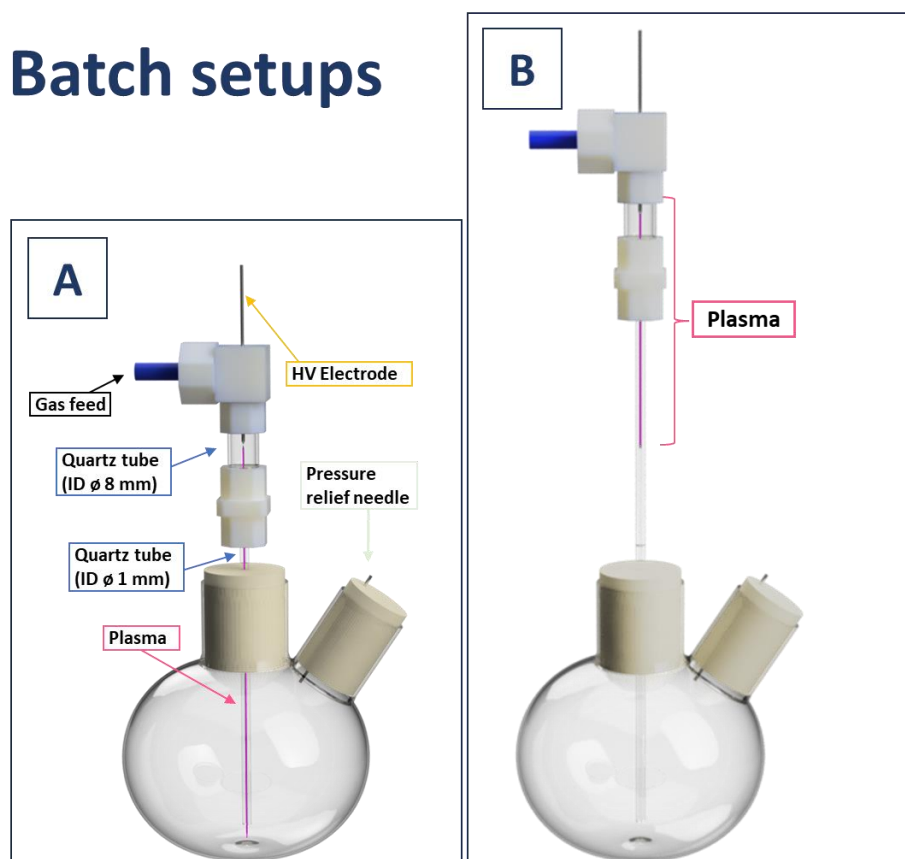
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## 1. Plasma set up:

The plasma set up was described in detail in our previous work.<sup>1</sup> Briefly, the plasma reactor consisted of a tungsten pin (1.8 mm diameter) acting as the HV electrode in the centre of a quartz tube (8 mm internal diameter and 10 mm outside diameter). In both cases, the plasma forming electrode sections were connected to reactors via narrower quartz tubing (1 mm internal diameter and 3 mm outside diameter) to carry the plasma/plasma generated species to the liquid interfaces. The argon gas was used as a feeding gas with 490 ml/min flow rate and the standard plasma settings were 20 kHz and  $3 \pm 0.5$  W.

The reaction set up used for the non-thermal plasma (NTP) assisted reactions (Figure S1) consisted of a 50 ml two-necked round bottom flask (RBF) and plasma generating probe. Both necks of the RBF were sealed with septa; one neck had a pierced hole to accommodate a quartz tube carrying plasma/plasma generated species to the liquid interface; the other was pierced with a needle for pressure control and to ensure the reactions could be carried out under the inert argon atmosphere. A magnetic stir bar was added to enable stirring. The setup in Figure S1a was used for direct NTP-liquid contact; the setup in Figure S1b was used for a control reaction where the NTP was not in direct contact with the reaction solution. Additionally, the clamps holding the RBF and the plasma generating probe were covered in Kaptan tape to avoid any arcing towards the metal part of the scaffold.



**Figure S1:** Plasma batch reactors. A: standard setup for direct plasma-solution interaction; B: extended quartz tube, plasma **was not** in direct contact with solution.

## 2. Additional experiments for macrocycle 1

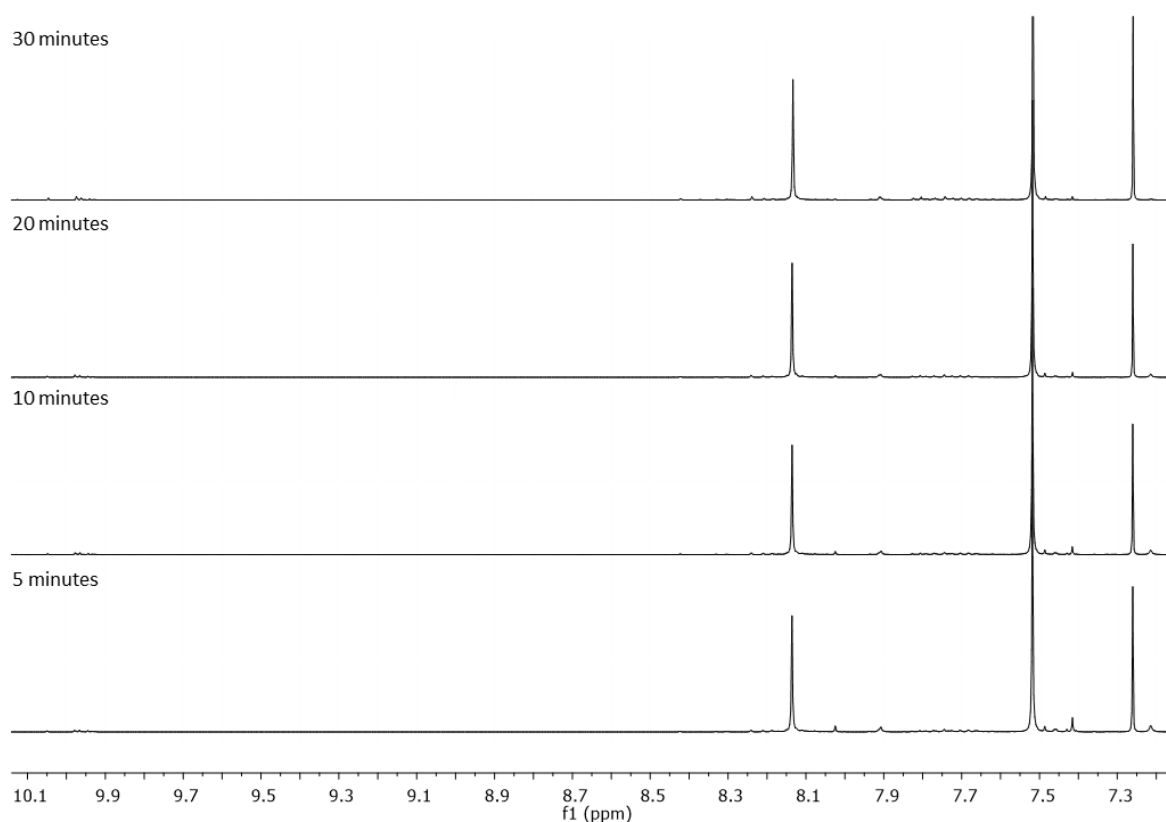
Control experiments were performed for macrocycle **1** and compared with the NTP reactions: a) batch reaction with no plasma performed at room temperature; b) batch reaction using plasma discharge above the solution, e.g., **not** in direct contact with solution (Figure 1).

For all reactions, the chosen concentration was 0.5 M, with 30 mL anhydrous chloroform in total, and the amine added dropwise over 3-4 minutes. The chirality of the products is assumed to be *R,R*- arising from the chirality of the diamine starting material.

For the non-contact plasma reactions, the plasma discharges were generated (3 W, 20 kHz) in a quartz tube with 40 cm length and 1.2 mm inner diameter. The distance from the electrode to the solution was 43 cm, whereas in the standard set up the distance was 15 cm. In each case, the reaction was run for 20 minutes.

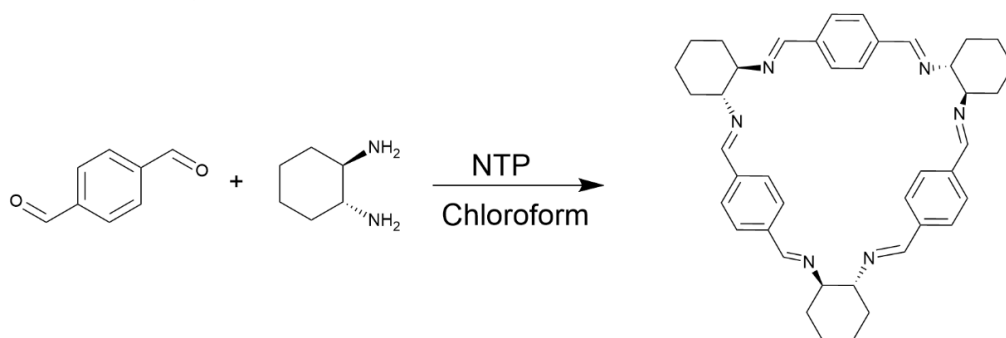
### 2.1 Batch reaction without plasma

Terephthalaldehyde (1.01 g, 7.5 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL), and a solution of (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (0.86 g, 7.5 mmol, 1 eq) in anhydrous chloroform (15 mL) was added dropwise under nitrogen. The reaction was left to stir at RT. Aliquots were taken at regular intervals, dried, redissolved in CDCl<sub>3</sub>, and characterised by <sup>1</sup>H NMR (Figure S2). After 30 minutes the solution was dried *in vacuo* to give a yellow solid (1.43 g, 90 % yield). No further purification was carried out. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.14, 7.52, 7.26, 3.36, 1.81, 1.47. HRMS (ES+) Calc; [M+H]<sup>+</sup> 637.4040 [3+3] m/z<sup>+</sup> found 637.3949 [3+3], [M+H]<sup>+</sup>. The data matched that found in the literature, integrations and peak picking can be seen in Figure S5.<sup>2</sup>



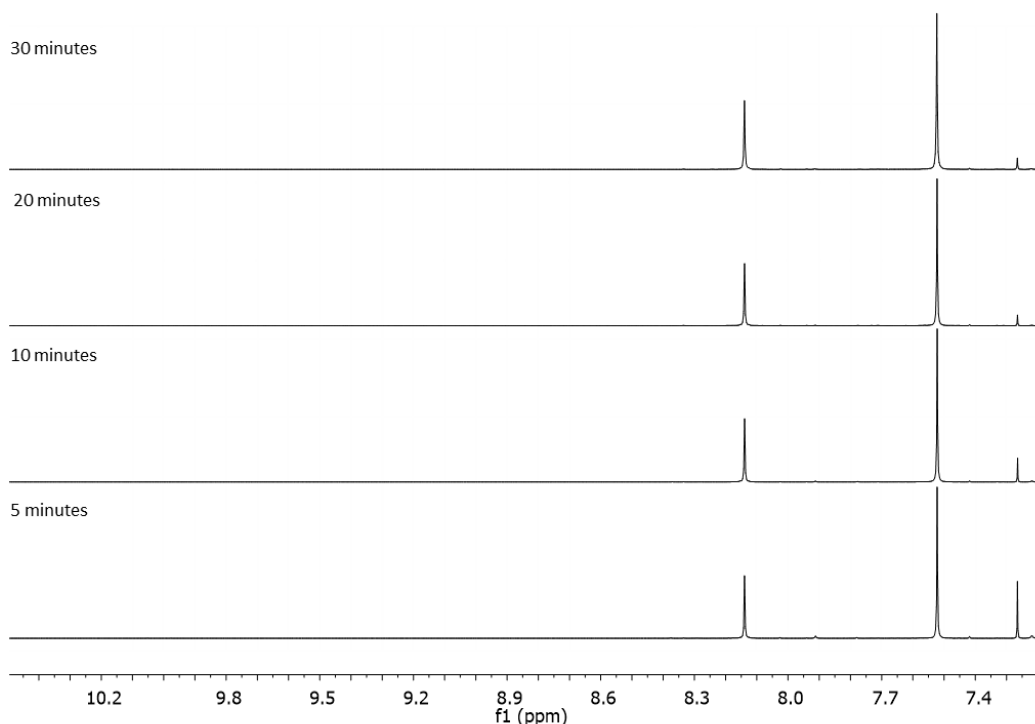
**Figure S2:** <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) samples of the synthesis of macrocycle **1** in batch, without plasma, 7.2 ppm – 10.2 ppm.

