Electronic Supplementary Information

Exploring *Gem*-Dimethyl Effect in the Formation of Imine-Based Macrocycles and Cages

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General Methods

Unless otherwise stated, all the chemicals and reagents were obtained commercially. Compounds **1**[1a], **2b**[1b], **2c**[1c] **and 8**[1d] were synthesized as per the reported procedures. Dry solvents were prepared by the standard procedures. Analytical thin layer chromatography was done on pre-coated silica gel plates (Kieselgel $60F_{254}$, Merck). Column chromatographic purifications were done with 100-200 mesh silica gel. NMR spectra were recorded in $CDCl_3$ on AV 200 MHz, AV 400 MHz or AV 500 MHz spectrometers. All chemical shifts are reported in δ ppm downfield to TMS and peak multiplicities as singlet (s), doublet (d), triplet (t), quartet (q), broad singlet (bs), and multiplet (m). Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd., Germany). IR spectra were recorded using $CHCl_3$ or Nujol on Bruker-FTIR spectrophotometer. Melting points were determined on a Buchi Melting Point B-540. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. MALDI-TOF/TOF mass spectra were obtained from ABSCIEX TOF/TOF™ 5800 mass spectrometer. Thermogravimetric analysis was carried out on NETSZCH TGA-DSC or METTLER TOLEDO, TGA/SDTA851e. The routine TGAs were done under N_2 gas flow (20ml or 50 ml/min) (purge + protective).

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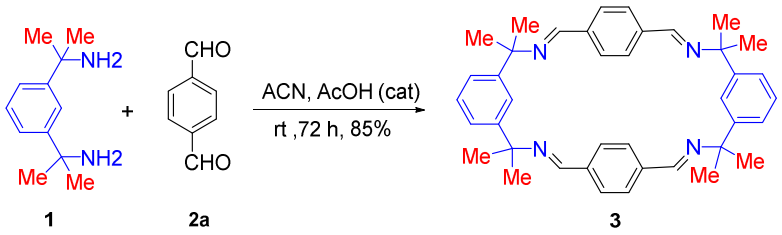
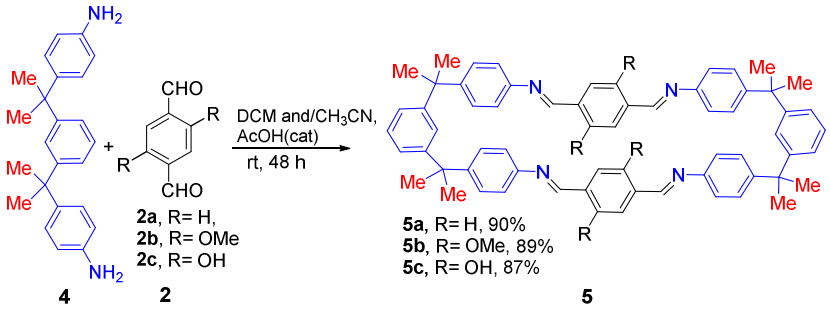
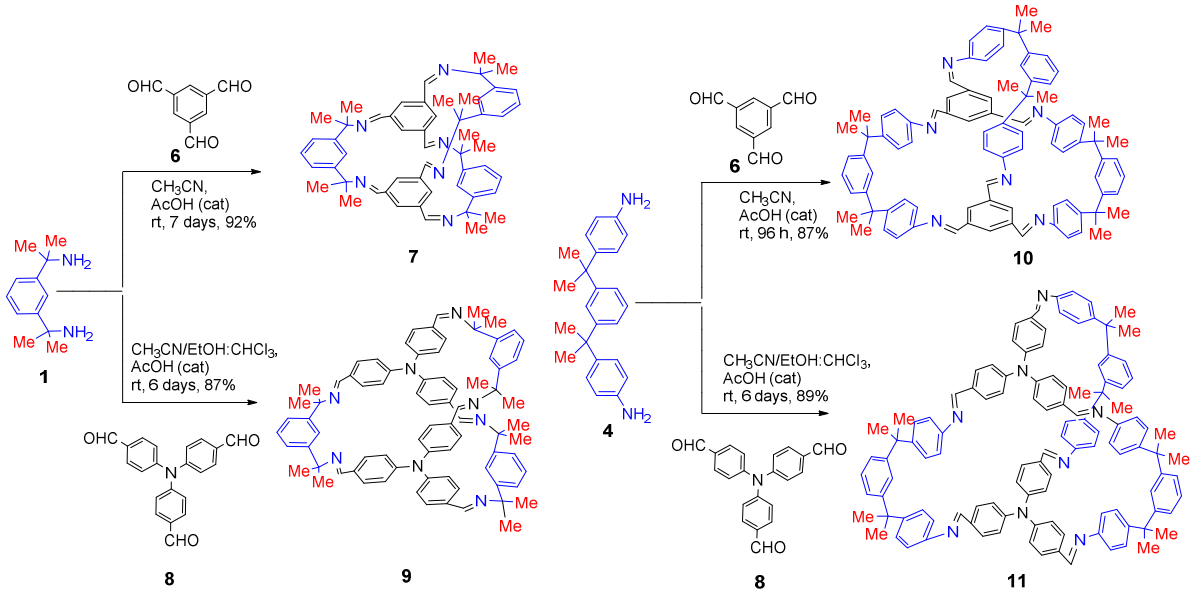


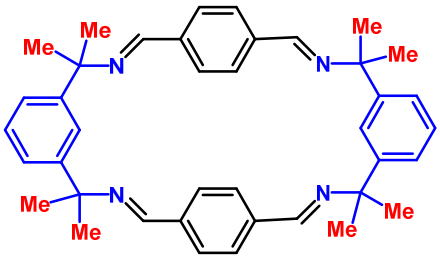
Scheme 1: Synthesis of macrocycle **3** using *gem*-dimethylamine **1**.



Scheme 2: Synthesis of macrocycles **5a-c** using *gem*-dimethylamine **4**.

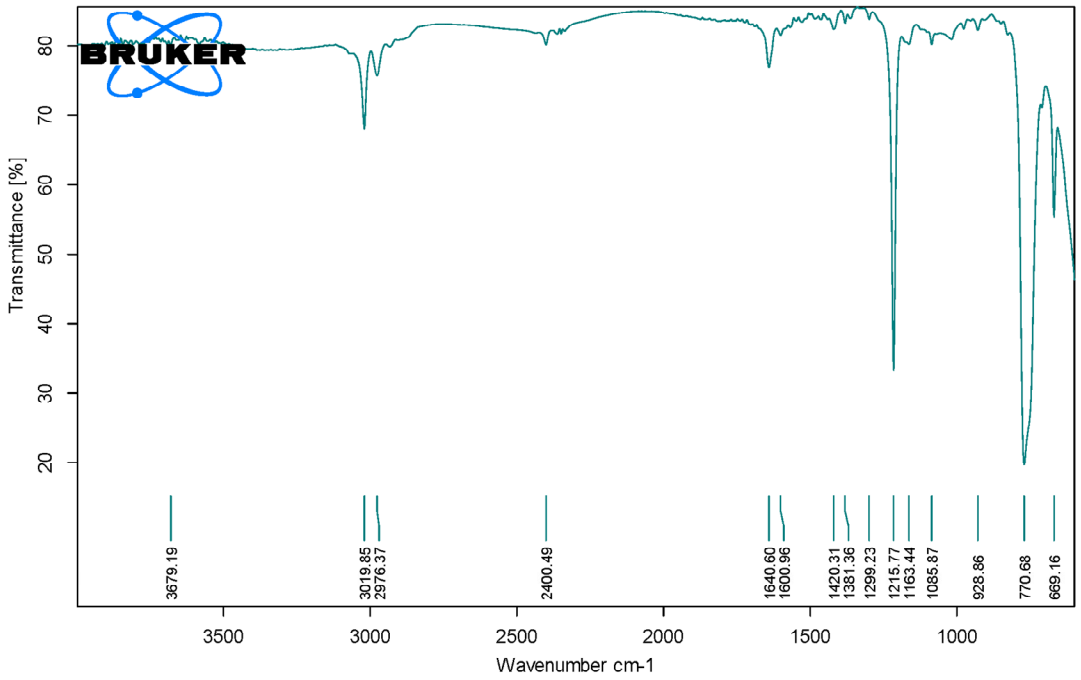


Scheme 3: Synthesis of cages **7**, **9** and **10** and **11** using *gem*-dimethylamines **1** and **4**.

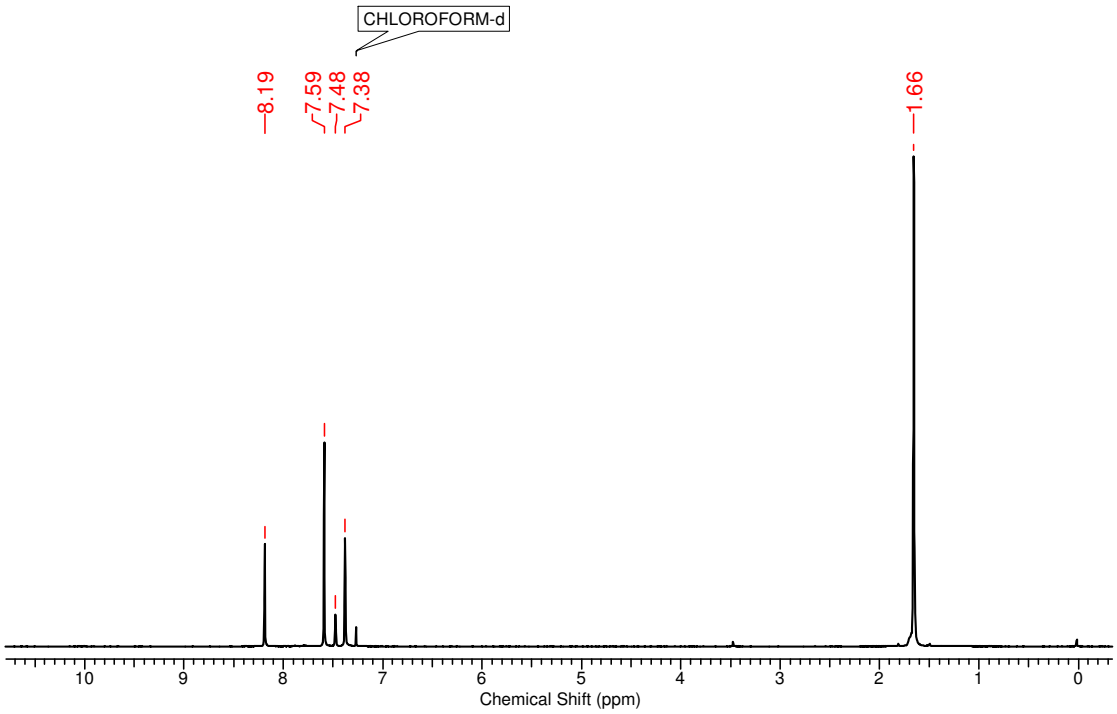


Macrocycle 3.

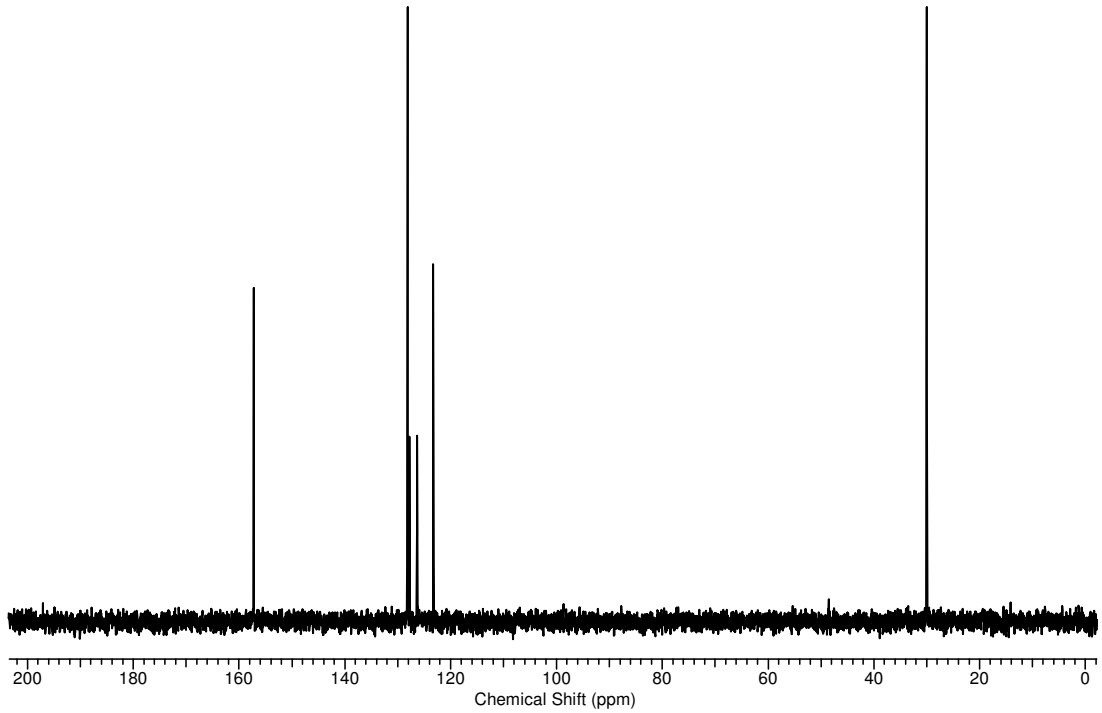
Method A (*under dilute condition*): A solution of **2a** (0.03 g, 0.22 mmol) in acetonitrile (ACN, 6 mL) was added slowly to a solution of **1** (0.043 g, 0.22 mmol) in ACN (6 mL) at room temperature. After complete addition of **2a**, a catalytic amount of acetic acid (20 µl) was added and the reaction mixture was kept undisturbed at ambient temperature for 72 h to get colourless crystals. The crystals were filtered and then washed with ACN. The crystal suitable for X-ray crystallography was removed directly from the sample vial to obtain crystal structure of the macrocycle **3**. Yield: 0.055 g, 85%; m.p: 233-235 °C; IR ($CHCl_3$) *v* (cm^{-1}): 3019 (m), 2976 (m), 1640 (CH=N), 1600 (Ar, C=C) (m), 1215; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 4H), 7.59 (s, 8H), 7.48 (s, 2H), 7.38 (s, 6H), 1.66 (s, 24H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.2, 148.1, 138.3, 128.0, 127.7, 126.3, 123.2, 63.0, 29.9; HRMS (*m/z*): calcd for $C_{40}H_{45}N_4$ $[M+H]^+$ 581.3639, found 581.3627.



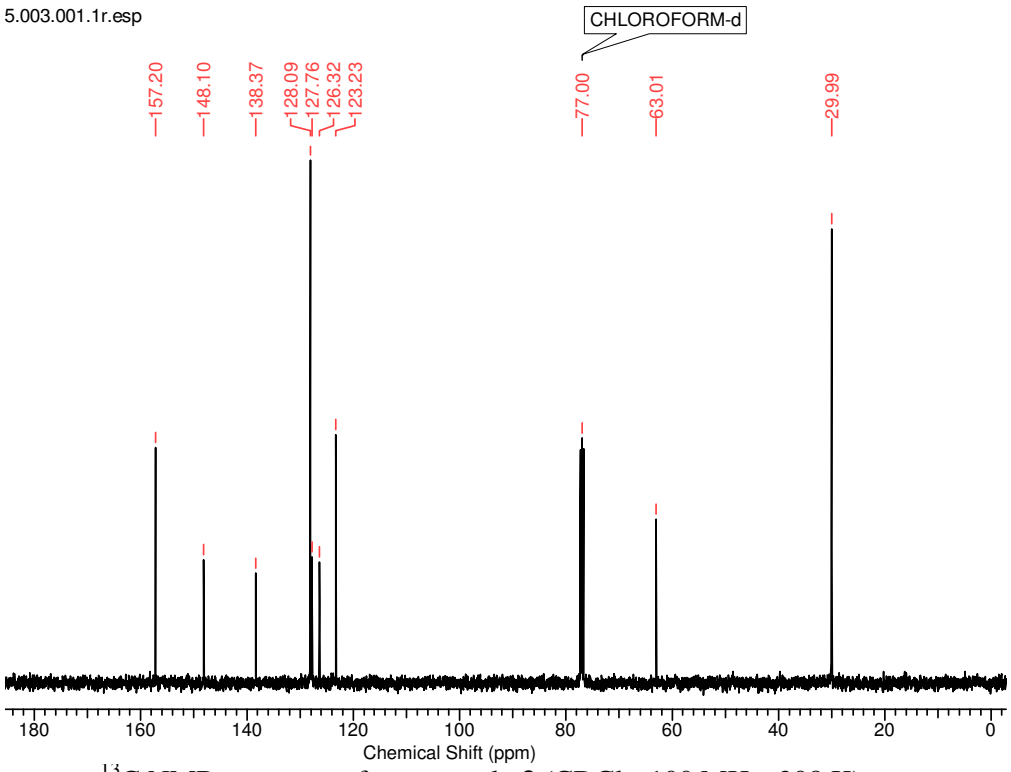
IR spectrum of macrocycle **3**



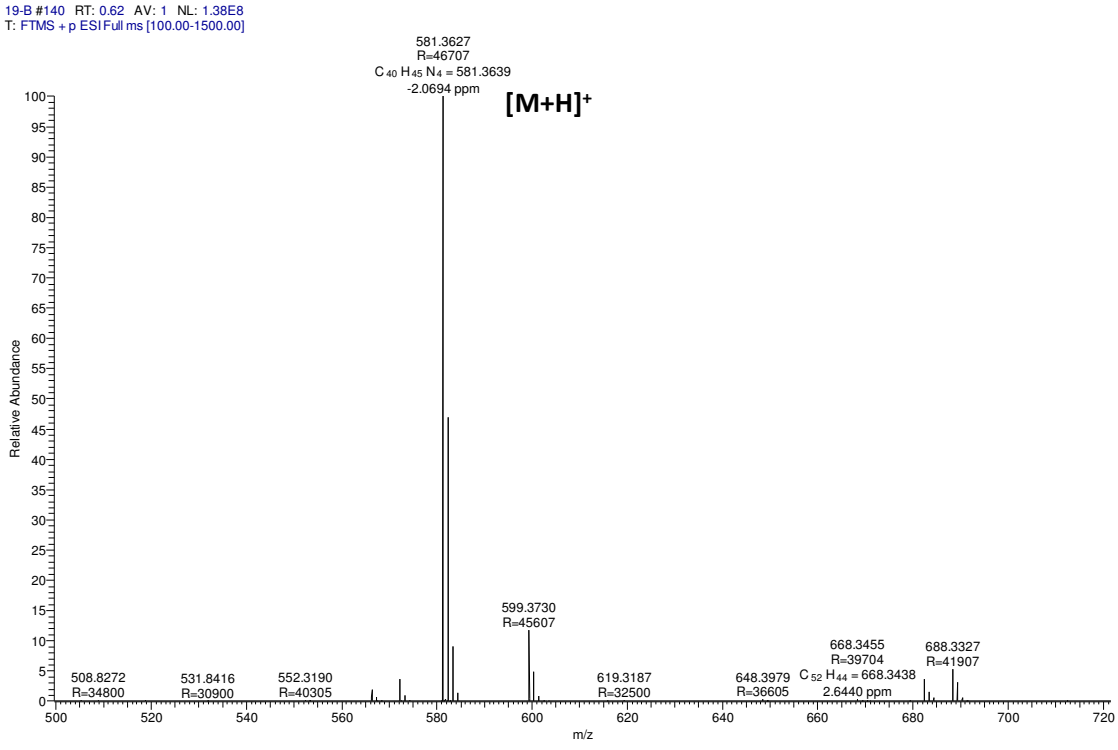
^{1}H NMR spectrum of macrocycle **3** ($CDCl_3$, 400 MHz, 298 K)



DEPT 135 spectrum of macrocycle **3** ($CDCl_3$, 100 MHz, 298 K)

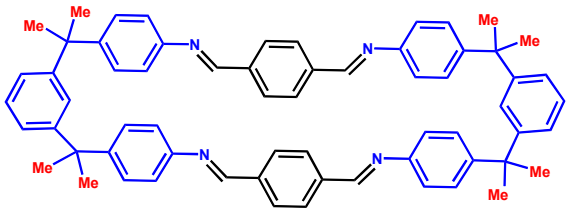


^{13}C NMR spectrum of macrocycle **3** ($CDCl_3$, 100 MHz, 298 K)

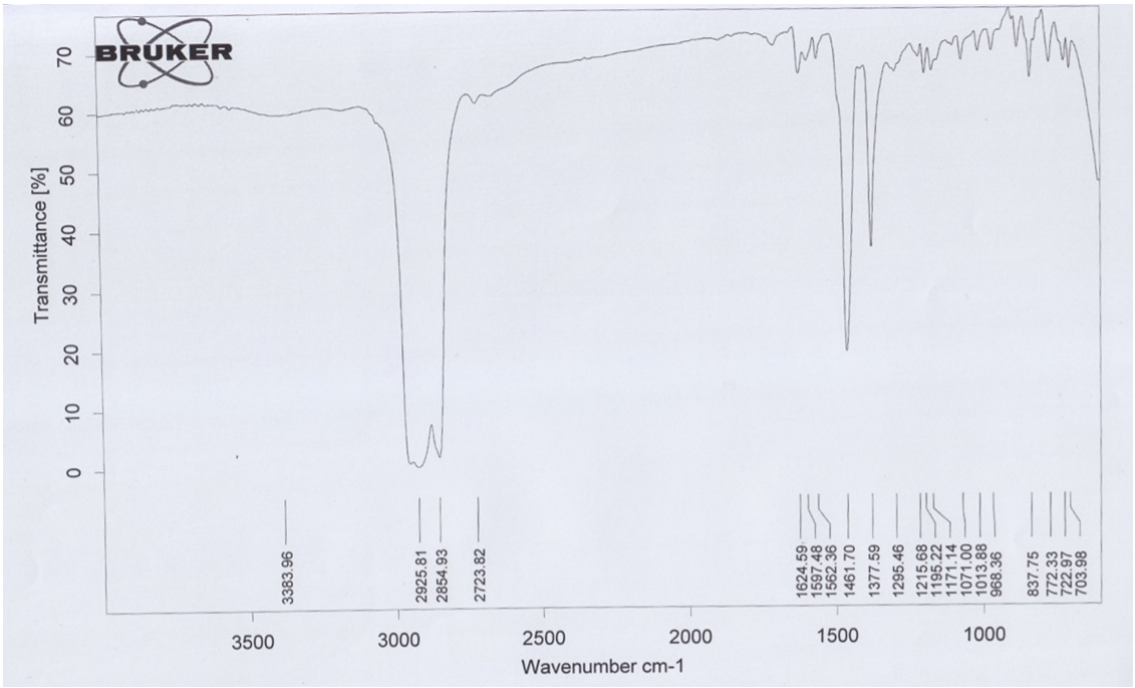


MS (HRMS) of macrocycle **3**

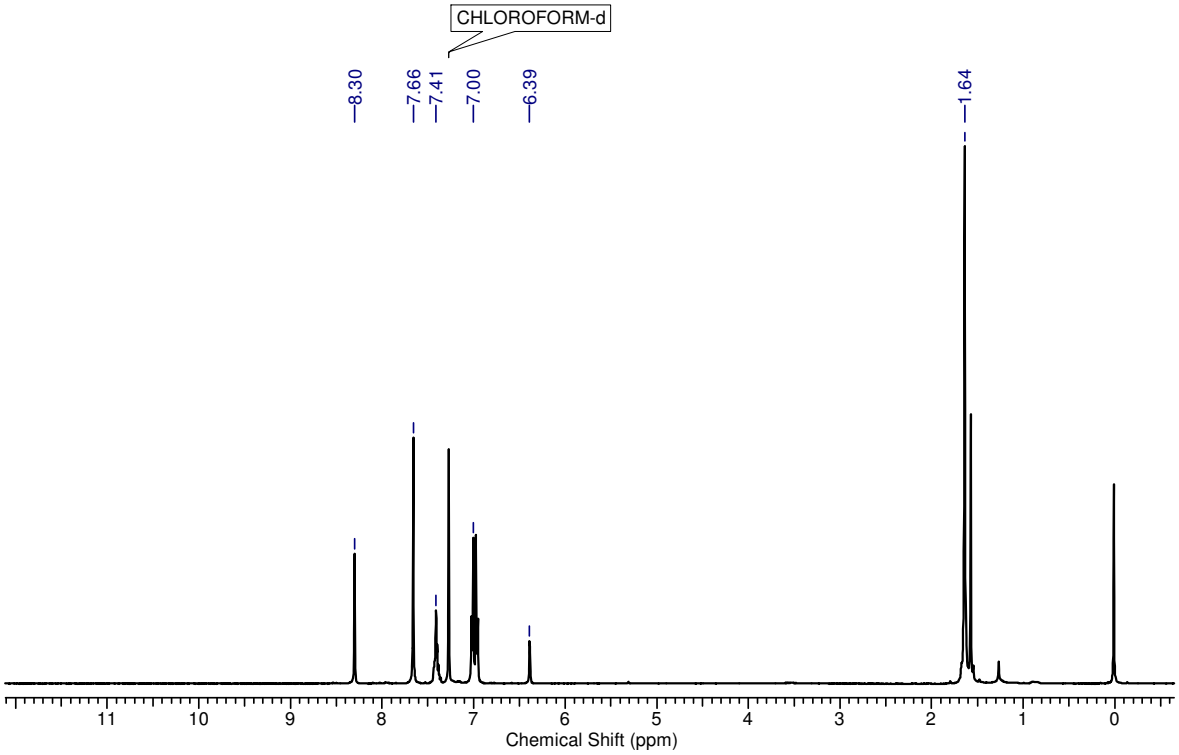
Macrocycle 5a.



