Supporting Information for:

Structurally Disfavoured Pseudopeptidic Macrocycles through Anion Templation

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General experimental procedures: Reagents and solvents were purchased from commercial suppliers (Adrich, Fluka or Merck) and were used without further purification. Compounds **3a,b** were prepared following previously reported procedures.

NMR spectroscopy: The NMR experiments were carried out either on a Varian INOVA 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) or a Varian MERCURY 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Chemical shifts are reported in ppm using TMS or residual non-deuterated solvent peaks as internal standards.

Mass spectrometry: Mass spectra were recorded on a hybrid QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface (Micromass, Manchester, UK). The desolvation gas as well as nebulizing gas was nitrogen at a flow of 700L/h and 20 L/h respectively. The temperature of the source block was set to 120 ºC and the desolvation temperature to 150ºC. A capillary voltage of 3.5 KV and 3.3 KV was used in the positive and negative scan mode, respectively. The cone voltage was typically set to 20 V to control the extent of fragmentation of the identified ions. Sample solutions were infused via syringe pump directly connected to the ESI source at a flow rate of 10 μL/min. The observed isotopic pattern of each intermediate perfectly matched the theoretical isotope pattern calculated from their elemental composition using the MassLynx 4.0 program. Mass spectra were also recorded on a Micromass Quattro LC spectrometer equipped with an electrospray ionisation source and a triple-quadrupole analyzer.

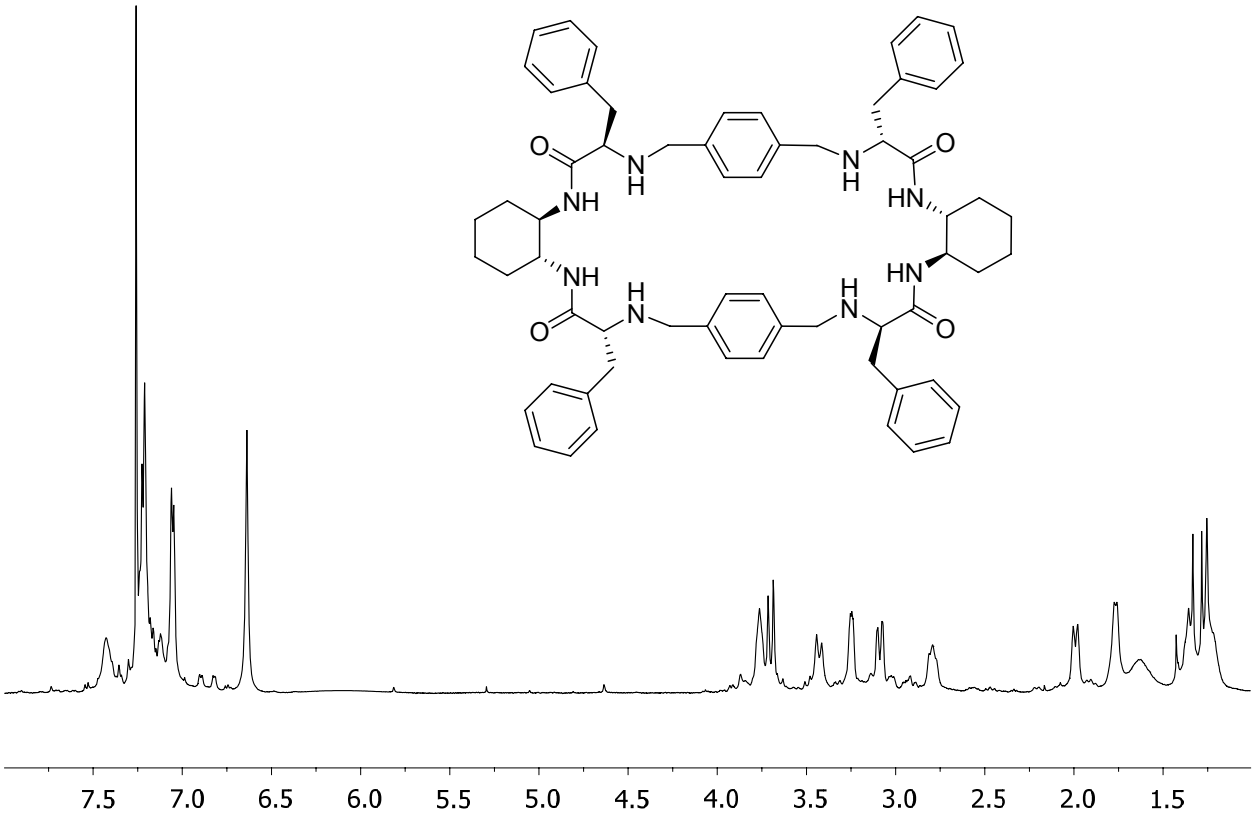
Anion templated macrocyclization reaction: synthesis of **6a** and **7a**. A solution of **5**·2TBA (126 mg, 0.194 mmol) in a 1 : 1 mixture of chloroform and degassed MeOH (4 mL) was added to a solution of **3a** (158 mg, 0.39 mmol) also in the same mixture of solvents (4 mL) under nitrogen atmosphere. Then, dialdehyde **4** (53 mg, 0.39 mmol in 3 mL of 1 . 1 $CHCl_3$: MeOH) was added and filled with additional 3-5 mL of solvent mixture until a final ~0.025 M concentration. The reaction was stirred at room temperature for 48 hours and, after that, $NaBH_4$ (119 mg, 3.10 mmol) was carefully added at 0ºC. The mixture was allowed to react for 24 hours before being hydrolyzed (conc. HCl) and evaporated to dryness. The residue obtained was re-dissolved in water and basified with 1M NaOH, the product extracted with chloroform, the combined organic layers dried and evaporated *in vacuum*. The products were purified by silica gel flash chromatography using CH_2Cl_2 as mobile phase while increasing slowly the polarity with MeOH (0% to 15%), several drops of aqueous NH_3 (~0.05%) were added to the mobile phase in order to improve the extraction of the product. The fractions that showed the same Rf were combined. Evaporation of the solvents yielded the products **6a** (firstly eluted, 98.7 mg, 0.097 mmol) and **7a** (secondly eluted, 29.6 mg, 0.019 mmol).

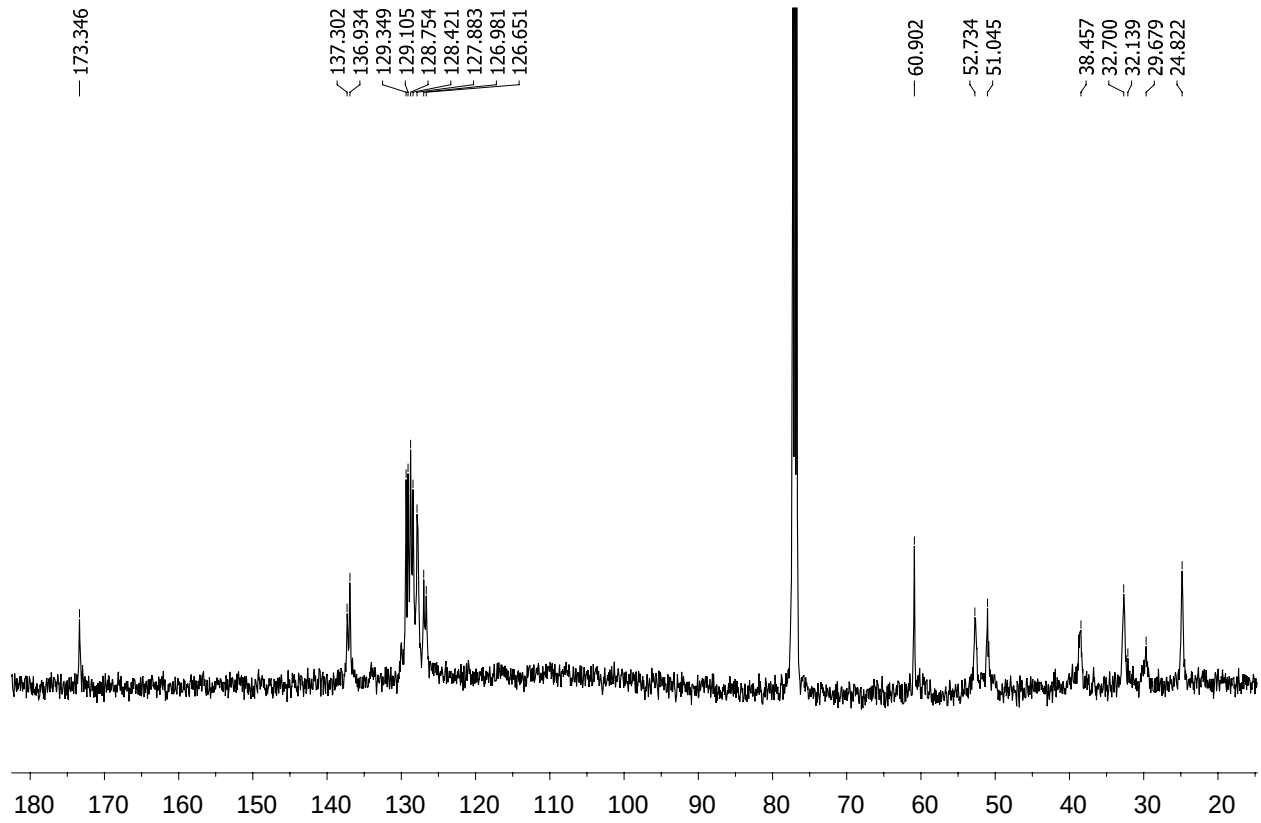
6a: ^{1}H NMR (500 MHz, $CDCl_3$, 303 K): 1.25-1.43 (m, 8H), 1.63 (bs, 4H, amine NH), 1.76 (bd, J = 7.3 Hz, 4H), 1.99 (bd, J = 12.1 Hz, 4H), 2.79 (bdd, $^{2}J_{HH}$ = 13.0 Hz and $^{3}J_{HH}$ = 7.9 Hz, 4H), 3.09 (bdd, $^{2}J_{HH}$ = 13.0 Hz and $^{3}J_{HH}$ = 3.8 Hz, 4H), 3.25 (bdd, $^{3}J_{HH}$ = 7.9 Hz and $^{3}J_{HH}$ = 3.8 Hz, 4H), 3.43 (d, $^{2}J_{HH}$ = 14.4 Hz, 4H), 3.70 (d, $^{2}J_{HH}$ = 14.4 Hz, 4H), 3.76 (bs, 4H), 6.64 (bs, 8H), 7.05 (bd, $^{3}J_{HH}$ = 6.5 Hz, 8H), 7.22 (m, 12H), 7.43 (bs, 4H, amide NH). ^{13}C NMR (125 MHz, $CDCl_3$, 303 K): 24.8, 29.7, 32.1, 38.5, 51.0, 52.7, 60.9, 126.7, 127.0, 127.8, 127.9, 128.4, 128.8, 129.1, 129.3, 136.9, 137.3, 173.3. ESI-TOF MS (m/z): 1043.6 [$(M+Na)^{+}$, 43], 1021.6 [$(M+H)^{+}$, 100], 513.3 [$(M+2H)^{2+}$, 100].