## 2.2 Reaction with plasma: standard conditions

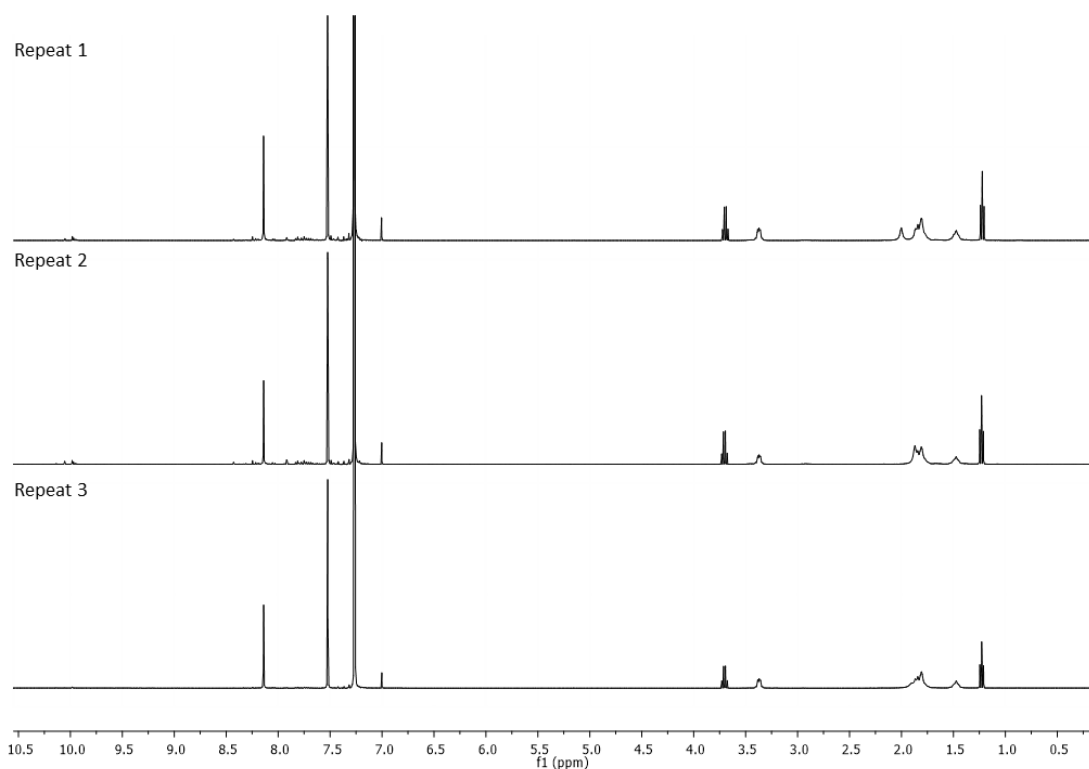


The reaction was performed using setup **1** shown in Fig 1a. The plasma settings used were 3.2 W, 13.2 kV; the flow rate of argon was set to 490 ml/min and the total reaction volume was 30 mL. Terephthalaldehyde (1.01 g, 7.5 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen and transferred to the argon-flushed RBF in the plasma set up via syringe and needle. In a separate flask, (1R,2R)-(-)-1,2-diaminocyclohexane (0.86 g, 7.5 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge was continued for 30 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR (Figure S3). At 30 minutes the reaction mixture was dried *in vacuo* to give a yellow solid (1.48 g, 93%). No further purification was carried out.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (s, 1H), 7.52 (s, 2H), 3.36 (m, 1H), 1.9 – 1.45 (m, cyclo-hex, 5.6 H). HRMS (ES+) Calc;  $[\text{M}+\text{H}]^+$  637.4040 [3+3]  $m/z^+$  found 637.3922 [3+3],  $[\text{M}+\text{H}]^+$ . The data matched that found in the literature.<sup>2</sup>

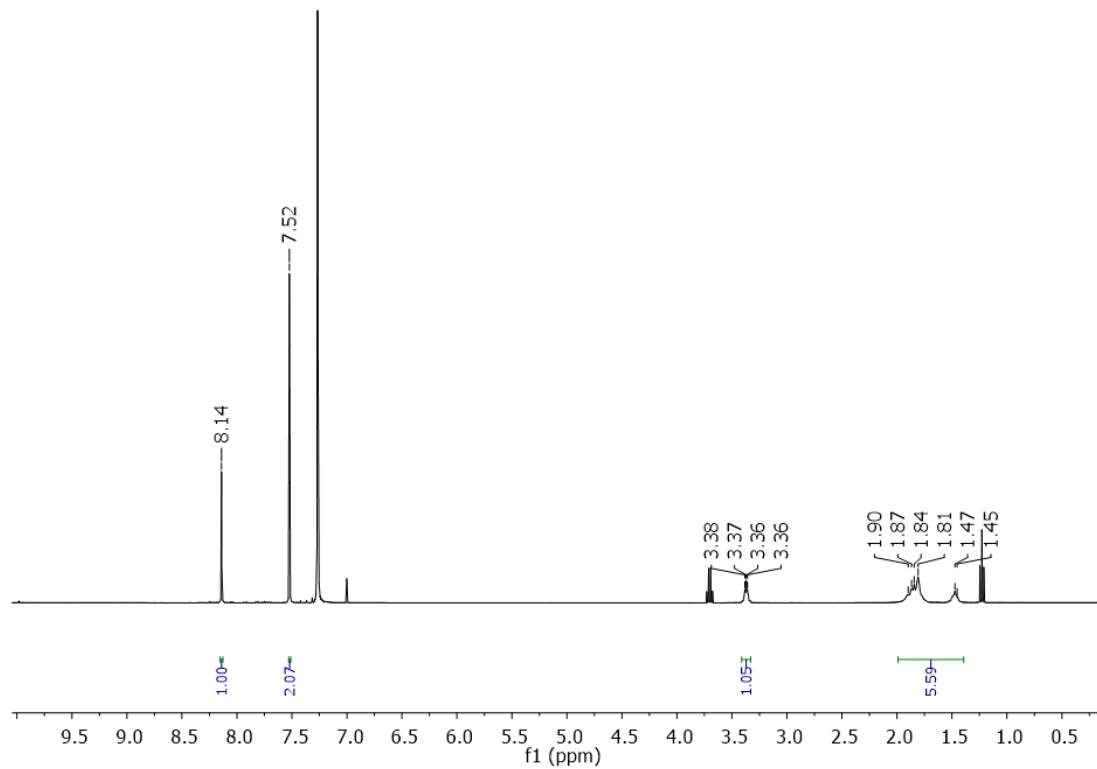
This procedure was repeated thrice more, at 20 minutes instead, to give yields of 93 %, 94% and 94 % (Figure S4).



**Figure S3:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) samples of the synthesis of macrocycle **1** in 30 minutes with plasma in contact with the solution, 7.2 ppm – 10.4 ppm.



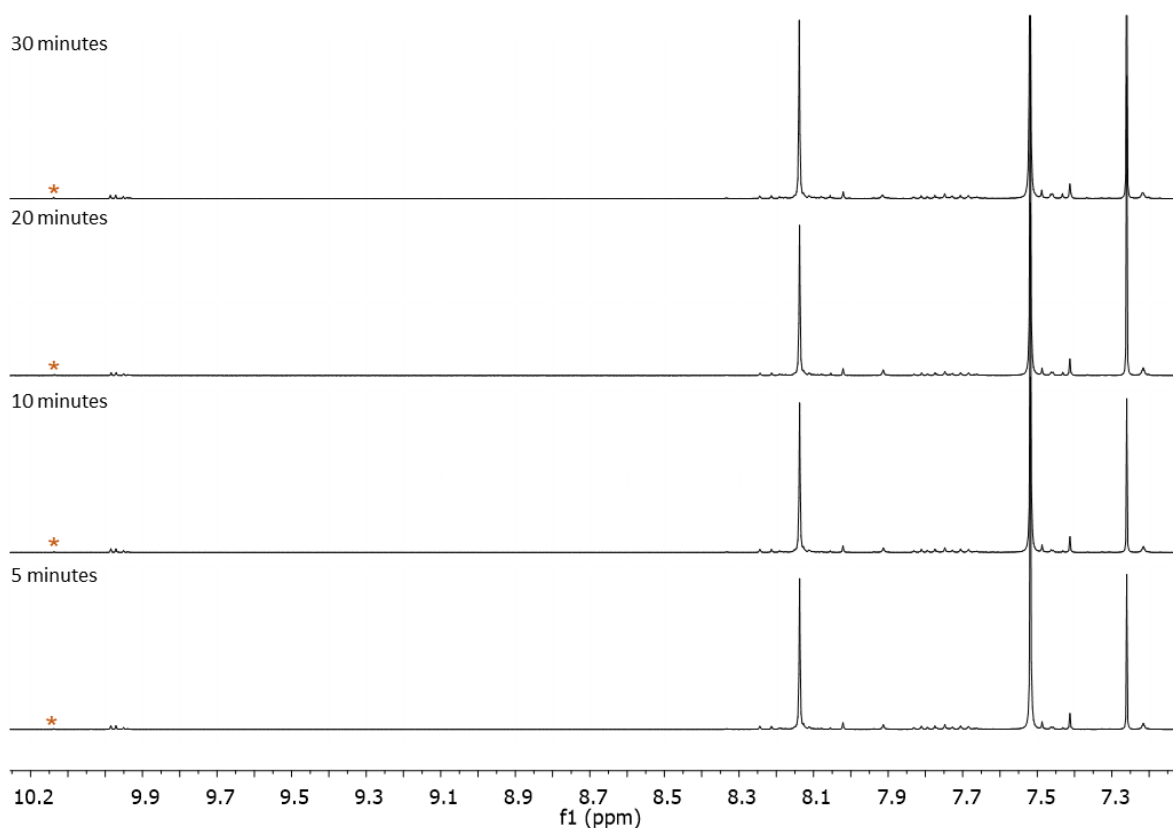
**Figure S4:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of repeats of NTP synthesis of macrocycle **1**, at 20 minutes.



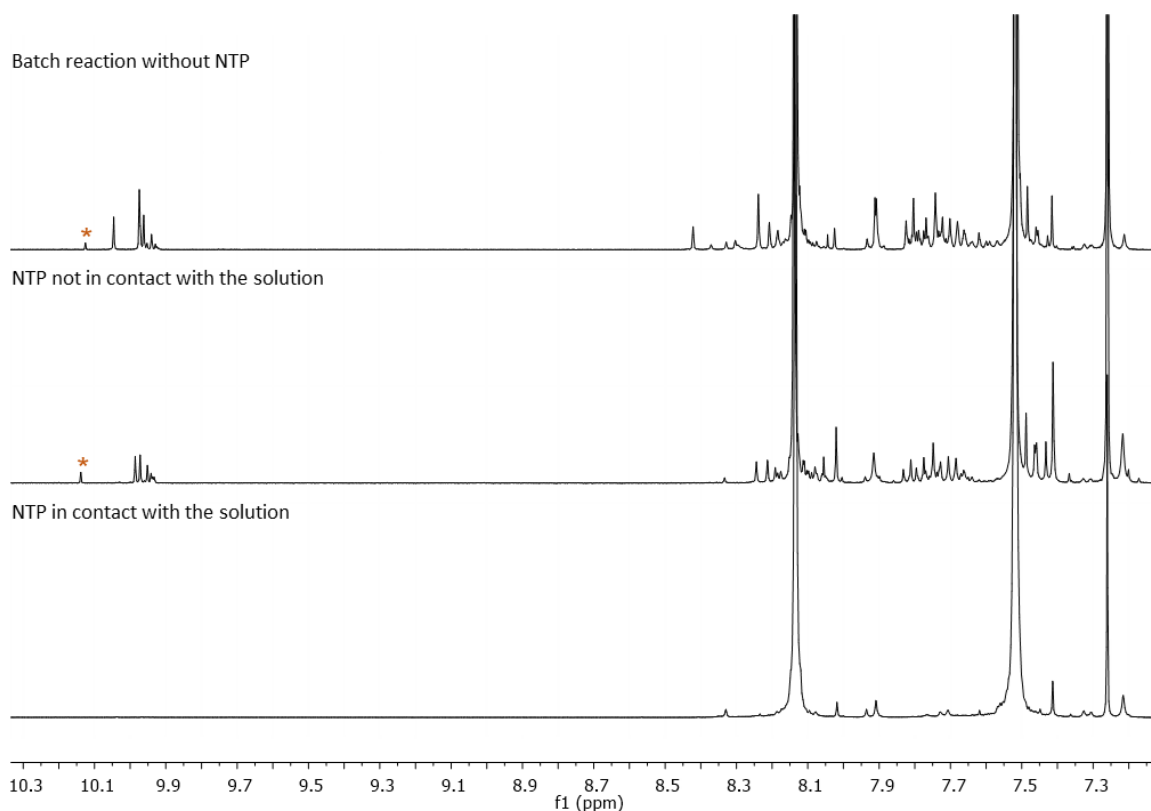
**Figure S5:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **1**, showing the integrations.

### 2.3 Reaction with plasma: no contact with solution

The reaction was performed using the setup shown in Figure S1b. Plasma settings were set to 3.2 W, 13.2 kV; the flow rate of argon was 490 ml/min and the total reaction volume was 30 mL. Terephthalaldehyde (1.01 g, 7.5 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen and transferred to the argon-flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (0.86 g, 7.5 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) in a separate flask under nitrogen. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 30 minutes, remaining in no contact with the reaction solution, and the reaction was monitored by <sup>1</sup>H NMR. After 30 minutes, the reaction mixture was dried *in vacuo* to give a yellow solid (1.35 g, 85 %). No further purification was carried out. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.14, 7.52, 7.26, 3.36, 1.81, 1.47. HRMS (ES+) Calc: [M+H]<sup>+</sup> 637.4040 [3+3], m/z<sup>+</sup> found: 637.5110 [3+3] [M+H]<sup>+</sup>. The data matched that found in the literature.<sup>2</sup>



**Figure S6:** <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) over 30 minutes for synthesis of macrocycle **1** when plasma is not in contact with solution, 7.2 ppm – 10.2 ppm. Orange asterisk indicates aldehyde peak relating to the starting material.



**Figure S7:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) at 30 minutes for synthesis of macrocycle **1** comparing (i) batch reaction without NTP (ii) NTP not in contact with the solution and (iii) NTP in contact with solution, 7.2 ppm – 10.2 ppm. All spectra have been magnified by the same amount. Orange asterisk indicates aldehyde peak relating to the starting material.

### 3. Screening parameters for NTP synthesis of macrocycle **1**

For  $^1\text{H}$  NMR analysis 0.5 mL of reaction solution was used at each time point except for 1.25 M, where 0.2 mL was used to avoid over-concentrating the NMR sample. In all instances, the NMR matches the literature,<sup>2</sup> but differs in purity.