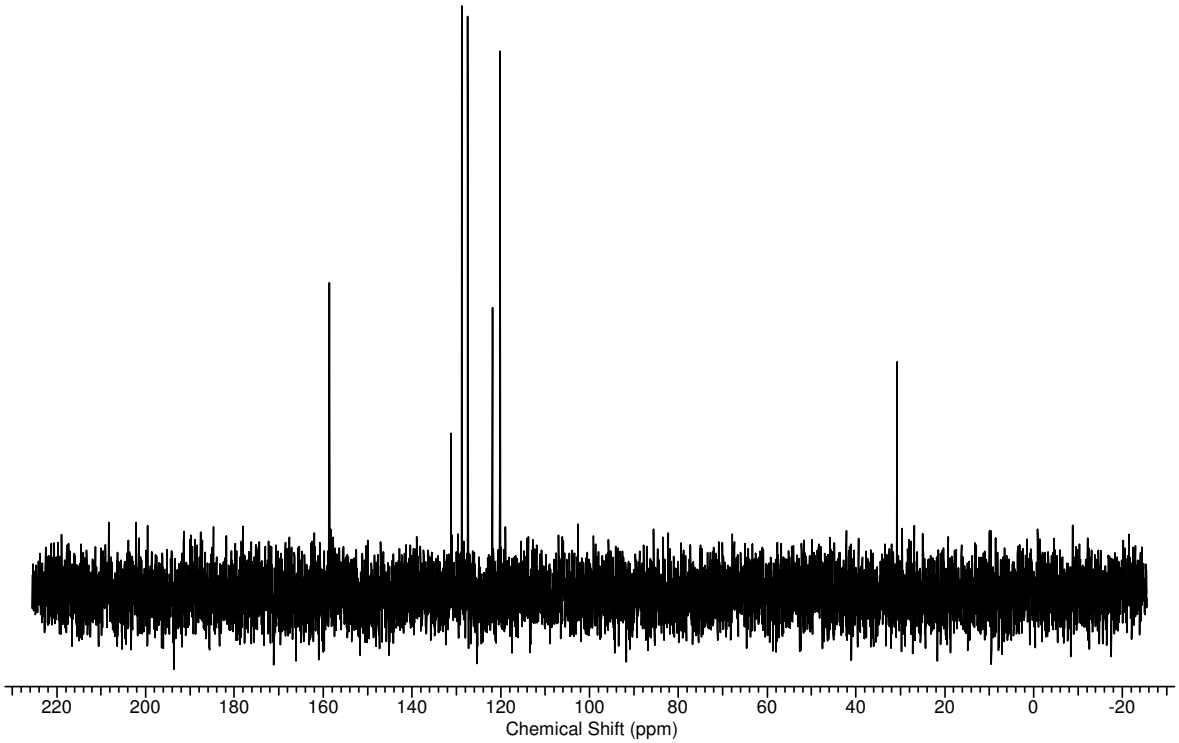
A solution of **2a** (0.015 g, 0.111 mmol) in DCM (7 mL) was added drop wise to a solution of **4** (0.038 g, 0.111 mmol) taken in a 20 mL glass vial containing DCM (7 mL). After complete addition of **2a**, a catalytic amount of acetic acid (20 µl) was added and the reaction mixture was kept undisturbed at room temperature for 48 h to get a yellow coloured solution having some crystals. Then, the reaction mixture was concentrated *in vacuo* then the residue obtained was directly recrystallised from hot *o*-dichlorobenzene (3mL) to give pale yellow crystals. The crystals were filtered and washed with diethyl ether. Yield: 0.045 g, (90%); m.p: 294 °C; IR (Nujol, ν (cm^{-1}) 2854, 1624 (CH=N), 1597 (Ar, C=C), 1377; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.30 (s, 4H), 7.66 (s, 8H), 7.45-7.36 (m, 6H), 7.04-6.93 (m, 16H), 6.39 (s, 2H), 1.64 (s, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 158.6, 150.3, 148.9, 131.2, 128.8, 127.4, 121.8, 120.1, 42.8, 30.7; MALDI-MS (*m/z*): calcd for $C_{64}H_{61}N_4$ $[M+H]^+$ 885.4896, found 885.7652.



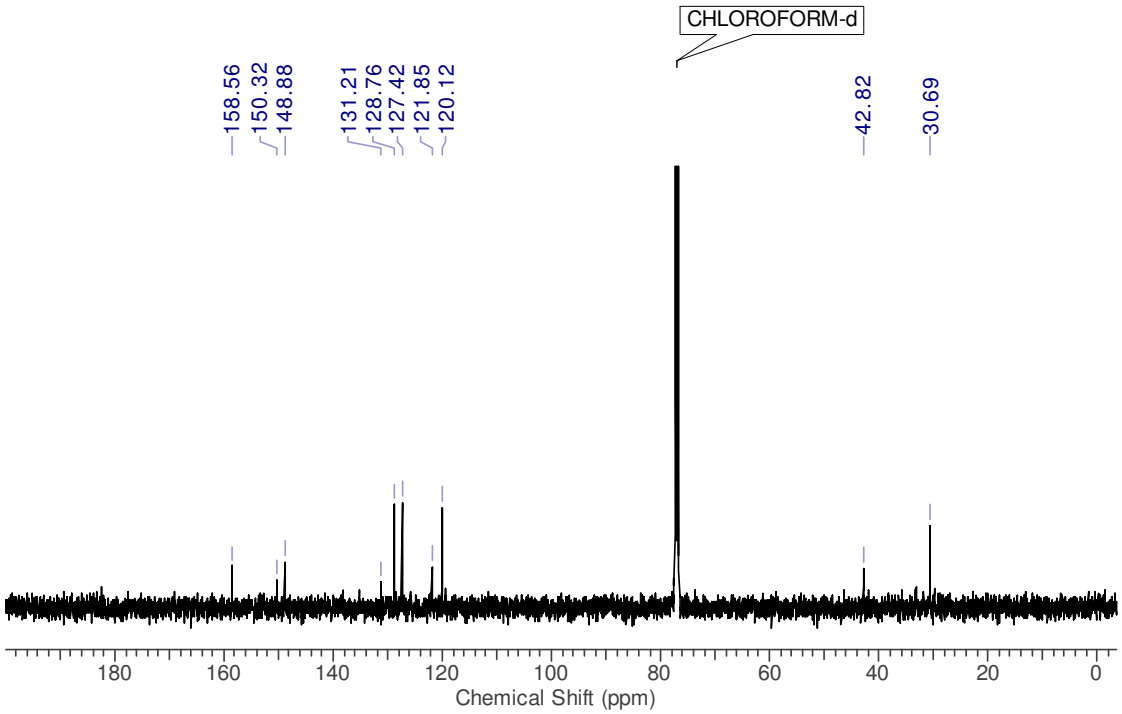
IR spectrum of macrocycle **5a**



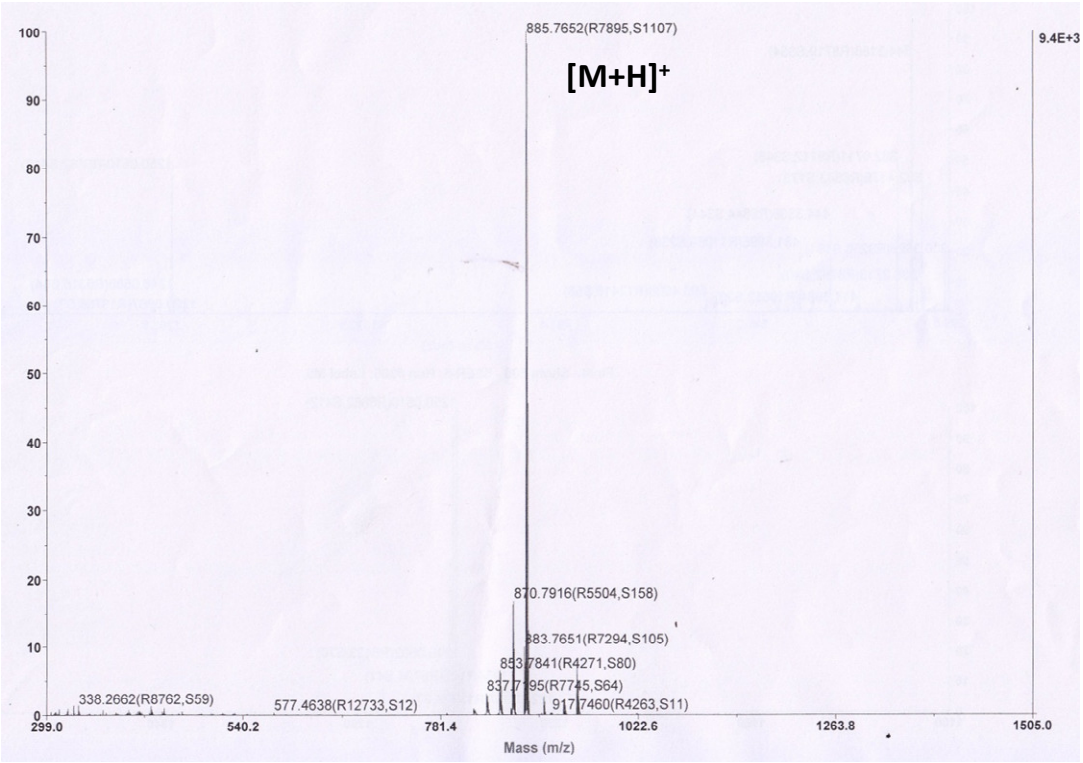
^{1}H NMR spectrum of macrocycle **5a** ($CDCl_3$, 400 MHz, 298 K)



DEPT 135 spectrum of macrocycle **5a** ($CDCl_3$, 100 MHz, 298 K). *Note*: Concentrated NMR sample could not be obtained owing to the poor solubility of **5a** in $CDCl_3$.

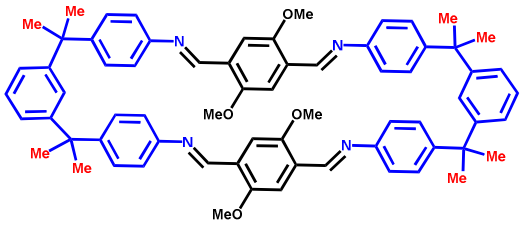


^{13}C NMR spectrum of macrocycle **5a** ($CDCl_3$, 100 MHz, 298 K). *Note:* Concentrated NMR sample could not be obtained owing to the poor solubility of **5a** in $CDCl_3$.

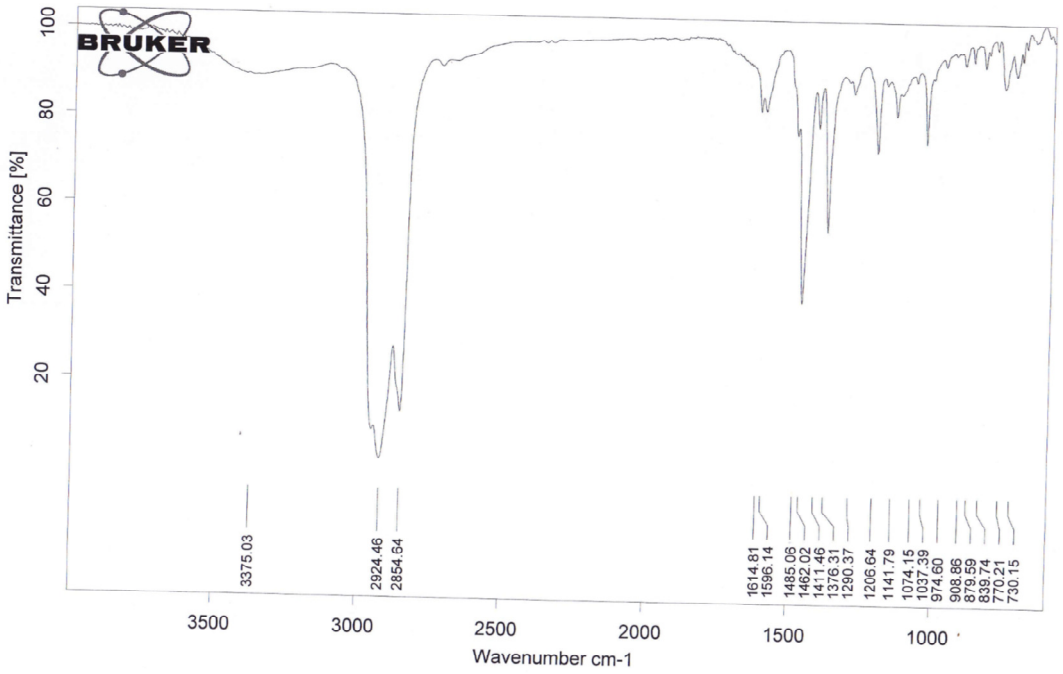


MALDI- MS of macrocycle **5a**

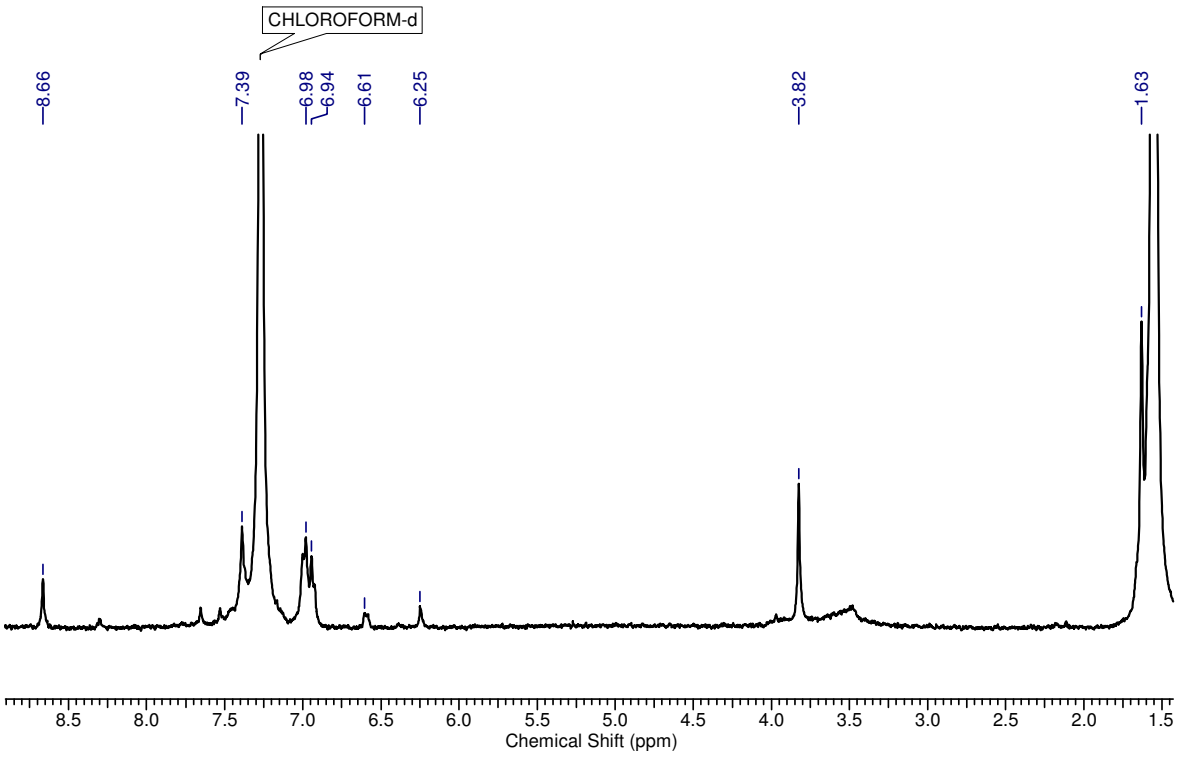
Macrocycle 5b.



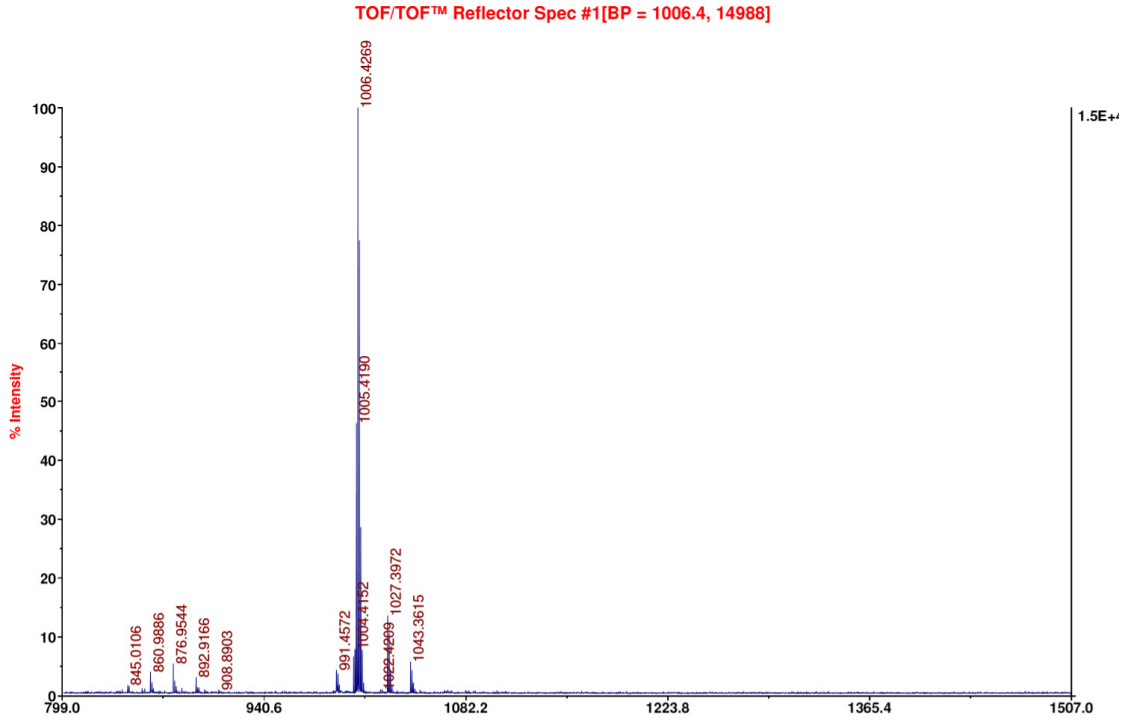
A solution of 1,5-dimethoxyterephthalaldehyde (**2b**, 10 mg, 0.051mmol) in ACN (2 mL) was added drop wise to a solution of *gem*-dimethylamine (**4**, 20 mg, 0.051 mmol) taken in a 4 mL glass vial containing DCM (2 mL). After complete addition of **2b**, a catalytic amount of acetic acid (5 µl) was added and the reaction mixture was kept undisturbed at room temperature for 48 h to get a yellow coloured solution having some crystals. Then, the reaction mixture was concentrated *in vacuo* then the residue obtained was directly recrystallised from hot *o*-dichlorobenzene (2mL) to give yellow coloured-needle shaped crystals. The crystals were filtered and washed with DCM. Yield: 0.023 g, (89%); m.p: >350 $^{\circ}$C; IR (Nujol, ν (cm^{-1}) 1624, 1596, 1485; Due to solubility issue, we could not obtain clear ^{1}H NMR and ^{13}C NMR of **5b**, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.66 (s, CH=N, 4H), 7.39-6.25 (Ar, 28H), 3.82 (br. s, OCH_3, 12H), 1.63 (br. s,CH_3 36H); MALDI- MS (*m/z*): $[M+H]^+$ 1005.4190.



IR spectrum of macrocycle **5b**

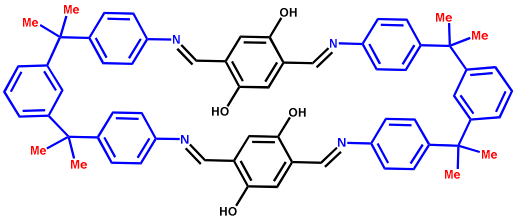


^{1}H NMR spectrum of macrocycle **5b** ($CDCl_3$, 400 MHz, 298 K). *Note:* Good quality NMR spectra could not be obtained owing to the poor solubility of **5b** in $CDCl_3$. The peak at δ=1.5 corresponds to $CDCl_3$-water.

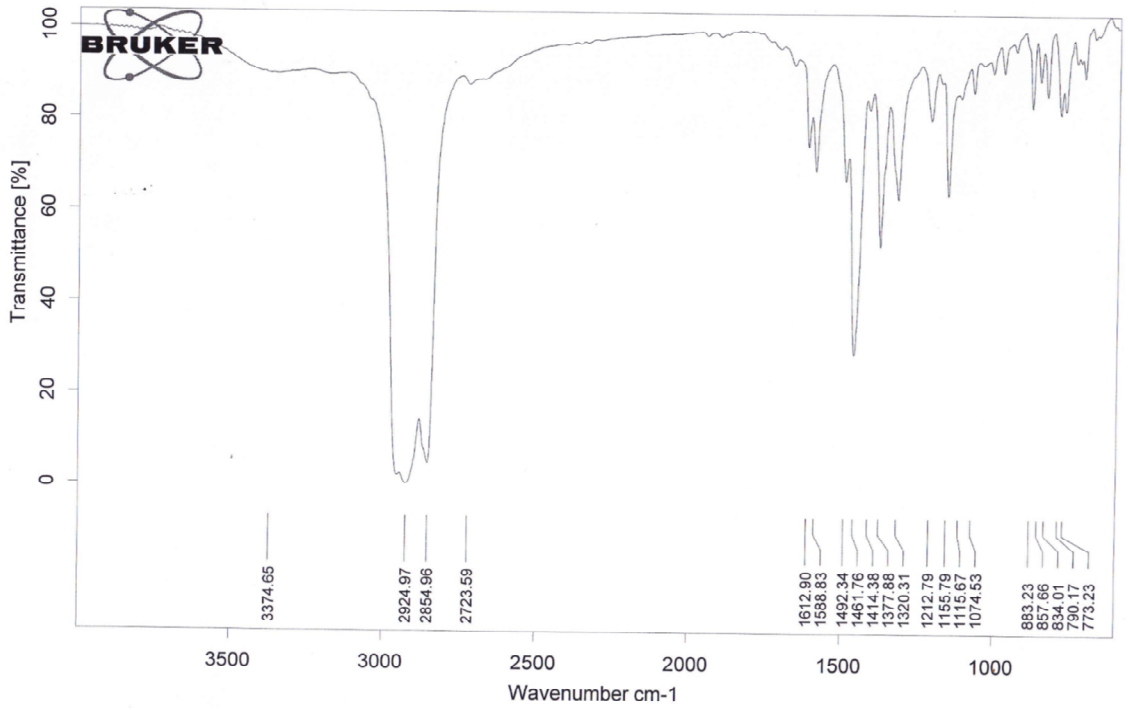


MALDI- MS of macrocycle **5b**

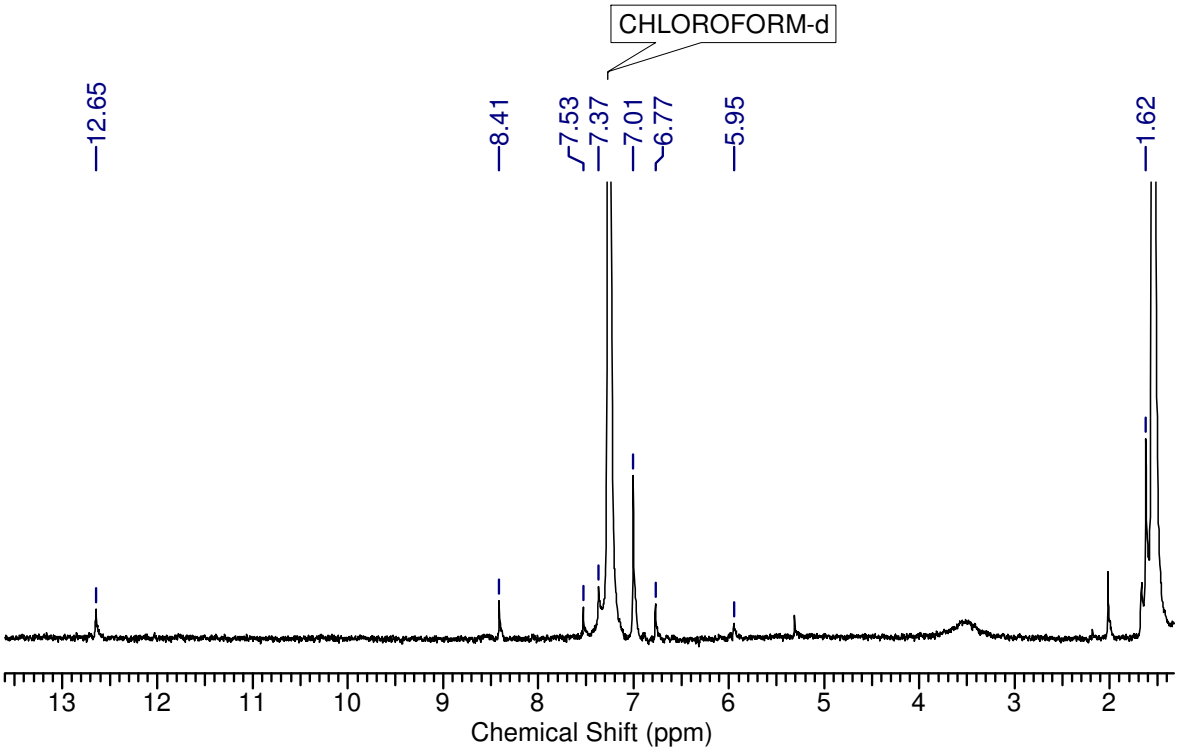
Macrocycle 5c.



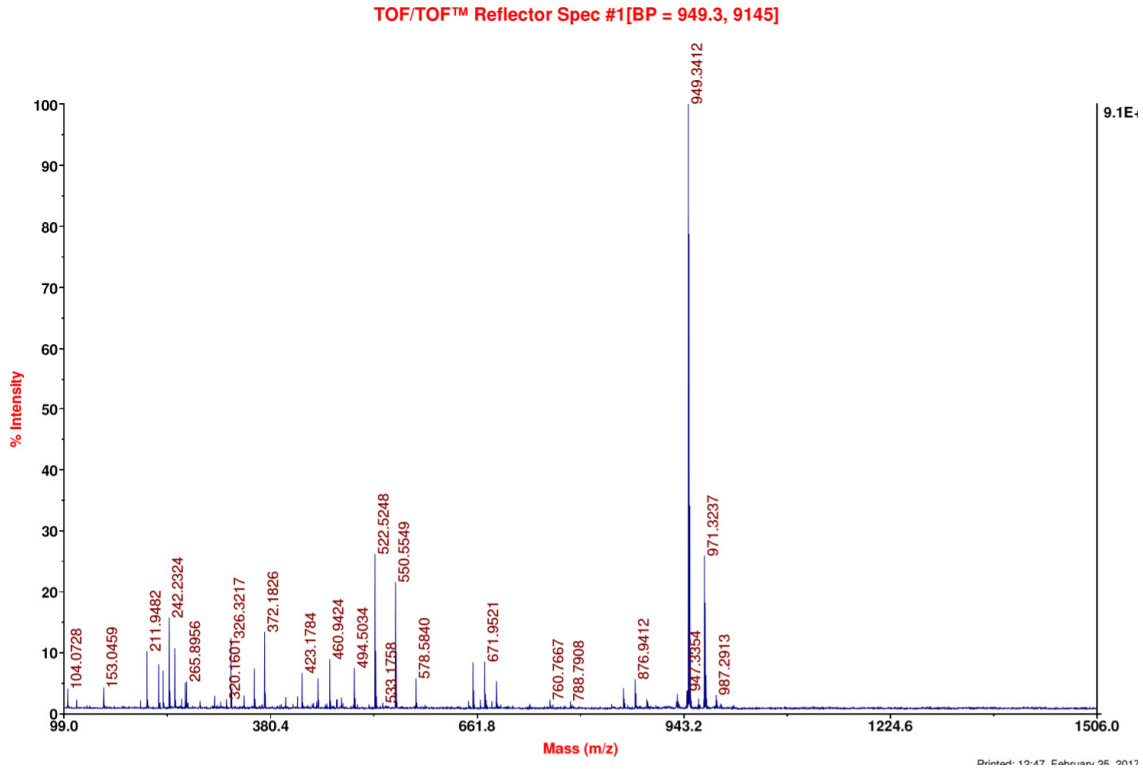
The synthesis of **5c** was carried out by utilizing the same procedure of **5b**. *Gem*-dimethylamine **4** (20 mg, 0.060 mmol), 2,5-dihydroxyterephthalaldehyde (**2c**, 10 mg, 0.06mmol), DCM (2 mL), ACN (2 mL), acetic acid (5 µl). Orange coloured-needle shaped crystals. Yield: 0.025 g, (87%); m.p: >410 $^{\circ}$C; IR (Nujol, ν (cm^{-1}):1612, 1588, 1492; Due to solubility issue, we could not obtain clear ^{1}H NMR and ^{13}C NMR of **5c**, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.65 (s, 4H), 8.41(s, CH=N, 4H), 7.54-5.9 (Ar, 28H), 1.62 (s, 36H); MALDI- MS (*m/z)*: $[M+H]^+$ is 949.34.