7a: ^{1}H NMR (500 MHz, $CDCl_3$, 303 K): 1.21-1.37 (m, 12H), 1.58 (bs, 6H, amine NH), 1.75 (bd, J = 7.2 Hz, 6H), 1.99 (bd, J = 12.2 Hz, 6H), 2.72 (bdd, $^{2}J_{HH}$ = 13.2 Hz and $^{3}J_{HH}$ = 8.2 Hz, 6H), 3.06 (bdd, $^{2}J_{HH}$ = 13.2 Hz and $^{3}J_{HH}$ = 3.0 Hz, 6H), 3.21 (bdd, $^{3}J_{HH}$ = 8.2 Hz and $^{3}J_{HH}$ = 3.0 Hz, 6H), 3.28 (d, $^{2}J_{HH}$ = 13.3 Hz, 6H), 3.62 (d, $^{2}J_{HH}$ = 13.3 Hz, 6H), 3.72 (bm, 6H), 6.74 (bs, 12H), 7.06 (bd, $^{3}J_{HH}$ = 6.3 Hz, 12H), 7.22 (m, 18H), 7.51 (bs, 6H, amide NH). ^{13}C NMR (125 MHz, $CDCl_3$, 303 K): 25.0, 29.9, 32.8, 39.3, 52.3, 52.9, 62.5, 127.1, 128.3, 129.4, 137.2, 138.0, 173.7. ESI-TOF MS (m/z): 584.4 [$(M+2Na)^{2+}$, 30], 766.5 [$(M+2H)^{2+}$, 18], 511.2 [$(M+3H)^{3+}$, 100]

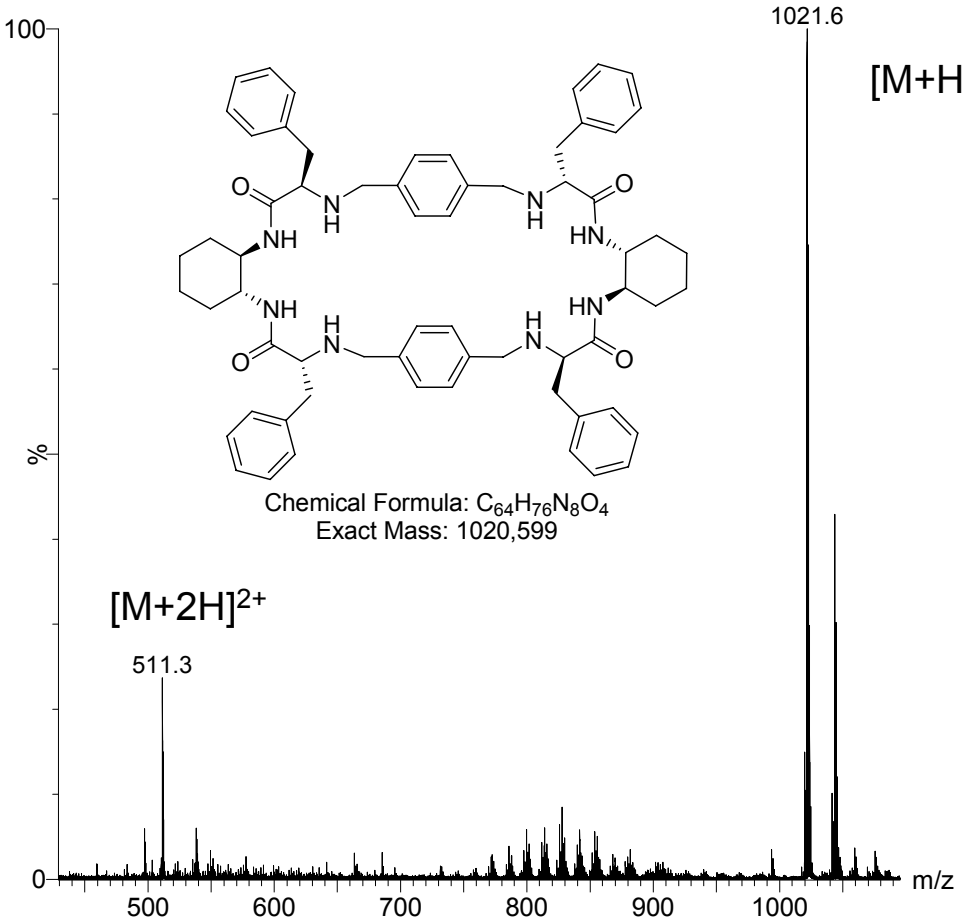
Following there are the copies of the ^{1}H NMR, ^{13}C NMR and high resolution ESI-TOF MS.

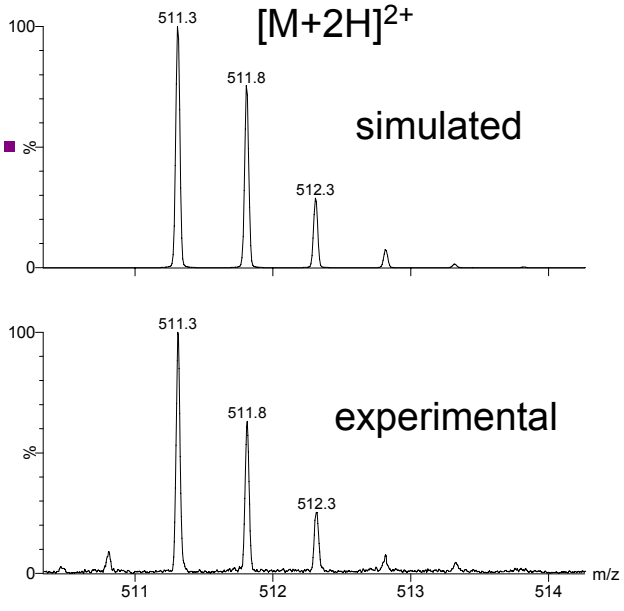
^{1}H and ^{13}C NMR spectra of **6a** ($CDCl_3$, 303 K)