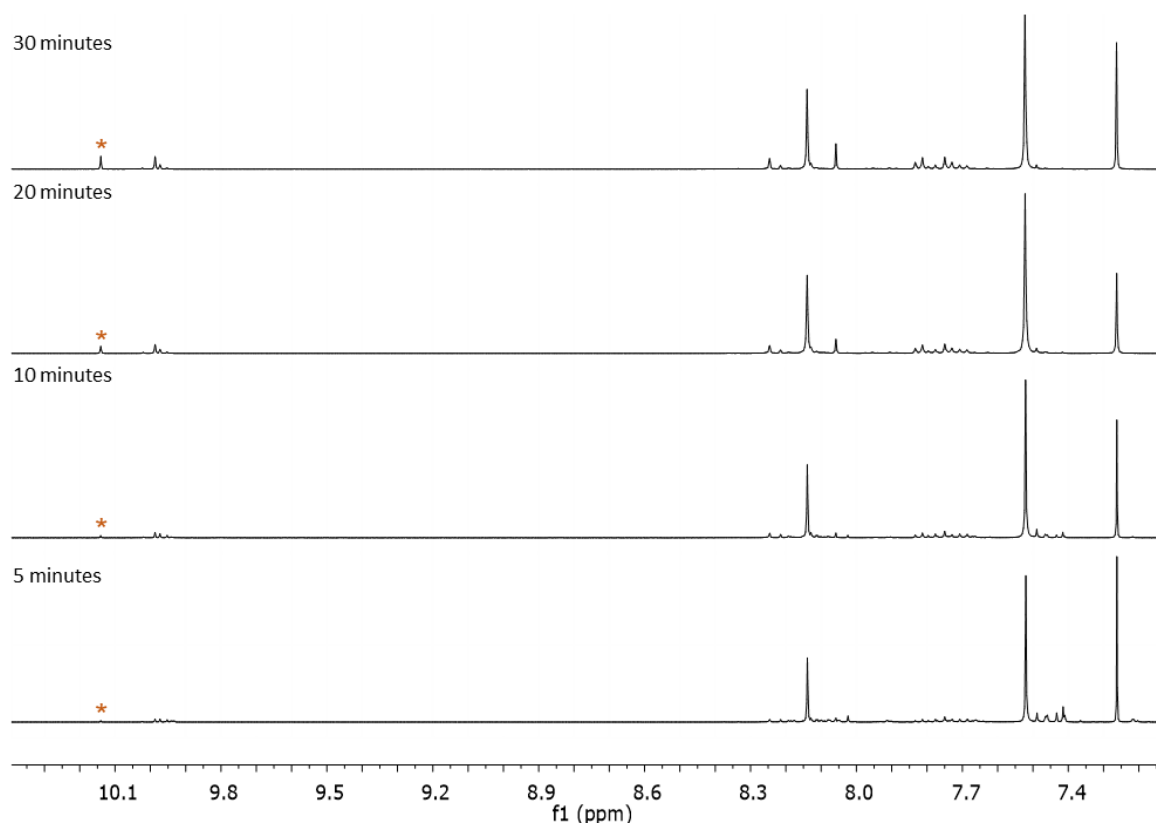
0.5 mL of reaction solution was used at each time point except for 1.25 M, where 0.2 mL was used to avoid over-concentrating the NMR sample. In all instances, the NMR matches the literature,<sup>2</sup> but differs in purity.

#### 3.1 Concentration

For all concentration changes, frequency, power, and voltage applied to generate the plasma was constant (3.2 W; 13.2 kV), the flow rate of argon was set to 490 ml/min and the total reaction volume was 30 mL.

**50mM:** Terephthalaldehyde (0.10 g, 0.75 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen and transferred to the argon-flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (0.09 g, 0.75 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 30 minutes,

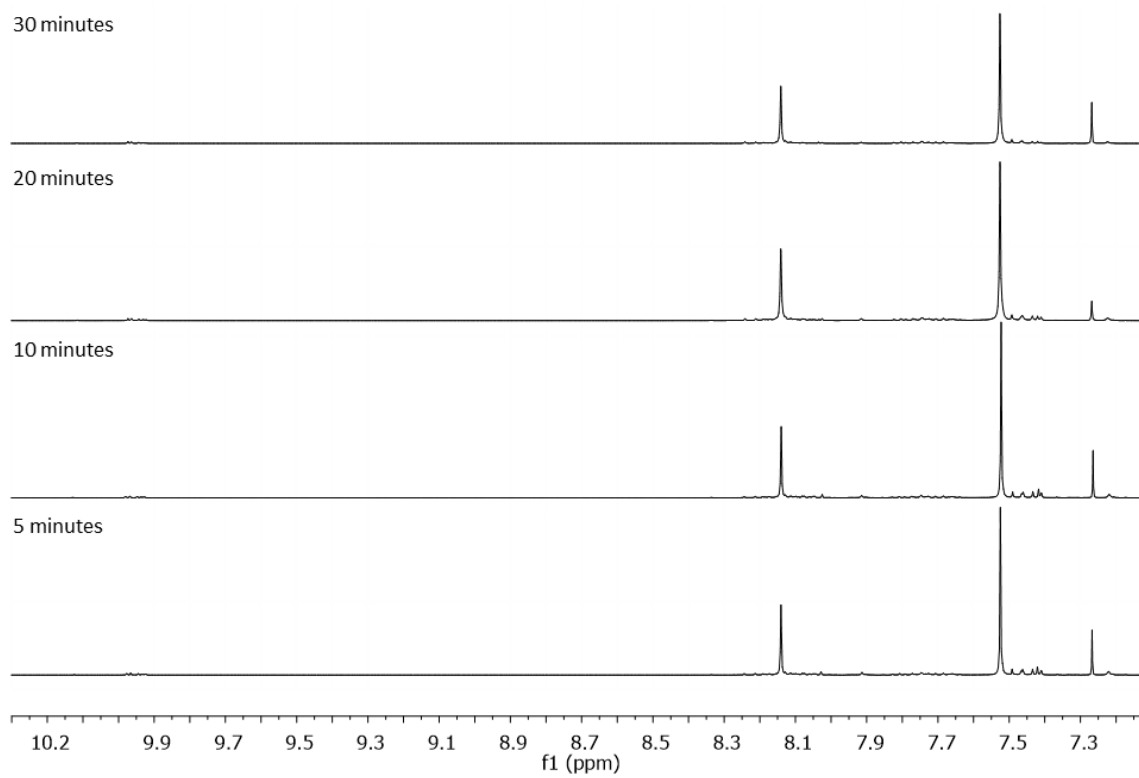
remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14, 7.52, 7.26, 3.36, 1.81, 1.47.



**Figure S8:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of macrocycle **1** over 30 minutes at 0.05 M, 7.2 ppm – 10.3 ppm. An orange asterisk indicates aldehyde peak relating to the starting material.

**1.25M:** Terephthalaldehyde (2.51 g, 18.75 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (2.14 g, 18.75 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 30 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14, 7.52, 7.26, 3.36, 1.81, 1.47



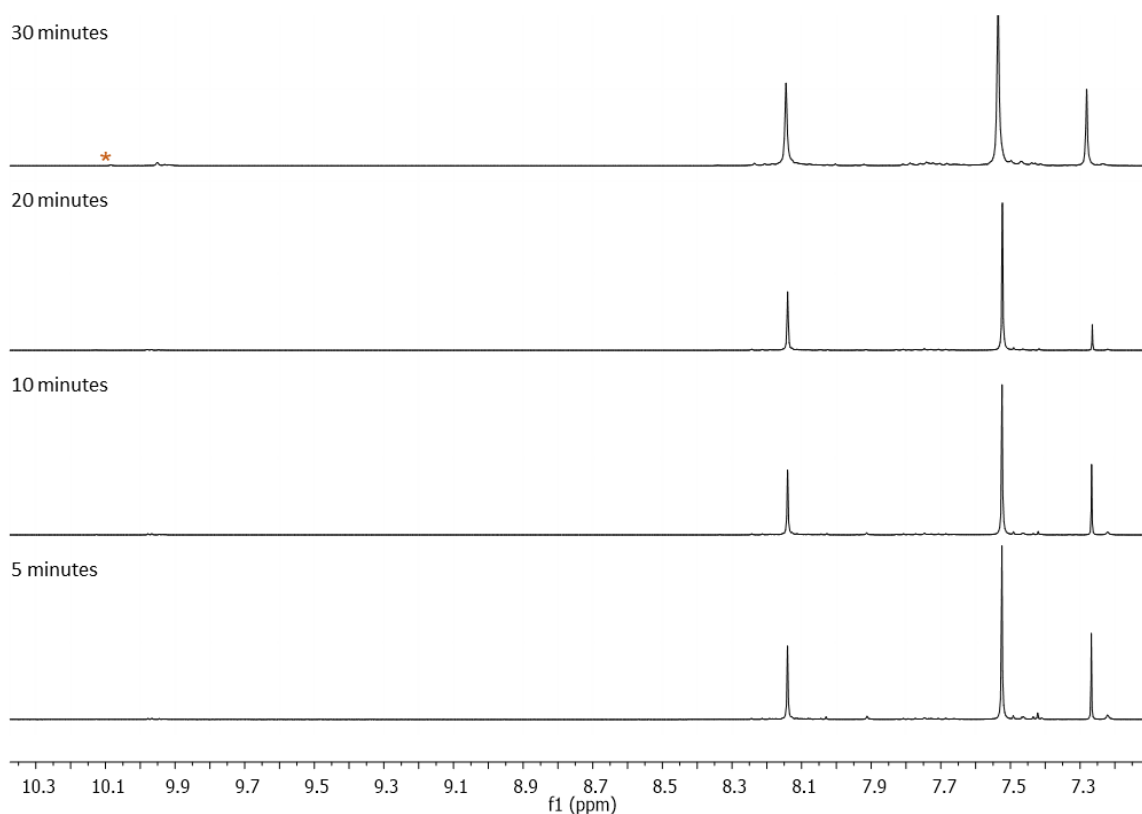


**Figure S9:** <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) of macrocycle **1** over 30 minutes at 1.25 M, 7.2 ppm- 10.3 ppm.

### 3.2 Volume

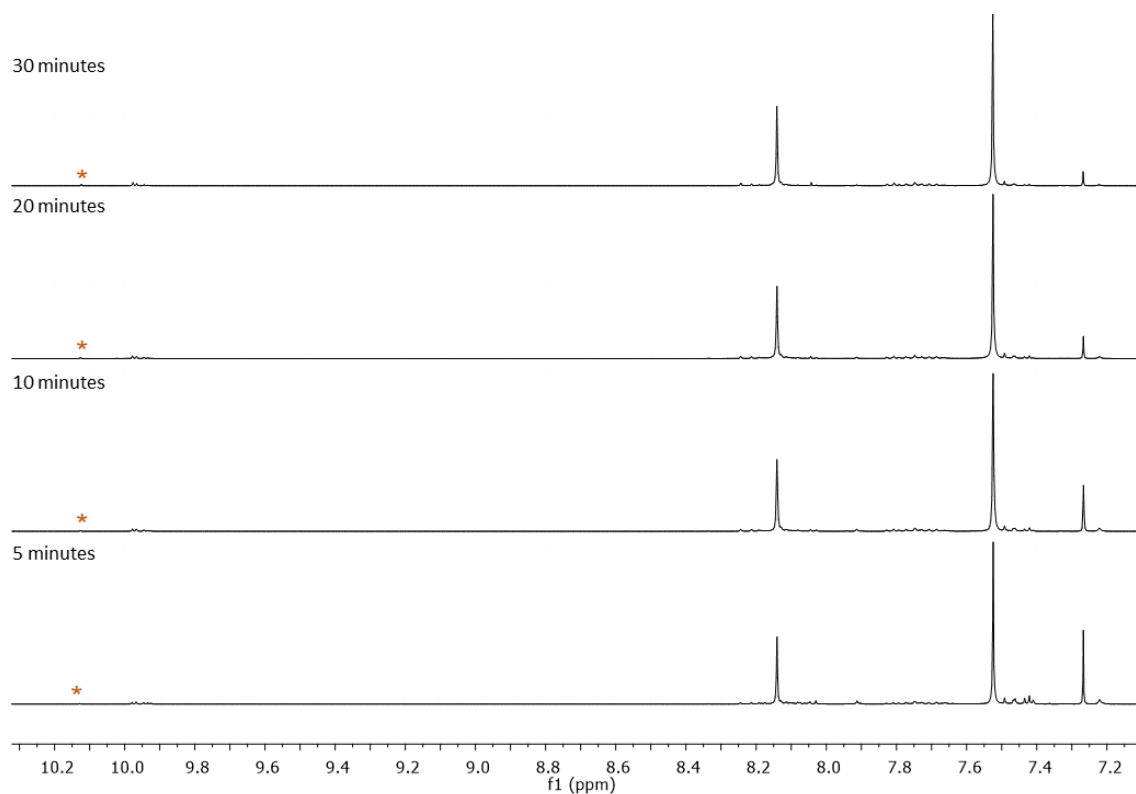
For all total volume changes (15 mL, 30 mL, 45 mL) the frequency, power and voltage applied to generate the plasma was constant (3.2 W; 13.2 kV), the flow rate of argon was set to 490 ml/min and the concentration was fixed at 0.5 M.

**15 mL:** Terephthalaldehyde (0.50 g, 3.75 mmol, 1 eq) was dissolved in anhydrous chloroform (7.5 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (0.43 g, 3.75 mmol, 1 eq) was dissolved in anhydrous chloroform (7.5 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 30 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14, 7.52, 3.36, 1.81, 1.47.



**Figure S10:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of macrocycle **1** over 30 minutes, at 15 mL total volume, 7.2 ppm – 10.3 ppm. Orange asterisk indicates aldehyde peak relating to the starting material.

**45 mL:** Terephthalaldehyde (1.51 g, 22.5 mmol, 1 eq) was dissolved in anhydrous chloroform (22.5 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (1.29 g, 22.5 mmol, 1 eq) was dissolved in anhydrous chloroform (22.5 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 30 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14, 7.52, 7.26, 3.36, 1.81, 1.47.