IR spectrum of macrocycle **5c**

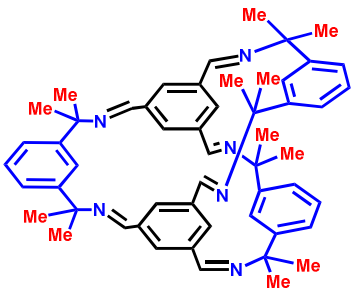


^{1}H NMR spectrum of macrocycle **5c** ($CDCl_3$, 400 MHz, 298 K). *Note:* Good quality NMR spectra could not be obtained owing to the poor solubility of **5b** in $CDCl_3$. The solvent impurity peaks at δ= 5.3 and δ=1.5 correspond to DCM and $CDCl_3$–water, respectively.

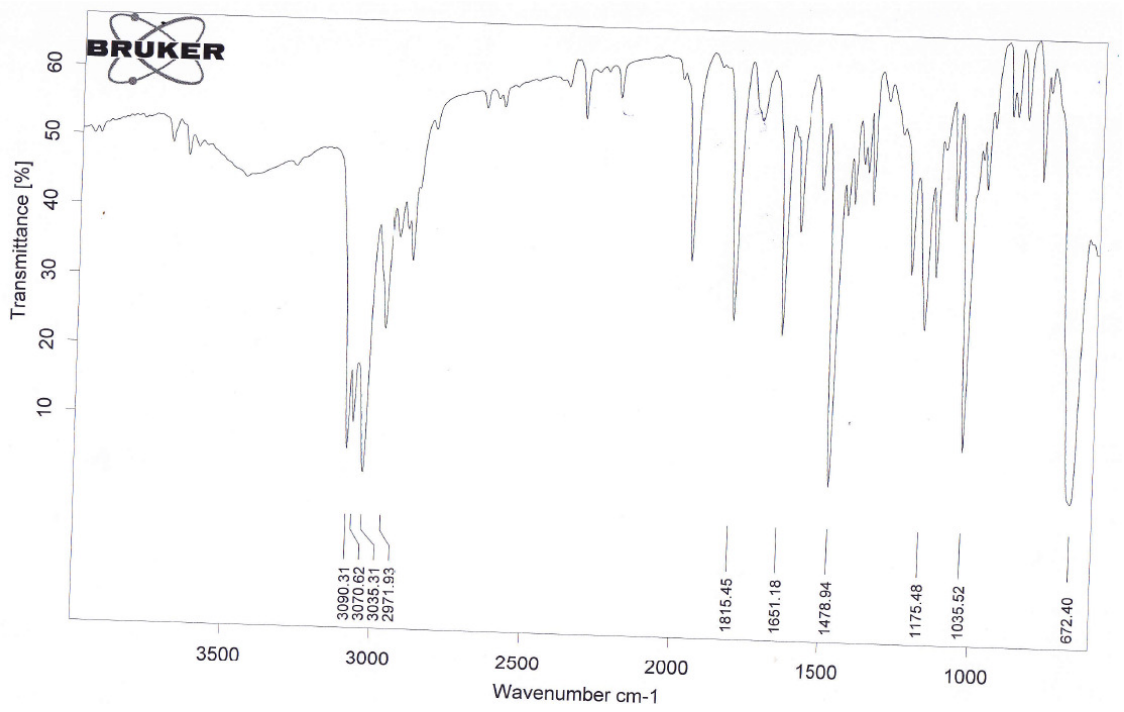


MALDI- MS of macrocycle **5c**

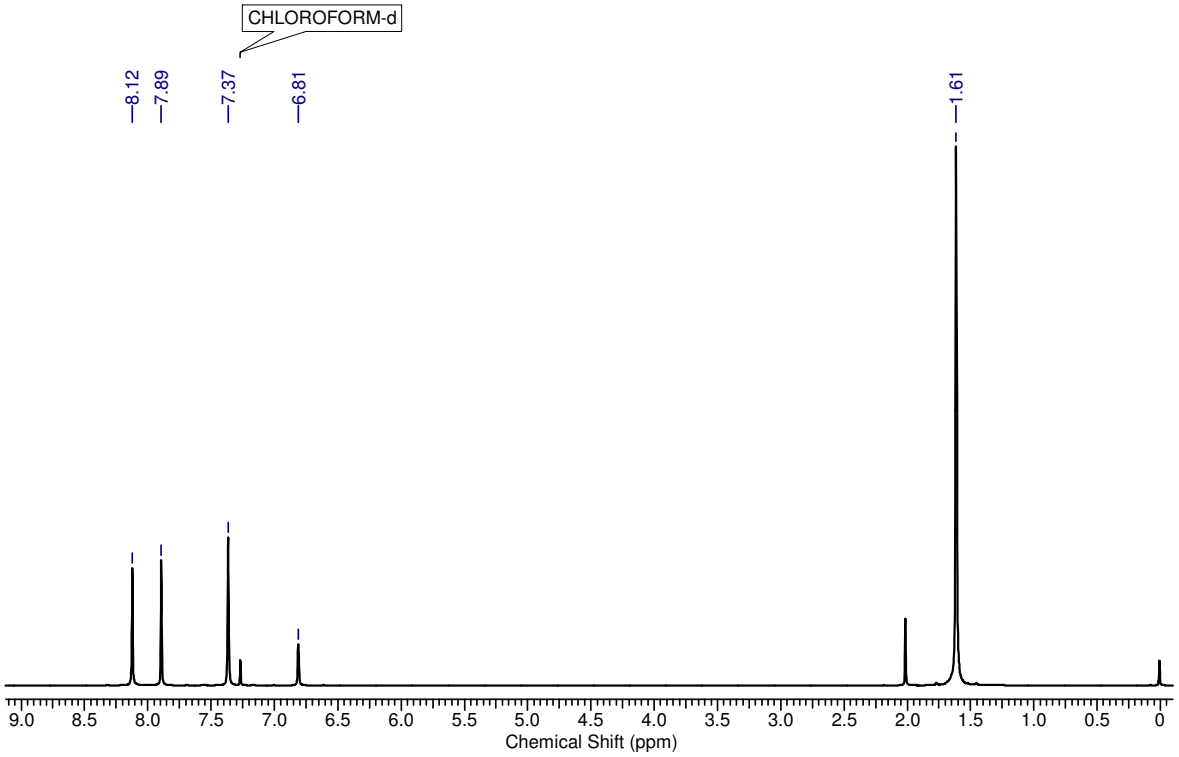
Cage 7.



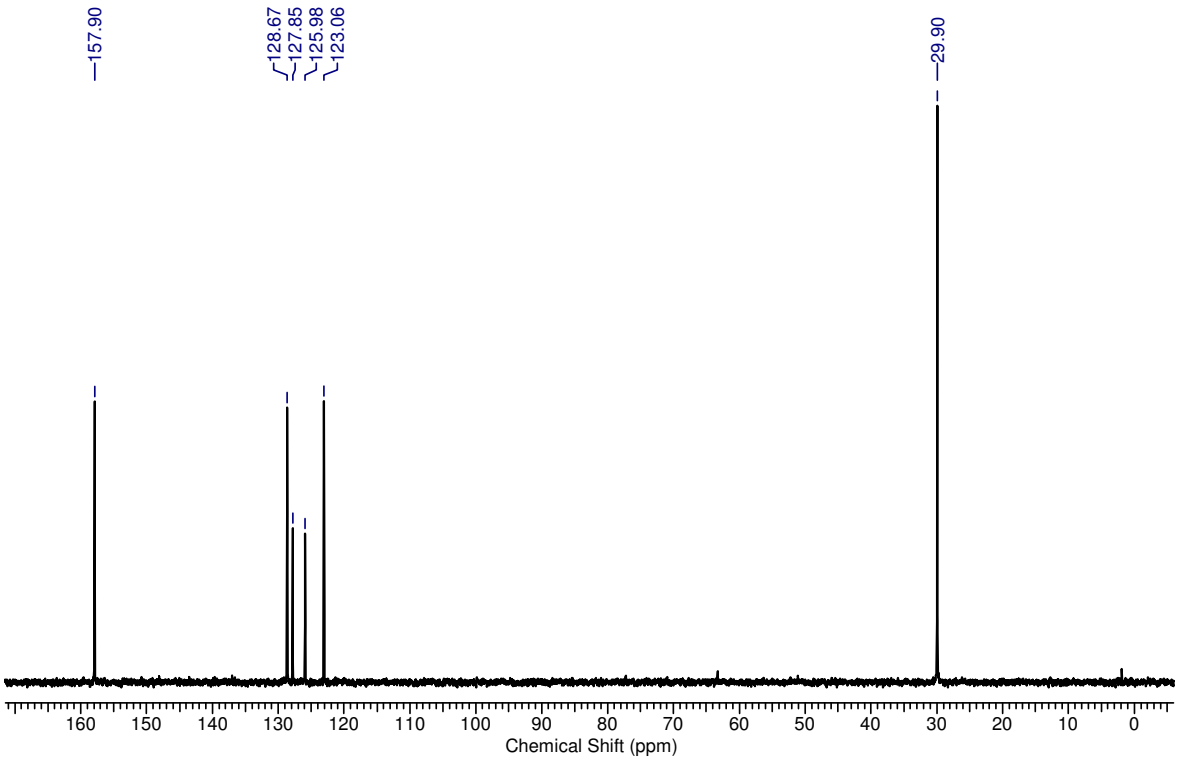
A solution of **6** (0.030 g, 0.185 mmol) in ACN (7 mL) was added slowly to a solution of **1** (0.053 g, 0.277 mmol in 7ml of ACN) taken in a 20 mL glass vial. After complete addition of **6**, a catalytic amount of acetic acid (50 µl) was added and the reaction mixture was kept undisturbed at room temperature for 7 days to obtain colourless, block-shaped crystals. The crystals were filtered and then washed with ACN to remove impurities. The crystal suitable for X-ray crystallography was removed directly from the sample vial to obtain crystal structure of the product **7**. Yield: 0.068 g, (92%); m.p: >340 °C; IR ($CHCl_3$, ν (cm^{-1})): 1651 (CH=N), 1478; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) : 8.12 (s, 6 H), 7.89 (s, 6 H), 7.37 (s, 9 H), 6.81 (s, 3 H), 1.61 (s, 36 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.9, 148.1, 137.0, 128.6, 127.8, 125.9, 123.0, 63.2, 29.9; HRMS(*m/z*): calcd for $C_{54}H_{61}N_6$ $[M+H]^+$ 793.4952, found 793.4916.



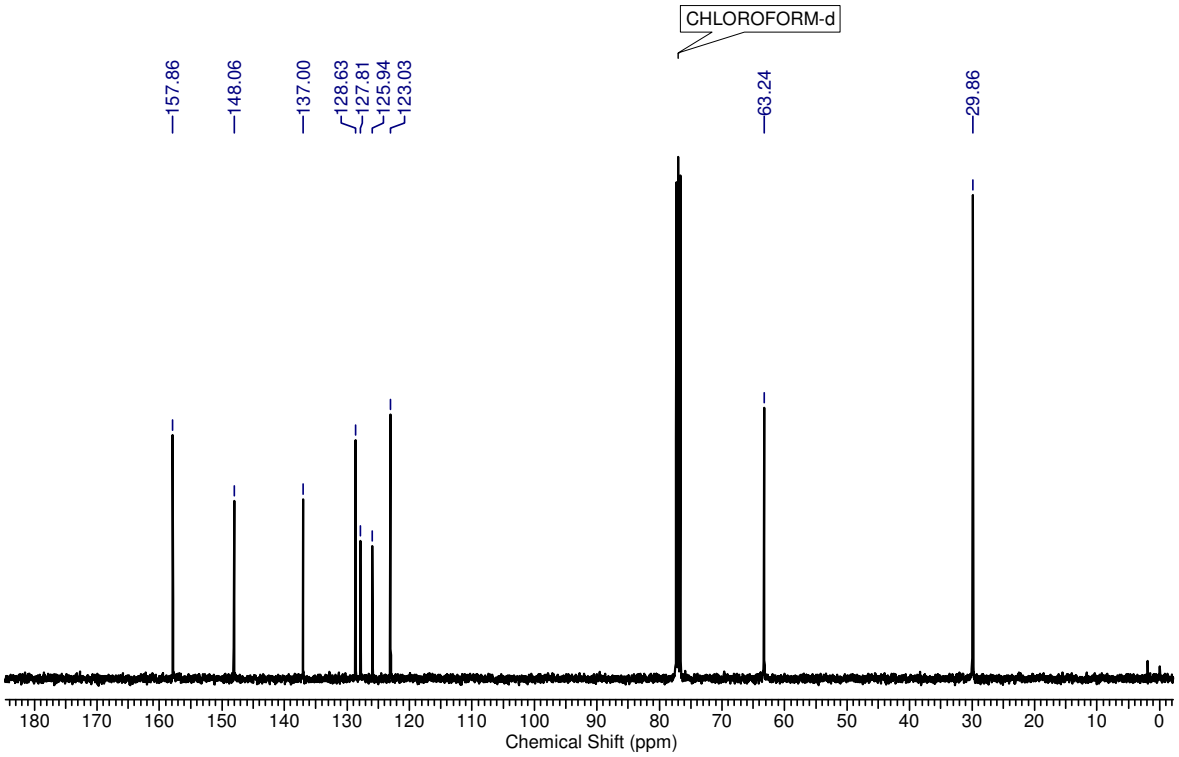
IR spectrum of cage **7**



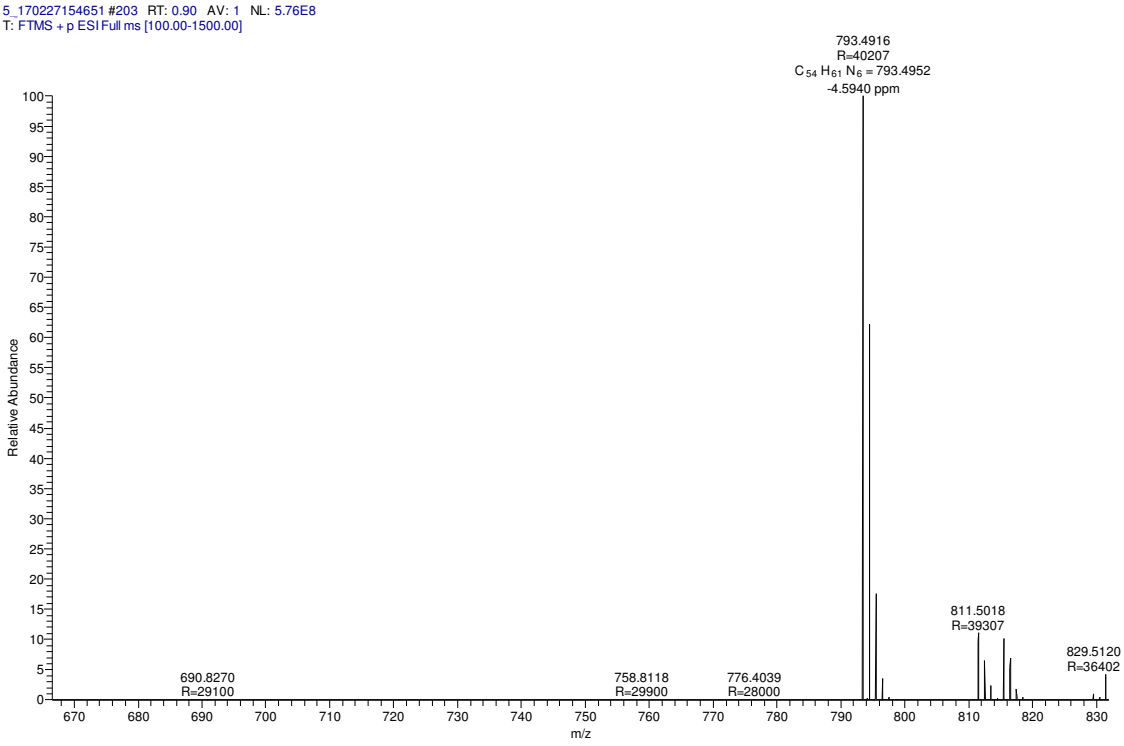
^{1}H NMR spectrum of cage **7** ($CDCl_3$, 400 MHz, 298 K)



DEPT 135 spectrum of cage **7** ($CDCl_3$, 100 MHz, 298 K)

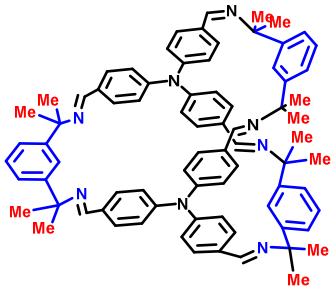


^{13}C NMR spectrum of cage **7** ($CDCl_3$, 100 MHz, 298 K)



MS (HRMS) of cage **7**

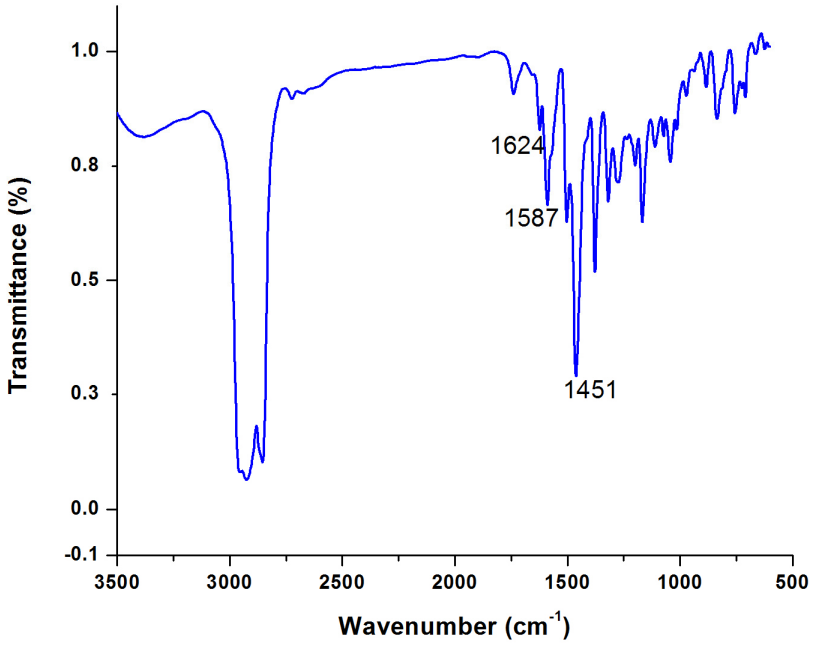
Cage 9.



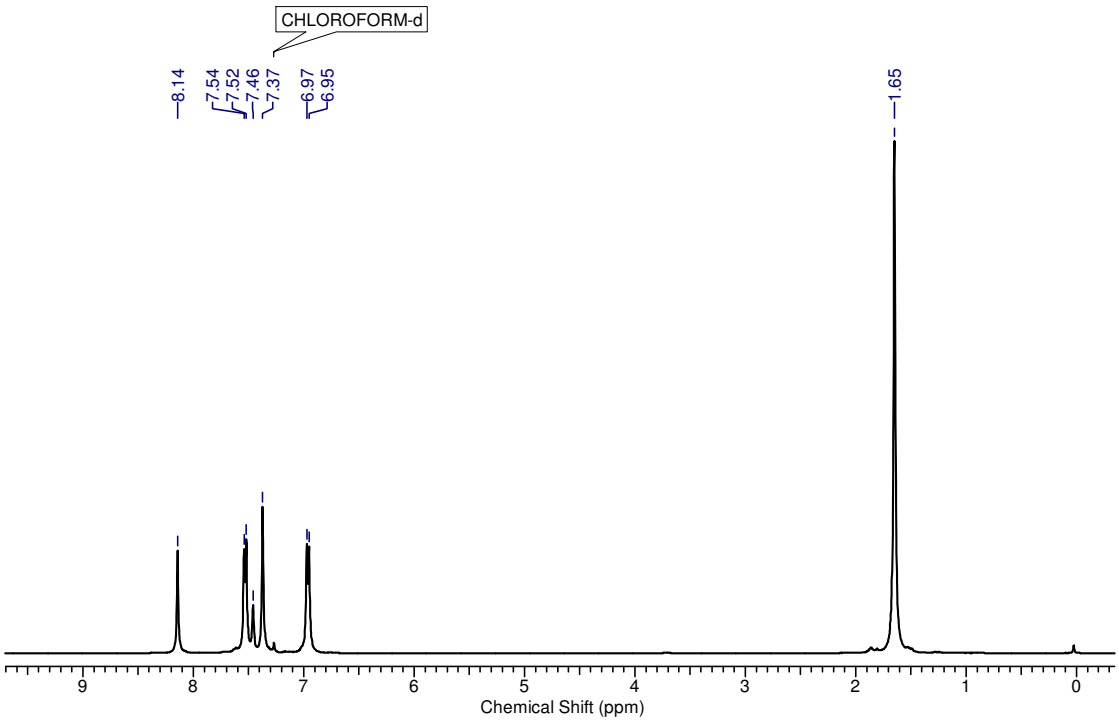
The synthesis of **9** was carried out by utilizing the same procedure of **7** using ACN as the solvent.

Gem-dimethylamine **1** (18.6 mg, 0.097 mmol), tris(4-formylphenyl)amine (**8**, 20 mg, 0.06mmol), ACN (10 mL), acetic acid (20 µl). Pale-yellow coloured-needle shaped crystals.

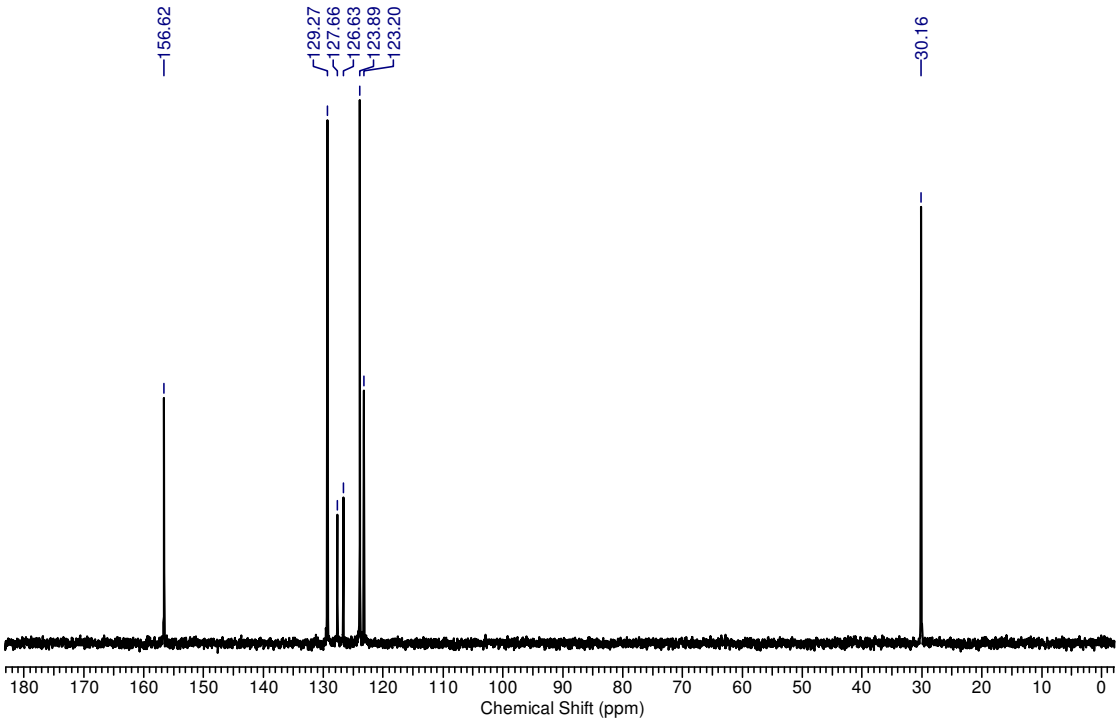
Yield: 0.030 g, (87%); m.p: >250 °C; IR (Nujol, ν (cm^{-1}): 1638 (CH=N), 1597; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) : 8.14 (s, 6H), 7.53 (d, J = 7.9 Hz, 12H), 7.46 (s, 3H), 7.37 (s, 9H), 6.96 (d, J = 7.9 Hz, 12H), 1.65 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 156.6, 148.3, 148.2, 132.0, 129.2, 127.6, 126.6, 123.8, 123.1, 62.7, 30.1; HRMS(*m/z*): calcd for $C_{78}H_{79}N_6$ $[M+H]^+$ 1127.6422, found 1127.6372.