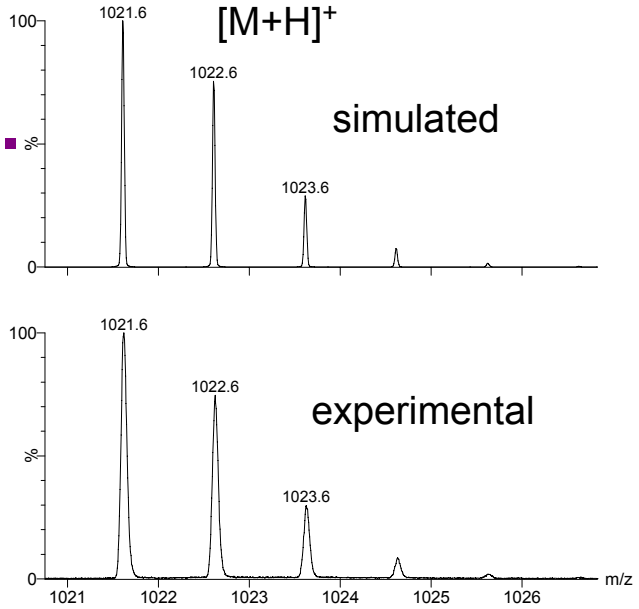




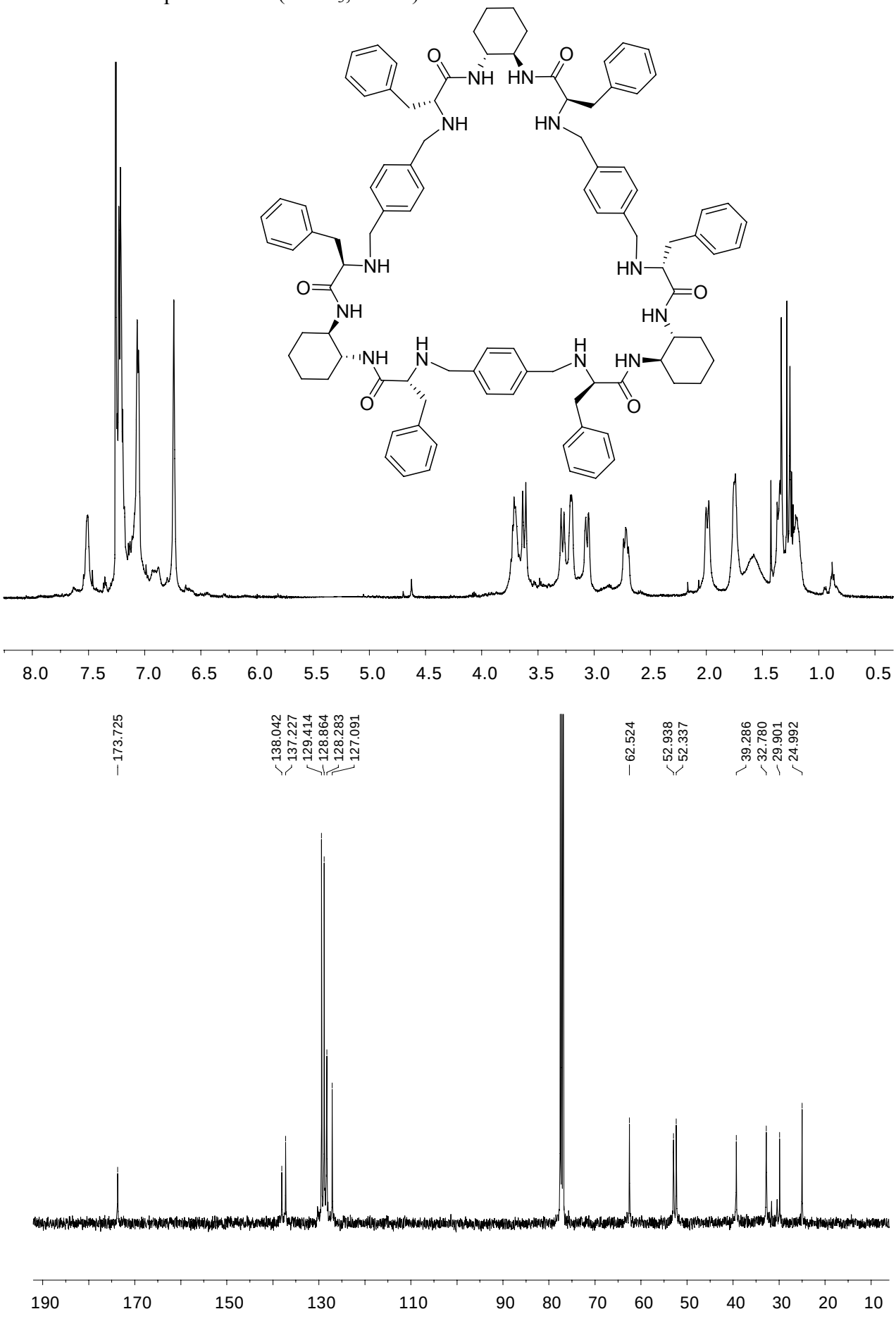
ESI-TOF mass spectrum of **6a**



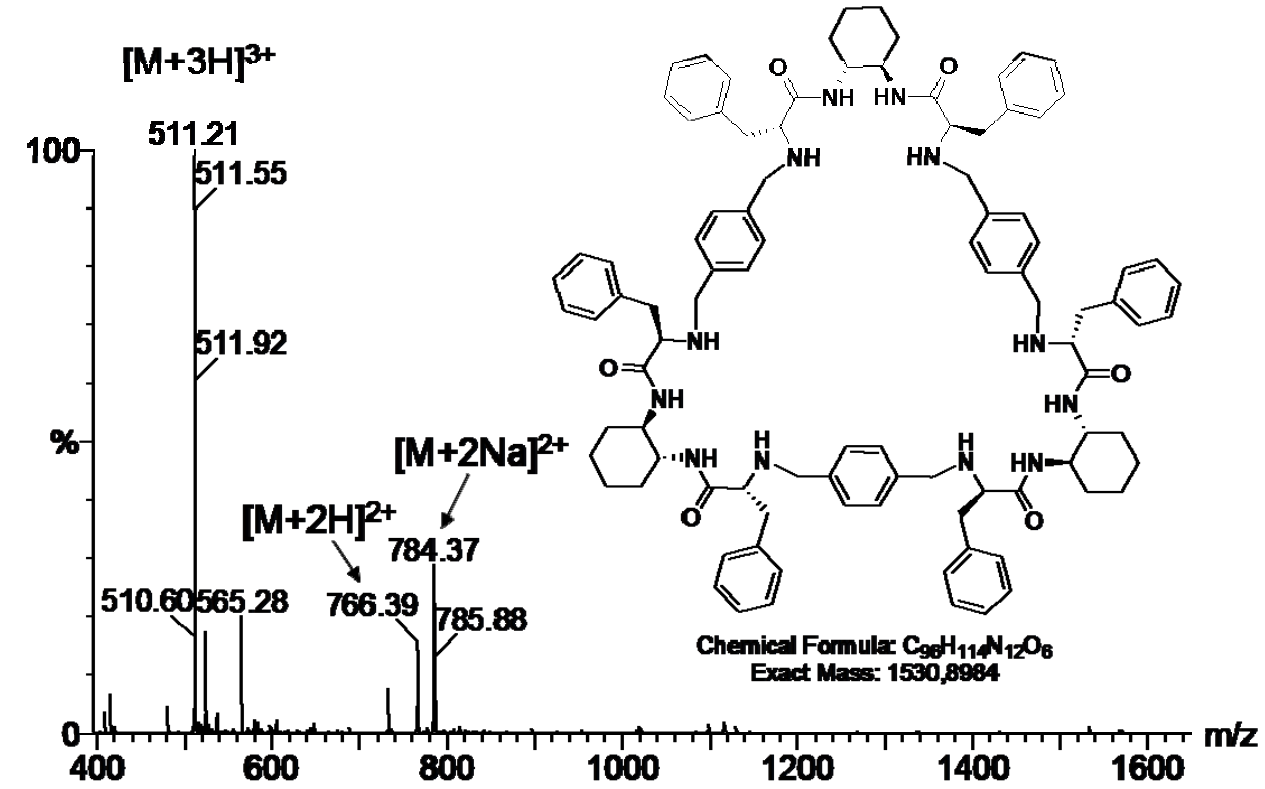


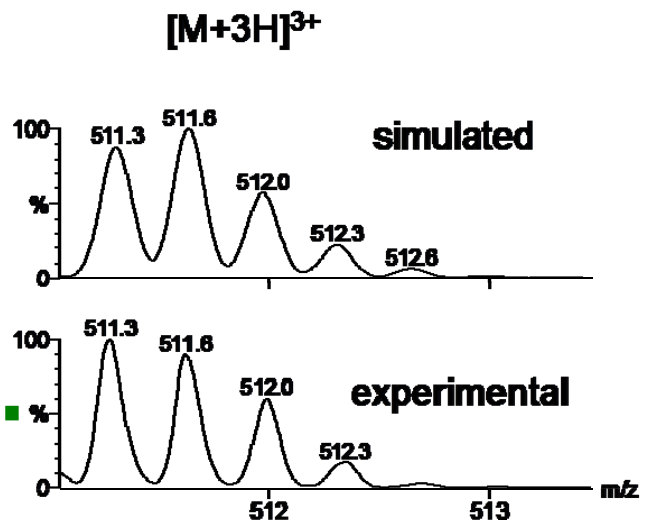


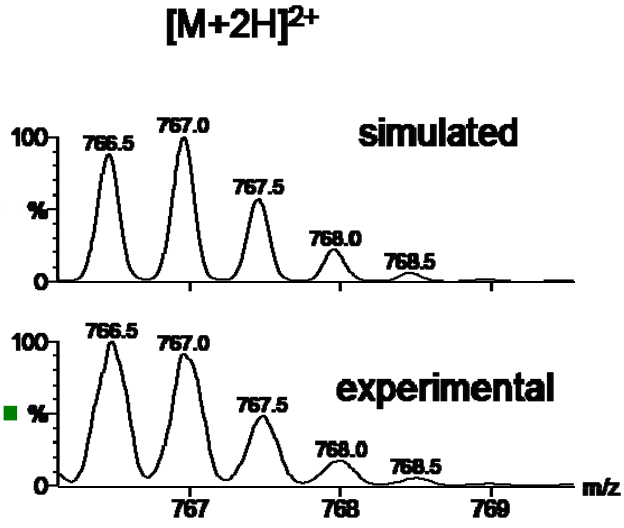
^{1}H and ^{13}C NMR spectra of **7a** ($CDCl_3$, 303 K)