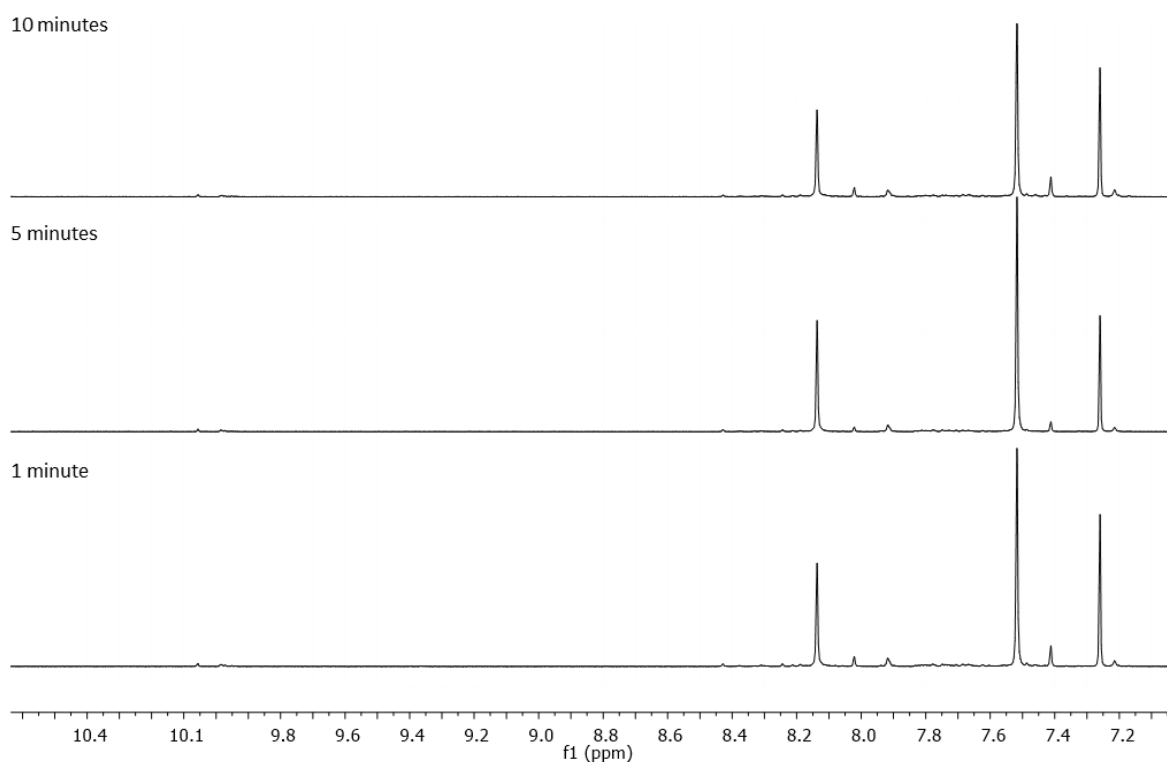


**Figure S11:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of macrocycle **1** over 30 minutes, at 45 mL total volume, 7.2 ppm – 10.3 ppm. Orange asterisk indicates aldehyde peak relating to the starting material.

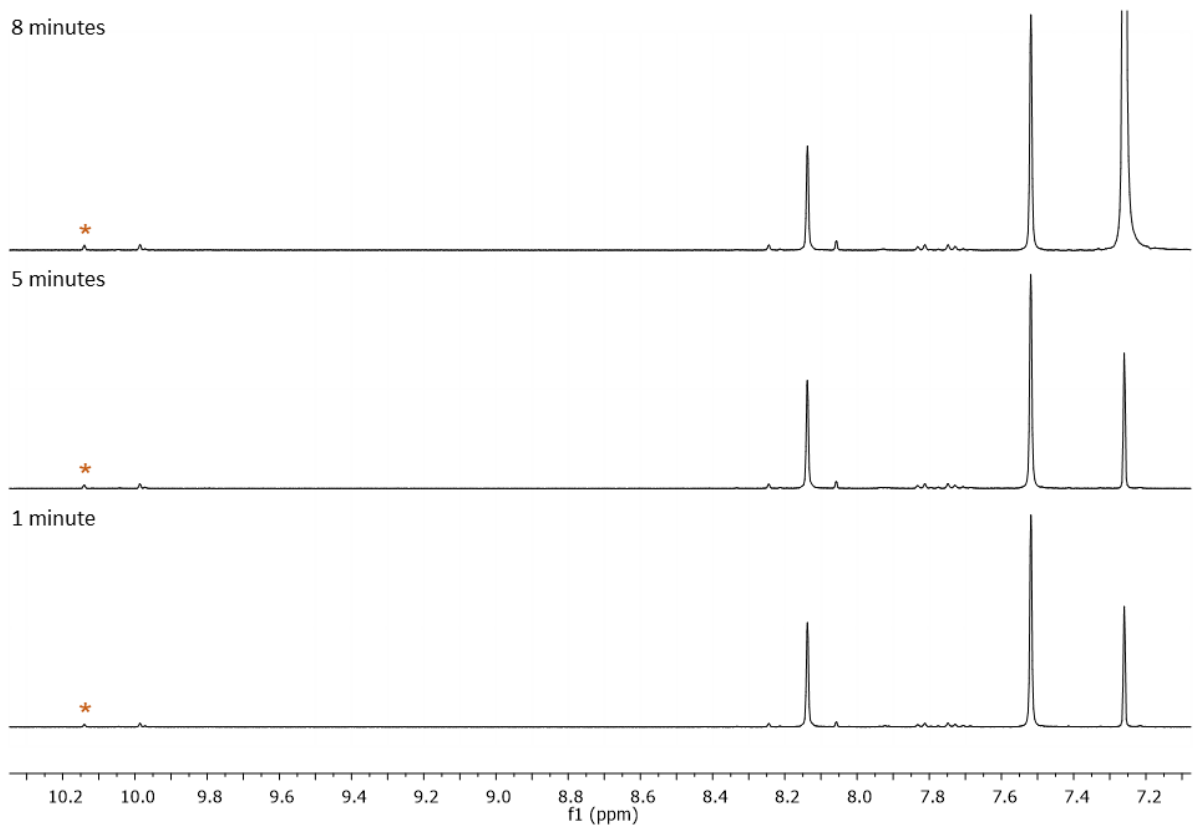
### 3.3 Power

For these experiments, the frequency (20 kHz) and the flow rate of feeding gas (490 ml/min) was kept constant. In the high power experiment the power was 4.5 W and corresponding voltage was 16-17 kV; the reaction was stopped at 10 minutes due to a power supply issue. The power for the low power experiment was 1.4 W and the corresponding voltage was 12 kV. For comparison purposes, the low power reaction was also stopped at 10 minutes.

Terephthalaldehyde (1.01 g, 7.5 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (0.86 g, 7.5 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 10 minutes, remaining in the contact with the reaction solution.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14, 7.52, 7.26, 3.36, 1.81, 1.47.



**Figure S12:**  $^1\text{H NMR}$  spectrum ( $\text{CDCl}_3$ ) of macrocycle **1** over 10 minutes, at low power, 7.2 ppm – 10.3 ppm.

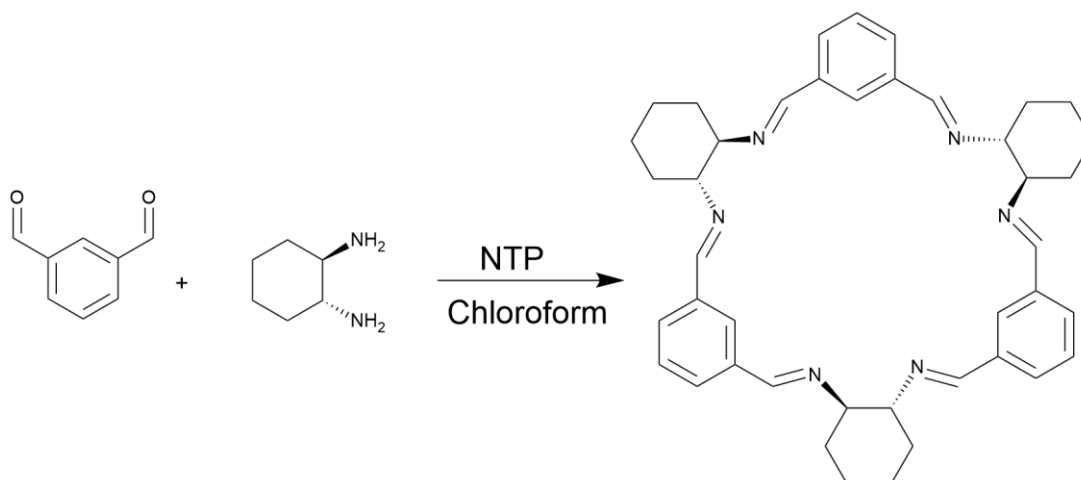


**Figure S13:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of macrocycle **1** over 10 minutes, at high power, 7.2 ppm -10.3 ppm (power cut off before 10 minutes). Orange asterisk indicates aldehyde peak relating to the starting material.

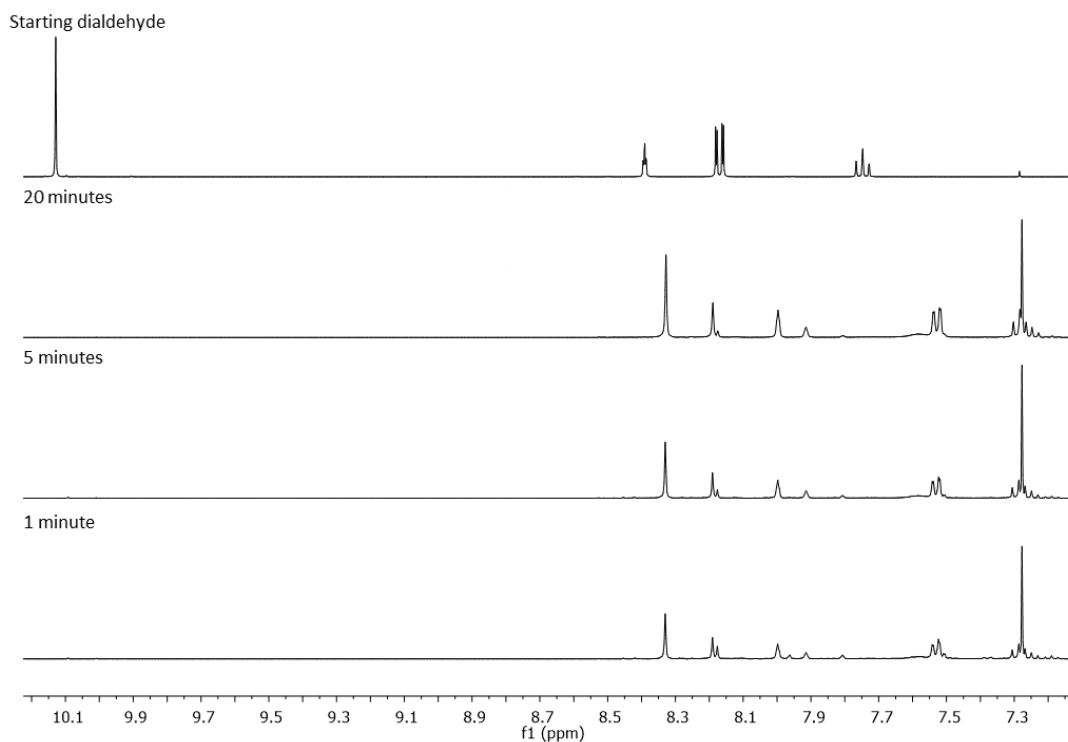
## 4. NTP synthesis of macrocycles 2-8

Plasma settings; frequency (20kHz), power (3.2 W) and voltage (14.2±0.5 kV).