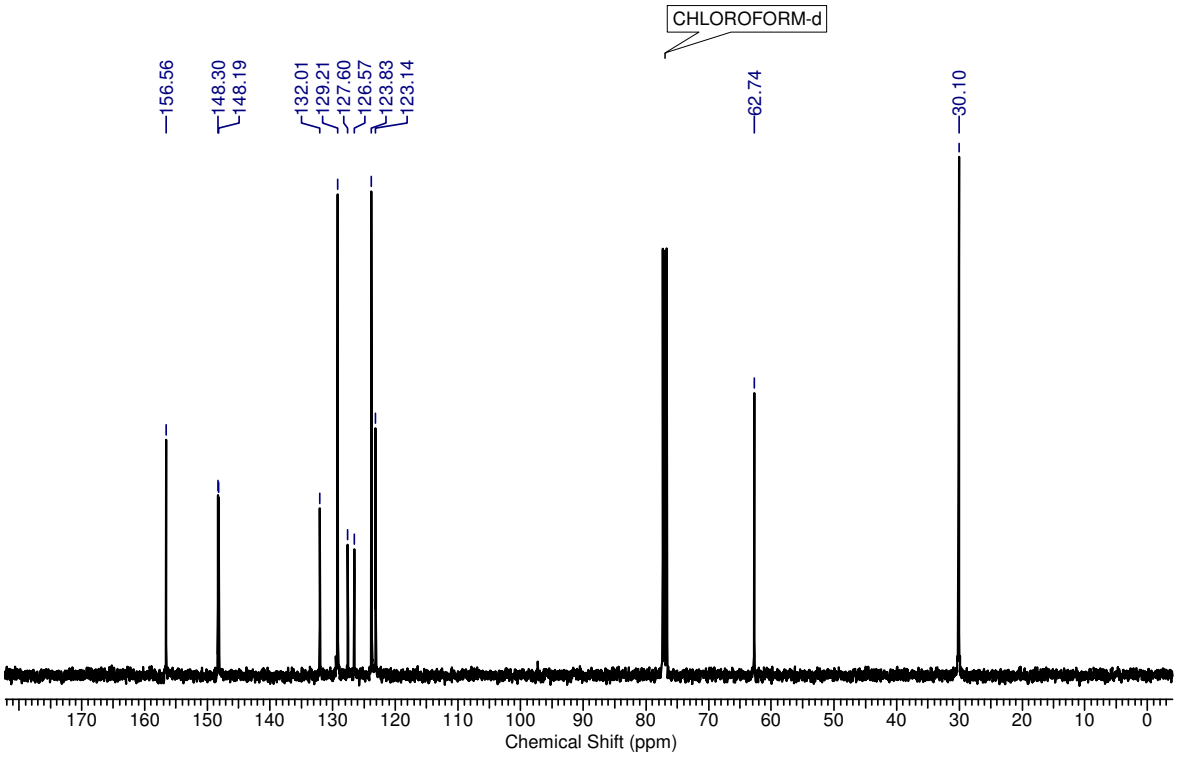
IR spectrum of cage **9**



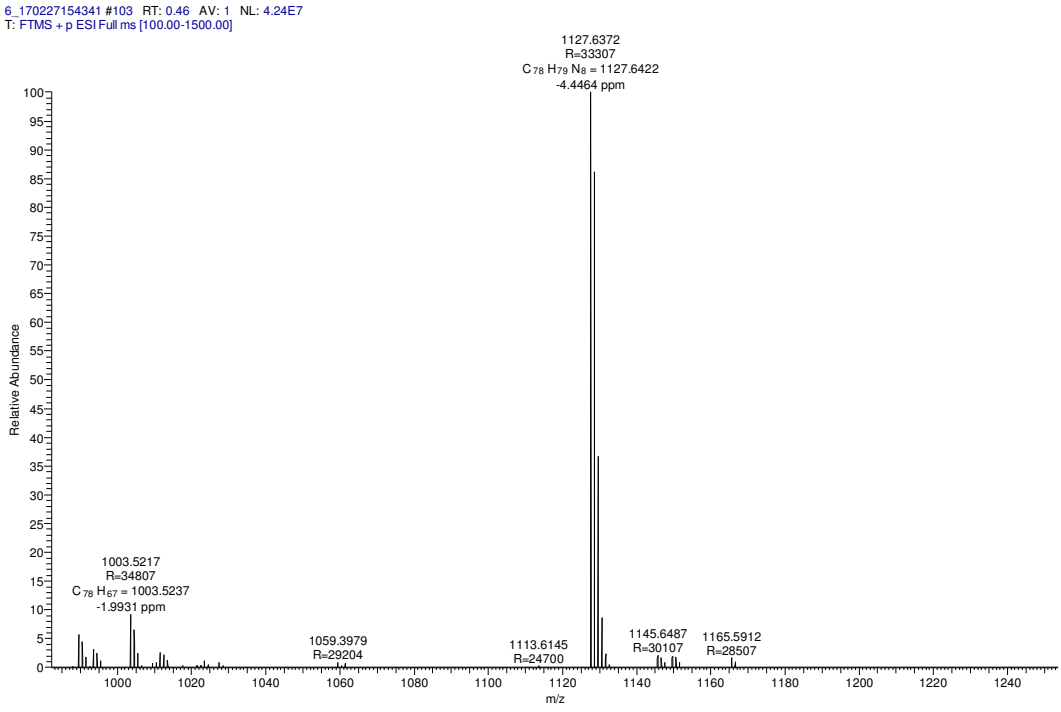
^{1}H NMR spectrum of cage **9** ($CDCl_3$, 400 MHz, 298 K)



DEPT 135 spectrum of cage **9** ($CDCl_3$, 100 MHz, 298 K)

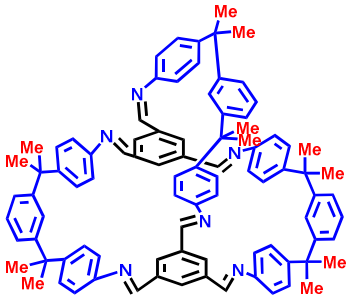


^{13}C NMR spectrum of cage **9** ($CDCl_3$, 100 MHz, 298 K)



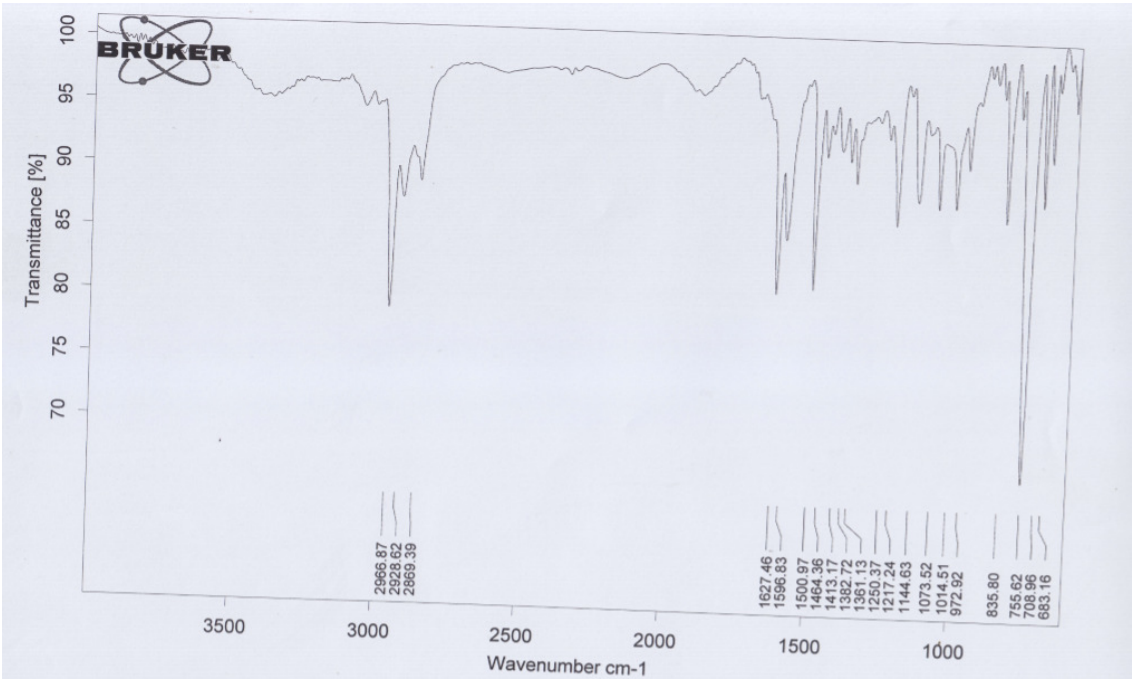
MS (HRMS) of cage **9**

Cage 10.

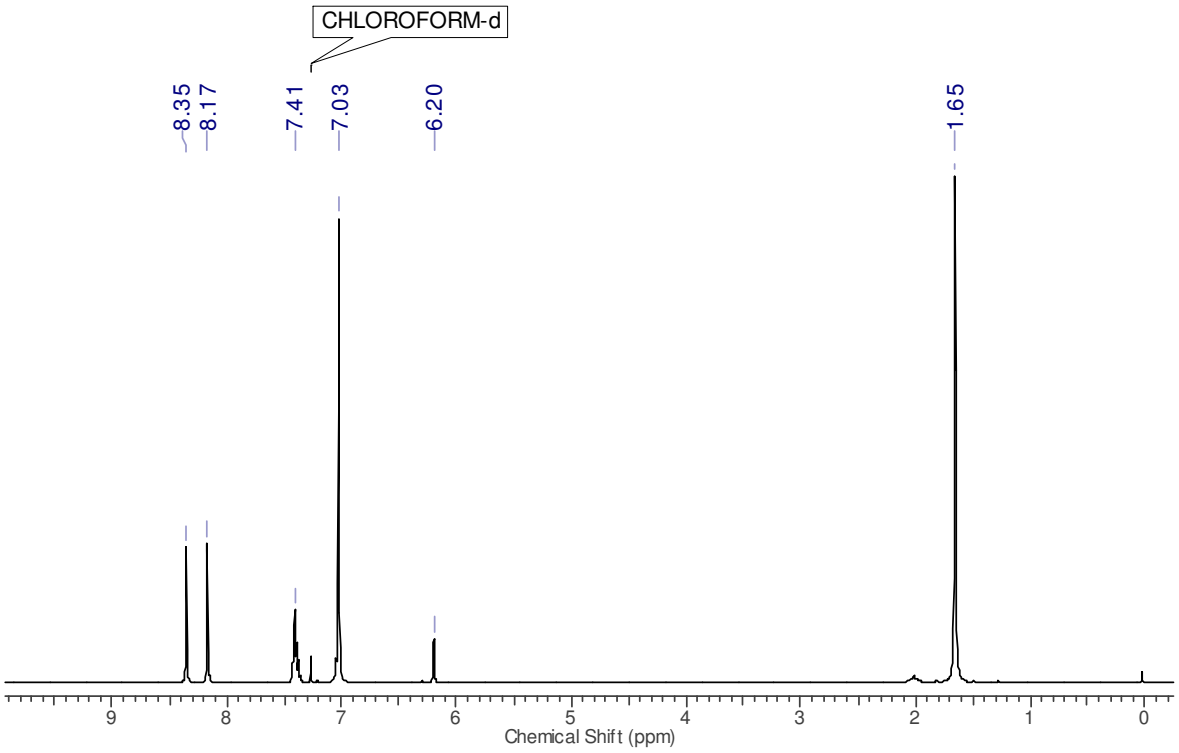


The synthesis of **10** was carried out by utilizing the same procedure of **7**.

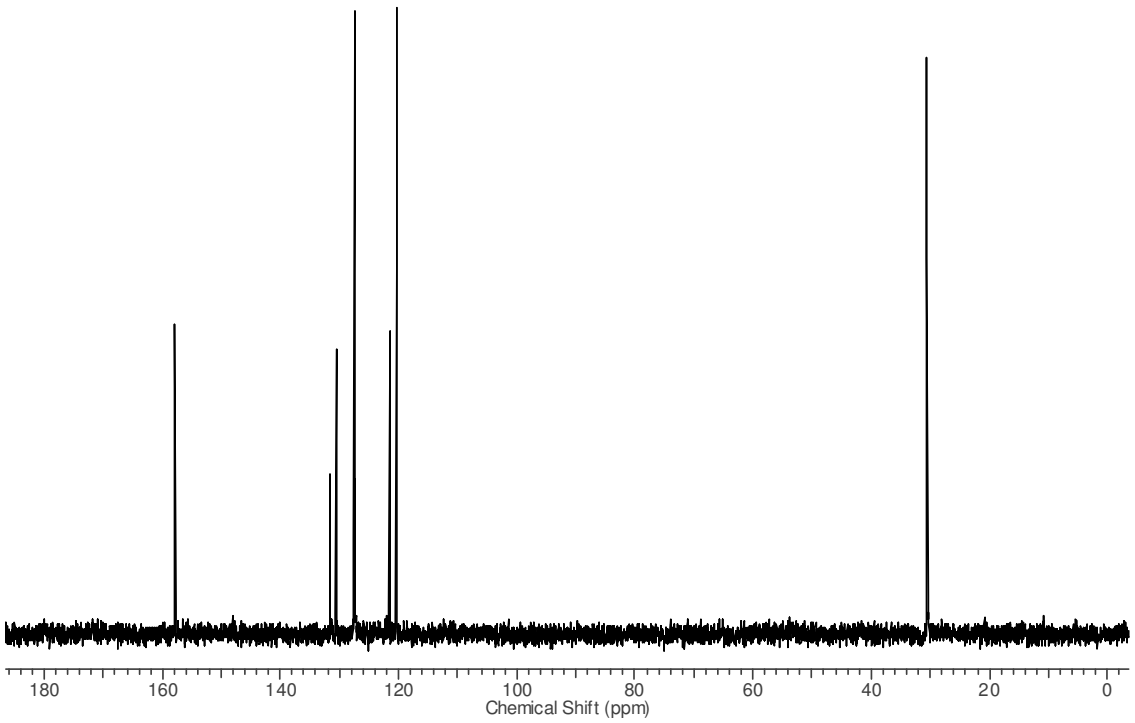
Benzene trialdehyde (**6**, 0.010 g, 0.061mmol), *gem*-dimethylamine **4** (0.032 g, 0.092 mmol) ACN (14 mL), acetic acid (50 µl). Pale yellow coloured, needle shaped crystals. The crystals were filtered and then washed with ACN. The crystal suitable for X-ray crystallography was removed directly from the sample vial to obtain crystal structure of the product **10**. Yield: 0.0336 g, (87%); m.p: 266-268 °C; IR ($CHCl_3$, ν (cm^{-1})): 2966 (s), 2928, 2869, 1627 (CH=N), 1596 (Ar, C=C), 1500; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) : 8.35 (s, 6H), 8.17 (s, 6H), 7.45-7.35 (m, 9H), 7.03 (s, 24H), 6.20 (s, 3H), 1.65 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.7, 150.7, 149.1, 148.1, 137.1, 131.5, 130.6, 127.5, 127.2, 121.5, 120.3, 42.8, 30.5; HRMS(*m/z*): calcd for $C_{90}H_{84}N_6$ $[M]^+$ 1248.6752, found 1248.6787.



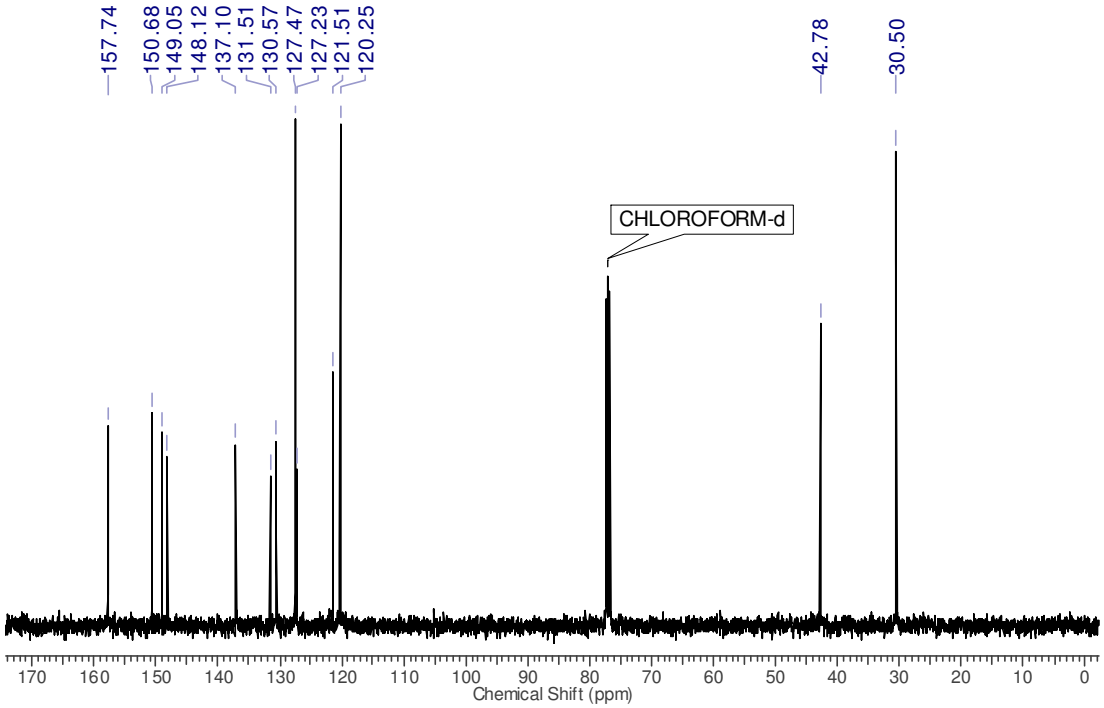
IR spectrum of cage **10**



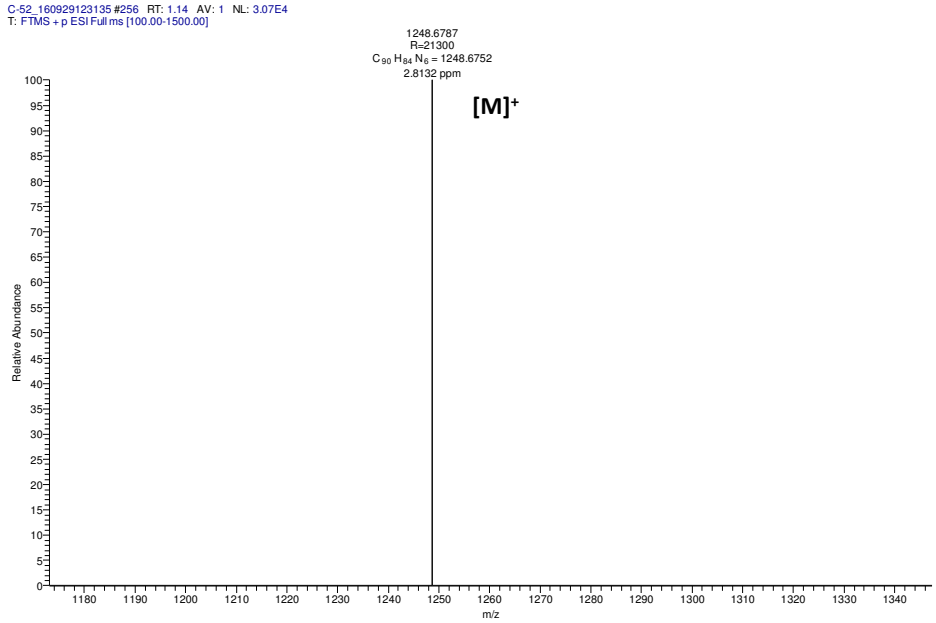
^{1}H NMR spectrum of cage **10** ($CDCl_3$, 400 MHz, 298 K)



DEPT 135 spectrum of cage **10** ($CDCl_3$, 100 MHz, 298 K)

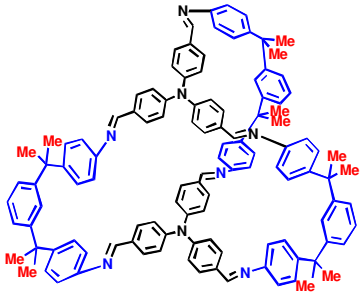


^{13}C NMR spectrum of cage **10** ($CDCl_3$, 100 MHz, 298 K)



MS (HRMS) of cage **10**

Cage 11.



Method 1 (*Acetonitrile as a solvent*)**:**

The synthesis of **11** was carried out by utilizing the same procedure of **7**.

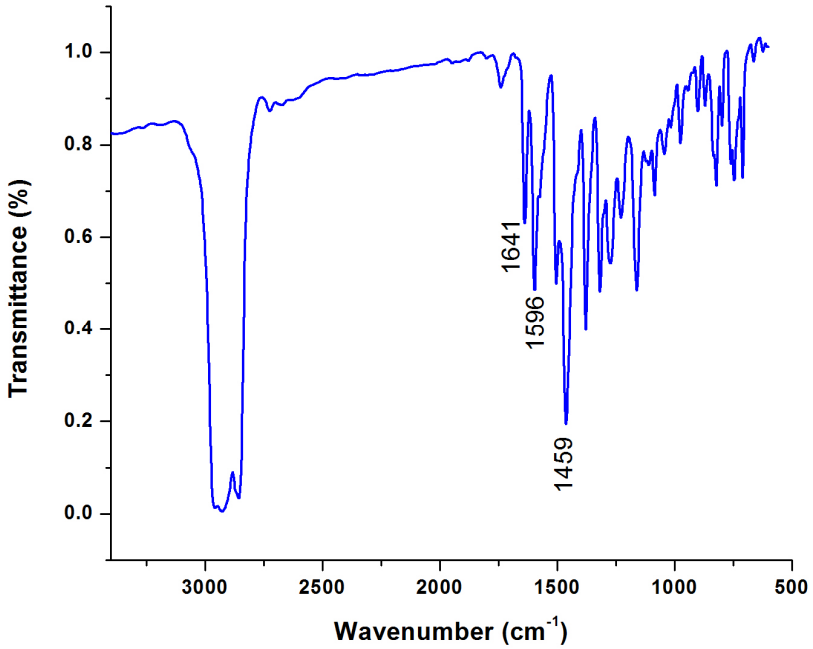
Gem-dimethylamine **4** (0.032g, 0.09 mmol), Tris(4-formylphenyl)amine (**8**, 20 mg, 0.06mmol), ACN (14 mL), acetic acid (20 µl). Pale yellow coloured, spongy-needle shaped crystals. The crystals were filtered and then recrystallised from ethanol/$CHCl_3$ (2:1). Yield: 0.043 g, (89%); Above 350 °C, filmed; IR (Nujol, *v* (cm^{-1}): 1636 (CH=N), 1595 (Ar, C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) : 8.27 (s, 6H), 7.66 (d, *J* = 7.9 Hz, 12H), 7.45 - 7.35 (m, 9H), 7.02 (dd, *J* = 8.5, 13.4 Hz, 24H), 6.95 - 6.90 (m, 12H), 6.55 (s, 3H), 1.64 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 158.5, 150.1, 149.4, 148.5, 148.4, 131.8, 131.1, 130.2, 127.4, 124.0, 122.0, 120.0, 42.8, 30.8; MALDI-MS(*m/z*): calcd for $C_{90}H_{84}N_6$ $[M]^+$ 1583.8, found 1584.0385.

Method 2 (*$CHCl_3$ as a solvent and ethanol as anti-solvent*)**:**

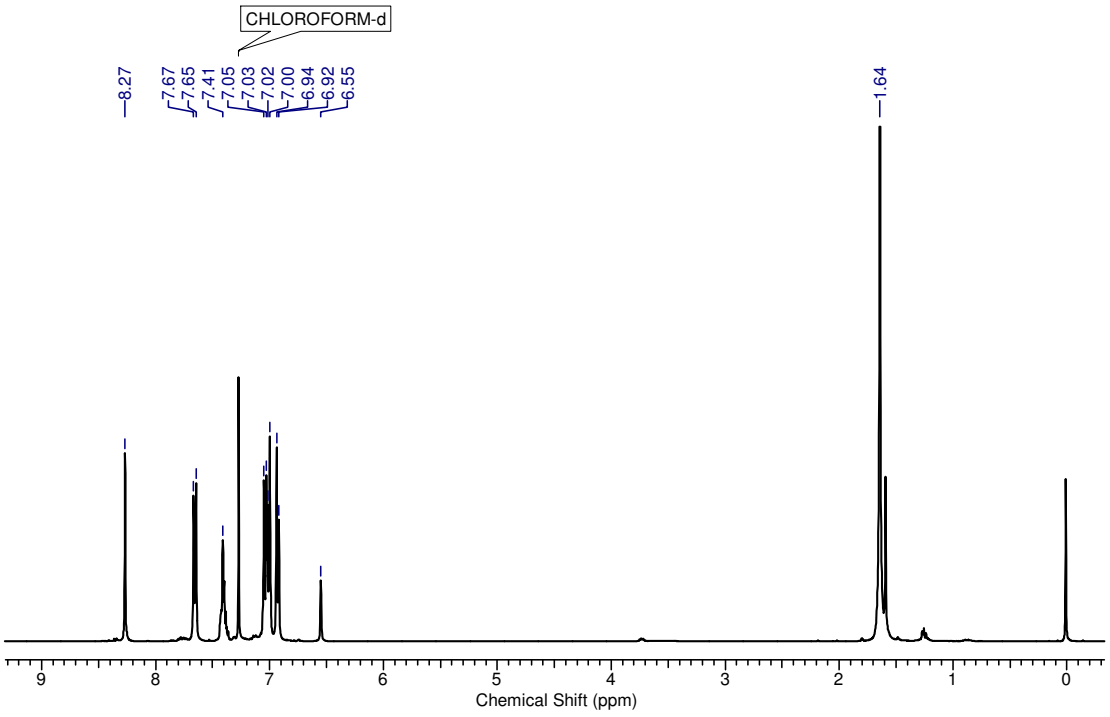
Reaction was performed in 20ml glass vial containing a screw cap.

Gem-dimethylamine (**4**, 0.032g, 0.09 mmol) was added to a solution of Tris(4-formylphenyl)amine (**8**, 20 mg, 0.06mmol) in $CHCl_3$ (7mL) at ambient temperature. The clear solution formed was kept without disturbance. After 24h, absolute ethanol (10ml) was added with slight shaking to get homogeneous solution. Then, the solution was kept without stirring for 7 days to obtain **11** as block shaped yellow crystals in good yields; 0.042 g (87%).