ESI-TOF mass spectrum of **7a**







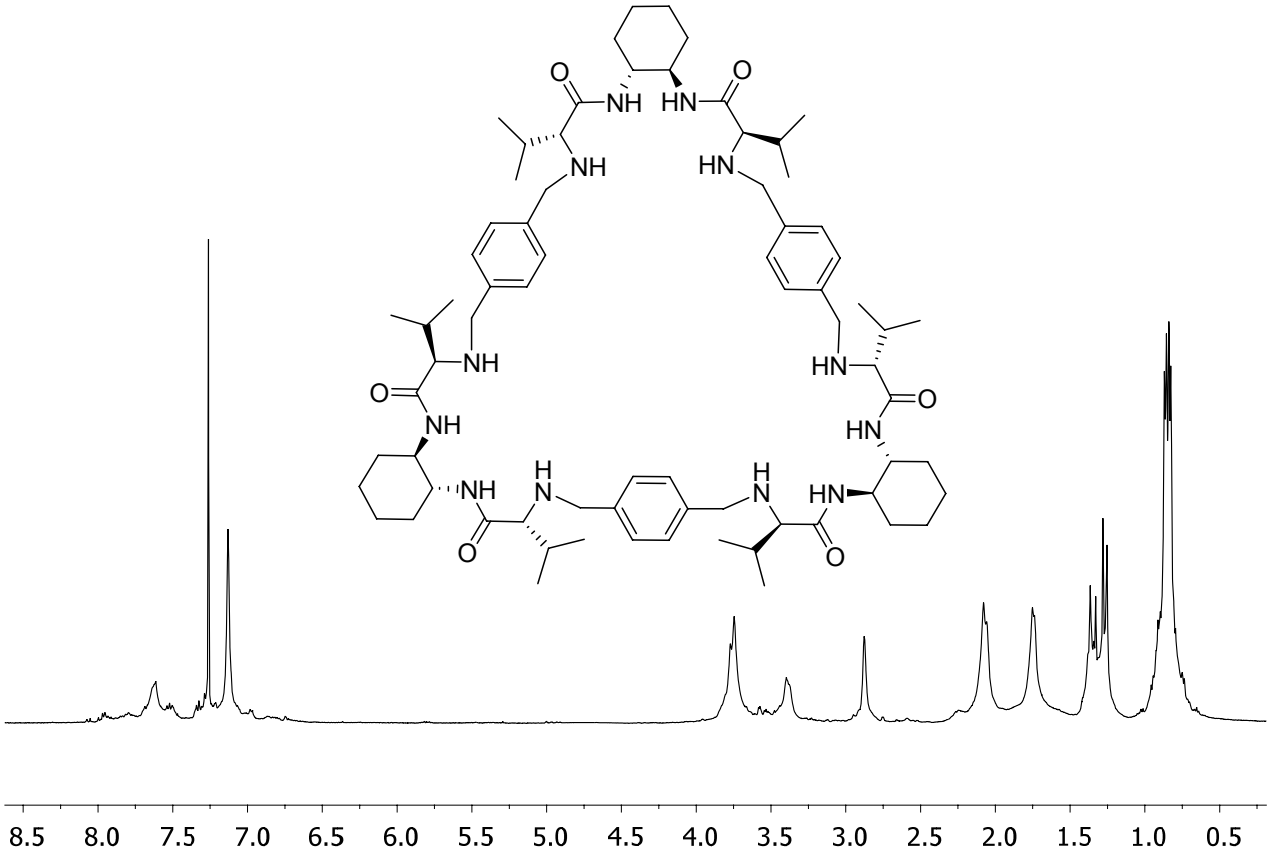
In the case of the Val derivative, **3b**, the anion templated imine-formation reaction can be performed either in the same mixture of solvents as for **3a** or in pure MeOH. The experimental procedure is as follows. A solution of **5**·2TBA (126 mg, 0.194 mmol) in a 1 : 1 mixture of chloroform and degassed MeOH (4 mL) was added to a solution of **3b** (121 mg, 0.39 mmol) also in the same mixture of solvents (4 mL) under nitrogen atmosphere. Then, dialdehyde **4** (53 mg, 0.39 mmol in 3 mL of 1 . 1 $CHCl_3$: MeOH) was added and filled with additional 3-5 mL of solvent mixture until a final ~0.025 M concentration. The reaction was stirred at room temperature for 48 hours, although a white precipitate was formed after several (<8) hours. After the 48 h of reaction, $NaBH_4$ (119 mg, 3.10 mmol) was carefully added at 0ºC. The mixture was allowed to react for 24 hours before being hydrolyzed (conc. HCl) and evaporated to dryness. The residue obtained was redissolved in water and basified with 1M NaOH, the product extracted with chloroform, the combined organic layers dried and evaporated *in vacuum*. The products were purified by silica gel flash chromatography using CH_2Cl_2 as mobile phase while increasing slowly the polarity with MeOH (0% to 15%), several drops of aqueous NH_3 (~0.05%) were added to the mobile phase in order to improve the extraction of the product. The fractions that showed the same Rf were combined. After that, we isolated the products **7b** (firstly eluted, 64.1 mg, 0.052 mmol) and **8b** (secondly eluted, 31.5 mg, 0.019 mmol) as white solids.

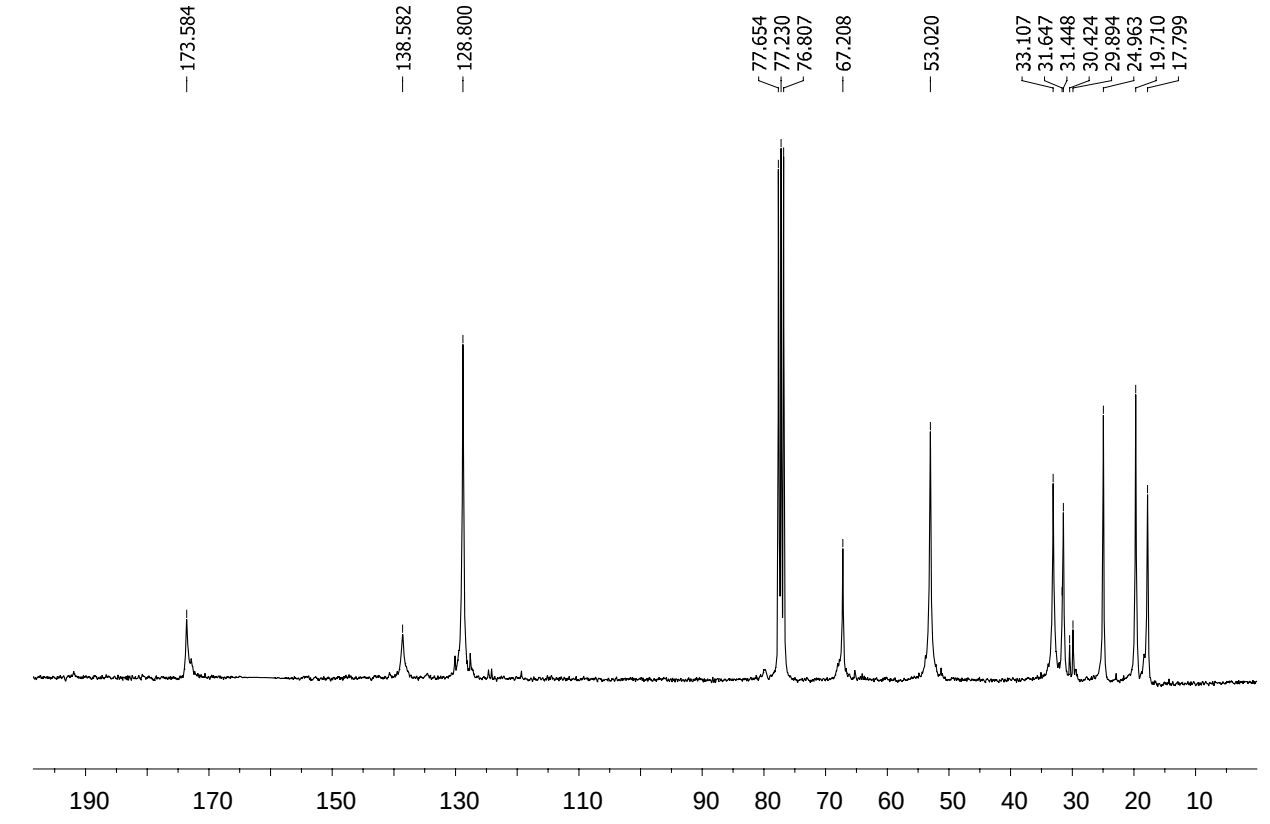
7b: ^{1}H NMR (500 MHz, $CDCl_3$, 303 K): 0.75-0.98 (m, 36H), 1.17-1.42 (m, 18H), 1.74 (m, 9H), 2.07 (m, 9H), 2.88 (bs, 6H), 3.39 (bd, J = 12.0 Hz, 6H), 3.65-3.84 (m, 6H overlapped with bd, J = 12.0 Hz, 6H), 7.13 (bs, 12H), 7.62 (bs, 6H amide NH). ^{13}C NMR (100 MHz, $CDCl_3$, 303 K): 17.8, 19.7, 24.9, 29.9, 30.4, 31.4, 31.6, 33.1, 53.0, 67.2, 128.8, 138.6, 173.6. ESI-TOF MS (m/z): 622.5 [$(M+2H)^{2+}$, 95], 415.3 [$(M+3H)^{3+}$, 100].

8b: ^{1}H NMR (500 MHz, $CDCl_3$, 303 K): 0.68-0.87 (m, 48H), 1.07-1.46 (m, 24H), 1.75 (m, 12H), 2.08 (m, 12H), 2.86 (bs, 8H), 3.44 (bs, *8*H), 3.72 (bm, 16H), 7.22 (bs, 16H), 7.63 (bs, 8H amide NH). ^{13}C NMR (100 MHz, $CDCl_3$, 303 K): 17.9, 19.8, 24.9, 29.9, 30.4, 31.4, 31.7, 33.0, 53.2, 67.6, 128.9, 138.7, 173.7. ESI-TOF MS (m/z): 840.6 [$(M+H+Na)^{2+}$, 70], 829.6 [$(M+2H)^{2+}$, 100], 553.4 [$(M+3H)^{3+}$, 20].