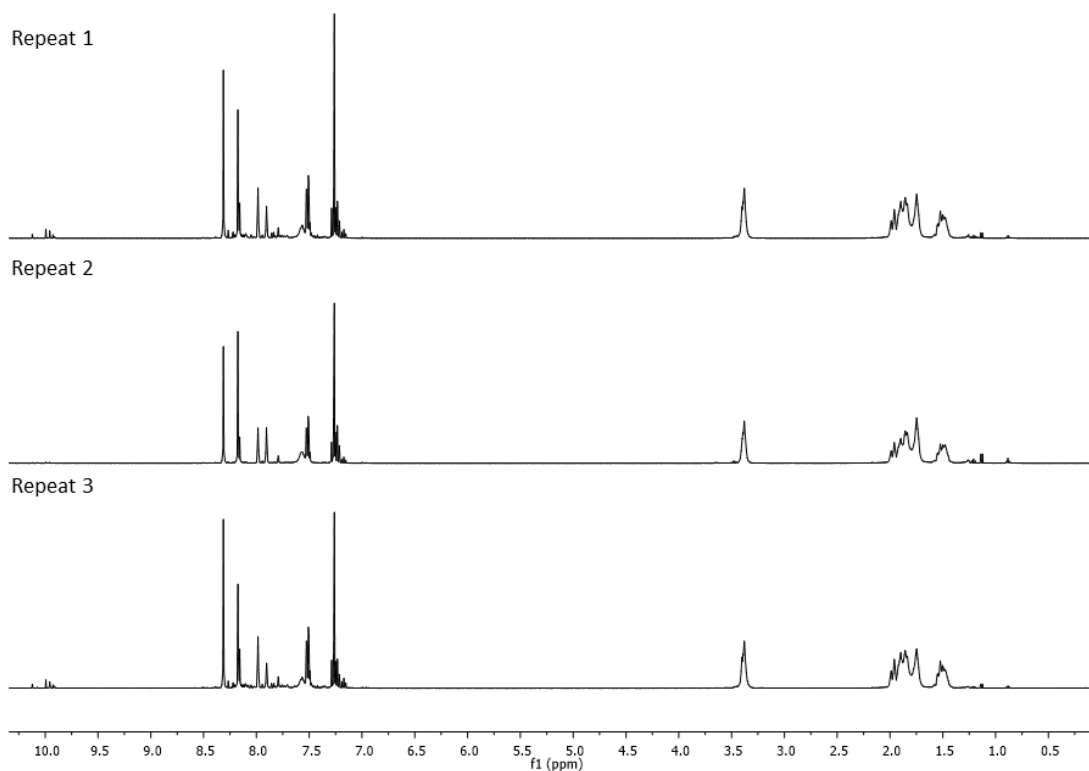
### 4.1 NTP synthesis of macrocycle 2



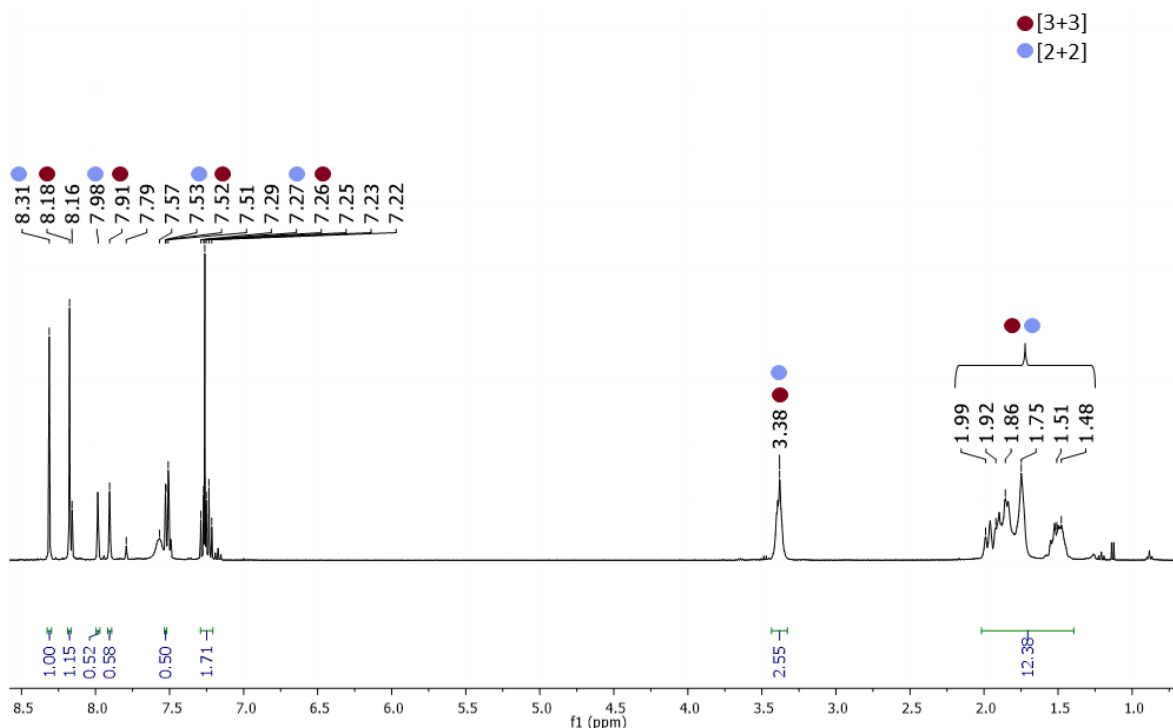
Isophthalaldehyde (1.01 g, 7.5 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (0.86 g, 7.5 mmol, 1 eq) was dissolved in anhydrous chloroform (15 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 20 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by <sup>1</sup>H NMR. After 20 minutes the reaction mixture was dried *in vacuo* to give a yellow solid (run in triplicate: 1.46 g, 1.55 g, 1.58 g to give yields of 92 %, 97 %, and 98 % respectively.) No further purification was carried out. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.31 (s, 1H, [2+2]), 8.18 (s, 1.14H, [3+3]), 7.98 (br s, 0.53H, [2+2]), 7.91 (br s, 0.59H, [3+3]), 7.53 (br s, [2+2]), 7.52 (br s, [3+3]), 7.27 (br s, [2+2]), 7.26 (br s, [3+3]) 3.38 (m, 2.55H, [2+2] and [3+3]), 1.99 – 1.48, (m, cyclo-hex, 12.38H, [2+2] and [3+3]). Integrals are calibrated to 1H for the imine peak for the [2+2] macrocycle to show relative amounts of each species in the mixture; peak integrals would be expected to have a ratio of 2:3 for [2+2]:[3+3]. Where integrals overlap or coincide with solvent peaks, no integration value has been given. HRMS (ES+) Calc; [M+H]<sup>+</sup> 425.2727 [2+2], 637.4040 [3+3], 849.5332 [4+4]; m/z<sup>+</sup> found 425.2700 [2+2], [M+H]<sup>+</sup>, 637.3922 [3+3], [M+H]<sup>+</sup>, 849.4954 [4+4], [M+H]<sup>+</sup>. The data match those reported in the literature.<sup>3</sup>



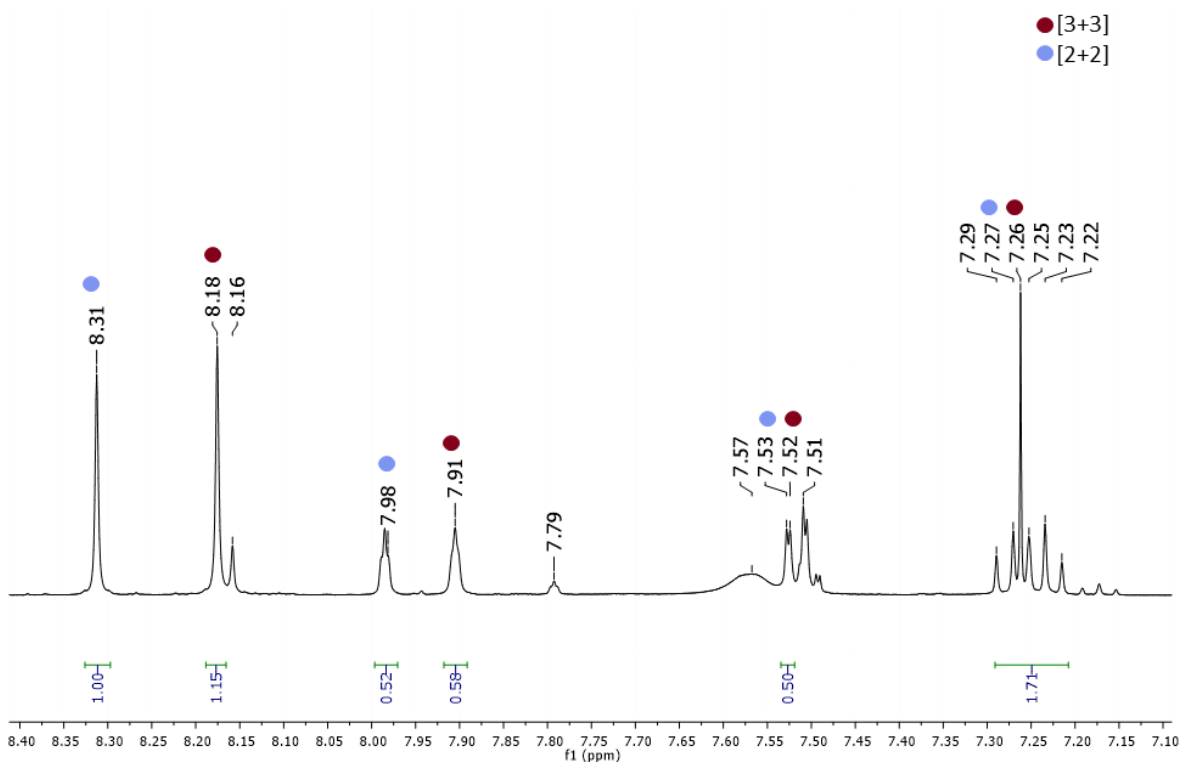
**Figure S14:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **2** over 20 minutes, with comparison to starting dialdehyde (6.6 ppm – 10.2 ppm).



**Figure S15:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) repeats of the 20-minute NTP synthesis of macrocycle **2**.



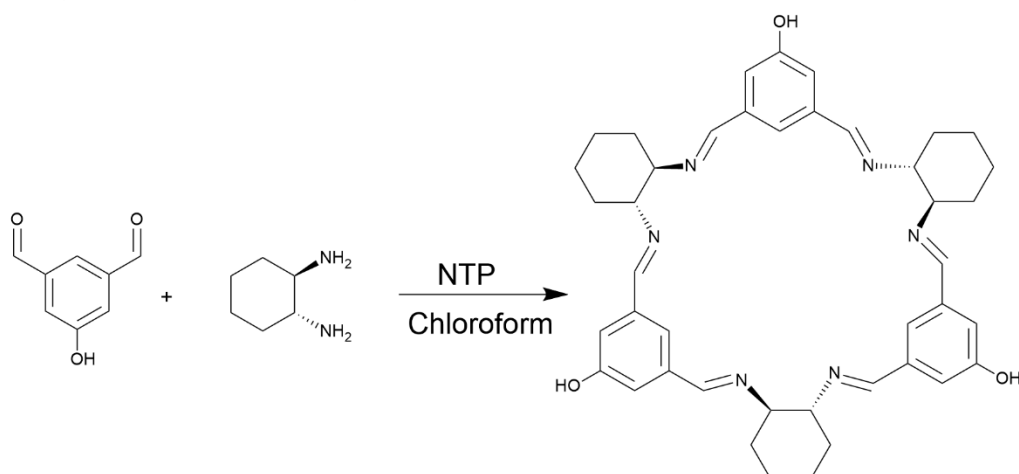
**Figure S16:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of macrocycle **2**, showing the integrals as relative values for the [2+2] and [3+3] species, calibrated to 1H for the [2+2] imine peaks.



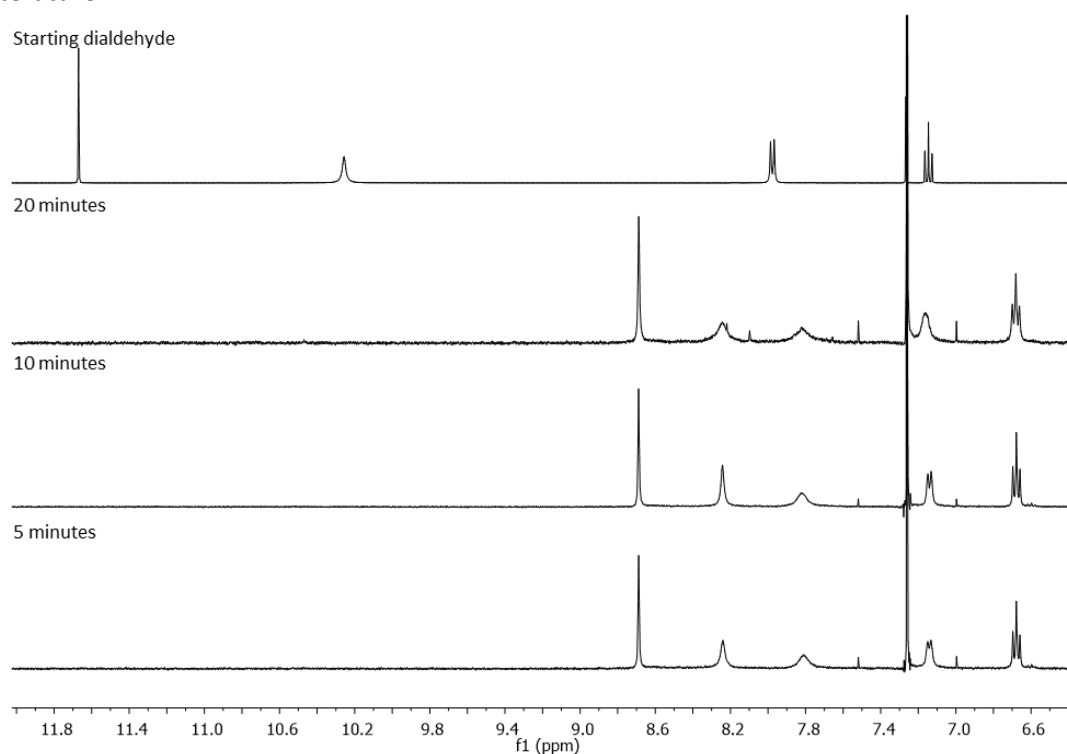
**Figure S17:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of macrocycle **2**, showing the integrals as relative values for the [2+2] and [3+3] species, calibrated to 1H for the [2+2] imine peaks, 7.10 ppm – 8.40 ppm. Additional peaks seen are assumed to be intermediate species and were not identified.



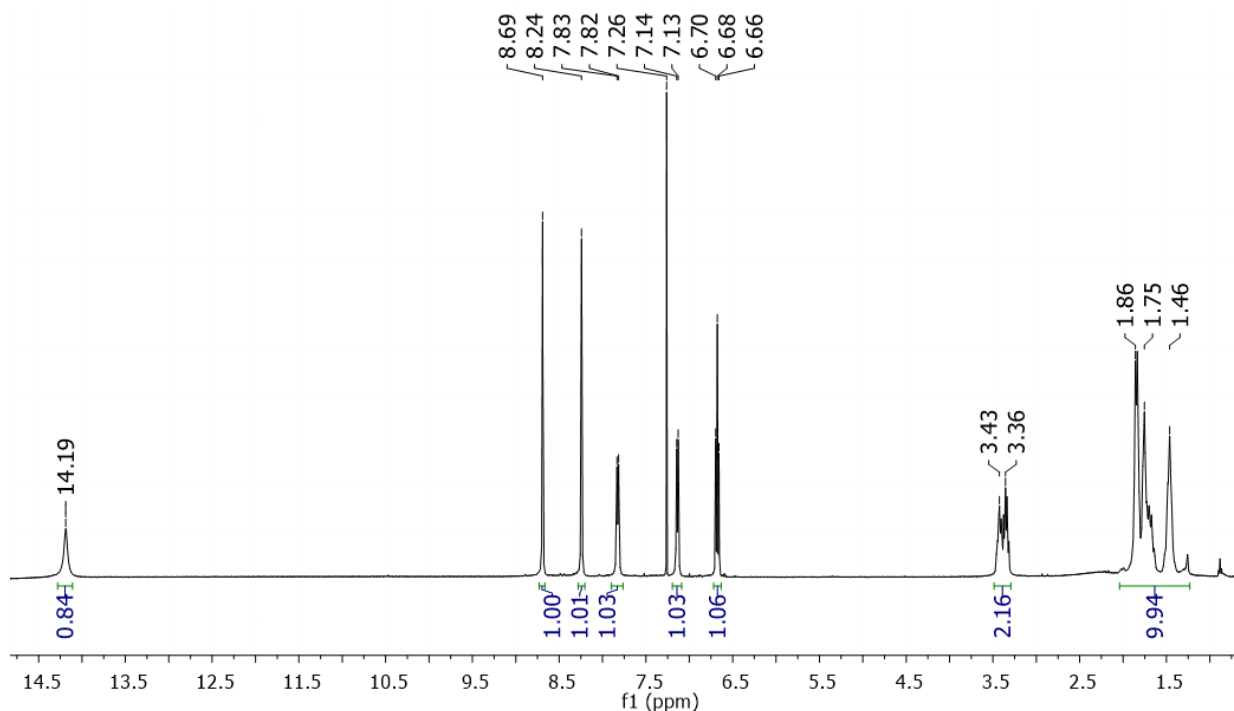
## 4.2 NTP synthesis of macrocycle 3



2-hydroxyisophthalaldehyde (0.0751 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1R,2R)-(-)-1,2-Diaminocyclohexane (0.0571 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 20 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR. After this the reaction mixture was dried *in vacuo* to give a yellow solid (0.11 g, 99 %). No further purification was carried out.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  14.19 (s, 0.84H), 8.69 (s, 1H), 8.24 (s, 1H), 7.82 (d, 1H), 7.13 (d, 1H), 6.70 – 6.66 (1H), 3.43 – 3.36 (b, 2.16H), 1.86 – 1.46 (m, cyclo-hex 9.94H). HRMS (ES+) Calc; [M+H]: 685.3888 [3+3],  $m/z^+$  found: 685.5023 [3+3], [M+H] $^+$ . The data match those reported in the literature.<sup>4</sup>

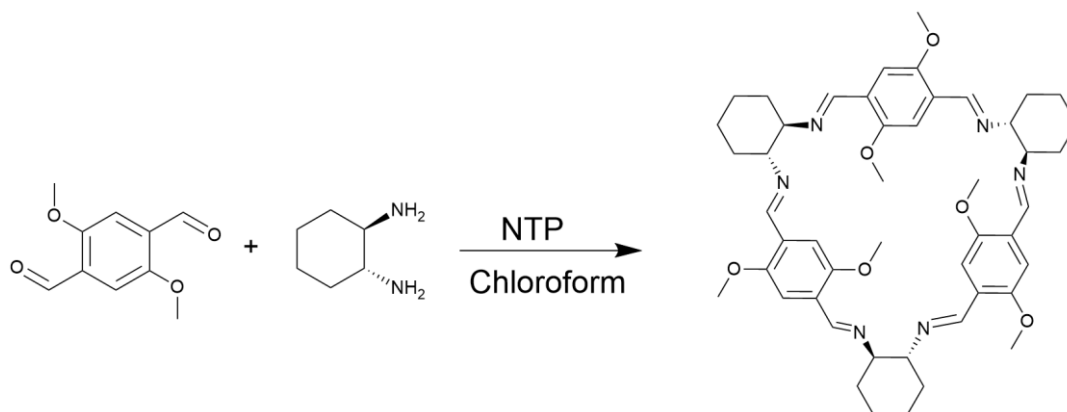


**Figure S18:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) NMR of NTP synthesis of macrocycle 3 over 20 minutes.