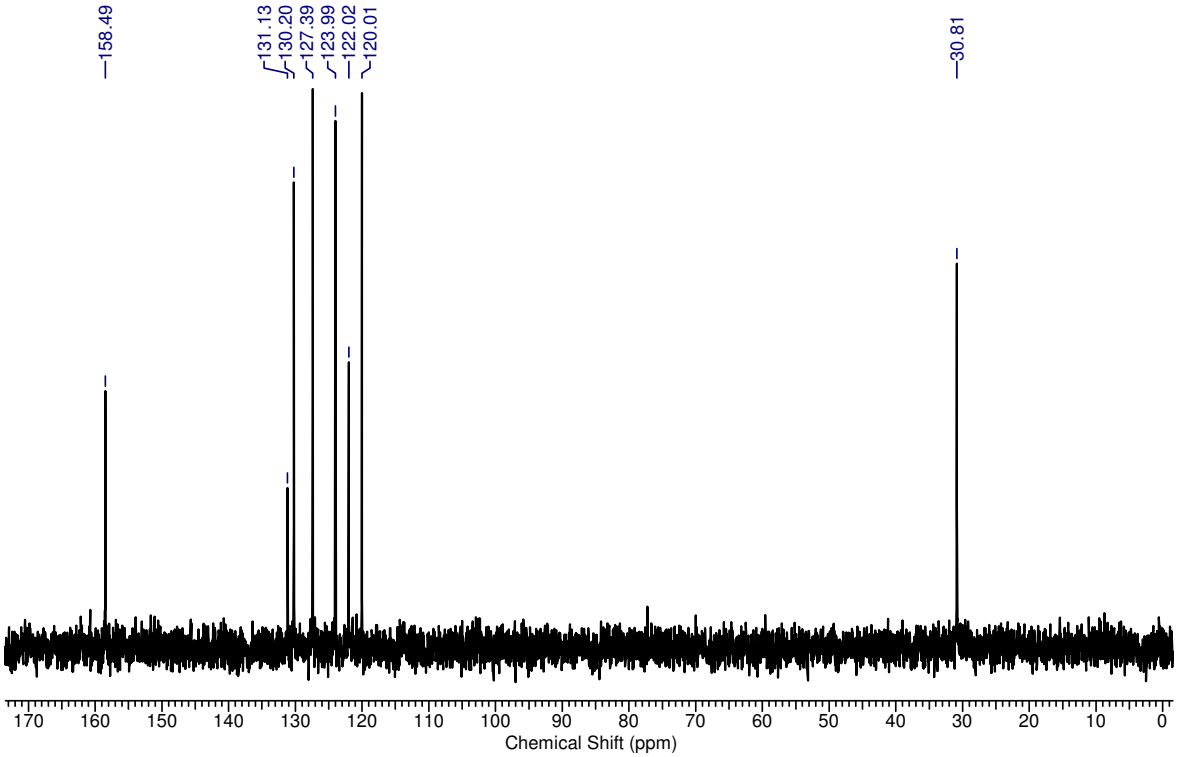
Note: Anti solvent ethanol was added for the purpose of getting macrocycles/cages as good quality crystals.



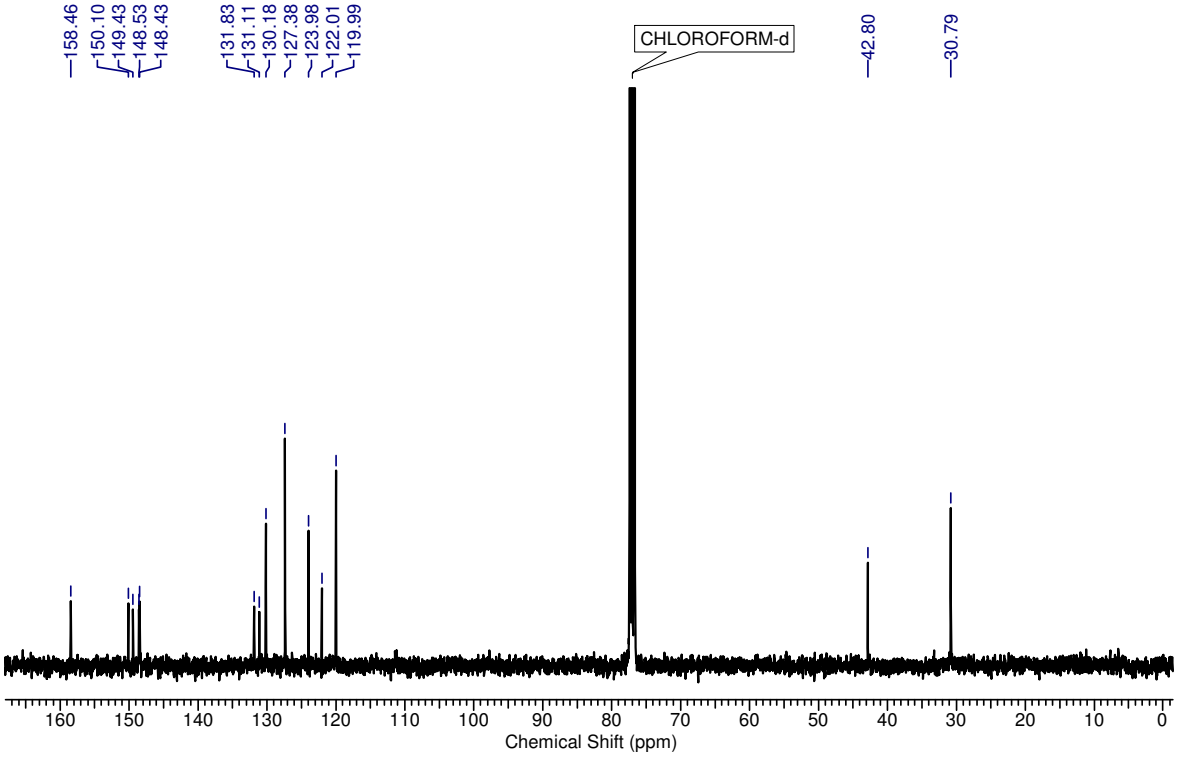
IR spectrum of cage **11**



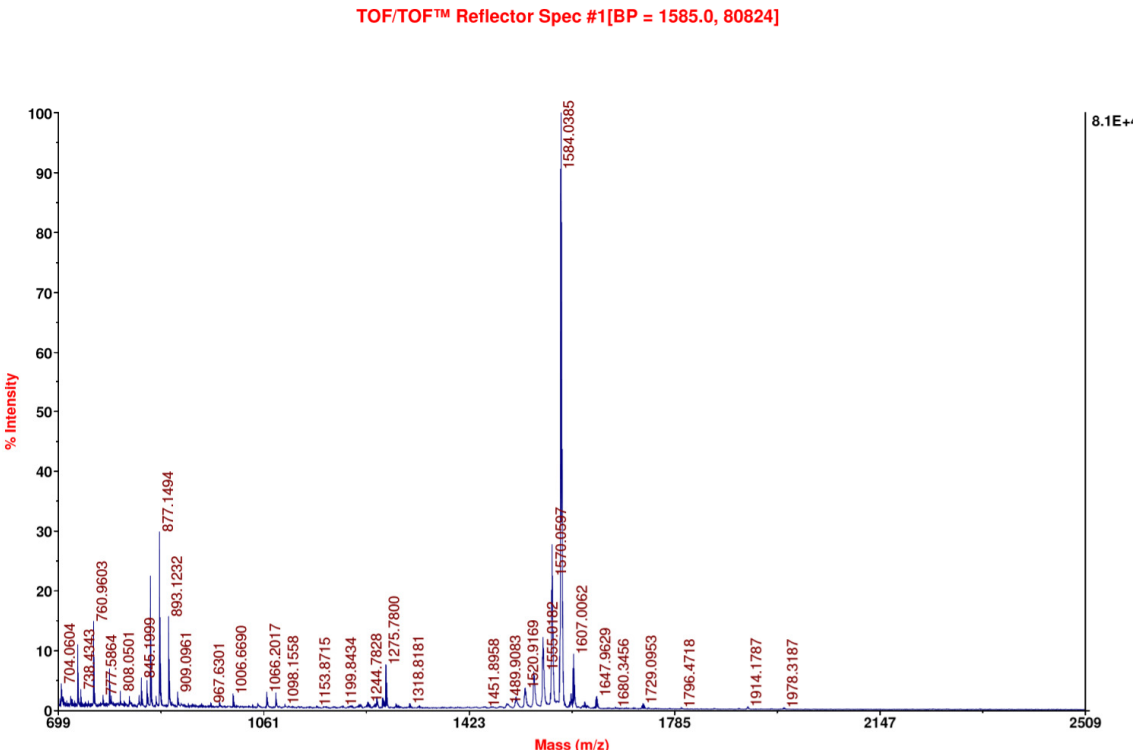
^{1}H NMR spectrum of cage **11** ($CDCl_3$, 400 MHz, 298 K)



DEPT 135 spectrum of cage **11** ($CDCl_3$, 100 MHz, 298 K)



^{13}C NMR spectrum of cage **11** ($CDCl_3$, 100 MHz, 298 K)



MALDI- MS of cage **11**

Macrocyclization under high concentrations.

1. Synthesis of macrocycle 3 in 1 M concentration:

To a 5 mL glass vial containing compound **2a** (0.136 g, 1.01mmol) and DCM (1 mL), **1** (0.199 mL, 1.01mmol) was added. The resultant clear solution was slowly hand-shaken for ~ 5-10 minutes, and then acetic acid (10 µl) was added to catalyze the reaction. The vial was tightly capped and kept undisturbed, without stirring at ambient temperature. After 24 h, the cap was partially opened to allow slow evaporation of solvent, over time, to afford crystals of **3**. The crystals were filtered with the aid of ACN to obtain first crop. The filtrate was concentrated *in vacuo* and the residue obtained was triturated with ACN to get a second crop. The combined yield of the crystalline material was 0.240 g (81%).

2. Synthesis of macrocycle 5a in 0.6 M concentration:

To a 5 mL glass vial containing compound **2a** (0.08g, 0.596 mmol) and DCM (1 mL), **4** (0.205 g, 0.596 mmol) was added. The resultant clear solution was slowly hand-shaken for ~ 5-10 minutes, and then acetic acid (10 µl) was added to catalyze the reaction. The vial was

tightly capped and kept undisturbed, without stirring at ambient temperature. After 36 h, the solution containing crystals was evaporated under reduced pressure and the residue was directly recrystallised from *o*-dichlorobenzene to afford yellow coloured plate-like crystal of **5a**. 0.235 g (89%).

3. Synthesis of Cage 10 in 0.5 M concentration:

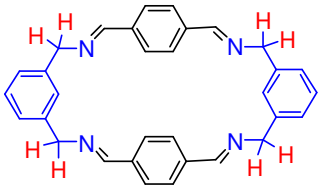
To a 5 mL glass vial containing compound **6** (0.0405 g, 0.2467 mmol) and DCM (0.5 mL), **4** (0.129g, 0.37 mmol) was added. The resultant clear solution was slowly hand-shaken for ~ 5-10 minutes, followed by addition of acetic acid (5 µl). Then, the vial was tightly capped and kept without stirring at ambient temperature for 36 h. After that, two drops of ethanol was added and the initially formed precipitate was dissolved by gentle shaking of the vial. The solution thus obtained was kept without stirring for 3 days to obtain **10** as pale yellow coloured crystals. Yield: 0.140 g (90%)

4. Synthesis of Cage 9 in 0.12 M concentration:

To a 5 mL glass vial containing compound **8** (0.040 g, 0.1214 mmol) in $CHCl_3$ (1 mL), **1** (0.035 g, 0.182 mmol) was added. The resultant clear solution was slowly hand-shaken for ~ 5 minutes, followed by which acetic acid (5 µl) was added to catalyze the reaction. Then, the vial was tightly capped and kept without stirring at ambient temperature for 36. After that, ethanol (2mL) was added and the initially formed precipitate was dissolved by gentle shaking of the vial. The solution thus obtained was kept without stirring for 3 days to obtain crystals of **9**. Yield: 0.056 g (82%). The crystal suitable for X-ray crystallography was removed directly from the sample vial to obtain crystal structure of the macrocycle **9**.

Note: Anti solvent ethanol was added for the purpose of getting macrocycles/cages as good quality crystals.

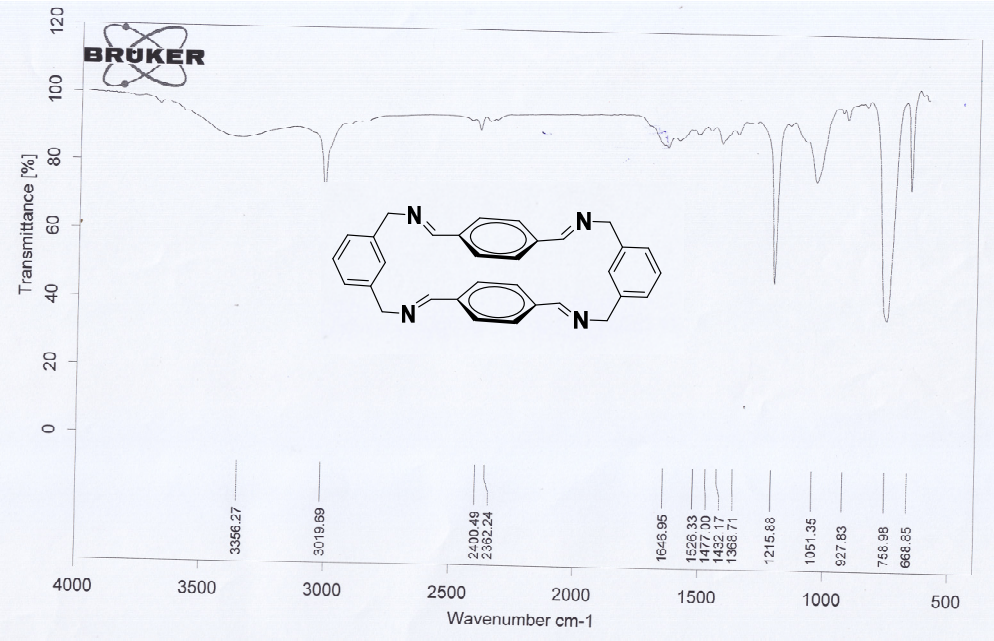
Preparation of macrocycle 3a under high dilute condition.



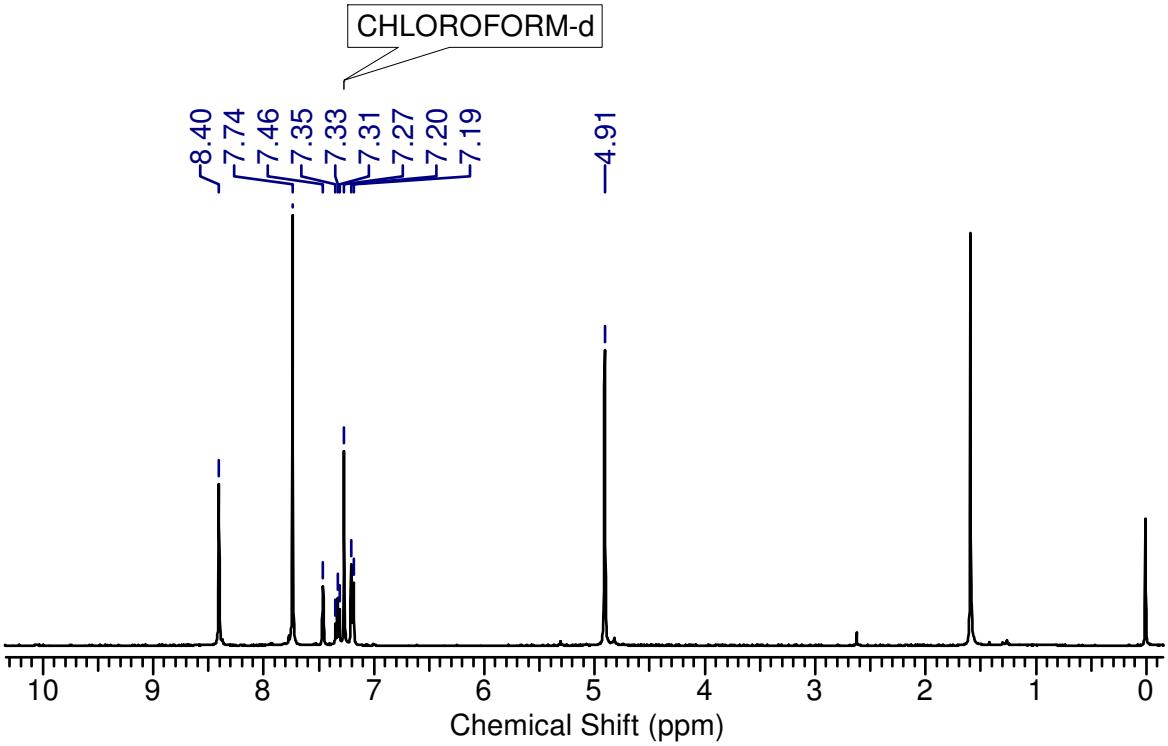
Macrocycle-**3a** was prepared by following the reported high dilution procedure[1e] (0.02 M in ACN, 48 h).

IR ($CHCl_3$, *v*): 1646(CH=N) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ(ppm) : 8.40 (s, 4H), 7.74 (s, 8H), 7.19-7.46 (m, 8H), 4.91 (s, 8H); ^{13}C NMR (100MHz, $CDCl_3$) δ(ppm): 161.8, 139.81,

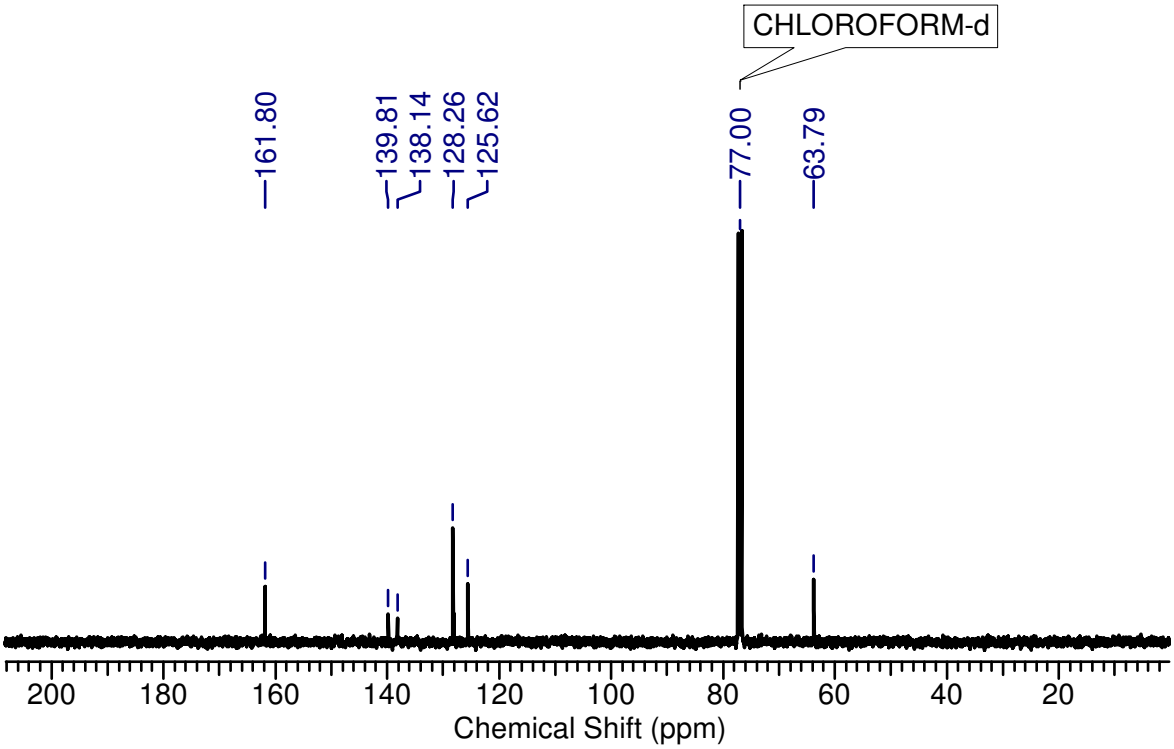
138.14, 128.26, 125.62, 63.79; MALDI-MS(m/z): calcd for $C_{32}H_{28}N_4$, $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$ 469.2314, 491.2212, 507.1951 found 469.1574, 491.1386, 507.1194.



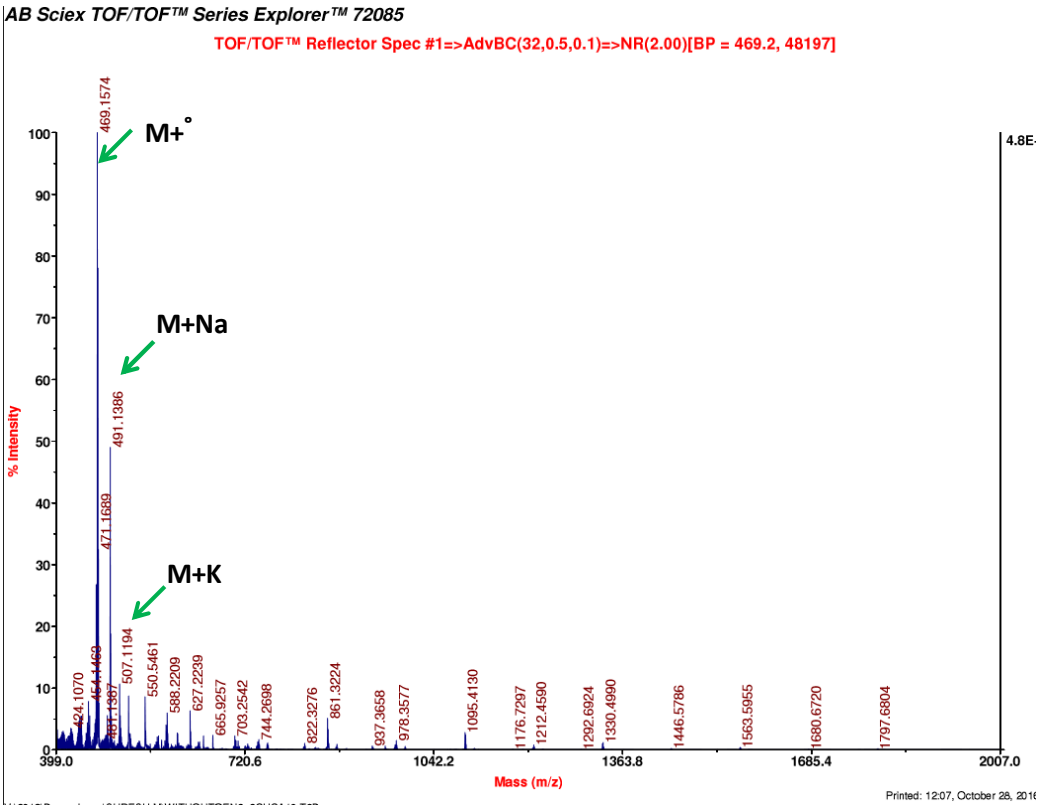
IR spectrum of macrocycle **3a**



^{1}H NMR spectrum of macrocycle **3a** ($CDCl_3$, 400 MHz, 298 K)

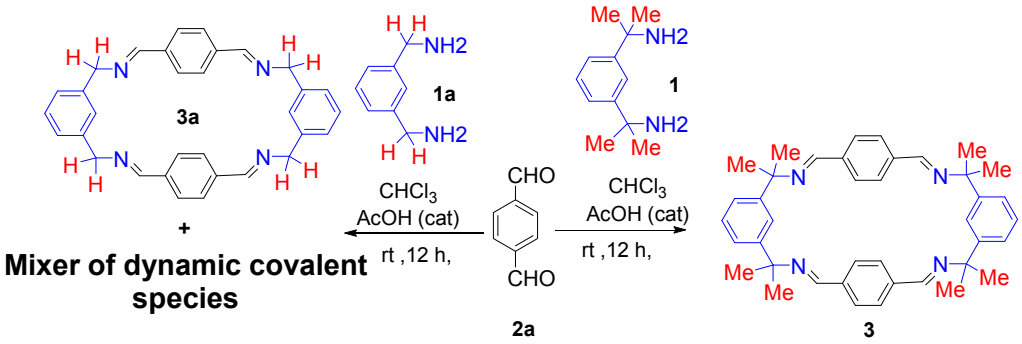


^{13}C NMR spectrum of macrocycle **3a** ($CDCl_3$, 100 MHz, 298 K)



MALDI-MS of macrocycle **3a**

A comparison study of imine-based macrocyclisation with and without *gem*-dimethyl groups in the amine at high concentrations.



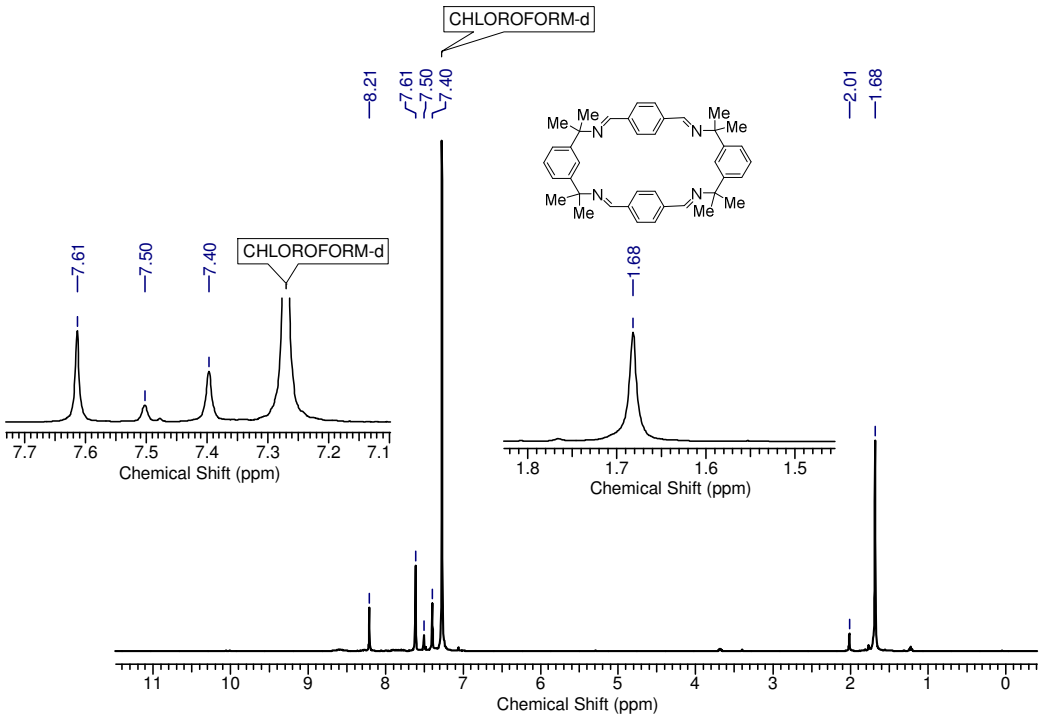
Scheme 4: Comparison of imine-based macrocyclisation with (**1**) and without (**1a**) *gem*-dimethyl groups in the amine at higher concentrations (0.09 M to 1 M).

The preparation of [2+2] macrocycle **3** (with the *gem*-dimethyl group) and its corresponding macrocycle **3a** without *gem*-dimethyl group were attempted in $CHCl_3$ at 1 M reaction concentrations by following the method which was mentioned in the high concentration reactions (the same experiment done already in DCM, except addition of anti-solvent ethanol, ESI page S26). In the former case, immediate precipitation has occurred, whereas in the later case clear solution was formed. After 12 h, both the cases reaction mixture was recorded ^{1}H-NMR and MALDI-MS, revealed that the formation mixture of dynamic oligomers in the former case (without *gem*-dimethylamine) and exclusively **3** in the later case, respectively. This experiment clearly suggests that almost full conversion of macrocycle **3** could be found in the solution. Similar observation was found even up to 0.091 M concentration as well.