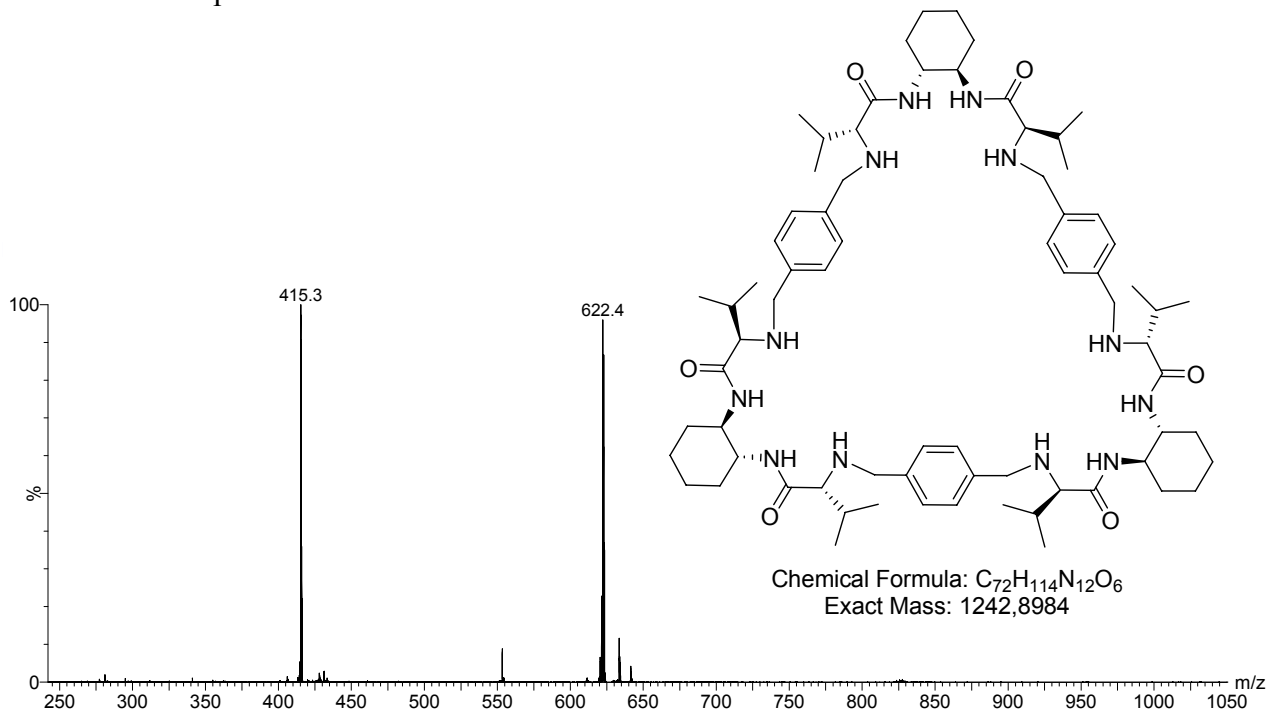
Following there are the copies of the corresponding ^{1}H and ^{13}C NMR spectra, as well as the high resolution ESI-TOF mass spectra with the experimental and simulated isotopic patterns.

^{1}H and ^{13}C NMR spectra of **7b** ($CDCl_3$, 303 K)