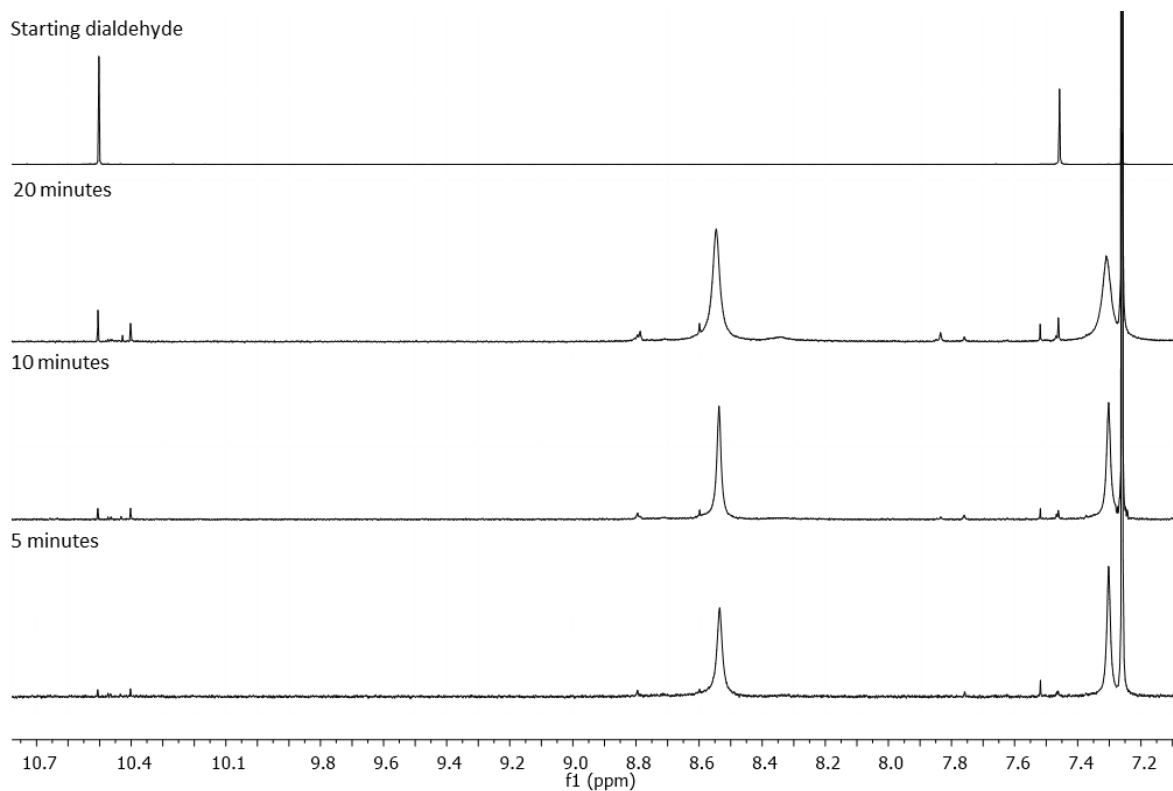


**Figure S19:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **3** at 20 minutes.

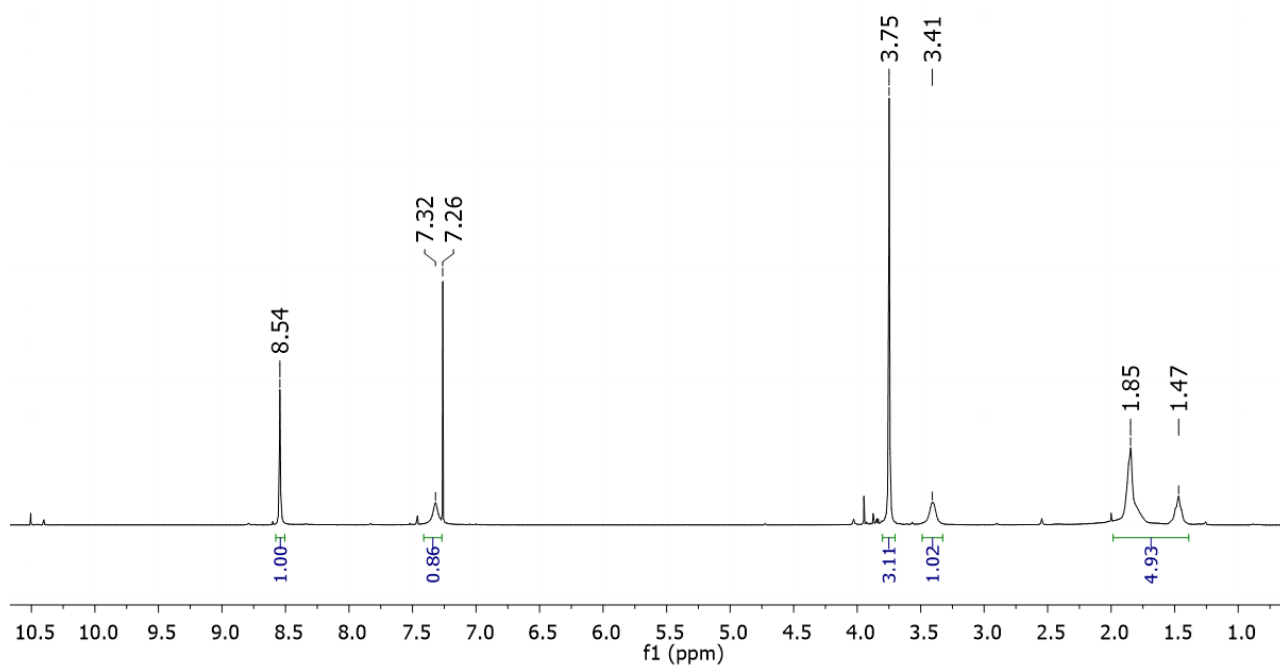
### 4.3 NTP synthesis of macrocycle **4**



2,5-dimethoxyterephthalaldehyde (0.10 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (0.06 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 20 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR. After this the reaction mixture was dried *in vacuo* to give a yellow solid (0.14 g, >99%). No further purification was carried out.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54 (s, 1H), 7.32 (b, 0.86H), 3.75 (s, 3.11H), 3.41 (m, 1.02H), 1.85 – 1.47 (m, cyclo-hex 4.93H). HRMS (ES+) Calc;  $[\text{M}+\text{H}]^+ = 817.5574$  [3+3],  $m/z^+$  found = 817.5846 [3+3],  $[\text{M}+\text{H}]^+$ . The data match those reported in the literature.<sup>5</sup>