Reaction quantity details:

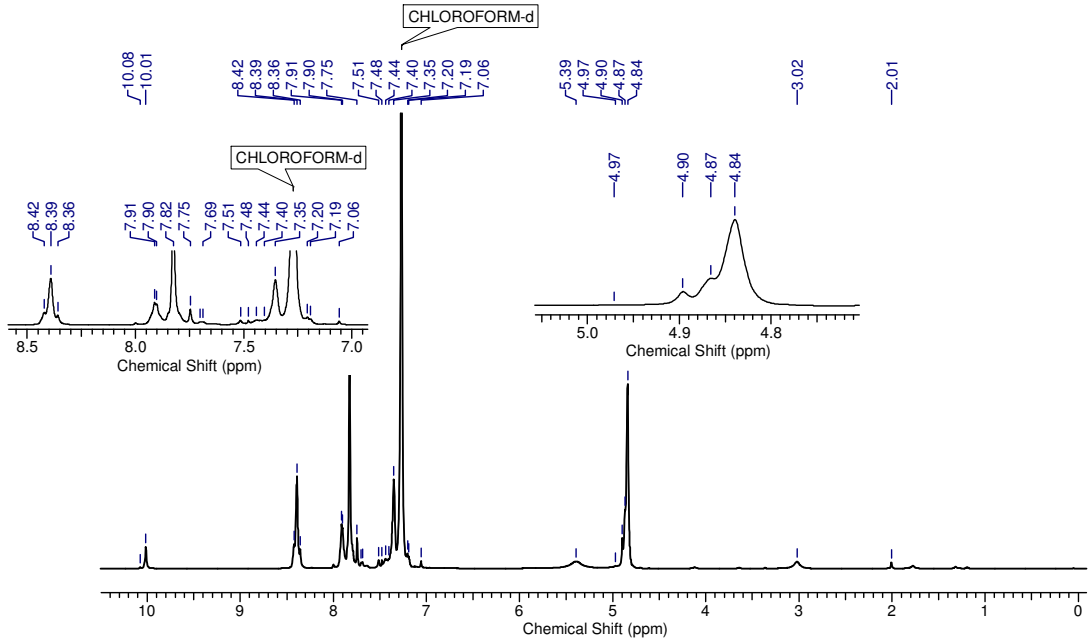
a) With *gem*-diemthyl groups: **2a** (0.136 g, 1.01 mmol), **1** (0.199 mL, 1.01 mmol), $CHCl_3$ (1 mL) and $AcOH_{(cat)}$(10 µL).

b) Without *gem*-diemthyl groups: **2a** (0.136 g, 1.01 mmol), **1a** (0.134 mL, 1.01 mmol), $CHCl_3$ (1 mL) and $AcOH_{(cat)}$(10 µL).

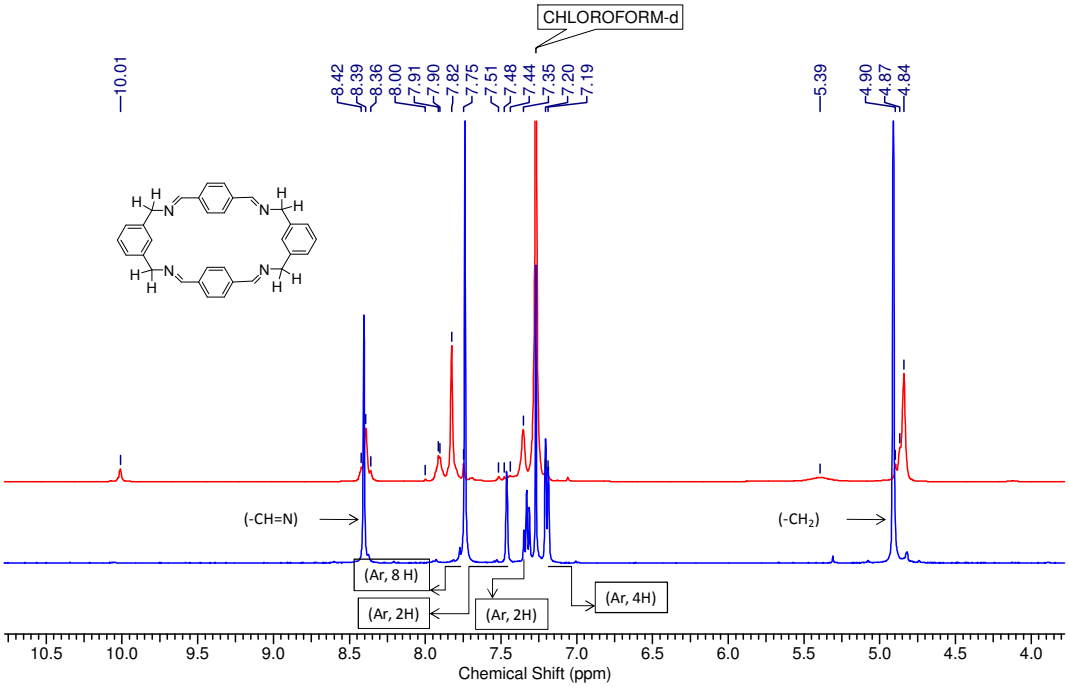


^{1}H-NMR spectrum of direct reaction mixture of macrocylisation performed for **3** under 1 M concentrations (in $CHCl_3$) shows the presence of almost only, [2+2] **macrocycle-3**.

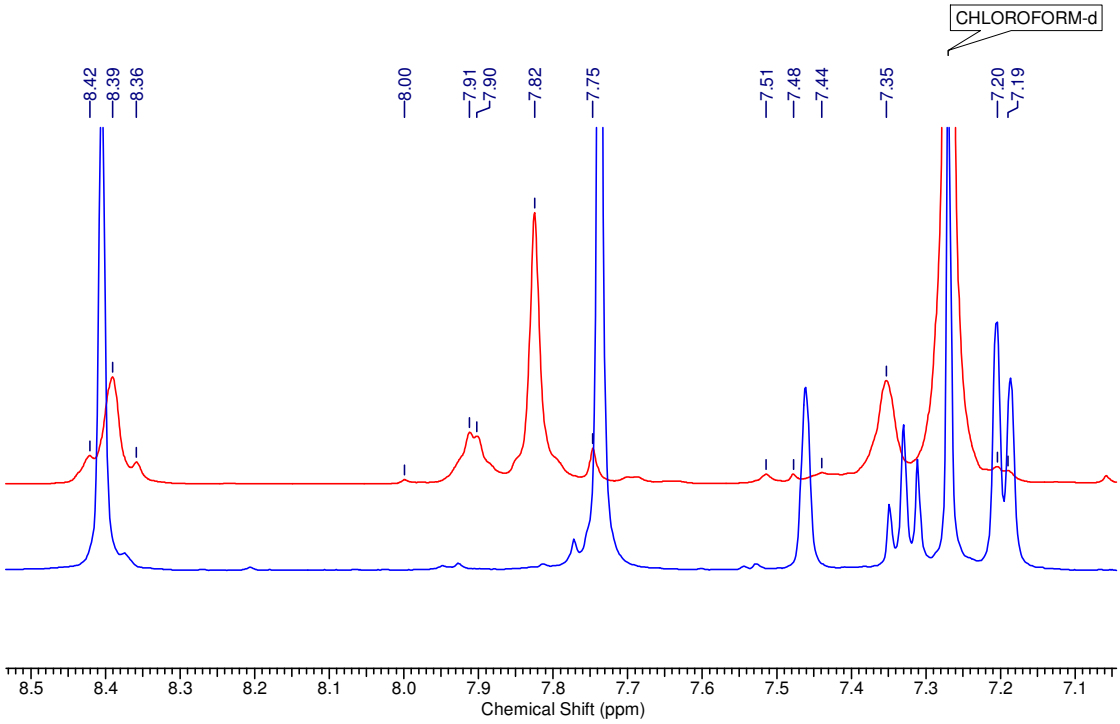
Note: The peak at δ=2.01 corresponds to CH_3COOH.



^{1}H NMR spectrum of direct reaction mixture of **macrocycle-3a** performed under 1 M concentrations (in $CHCl_3$) shows the presence of various dynamic combinatorial library (DCL). Note: The peak at δ=2.01 corresponds to CH_3COOH



^{1}H-NMR spectrum comparison of pure **macrocycle-3a** (prepared by high dilution method) and direct reaction mixture of macrocyclisation performed for **3a** at 1 M concentration.



^{1}H-NMR spectrum comparison of pure **macrocycle-3a** (prepared by high dilution method) and direct reaction mixture of macrocyclisation performed for **3a** at 1 M concentration (Aromatic region expanded).

Macrocycle-3a formation at 0.09 M concentration

To a 20 mL glass vial, solution of **2a** (0.049 g, 0.367 mmol in 4 mL $CHCl_3$) was added instantly to **1a** (0.05 g, 0.367 mmol) without stirring at room temperature (while doing addition immediate milky precipitate was observed). After complete addition of **1a**, a catalytic amount of acetic acid (10 µL) was added (amount precipitate rapidly increased) and followed by the reaction mixture was kept undisturbed at room temperature for a week. Then the reaction mixture with precipitate was evaporated under vacuum, the residue obtained was washed with diethyl ether for a couple of times to get a clear solid. Further, the material was characterized by IR, NMR, MALDI-MS.

IR (Nujol, *v*):1702(C=O), 1645(CH=N) cm^{-1}; DMSO-d6 soluble part of the substance recorded ^1H NMR showed clearly distinct oligomeric peaks. MALDI-MS showed many peaks with a characteristic of various oligomers.

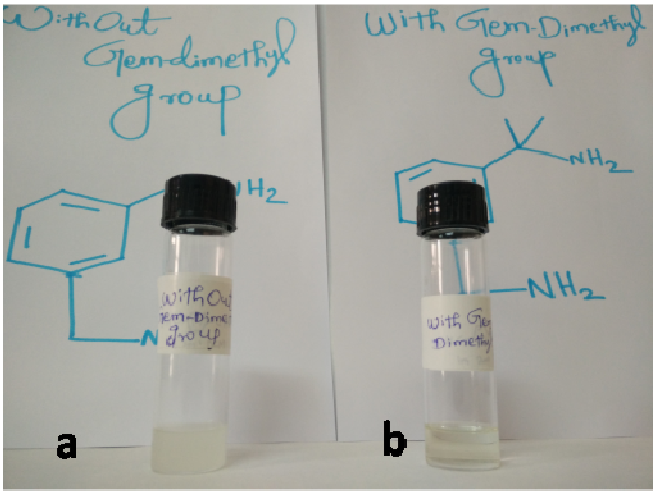
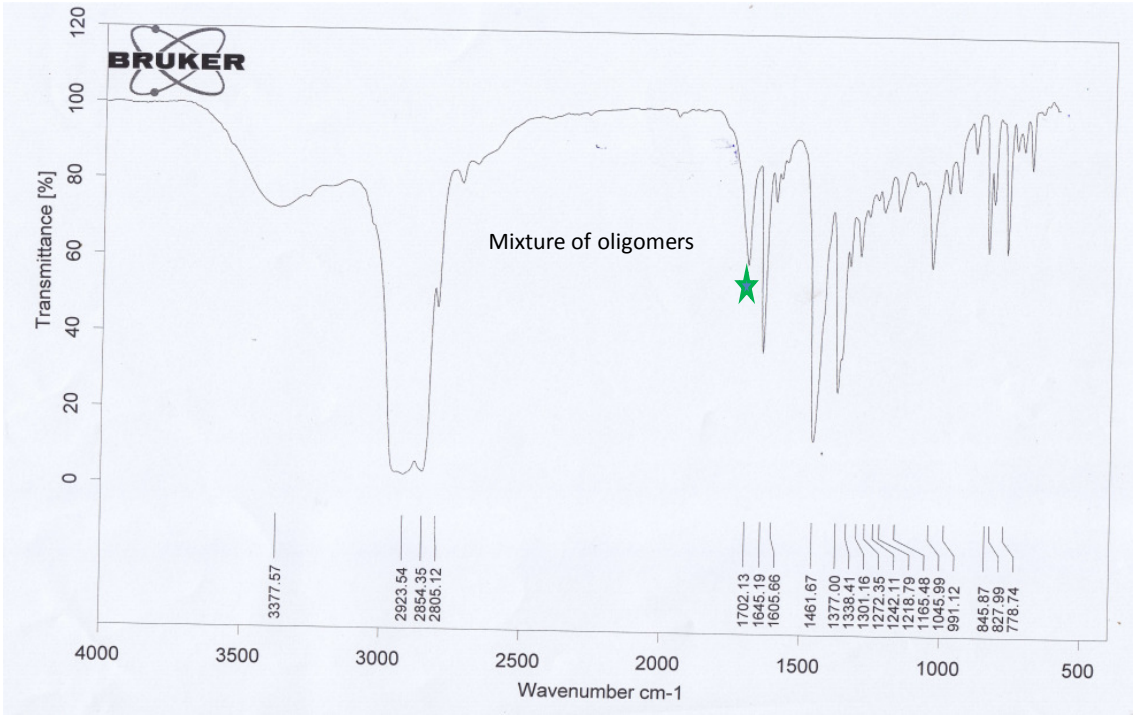
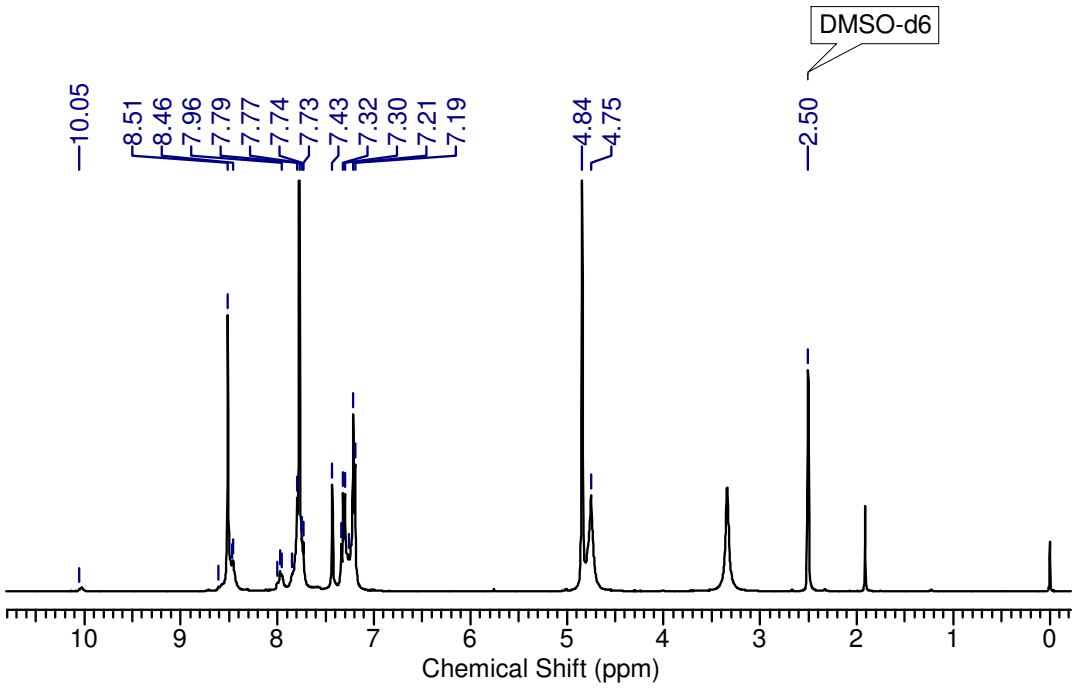


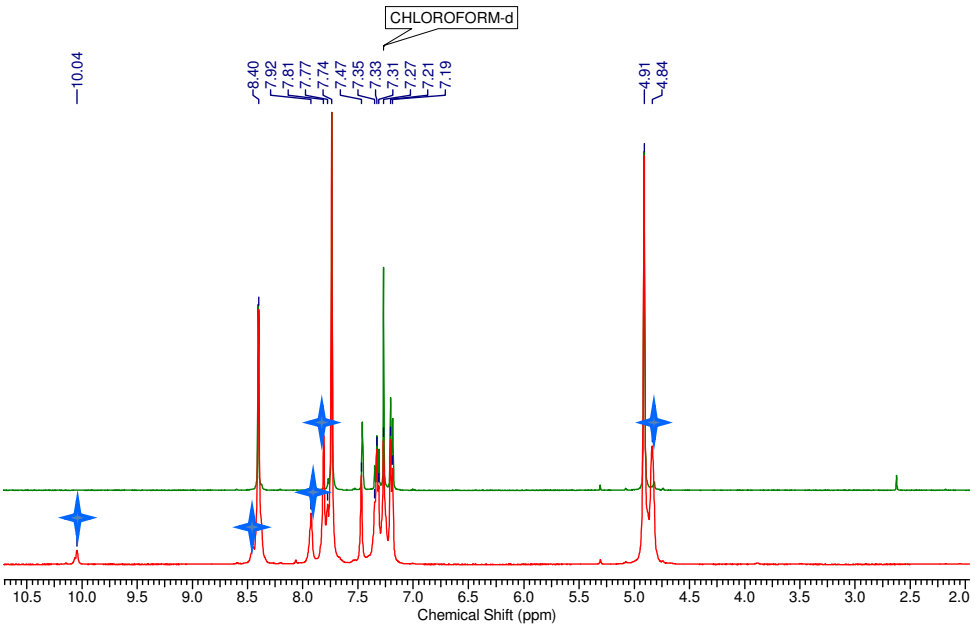
Fig. 1 Comparison of imine-based macrocyclisation with (**1**) and without (**1a**) *gem*-dimethyl groups in the amine at 0.09 M concentration. After instant mixing of amines **1a** and **1** with dialdehyde **2a**, separately. a) Instantly formed precipitate in macrocyclisation of **3a** b) Clear solution formed in macrocyclisation of **3**.



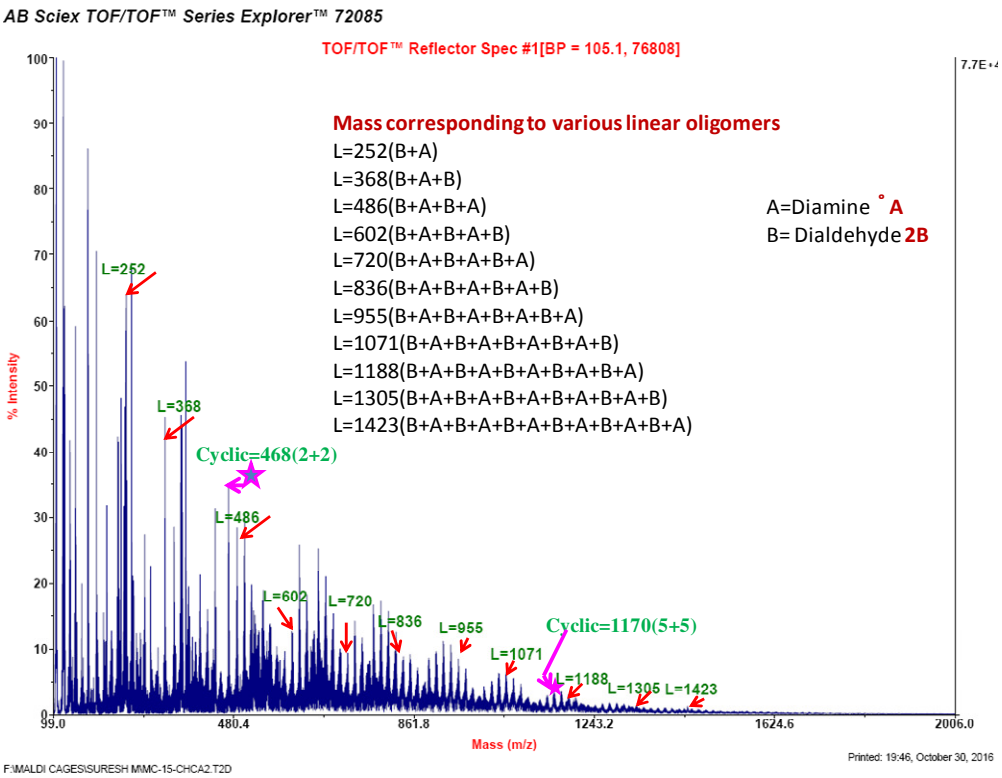
IR spectrum of imine-based macrocyclisation performed for **3a** (at 0.09 M concentration)



^{1}H-NMR spectrum of imine-based macrocyclisation performed for **3a** (at 0.09 M concentration) shows various DCL (DMSO-d^{6}, 400 MHz, 298 K).



Comparison of ^{1}H-NMR spectrum of imine-based macrocyclisation performed for **3a** at 0.09 M (red) and pure-**3a** synthesized by high dilution method (green). *Note*: Additional peaks are indicated in blue stars which correspond to other DCL).



MALDI-MS of mixture of oligomers found in imine-based macrocyclisation performed for **3a** (at 0.09 M concentration)

Effect of *gem*-dimetheyl groups in reaction equilibrium of the imine-based macrocyclisation studied using ^{1}H-NMR

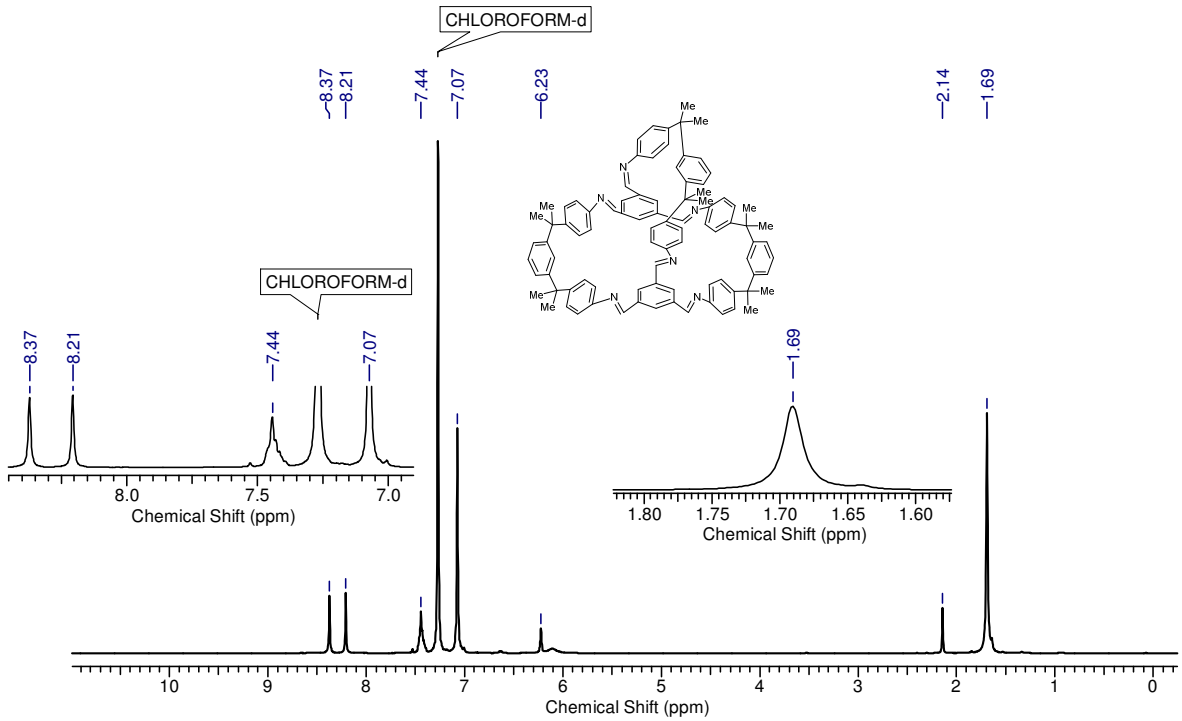
In general, in order to study equilibrium of the dynamic covalent library (DCL), the reaction should be performed in the solvent, in which all the DCL components are soluble. The reaction mixture directly could be analyzed by ^{1}H-NMR (ref). Herein, macrocycles **3**, **10** and their DCL are completely soluble in $CHCl_3$. Therefore, the macrocyclisation of **3** and **10** have taken as exemplary systems to study the effect of *gem*-dimethyl groups in the equilibrium of the imine-based macrocyclisation. The macrocyclisation reactions for the formation of **3** and **10** were conducted in $CHCl_3$, at high concentrations 1 M and 0.5 M, respectively. After 12 h, both the reaction mixtures were directly taken from the reaction vial and ^{1}H-NMR was recorded, separately. The results of the 1H-NMR have undoubtedly revealed the presence of [2+2] macrocycle (see: ^{1}H-NMR ESI, page 31, top) and [2+3] cage (see ^{1}H-NMR shown below page, S37) correspondingly.

Note: Reaction quantity details: a) For **cage-10**: **6** (0.0405 g, 0.2467 mmol), **4** (0.129g, 0.37 mmol), $CHCl_3$ (0.5 mL) and $AcOH_{(cat)}$(10 µL).

Presumably, due to the presence of *gem*-dimethyl groups in the dynamic combinatorial libraries (DCL), increase of ΔS^o or decrease of ΔH^o or both in the system, could highly thermodynamically favors the cyclisation [a) Michael E. Jung and Grazia Piizzi, Chem. Rev. 2005, 105, 1735-1766; b) Allinger, N. L., Zalkow, V. *J. Org. Chem.* 1960, **25**, 701) and makes equilibrium always shifts drastically towards the macrocycle formation (almost negligible amount starting materials and other species).

On the other hand, similar experiment was conducted for the formation **macrocycle-3a** in $CHCl_3$, at 1 M concentration, wherein ^{1}H-NMR (ESI, page S31-32) clearly showed the presence of many DCL components in the equilibrium of the reaction mixture.

Note: To maintain the high concentration while recording ^{1}H-NMR, 450 µl of the reaction solution and 100 µl of $CDCl_3$ was used.



^{1}H NMR spectrum of direct reaction mixture of macrocyclisation performed for **10** under 1 M concentrations (in $CHCl_3$) shows the presence of almost only, [2+3] **cage-10**.

Note: The peak at δ=2.14 corresponds to CH_3COOH

Thermogravimetric analysis:

Thermogravimetric analysis was carried out on NETSZCH TGA-DSC or METTLER TOLEDO, TGA/SDTA851e. The routine TGAs were done under N_2 gas flow (20ml or 50 ml/min) (purge + protective).