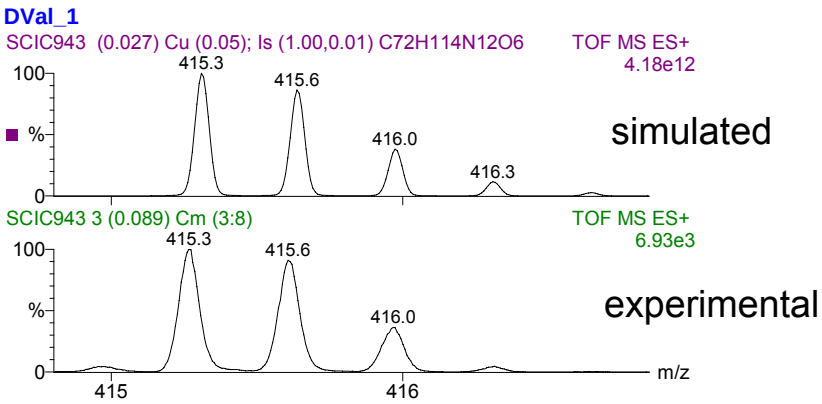




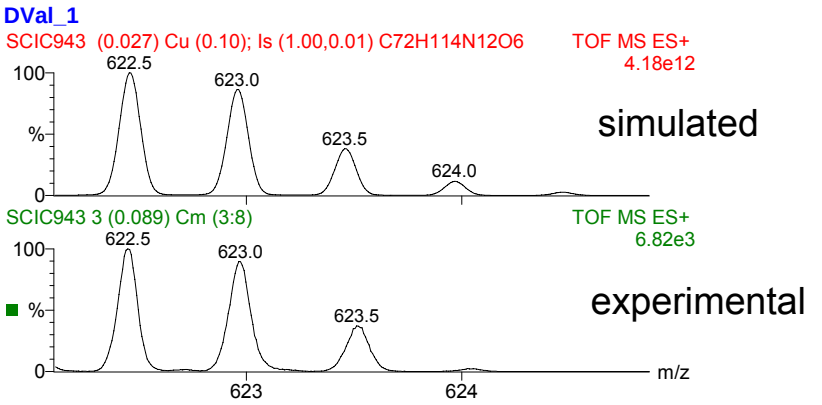
ESI-TOF mass spectrum of **7b**



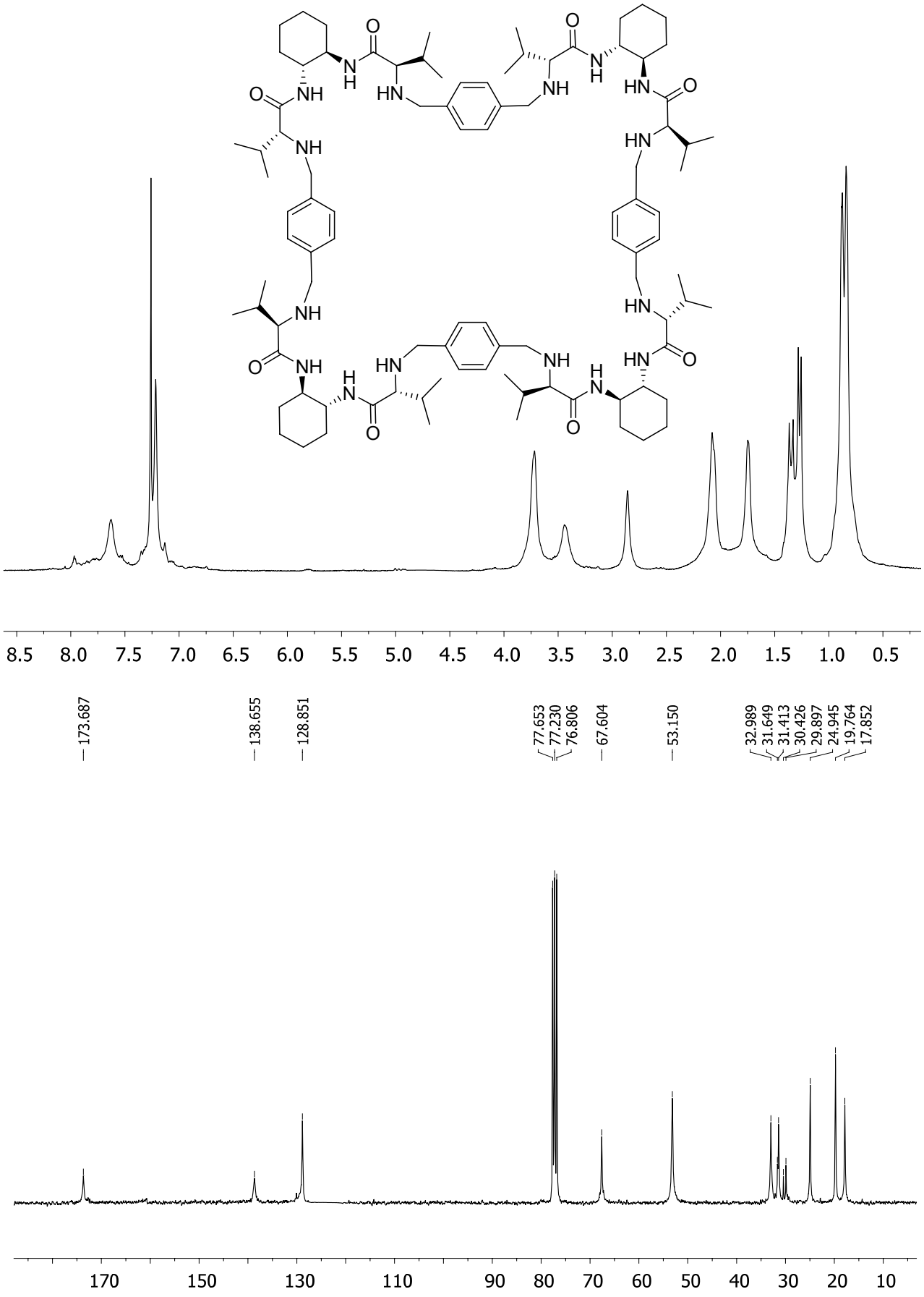
$[M+3H]^{3+}$



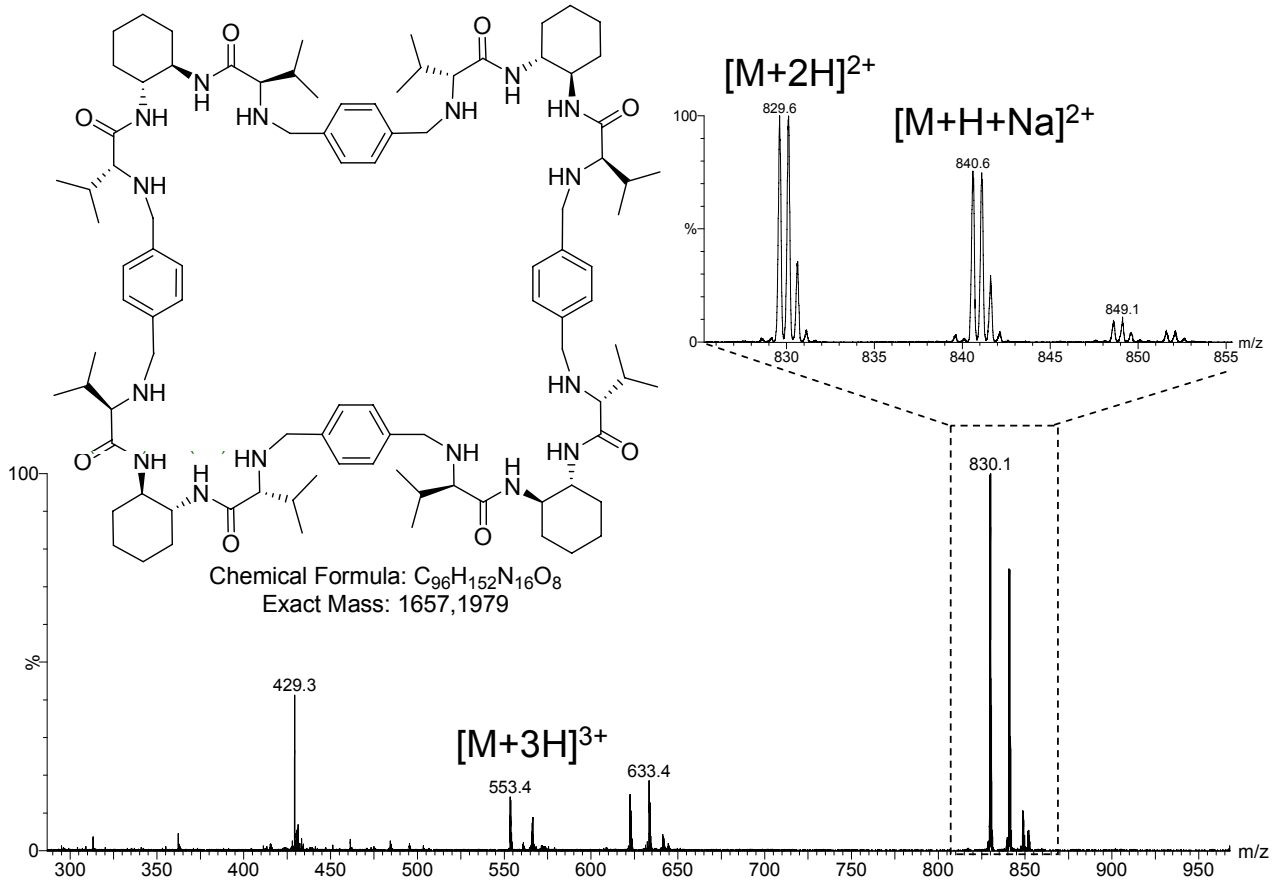
$[M+2H]^{2+}$

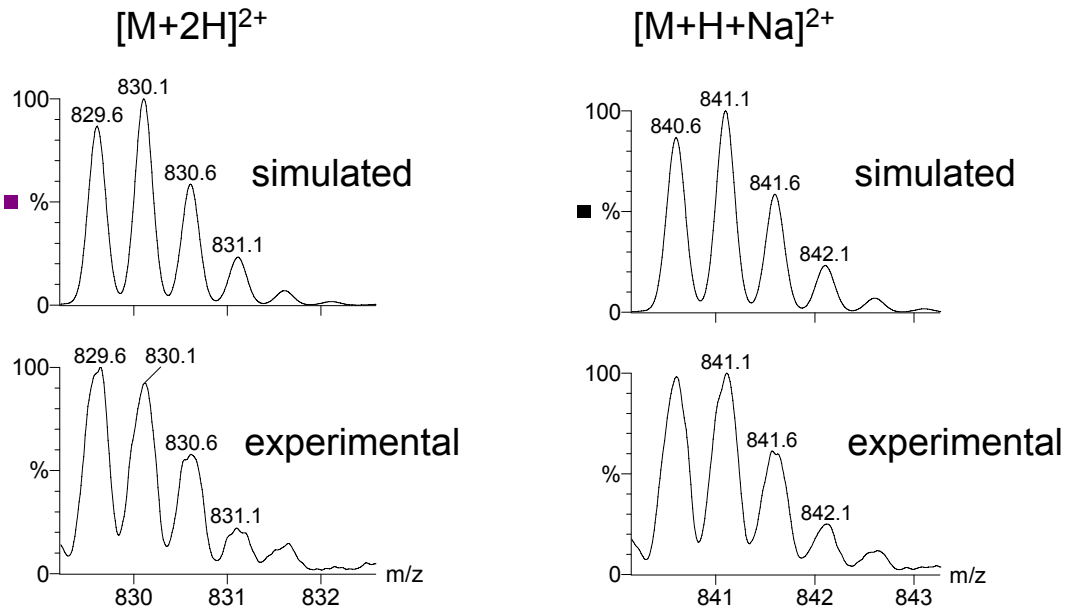


^{1}H and ^{13}C NMR spectra of **8b** ($CDCl_3$, 303 K)



ESI-TOF mass spectrum of **8b**



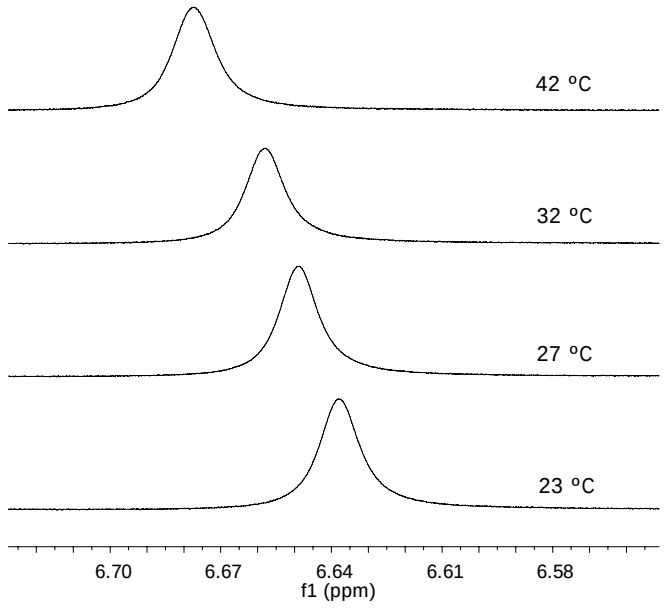


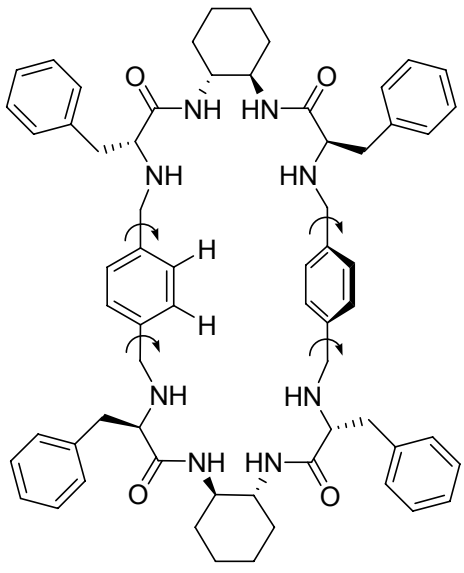
Solution studies (by NMR) of the synthesized macrocycles

In order to obtain some correlation between the spectroscopic data in solution and the conformational constraints of the cycles, the ^{1}H NMR spectra (500 MHz, 303 K) of the synthesized macrocycles (**6a**, **7a**, **7b** and **8b**) have been carefully compared. Despite the spectra showed broad signals, a regular trend was observed for a proton signal, which seems to be diagnostic for the strain of the cycles. The signal corresponding to the *p*-phenylene moiety is a good molecular probe for that conformational constraint. We observed that the smaller is the macrocycle, the lower is the chemical shift value for that proton (see following table).

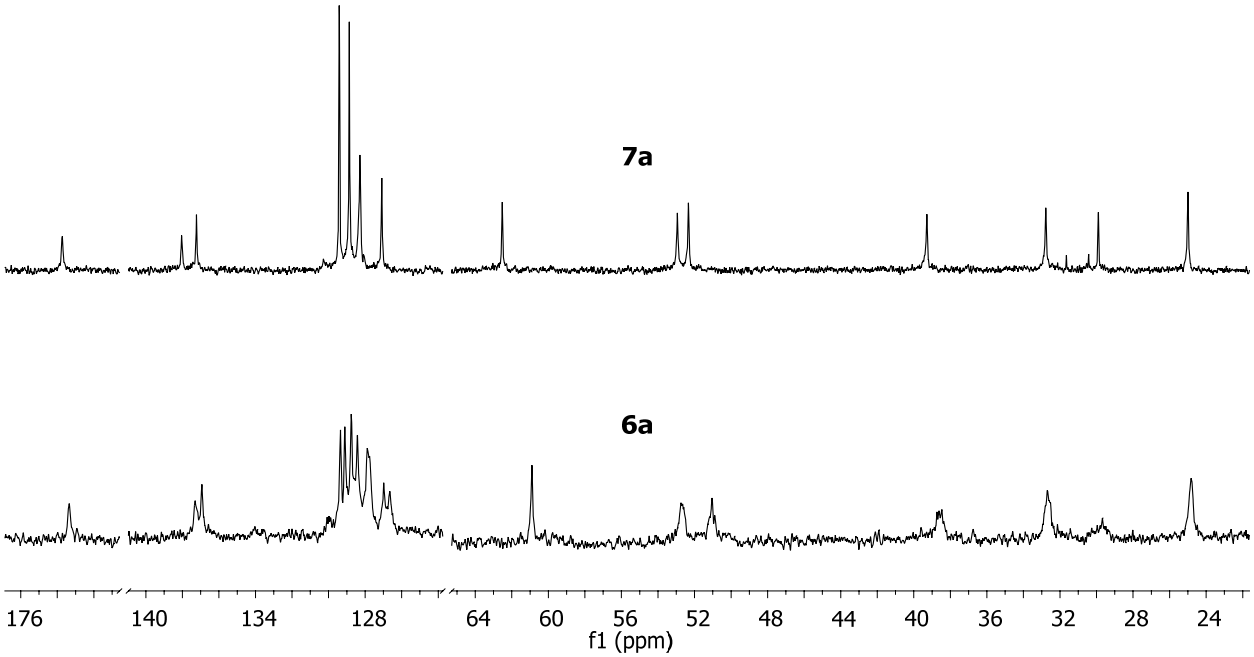
Compound	Macrocyclic size (n in Scheme 1 of manuscript)	^{1}H NMR chemical shift
6a (Phe)	[2+2] (1)	6.64
7a (Phe)	[3+3] (2)	6.74
7b (Val)	[3+3] (2)	7.13
8b (Val)	[4+4] (3)	7.22