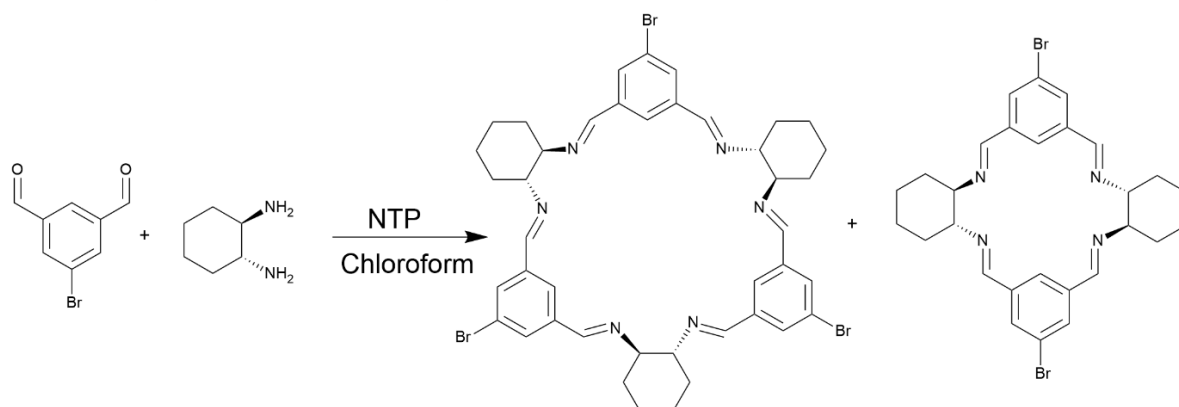


**Figure S20:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **4** over 20 minutes (6.7 ppm – 10.8 ppm).

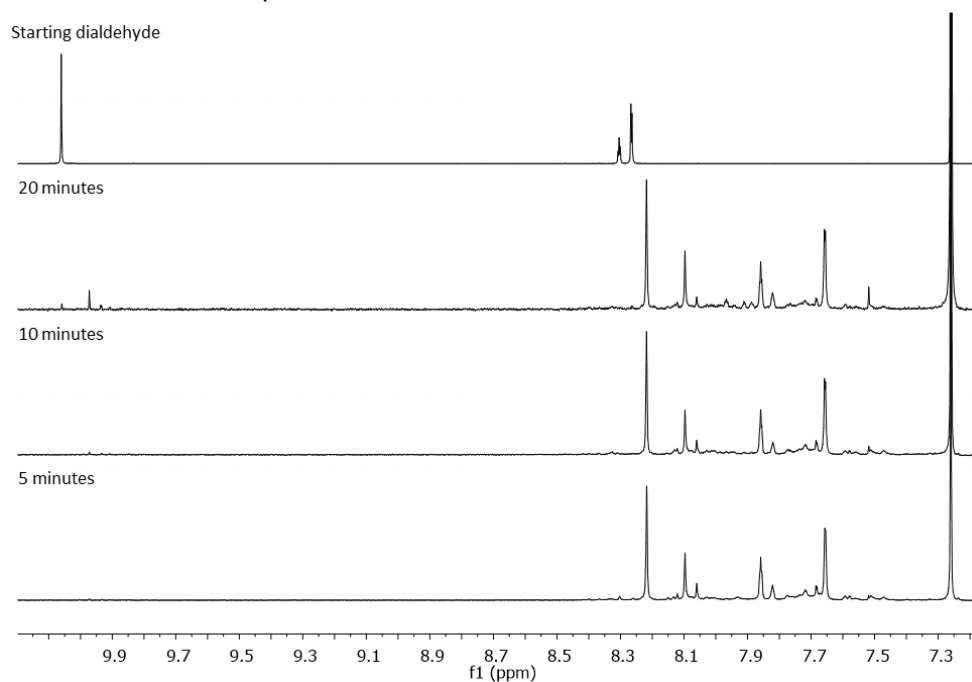


**Figure S21:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **4** at 20 minutes.

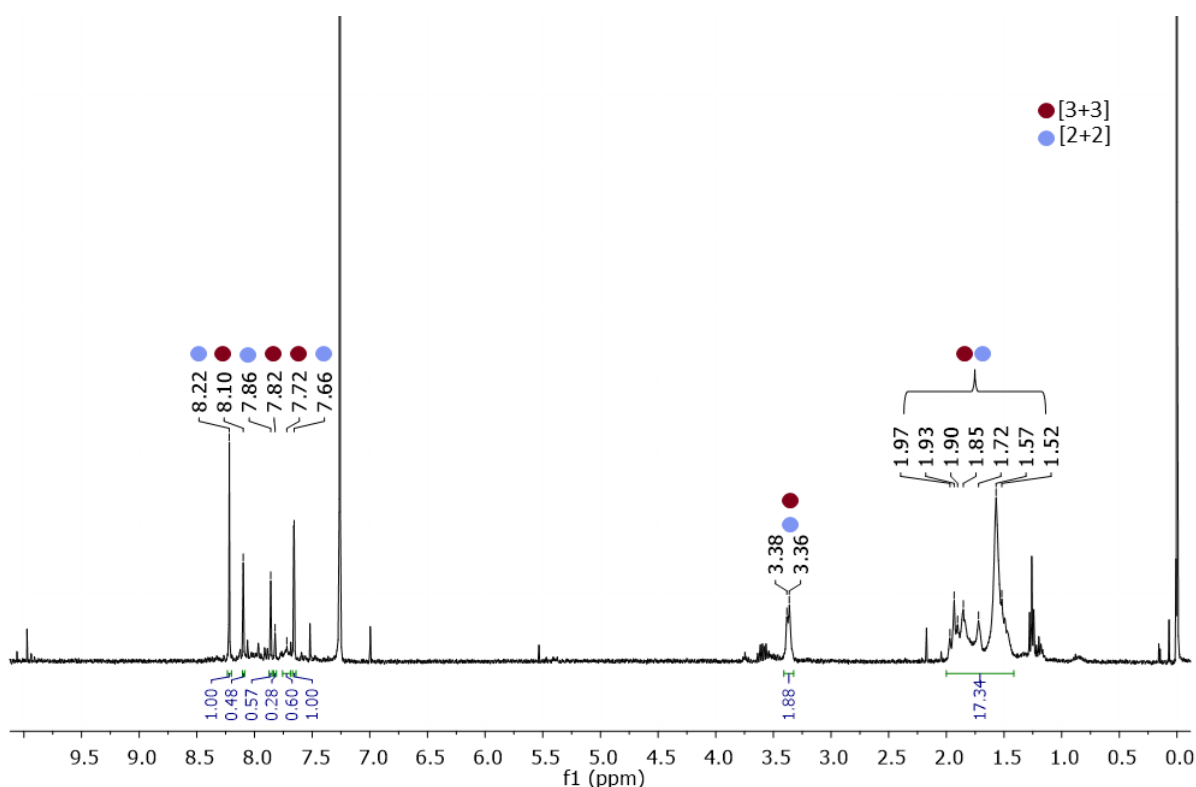
#### 4.4 NTP synthesis of macrocycle 5



5-bromoisophthalaldehyde (0.11 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (0.0571 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 20 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR. After 20 minutes the reaction mixture was dried *in vacuo* to give a white/pale yellow solid (0.12 g, 82 %). No further purification was carried out.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.22 (s, 1H, [2+2]), 8.10 (s, 0.48H, [3+3]), 7.86 (m, 0.57H, [2+2]), 7.82 (m, 0.28H, [3+3]), 7.72 (broad s, 0.60H, [3+3]), 7.66 (d, 1H, [2+2]), 3.36-3.38 (m, 1.88H, [2+2] and [3+3]), 1.97 – 1.52 (m, cyclo-hex, 17.34H, [2+2] and [3+3]). Integrals are calibrated to 1H for the imine peak for the [2+2] macrocycle to show relative amounts of each species in the mixture; peak integrals would be expected to have a ratio of 2:3 for [2+2]:[3+3]. HRMS (ES+) Calc;  $[\text{M}+\text{H}]^+ = 581.0937$  [2+2], 871.1356 [3+3],  $m/z^+$  found;  $[\text{M}+\text{H}]^+ = 583.2269$  [2+2], 875.2955 [3+3]. The data match those reported in the literature.<sup>6,7</sup>

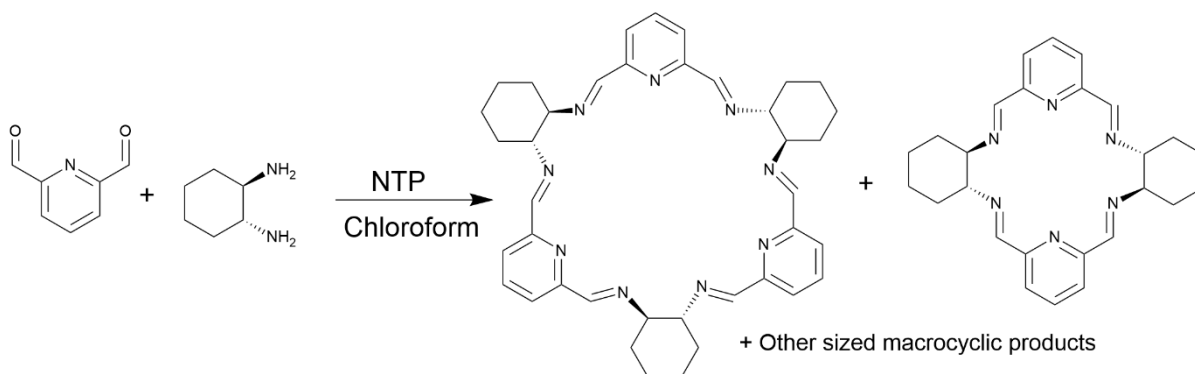


**Figure S22:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle 5 over 20 minutes (7.0 ppm – 10.2 ppm).



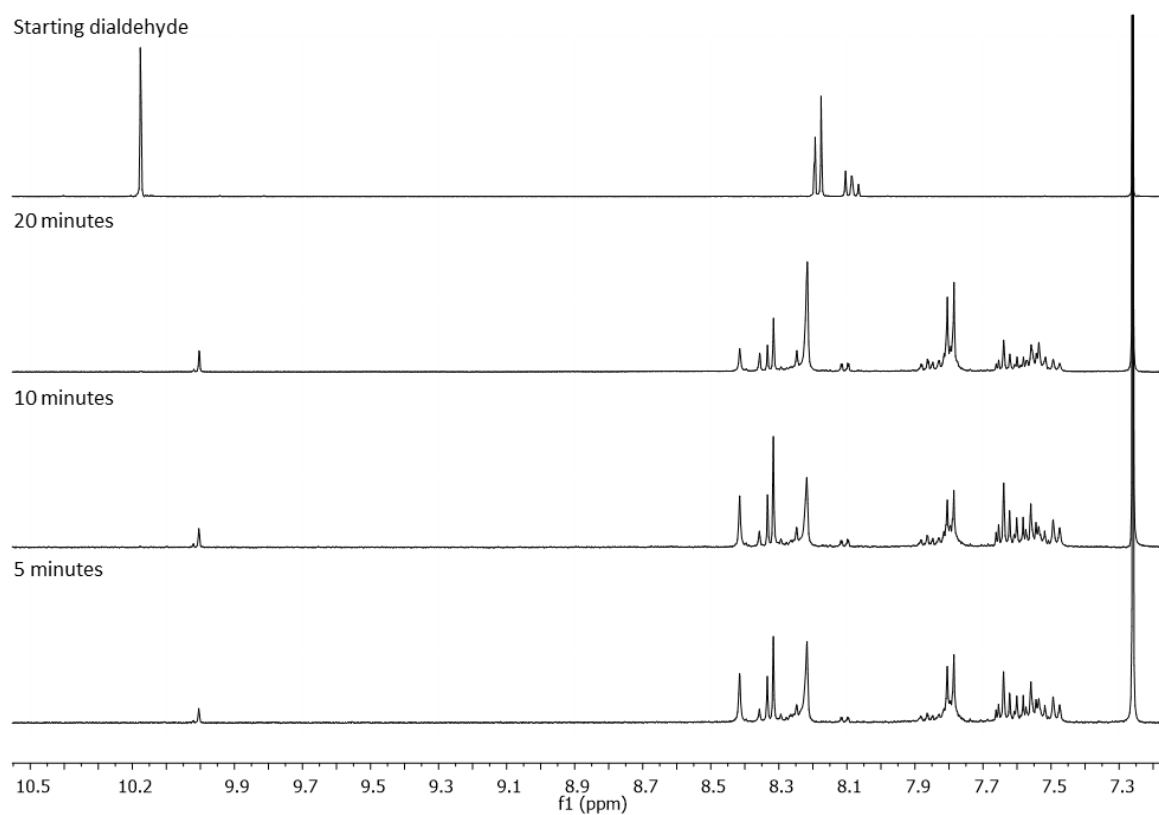
**Figure S23:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **5** at 20 minutes, showing the integrals as relative values for the [2+2] and [3+3] species, calibrated to 1H for the [2+2] imine peaks.

#### 4.5 NTP synthesis of macrocycle **6**

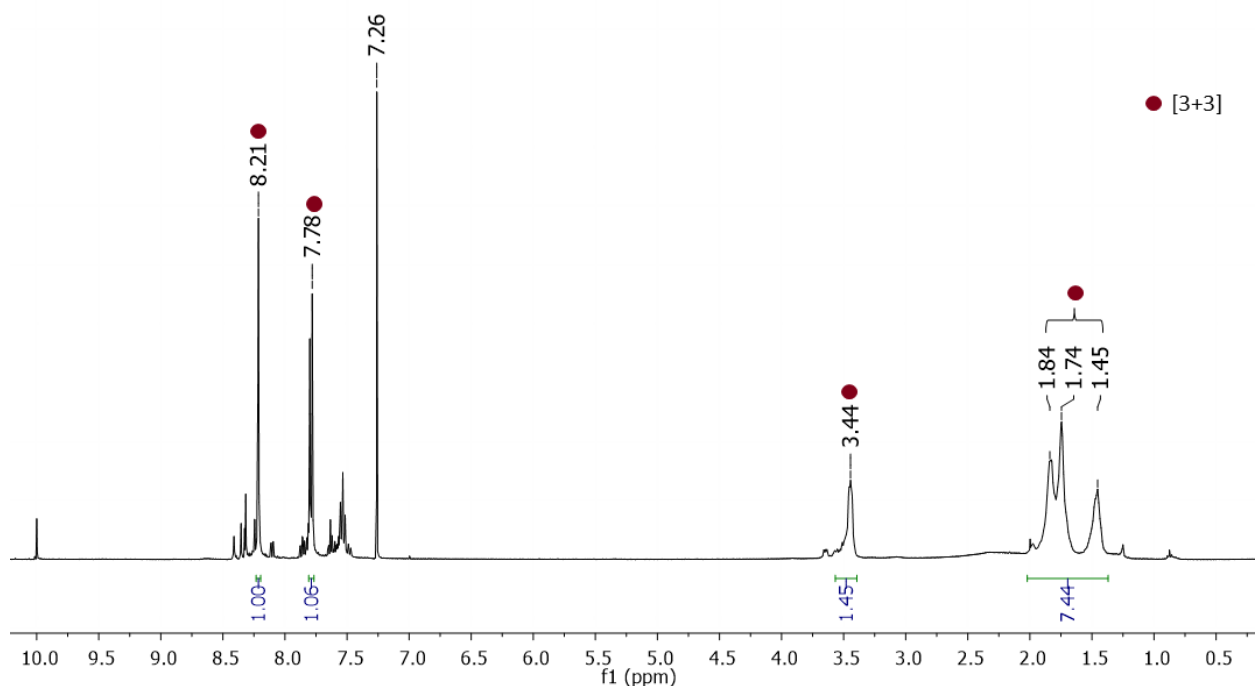


Pyridine-2,6-dicarbaldehyde (0.08 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (0.06 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 20 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR. After 20 minutes the reaction mixture was dried *in vacuo* to give a yellow solid (0.10 g, 90 %). No further purification was carried out.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (s, 1H), 7.78 (s, 1H), 3.45 (m, 1.45H), 1.84 – 1.45 (m, 7.44H). HRMS (ES+) Calc;  $[\text{M}+\text{H}]^+$  = 427.2632 [2+2], 640.3898 [3+3], 853.5164 [4+4]  $\text{m/z}^+$  found 640.3760 [3+3],  $[\text{M}+\text{H}]^+$ , 853.4786 [4+4],  $[\text{M}+\text{H}]^+$ . The data match those reported in the

literature for the [3+3] species,<sup>8</sup> however the other peaks present are not assigned in the literature – these could be alternative sized species, as suggested by mass spectroscopy data, or intermediates to the [3+3] macrocycle.

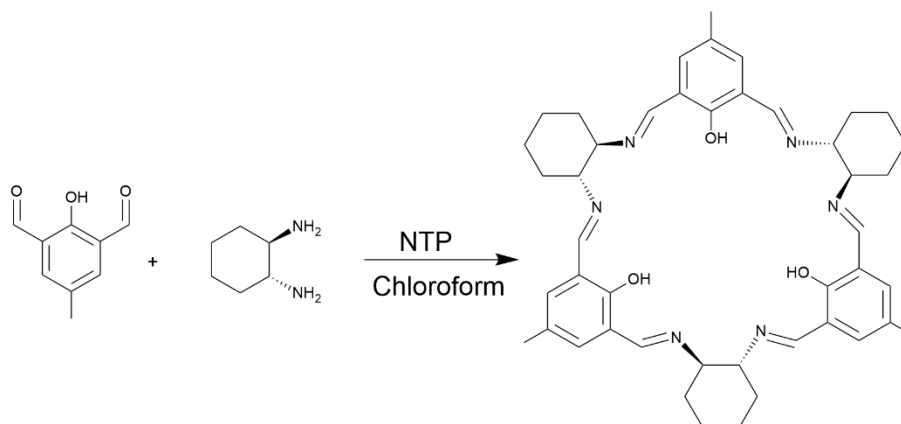


**Figure S24:** <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) of NTP synthesis of macrocycle **6** over 20 minutes (7.2 ppm – 10.1 ppm)

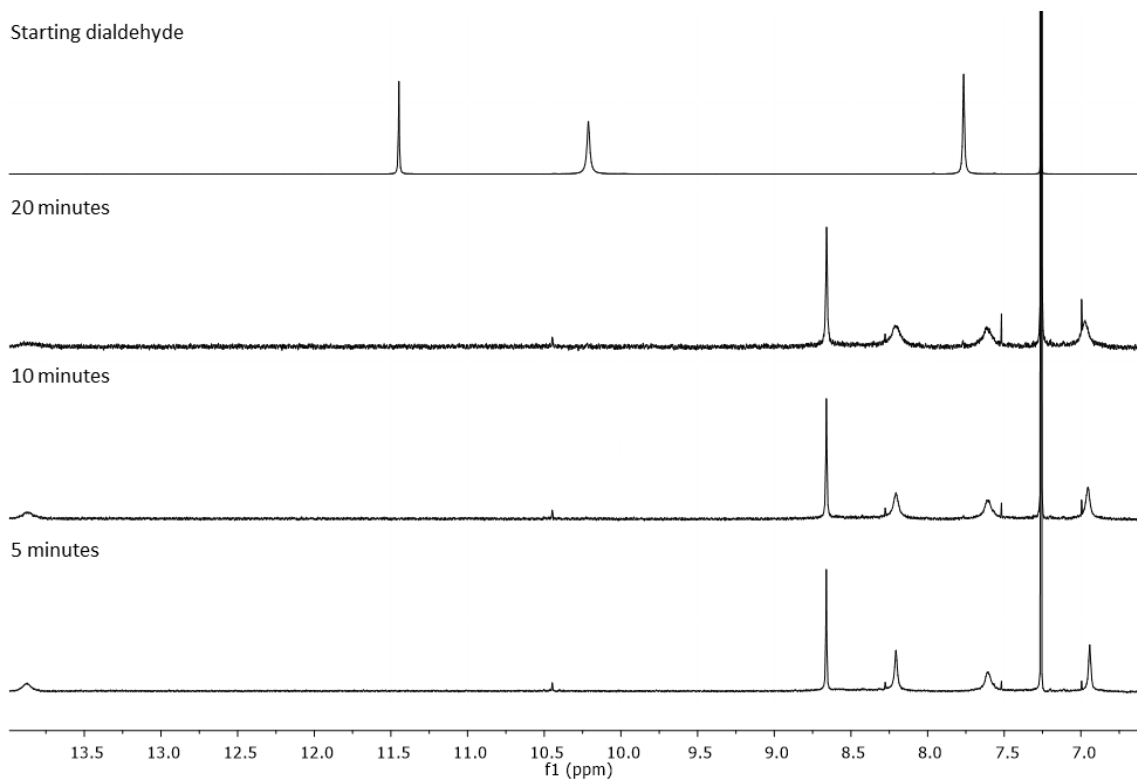


**Figure S25:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **6** at 20 minutes with the proton peaks corresponding to the [3+3] species reported in the literature labelled with a red circle.<sup>8</sup> The integration is not as expected but this is likely due to there being a mixture of different species present.