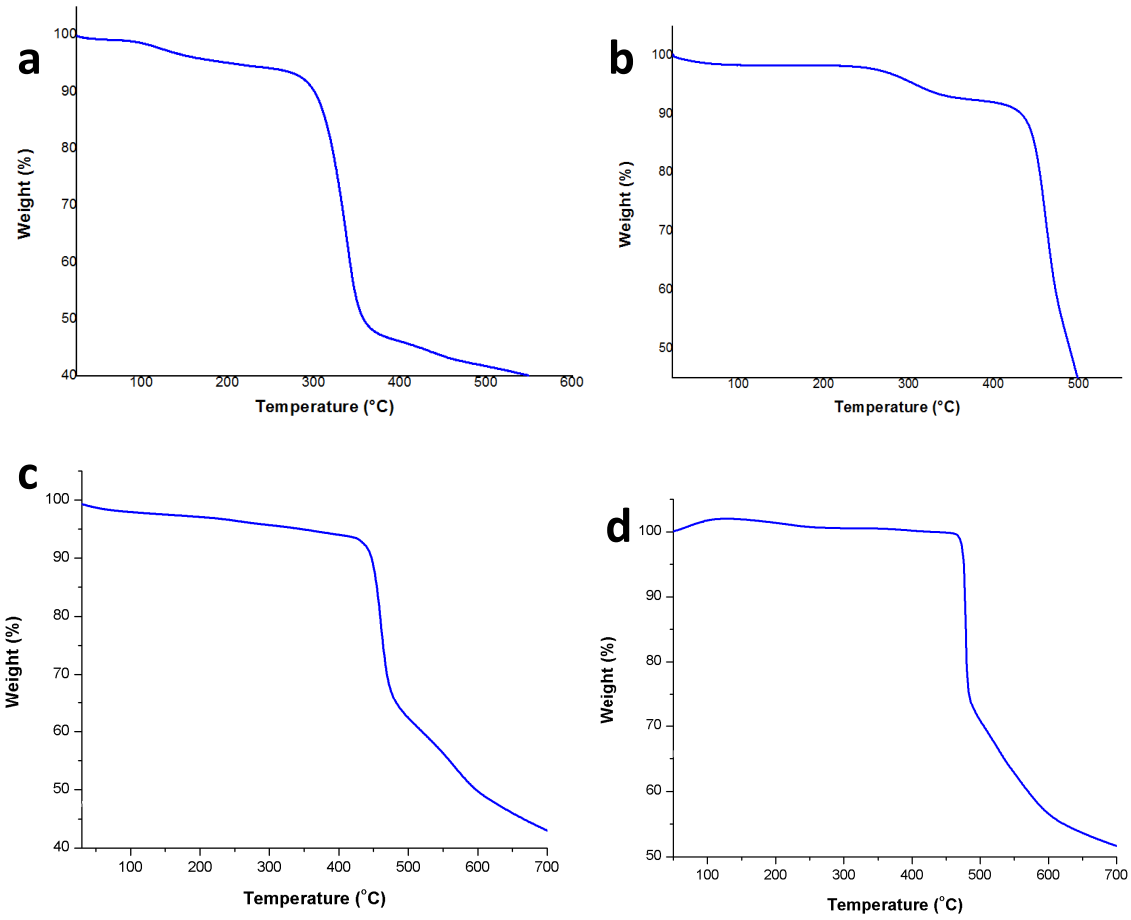


Fig. 2 TGA data of macrocycles. a) Macrocycle-**3** heated to 600 °C at the rate of 5 °C /min. b) Macrocycle-**5a** heated to 600 °C at the rate of 5 °C /min. c) Macrocycle-**5b** heated to 700 °C at the rate of 10 °C /min. d) Macrocycle-**5c** heated to 700 °C at the rate of 10 °C /min.

Note: Except macrocycle-**3,** rest of the macrocycle**s** showed decomposition temperature above 400 °C.

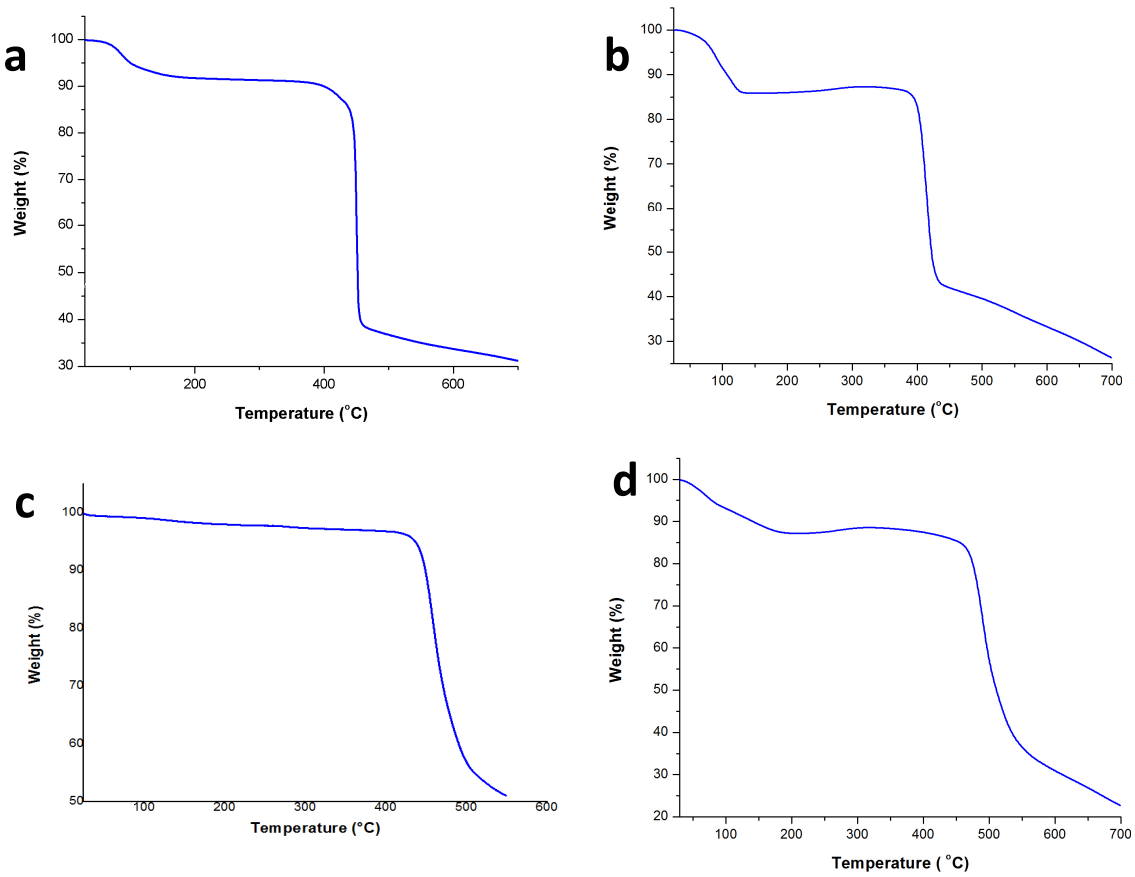


Fig. 3 TGA data of cages. a) Cage-**7** heated to 700 °C at the rate of 10 °C /min. b) Cage-**9** heated to 700 °C at the rate of 10 °C /min. c) Cage-**10** heated to 600 °C at the rate of 5 °C /min. d) Cage-**11** heated to 700 °C at the rate of 10 °C /min.

Note: All the cages showed decomposition temperature about 400 °C.

X-ray Crystallography:

X-ray intensity data measurements of macrocycles **7, 9** and **10** were carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Cu micro-focus sealed tube diffraction source (CuK_α= 1.54178 Å) at 100(2) K temperature. The X-ray generator was operated at 50 kV and 1.1 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 40 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[2a] On the other hand X-ray intensity data measurements of macrocycles **3** and **5a** were carried out on a Bruker SMART APEX II CCD diffractometer with graphite monochromatized (MoK_α= 0.71073 Å) radiation at 100(2) K. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[2b] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[3] All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on the parent atoms. An *ORTEP* III[3] view of the compounds was drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii. The crystallographic data are sumarised in Table 1.

Table 1:

Crystal Data	**3**	**5a**	**7**	**9**	**10**
Formula	$C_{40}H_{44}N_4$	$C_{64}H_{60}N_4$	$2(C_{54}H_{60}N_6)$, $3(C_2H_3N)$	$C_{78}H_{78\ N8}$, $2(CHCl_3)$	$C_{90}H_{84}N_6$
M_r	580.79	885.16	1709.31	1366.22	1249.63
Crystal Size, mm	0.31 x 0.24 x 0.18	0.44 x 0.37 x 0.24	0.250 x 0.130 x 0.070	0.230 x 0.110 x 0.090	0.35 x 0.15 x 0.11
Temp. (K)	150 (2)	200 (2)	100 (2)	100 (2)	100 (2)
Crystal Syst.	monoclinic	monoclinic	triclinic	monoclinic	triclinic
Space Group	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
a/Å	8.8258(2)	16.1510(4)	16.593(2)	24.2039(9)	9.9660(5)
b/Å	6.0141(2)	17.5803(5)	17.657(2)	14.9856(6)	20.4442(12)
c/Å	30.3167(8)	8.6794(2)	17.872(3)	19.4818(8)	21.3571(12)
α/^{0}	90	90	102.170(5)	90	109.652(3)
β/^{0}	96.3860(10)	96.025(2)	92.478(7)	98.2140(10)	100.622(3)
γ/^{0}	90	90	98.250(4)	90	98.052(3)
V/Å^3	1599.20(8)	2450.81(11)	5051.2(11)	6993.75	3930.6(4)
Z	2	2	2	4	2
D_{calc}/g cm^{-3}	1.206	1.199	1.124	1.298	1.056
μ/mm^{-1}	0.071	0.070	0.067	2.635	0.467
F(000)	624	944	1836	2872	1332

Ab. Correct.	multi-scan	multi-scan	multi-scan	multi-scan	multi-scan
T_{min}/ T_{max}	0.978/0.987	0.970/0.984	0.984/ 0.995	0.582/0.797	0.854/0.950
$2\theta_{max}$/°	57.38	52.0	28.243	89.698	149.1
Total reflns.	26842	14923	190004	72317	24629
Uniq.reflns.	4114	4607	24834	15946	15110
Obs. reflns.	3732	3117	21423	10501	9907
h, k, l (min, max)	(-11, 11), (-8, 8), (-40, 40)	(-18, 19), (-21,21), (-10, 10)		(-30, 31), (-16, 19), (24, 25)	(-12, 11), (-25, 25), (-26, 26)
R_{int}	0.0270	0.0360	0.0322	0.0789	0.0504
No. of para	204	311	1161	861	877
R1 [$I > 2\sigma(I)$]	0.0505	0.0622	0.0451	0.0592	0.0739
wR2[$I > 2\sigma(I)$]	0.1179	0.1133	0.1484	0.1615	0.1935
R1 [all data]	0.0562	0.1032	0.0519	0.1031	0.1110
wR2 [all data]	0.1214	0.1291	0.1484	0.1615	0.2142
goodness-of-fit	1.112	1.076	1.079	1.027	1.016
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	+0.370, -0.229	+0.240, -0.193	0.400, -0.227	1.117, -0.758,	+0.537, -0.288
CCDC no.	1524539	1524540	1538148	1538147	1524541

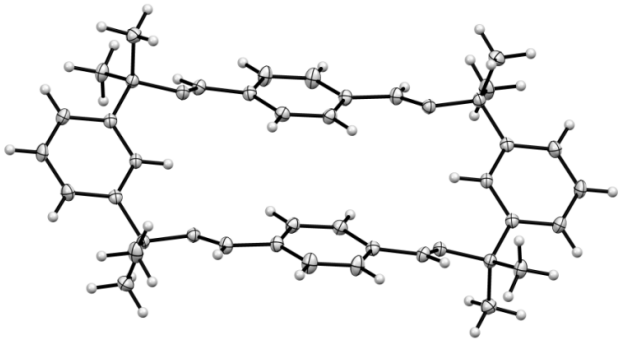


Fig. 4 ORTEP diagram of the macrocycle **3** (thermal ellipsoids are shown in 50% probability level).

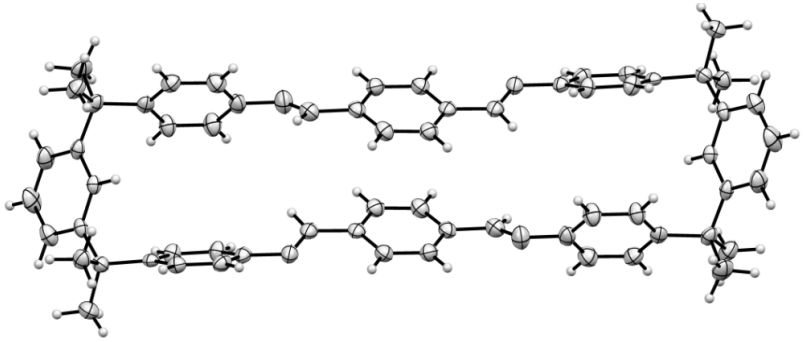


Fig. 5 ORTEP diagram of the macrocycle **5** (thermal ellipsoids are shown in 50% probability level).

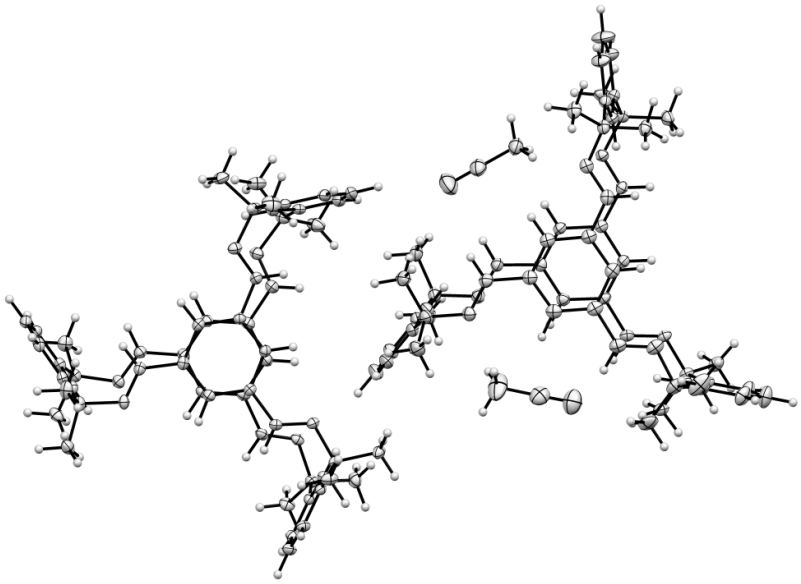


Fig. 6 ORTEP diagram of the two conformational isomers of macrocycle **7** with acetonitrile (thermal ellipsoids are shown in 50% probability level).

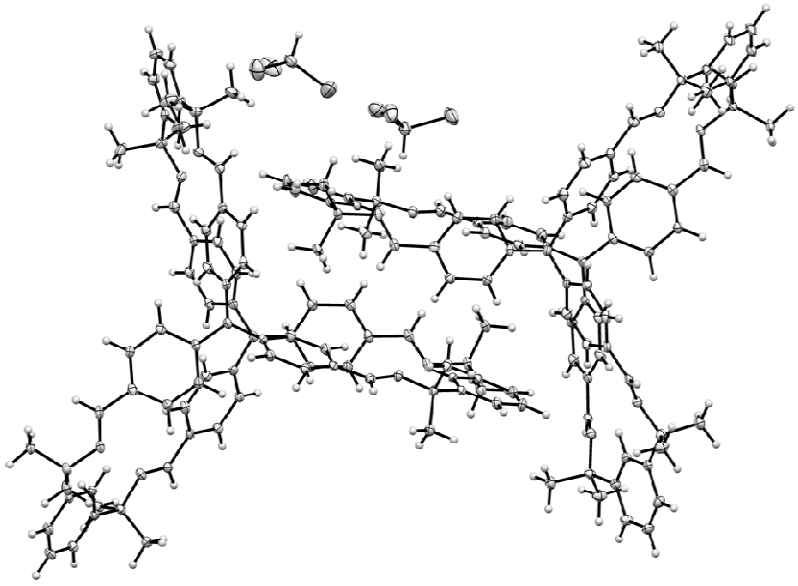


Fig. 7 ORTEP diagram of the two conformational isomers of macrocycle **9** with chloroform (thermal ellipsoids are shown in 50% probability level).

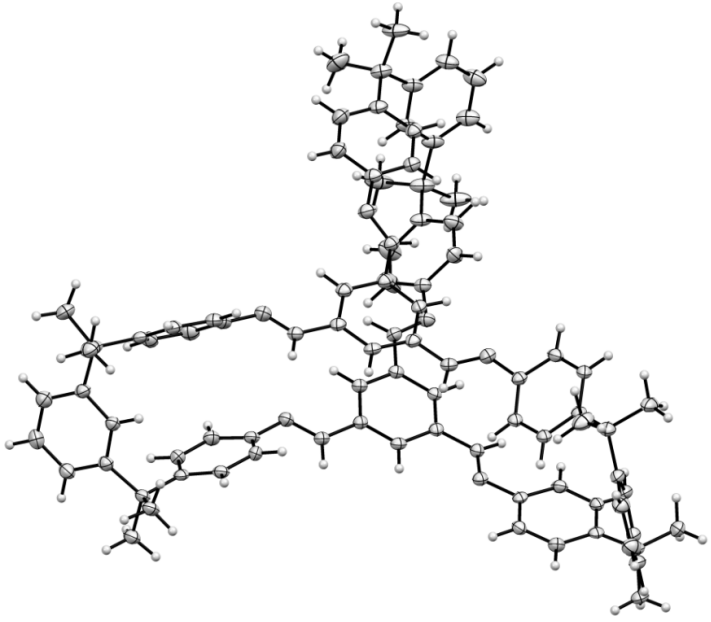


Fig. 8 ORTEP diagram of the macrocycle **10** (thermal ellipsoids are shown in 50% probability level).

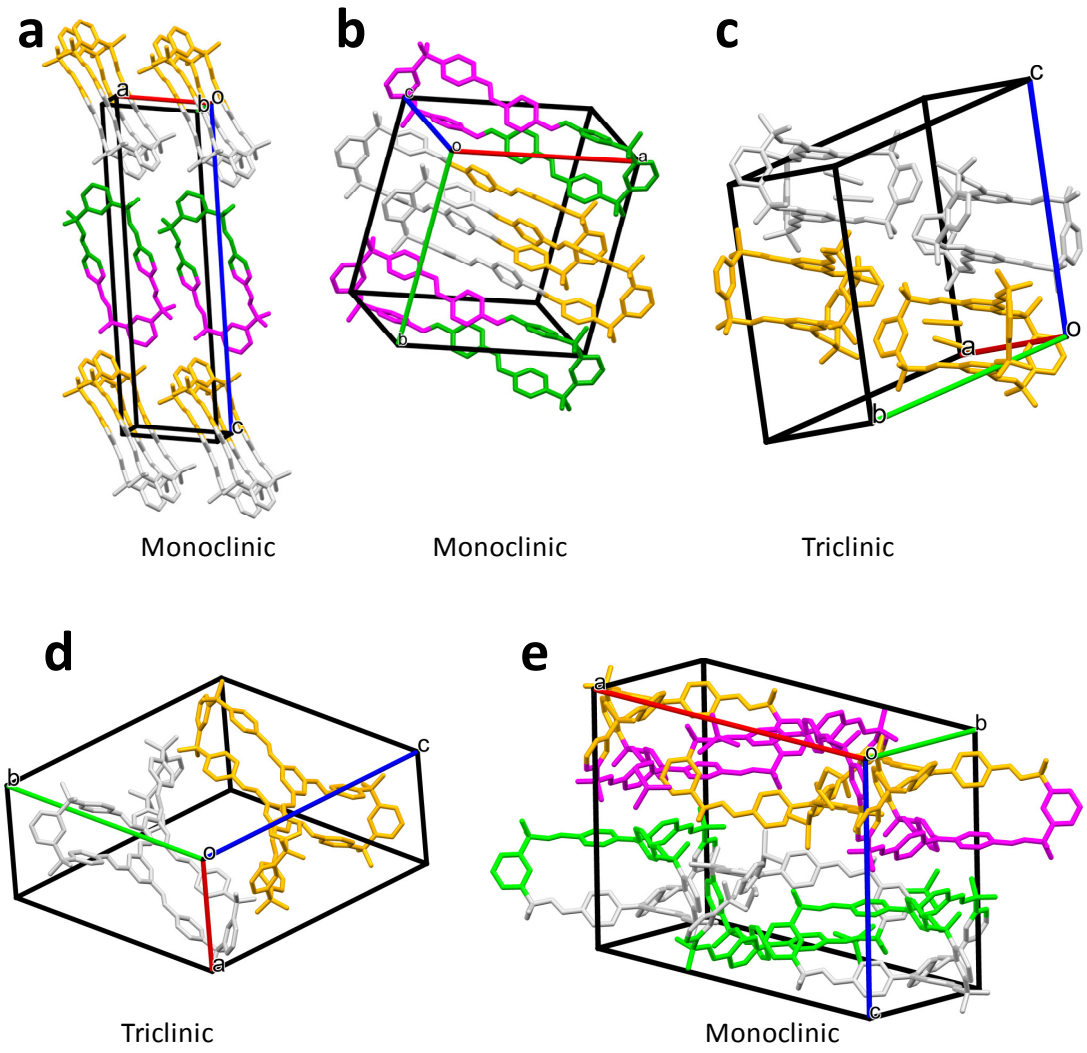


Fig. 9 Unit cells of macrocycle/cages with symmetry operation. a) Macrocycle-**3**, b) Macrocycle-**5a**, c) Cage-**7**, d) Cage-**10**, e) Cage-**9**.

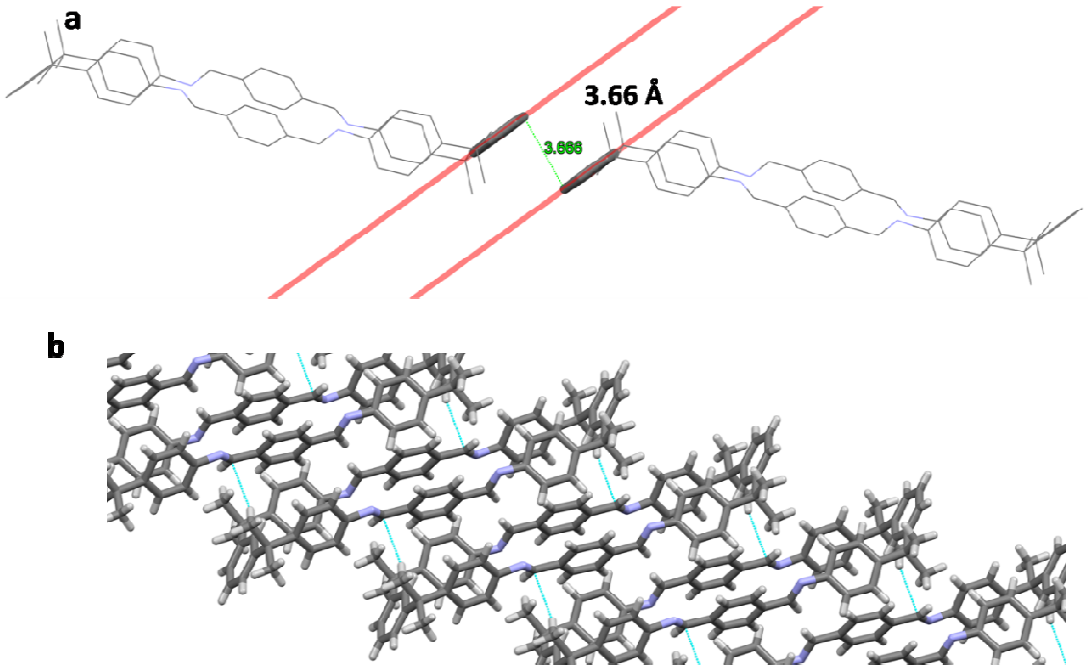


Fig. 10 CH-π and π-π stacking interaction in the Macrocycle 5a. a) Terminal benzene ring of the macrocycle **5a** showing intermolecular parallel displaced π-π stacking with the distance of 3.6 Å. b) X-ray crystal structure of macrocycle **5a** showing continuous intermolecular CH-π interactions.

Note: The presence of large number of continuous intermolecular CH-π and π-π stacking interactions is presumably the reason for the reduced solubility of macrocycle **5a**.

Microscopic crystals-images of macrocycles 5b and 5c.

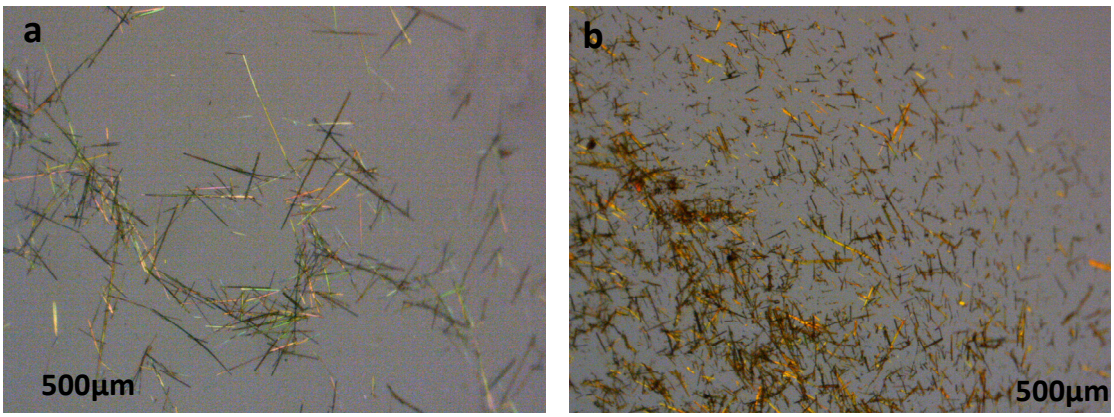


Fig. 11 a) Yellow coloured crystals of macrocycle **5b**; b) Organge coloured crystals of macrocycle **5c**.