This effect can be explained attending to the conformation observed in the crystal structure of 6a. This macrocycle sets the *p*-phenylene moieties in a perpendicular disposition (T-shaped) where the aromatic C-H atoms of one *p*-phenylene substructure is in the shielding zone of the anisothropy cone of the other *p*-phenylene moiety. This effect should be larger for the smaller macrocycles, since the corresponding *p*-phenylene moieties are closer. Obviously, in solution, the situation is dynamic and we observed a symmetrical structure, although the shielding effect is evident from the comparison of the corresponding chemical shifts of macrocycles of different sizes. If our interpretation is correct, this shielding effect must be reduced if we increase the temperature. The heating process will fasten the rotation of the *p*-phenylene moieties and the shielding effect due to the T-shaped disposition will be attenuated. That is exactly what we observed experimentally, as depicted in the following figure, which shows the stacked partial ^{1}H NMR spectra (500 MHz) of **6a** as the free amine in $CDCl_3$ (10 mM) at four different temperatures.





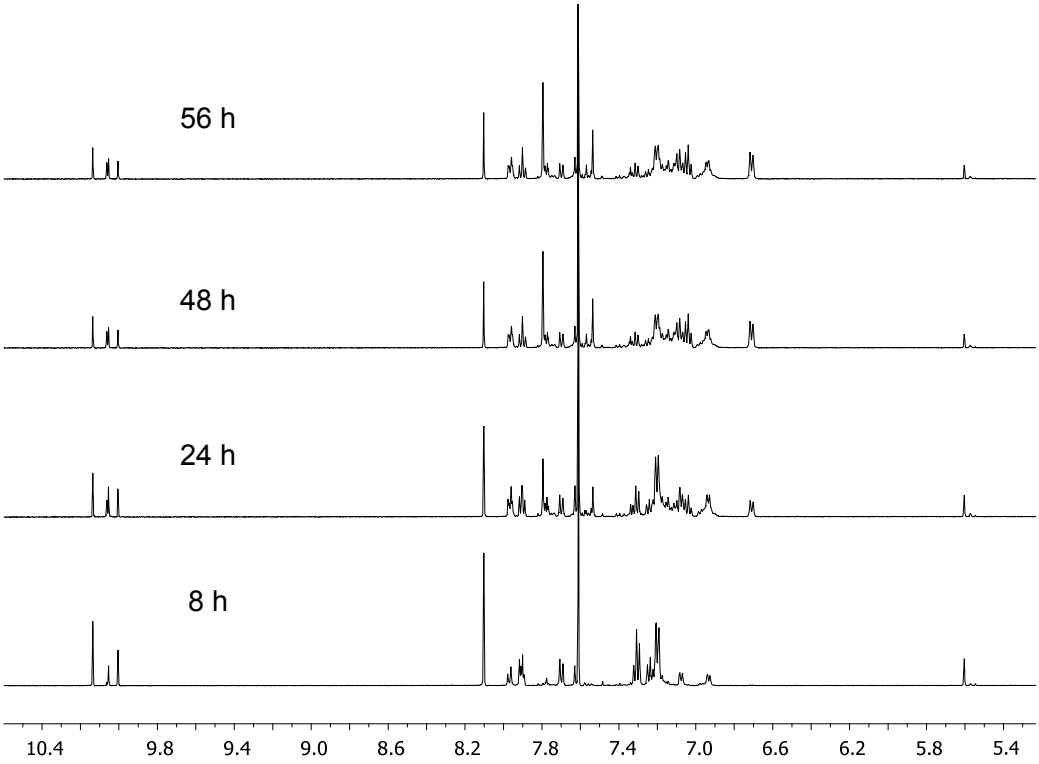
We also compared the ^{13}C NMR spectra of the smaller and larger macrocycle of the same family (**6a** versus **7a**) both of them acquired in the same conditions (20 mM in $CDCl_3$, 125 MHz, 303 K).



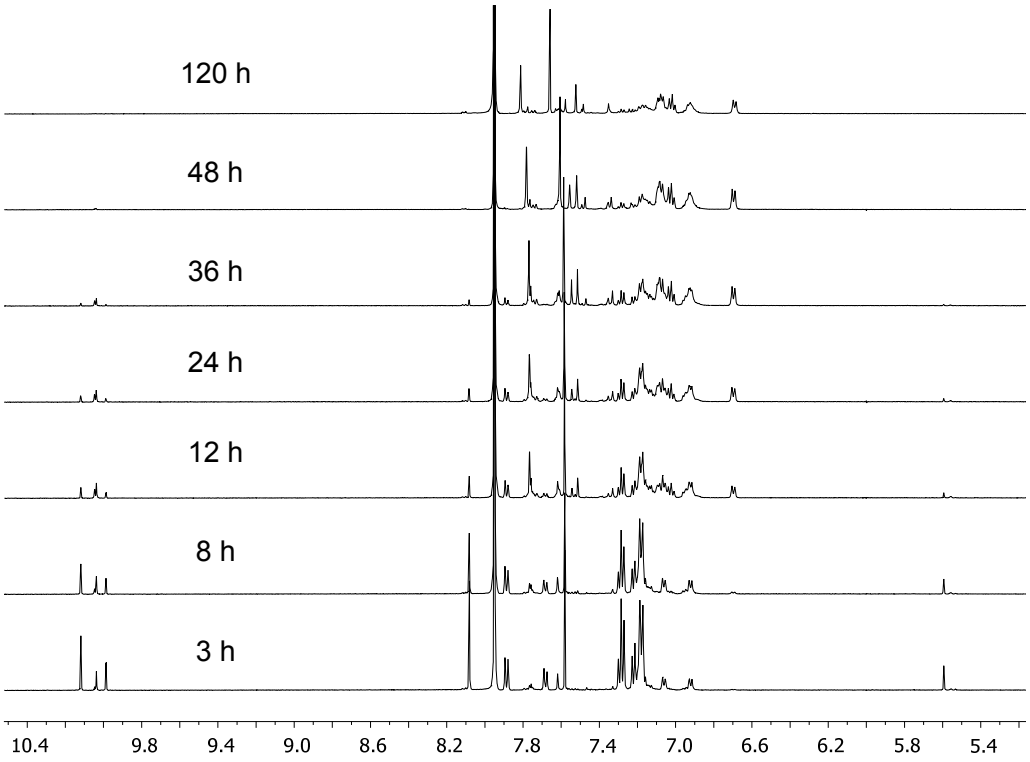
Interestingly, the spectrum of **6a** showed much broader signals than the one of **7a** both in the aromatic and in the aliphatic regions. Moreover, for **6a**, most of the aromatic signals split off supporting the presence of different conformers in solution in slow exchange in the ^{13}C NMR timescale. This observation nicely correlates with the structures obtained in the solid state, where different conformations due to the disposition of the aromatic rings (both *p*-phenylene and benzyl side chains) were observed.
Overall, ^{1}H NMR (including VT-NMR) and ^{13}C NMR data strongly support the strained disfavoured geometry of **6a** in solution.