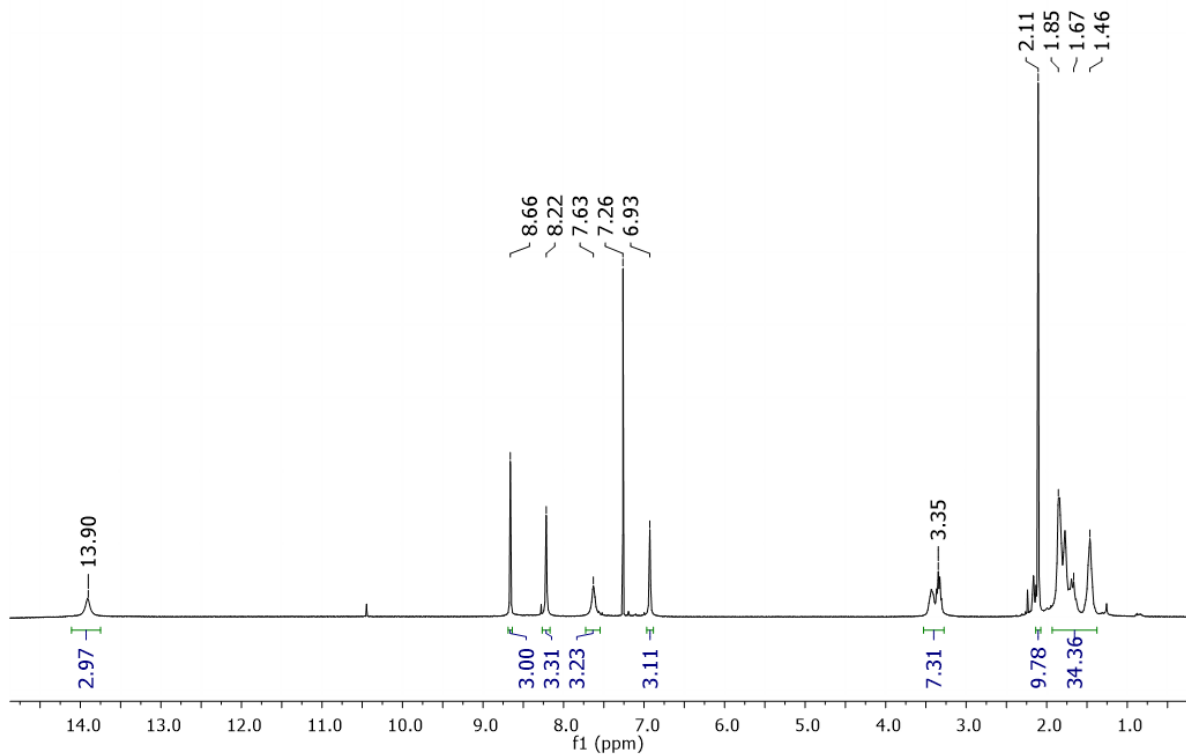
#### 4.6 NTP synthesis of macrocycle **7**



2,6-Diformyl-4-methyl-phenol (0.08 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane (0.06 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 20 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR. After 20 minutes the reaction mixture was dried *in vacuo* to give an orange solid (0.12 g, 94 %). No further purification was carried out.  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.90 (broad s, 2.97H), 8.66 (s, 3H), 8.22 (s, 3.31 H), 7.63 (broad s, 3.23), 6.93 (s, 3.11H), 3.35 (m, 3.35H), 2.11 (s, 9.78H), 1.85-1.46 (m, cyclo-hex, 34.36H). **HRMS** (ES+) Calc;  $[\text{M}+\text{H}]^+ = 727.4357$  [3+3]  $m/z^+$ , found 727.5530 [3+3],  $[\text{M}+\text{H}]^+$ . The data match those reported in the literature.<sup>9</sup>



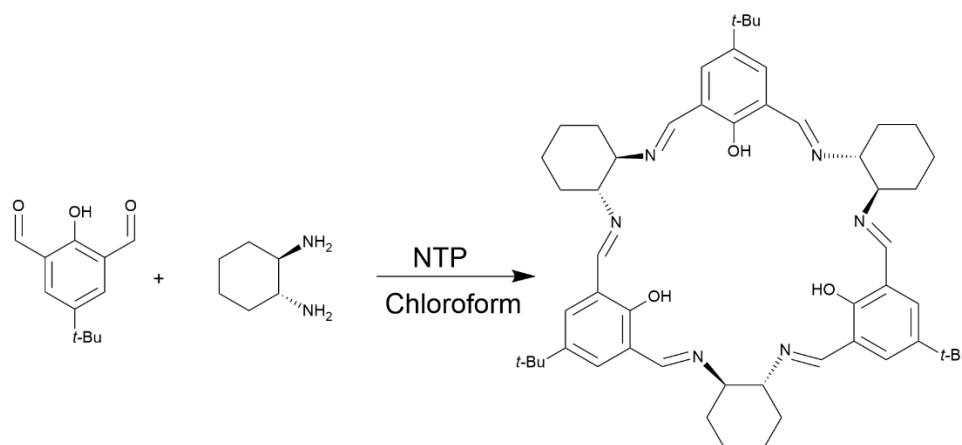
**Figure S26:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **7** over 20 minutes (7.0 ppm – 10.4 ppm).



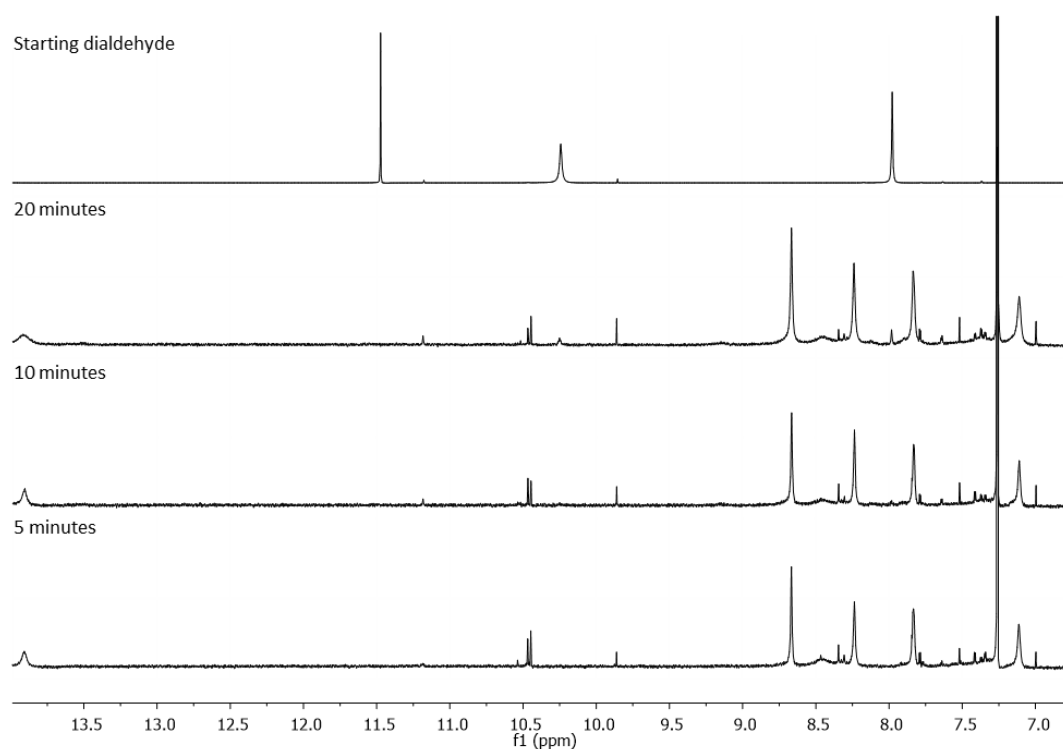
**Figure S27:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **7** after 20 minutes.



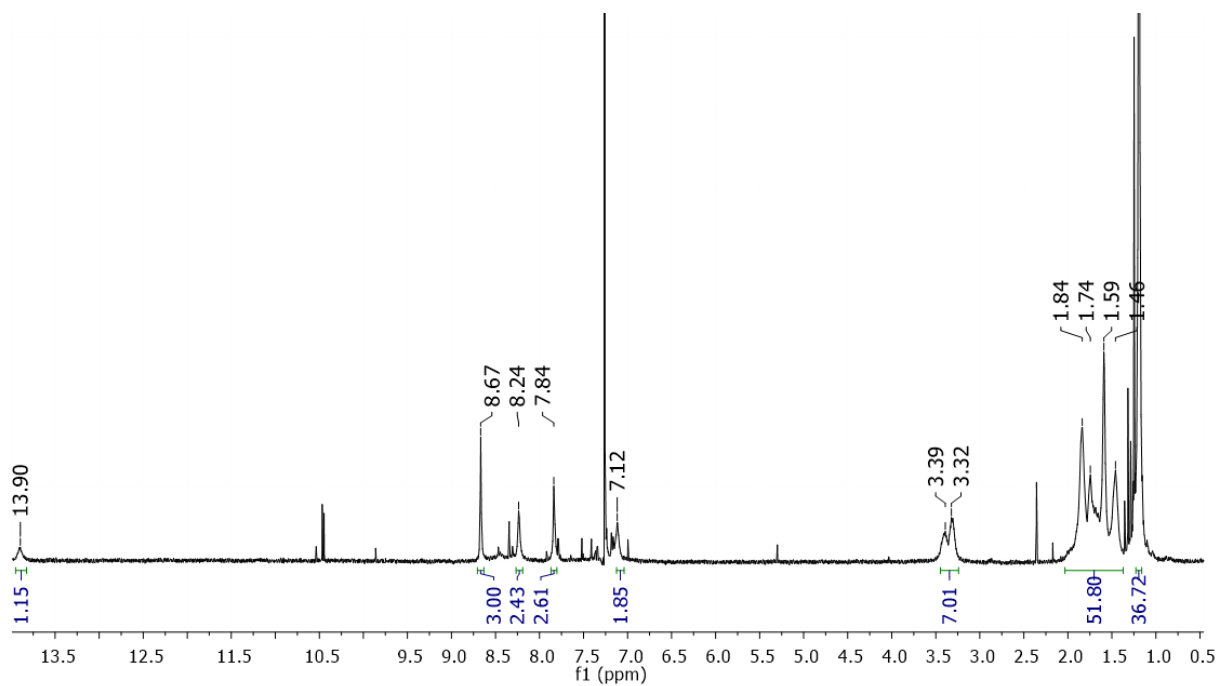
## 4.7 NTP synthesis of macrocycle **8**



4-tert-butyl-2,6-diformyl phenol (0.08 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen and transferred to the argon flushed RBF in the plasma set up. (1R,2R)-(-)-1,2-Diaminocyclohexane (0.06 g, 0.5 mmol, 1 eq) was dissolved in anhydrous chloroform (10 mL) under nitrogen in a separate flask. The NTP discharge was turned on and the amine was added dropwise using a syringe pump over a period of 3.5 minutes. The plasma discharge continued for 20 minutes, remaining in the contact with the reaction solution, and the reaction was monitored by  $^1\text{H}$  NMR. After 20 minutes the reaction mixture was dried *in vacuo* to give an orange solid (0.13 g, 91%). No further purification was carried out.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.90 (broad s, 1.15H), 8.67 (s, 3H), 8.24 (s, 2.43H), 7.84 (m, 2.61H), 7.12 (b, 1.85H) 3.39 - 3.32 (m, 7H), 1.84 - 1.46 (m, cyclo-hex, 51.80H) 1.19 (m, 36.72H). HRMS (ES+) Calc;  $[\text{M}+\text{H}]^+ = 853.5766$  [3+3],  $m/z^+$  found = 853.5503 [3+3],  $[\text{M}+\text{H}]^+$ . The data match those reported in the literature.<sup>10</sup>



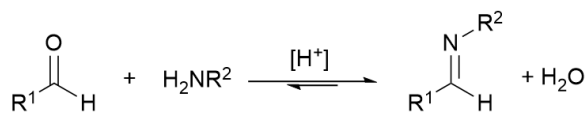
**Figure S28:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **8** over 20 minutes (6.9 ppm – 10.5 ppm)



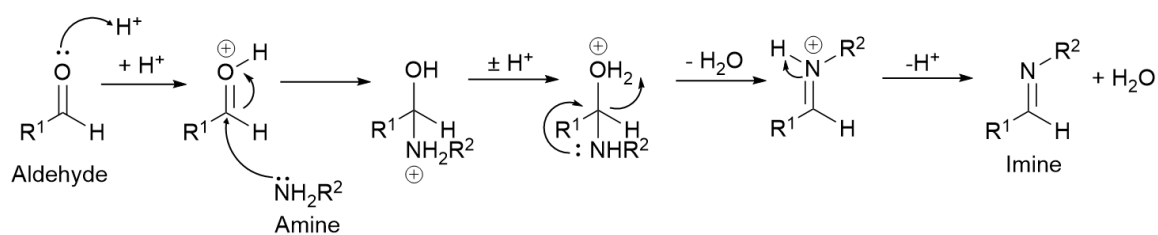
**Figure S29:**  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) of NTP synthesis of macrocycle **8** at 20 minutes.

## 5. Mechanism

Overall Reaction Scheme:



Imine Condensation Mechanism:



**Figure S30:** Scheme of imine formation

## 5. References

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