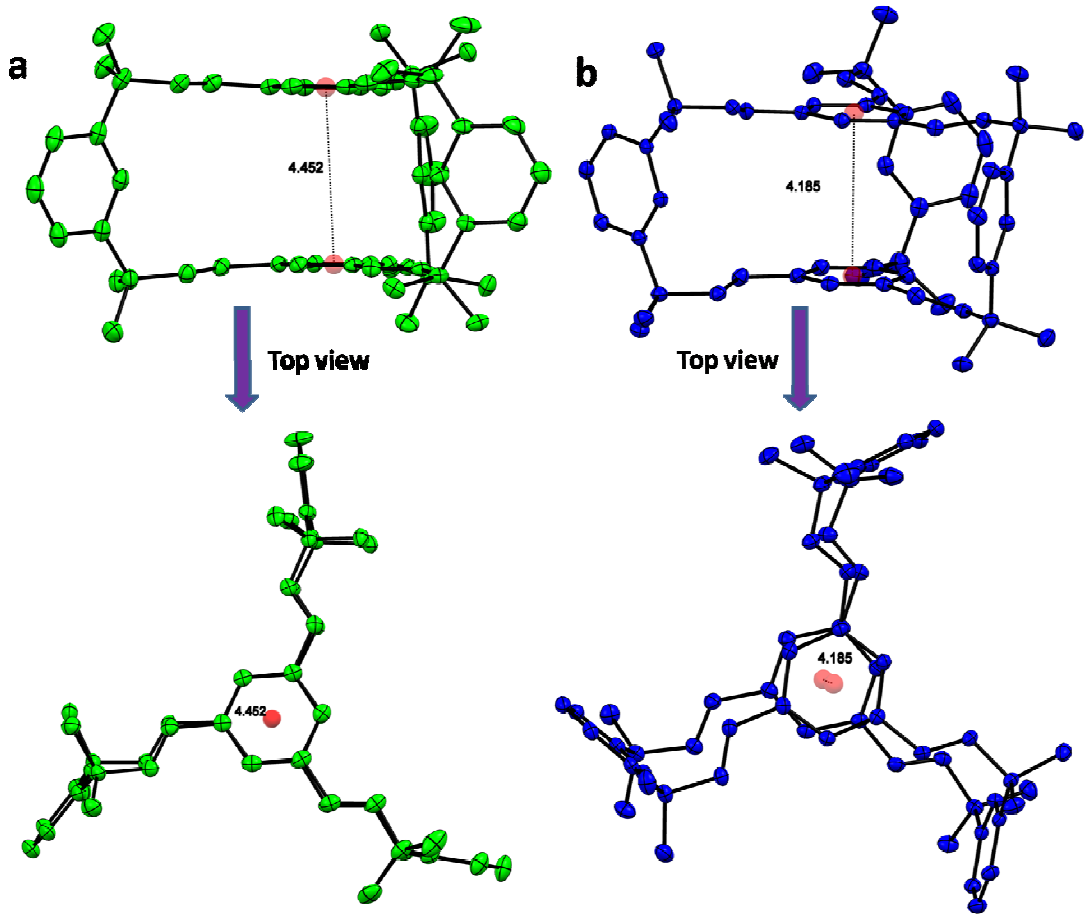


Fig. 12 Side and top views of the two types of isomers found in the unit cell of cage-7. a) The distance between the central benzene ring is 4.452 Å and the central benzene rings were found to be in the fully-eclipsed manner, b) The distance between the central benzene ring is 4.185 Å and the central benzene rings were found to be in a slightly displaced manner.

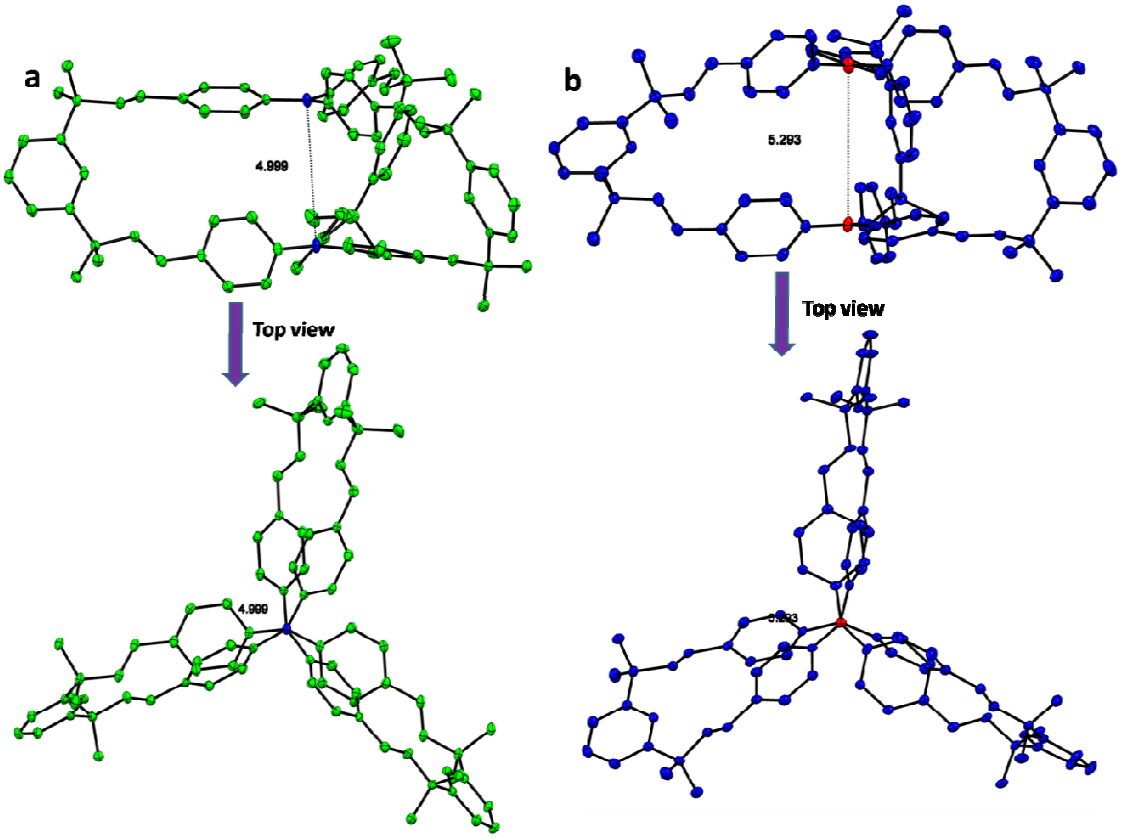


Fig. 13 Side and top views of the two types of isomers found in the unit cell of cage-9. a) The distance between the central nitrogen atoms (blue coloured) is 4.99 Å. b) The distance between the central nitrogen atoms (red coloured) is 5.293 Å.

Discontinuous extrinsic voids in cage **7**:

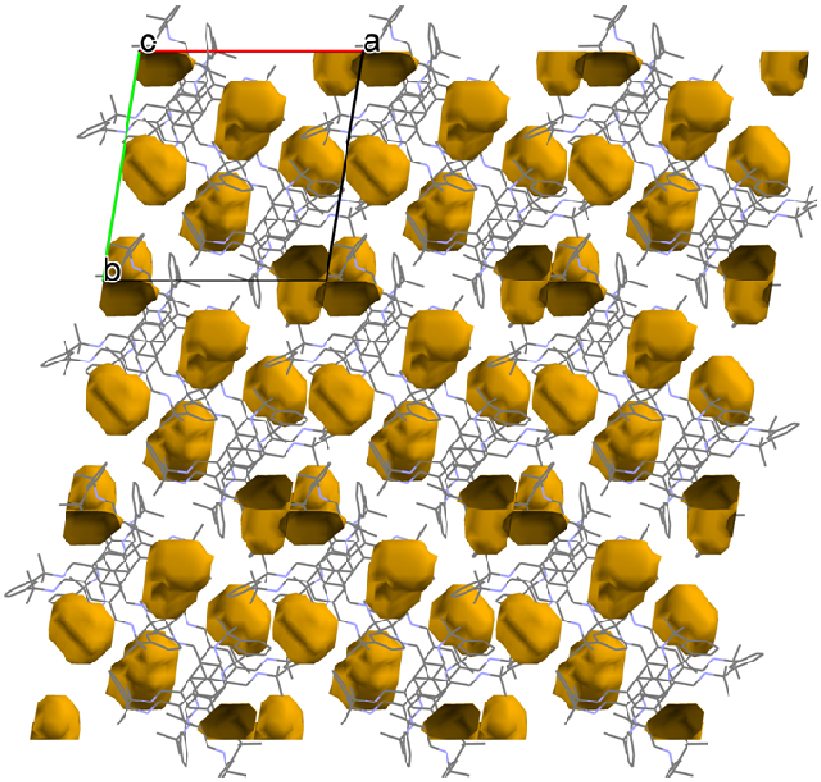


Fig. 14 Manual deletion solvent molecules (ACN) from the crystal lattice of cage-**7** generate discontinuous extrinsic voids amounting 262.13 $Å^3$ per unit cell (5.2% of the cell volume).

Note: The voids are calculated using contact surface with the probe radius 2.0 Å.

Generation of extrinsic voids in cage **10**:

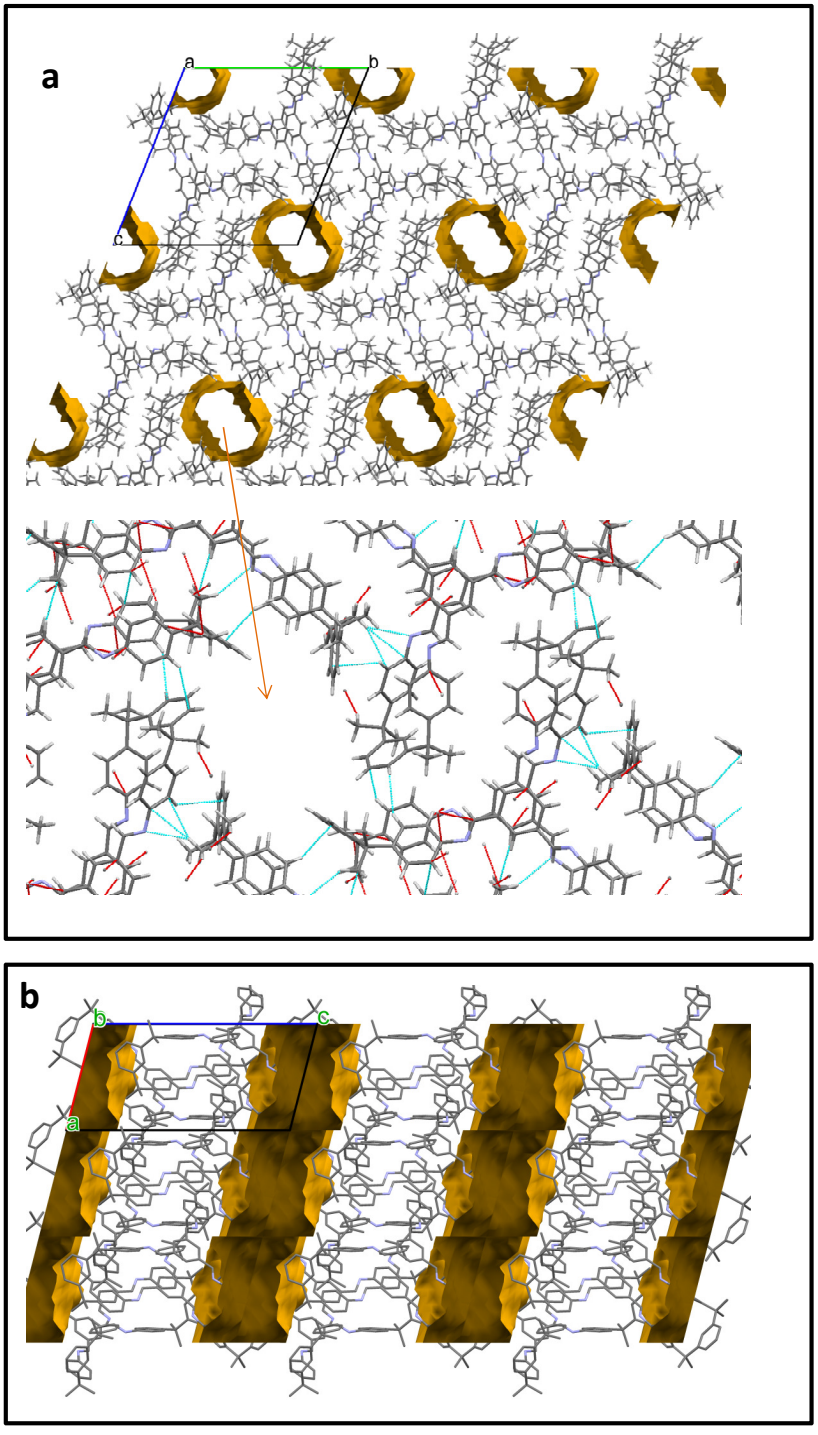


Fig. 15 a) The successive association (through C-H…N, marginal C-H···π and other Van der Waals forces.) of six propeller-shaped cage **10** constitutes the hexagonal one-dimensional network along the a-axis. b) The voids generated along a-axis are calculated using contact surface with the probe radius 2.0 Å revealing voids amounting to 507.18 $Å^3$ per unit cell (12.9% of the cell volume).

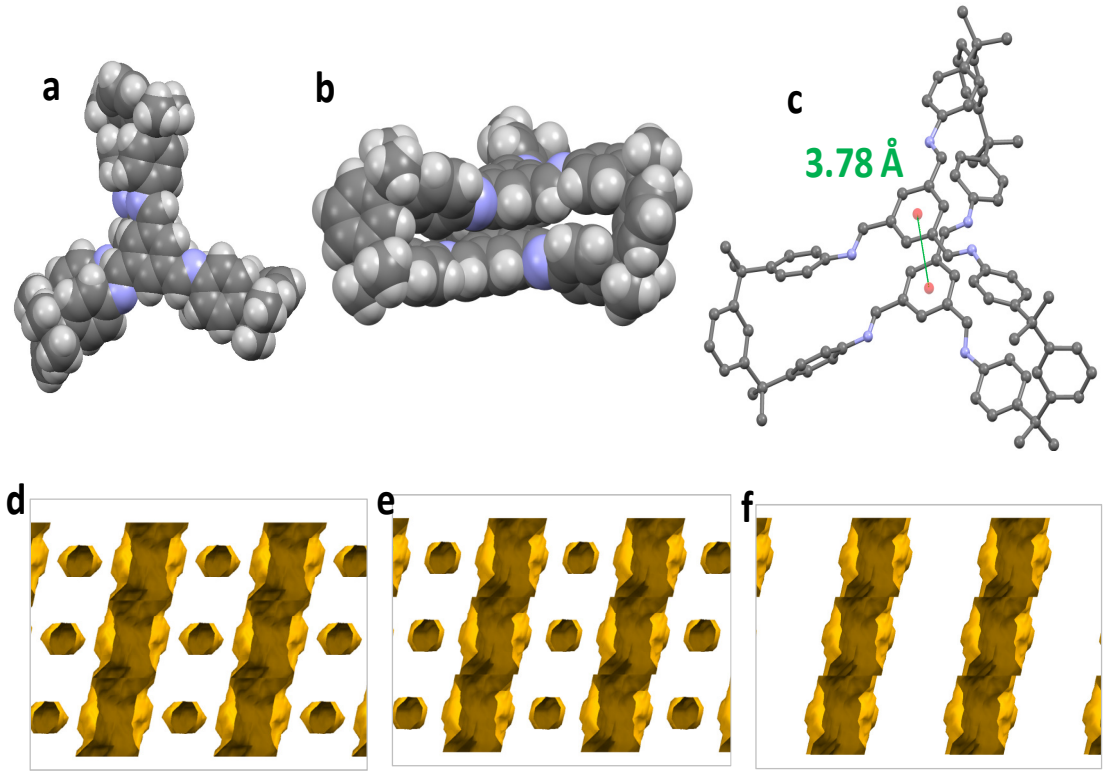


Fig 16 a) Space-filling model of a three-bladed fan-like *pseudo* co-facial cage crystal structure of **10** viewed from the top. b) Side view of the crystal structure of **7** shows negligible intrinsic voids (space-fill model). c) Crystal structure of **7** (ball and stick model) shows the distance between the two central benzene rings to be 3.78 Å. d) Connolly surfaces generated for hydrogen showing the channels/voids (probe radii: 1.42 Å), e) Connolly surfaces generated for carbon dioxide showing the channels/voids (probe radii: 1.72 Å) and f) Connolly surfaces generated for nitrogen showing the channels/voids (probe radii: 1.82 Å).

Note: The 1-D channels present in crystals of **10** have a void diameters which are little larger than the kinetic diameter of many gasses (S. Sircar, *Ind. Eng. Chem. Res*., 2006, **45**, 5435).

Powder X-ray diffraction (PXRD):

Powder X-ray diffraction (XRD) patterns were recorded on a PANalytical X'Pert PRO X-ray diffractometer, using Cu Kα radiation.

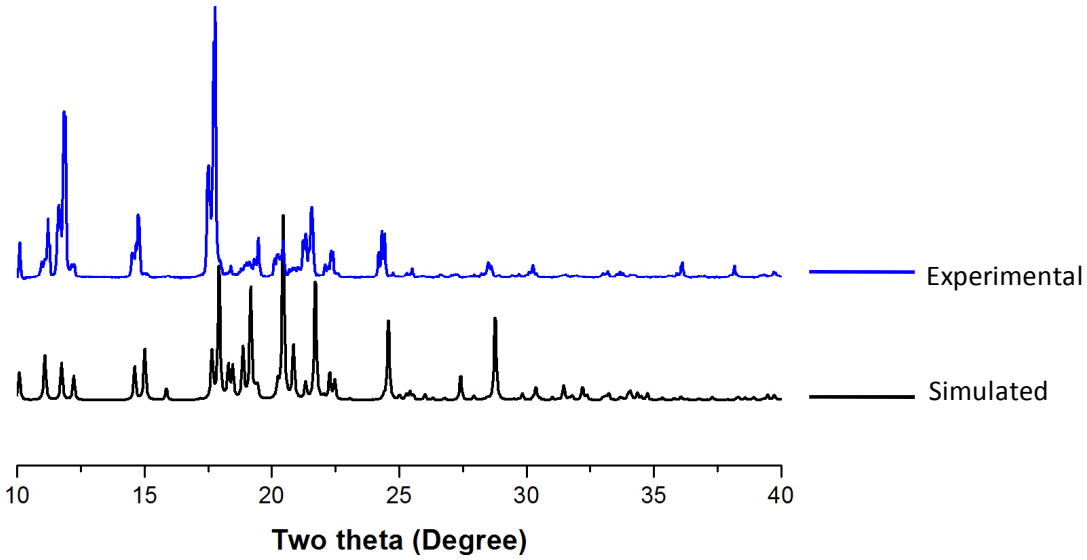


Fig.17 Comparison of experimental (blue) and simulated (black) PXRD (from the single crystal structure) patterns of macrocycle **3**.

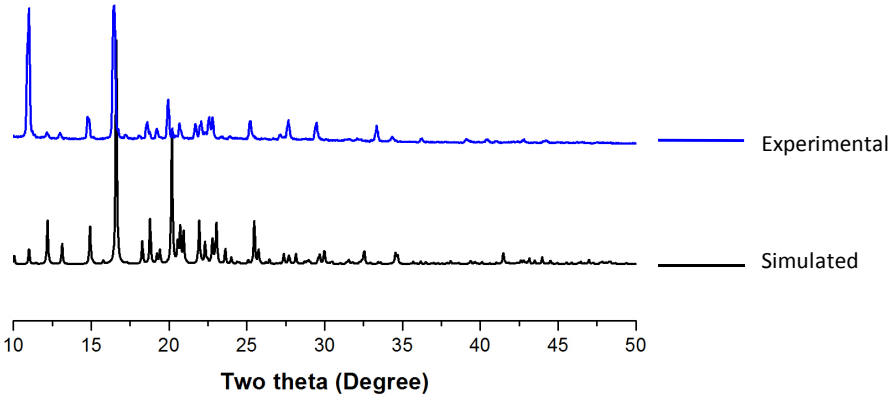


Fig. 18 Comparison of experimental (blue) and simulated (black) PXRD (from the single crystal structure) patterns of macrocycle **5a**.

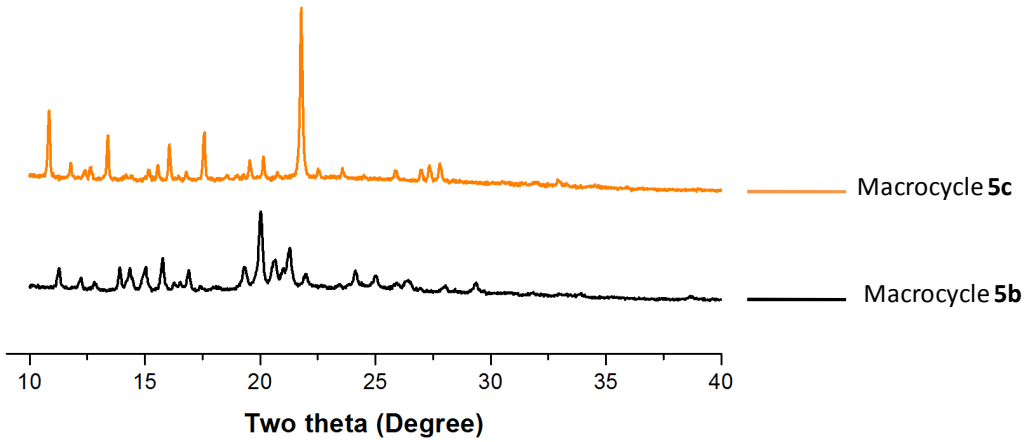


Fig. 19 Powder X-ray diffraction patterns for macrocycle **5b** (black) and **5c**.

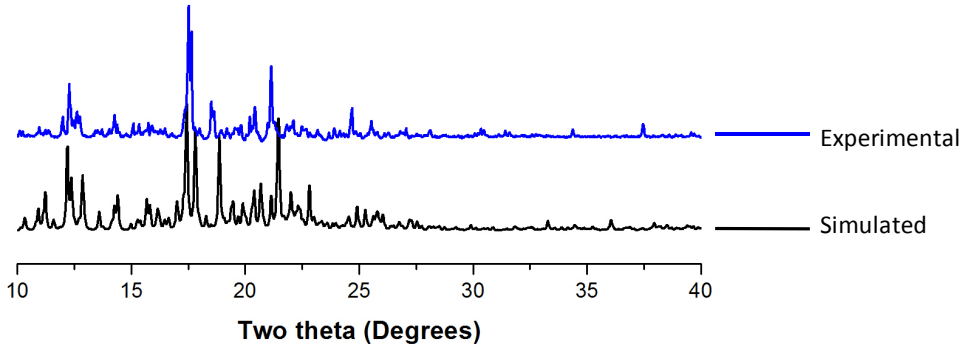


Fig. 20 Comparison of experimental (blue) and simulated (black) PXRD (from the single crystal structure) patterns of cage **7**.

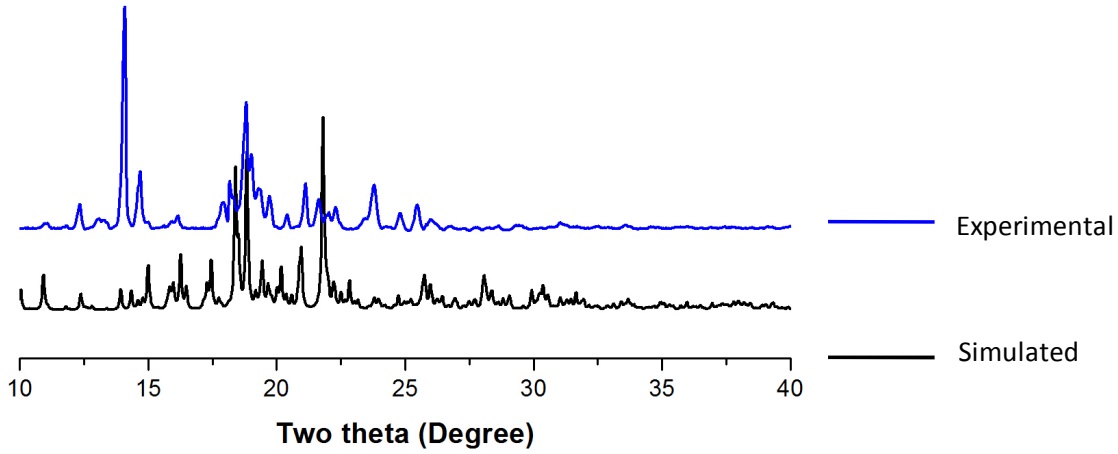


Fig. 21 Comparison of experimental (blue) and simulated (black) PXRD (from the single crystal structure) patterns of cage **9**.

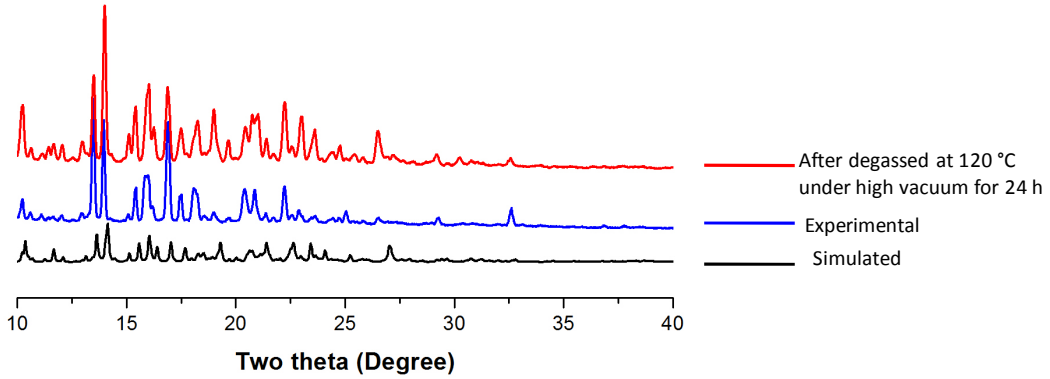


Fig. 22 Comparison of powder X-ray diffraction patterns for **10** recorded for the bulk sample as synthesized (middle, blue), simulated PXRD from the single crystal structure for **10** (bottom, black) and after degassed at 120 °C under high vacuum for 24 h (top, red).

Note 1: The experimental PXRD data were collected at room temperature while the single crystal X-ray data that used to generate the simulated pattern were collected at 100 K.

Note 2: There was no change in the experimental PXRD data before and after degassing at 120 °C under high vacuum for 24 h, which suggested that the crystals are stable under these conditions.

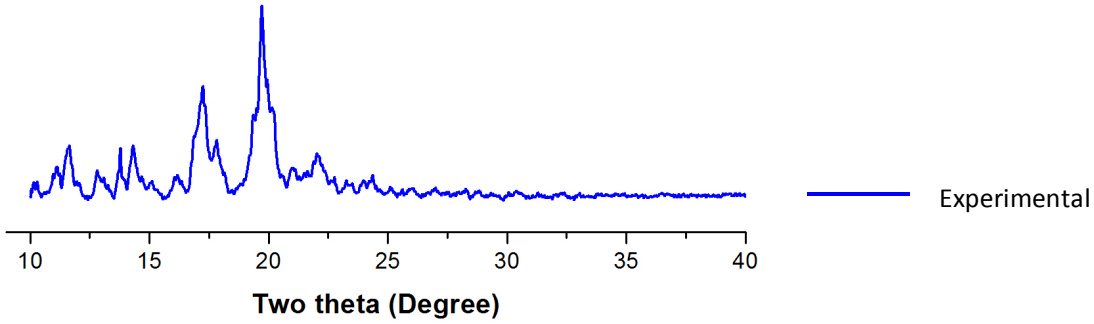


Fig. 23 Powder X-ray diffraction pattern of cage **11**.

References

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2. (a) Bruker (2016). *APEX3*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA; b) Bruker (2006). *APEX3*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
3. (a) G. M. Sheldrick, *Acta Crystallogr*., 2008, **A64**, 112; b) L. J. Farrugia, *J. Appl. Cryst.* 1997, **30**, 565–565.