Characterization of the dynamic mixture of oligoimines: NMR spectra

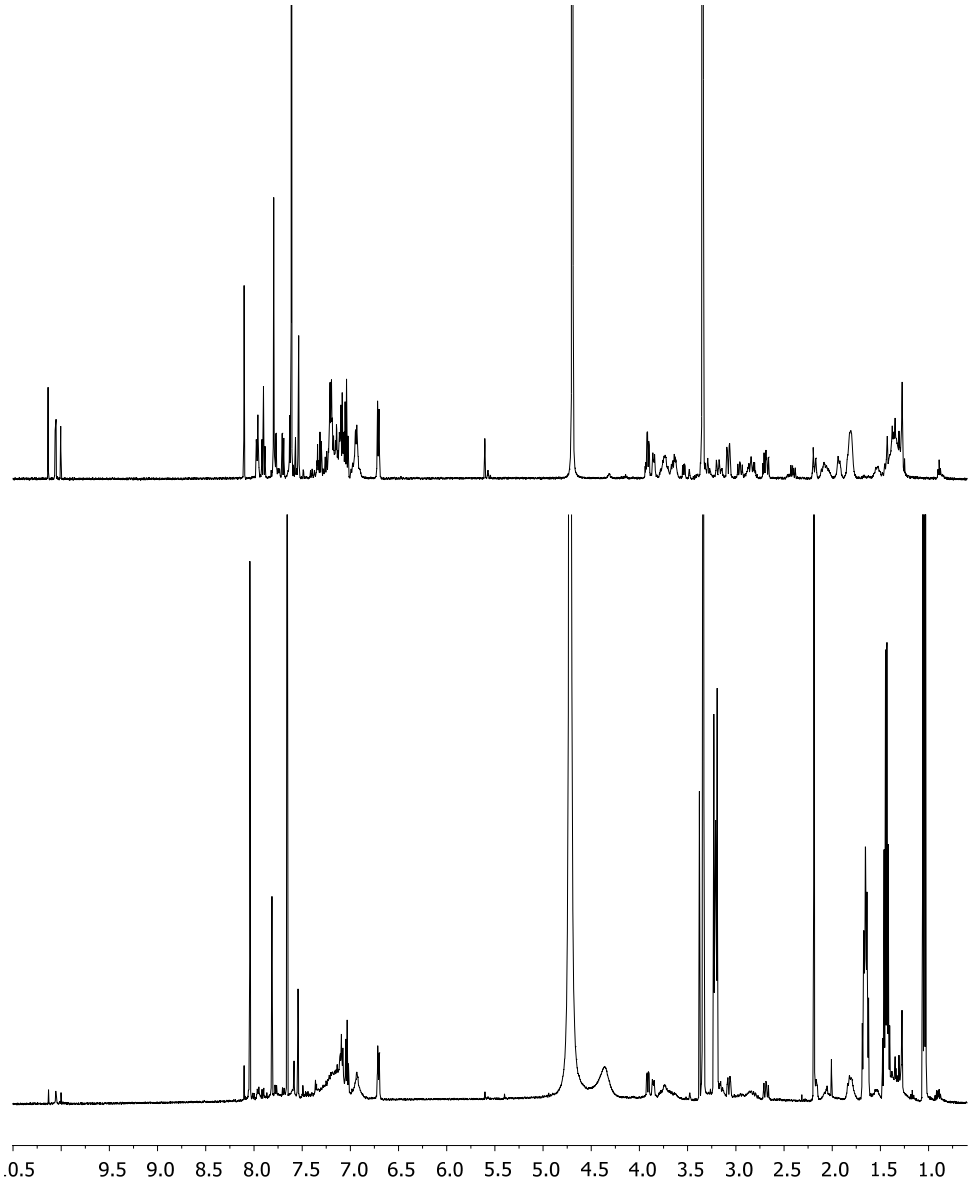
Stack of the ^{1}H NMR spectra of an equimolecular mixture of (**3a** + **4**) versus time. The corresponding times are shown for every trace. After 48 hours, the reaction has reached equilibrium and the presence of open chain oligomers is evident from the signals at 10.05 and 10.06 ppm.



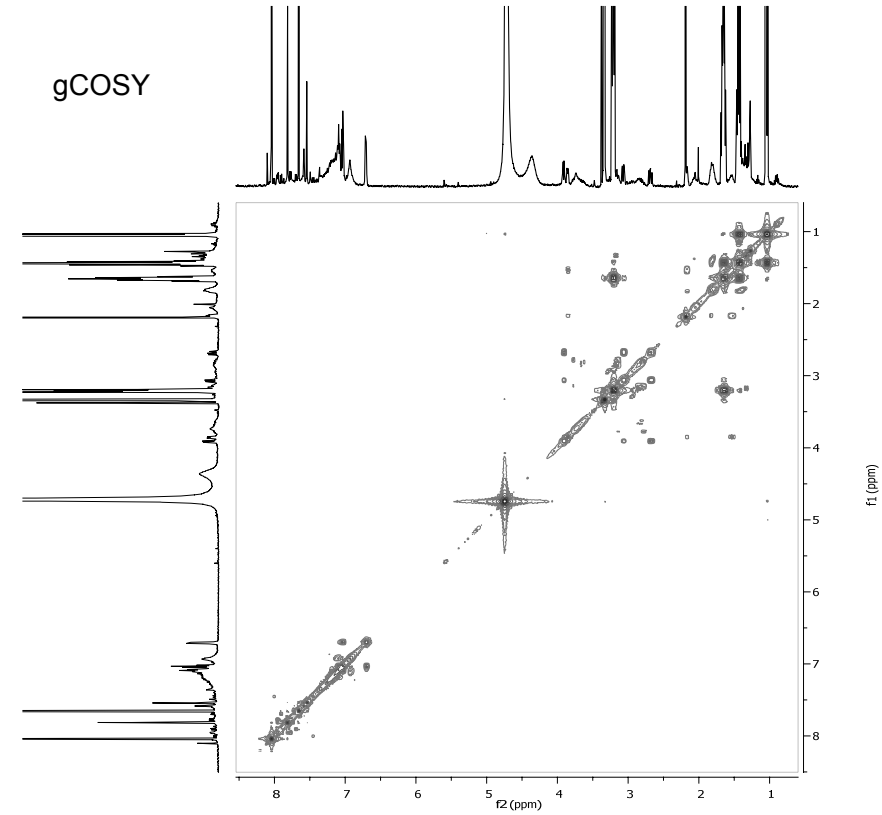
Stack of the evolution of partial ^{1}H NMR spectra of a mixture of (**3a** + **4** + 0.5 eq. of **5**) versus time. The corresponding times after mixing are shown for every trace.

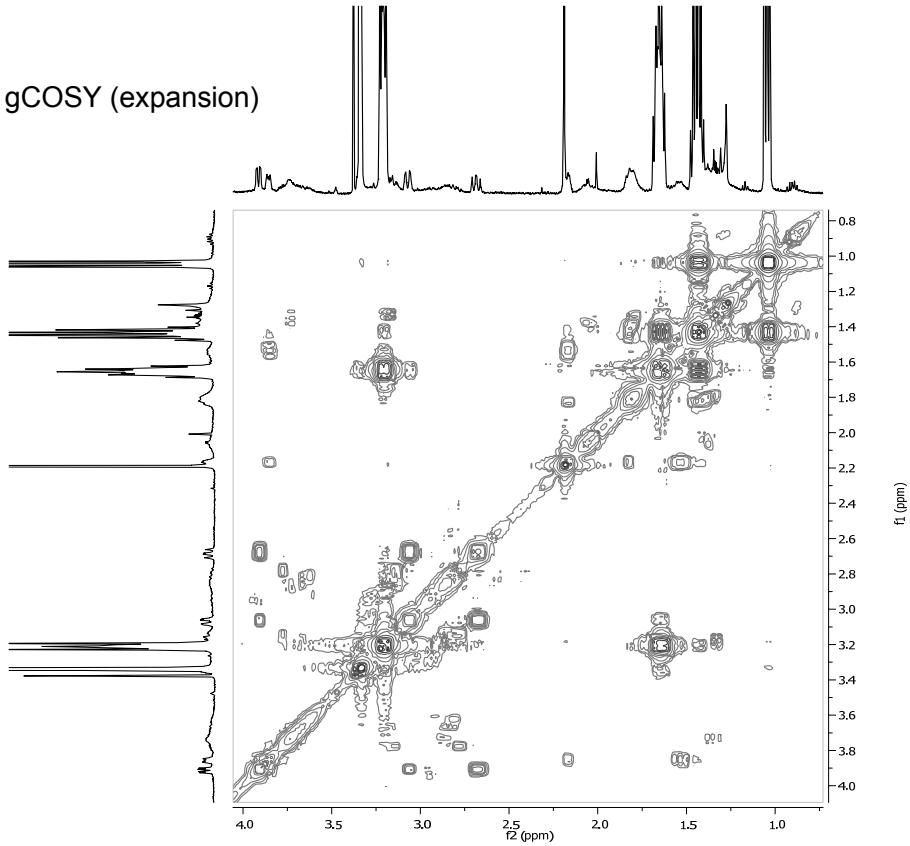


^{1}H NMR spectra of the equilibrated (>48 h) reaction mixture (**3a**+**4**) in the absence (upper trace) and the presence (lower trace) of 0.5 equivalents of the template (**5**)



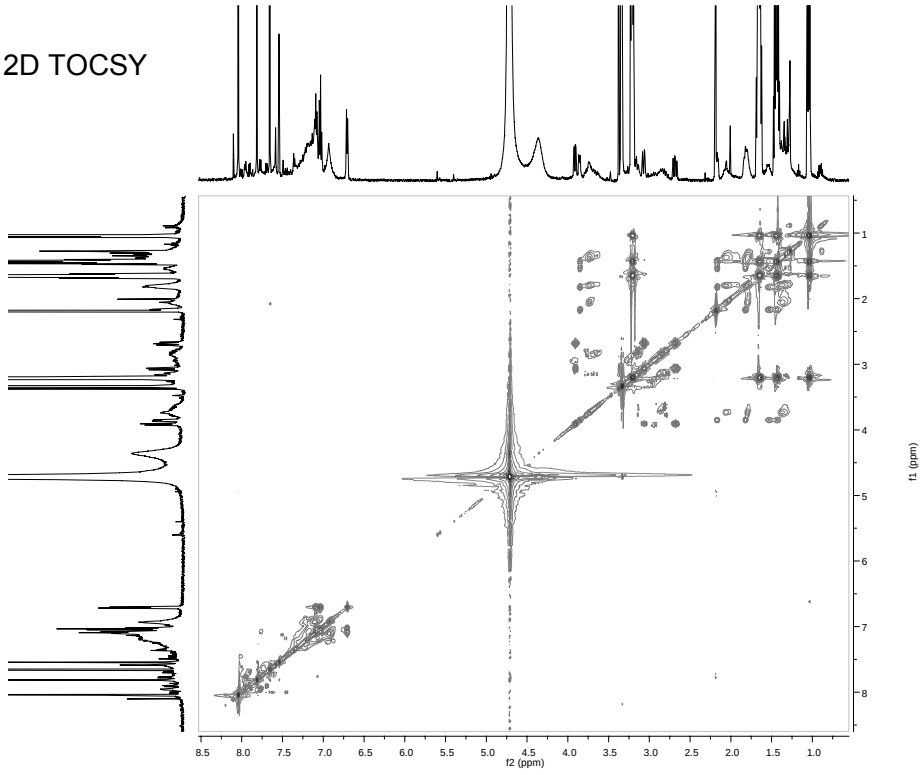
gCOSY spectrum (500 MHz, 1 : 1 $CDCl_3$: CD_3OD, 296 K) of the equilibrated mixture (**3a**+**4**+**5**)



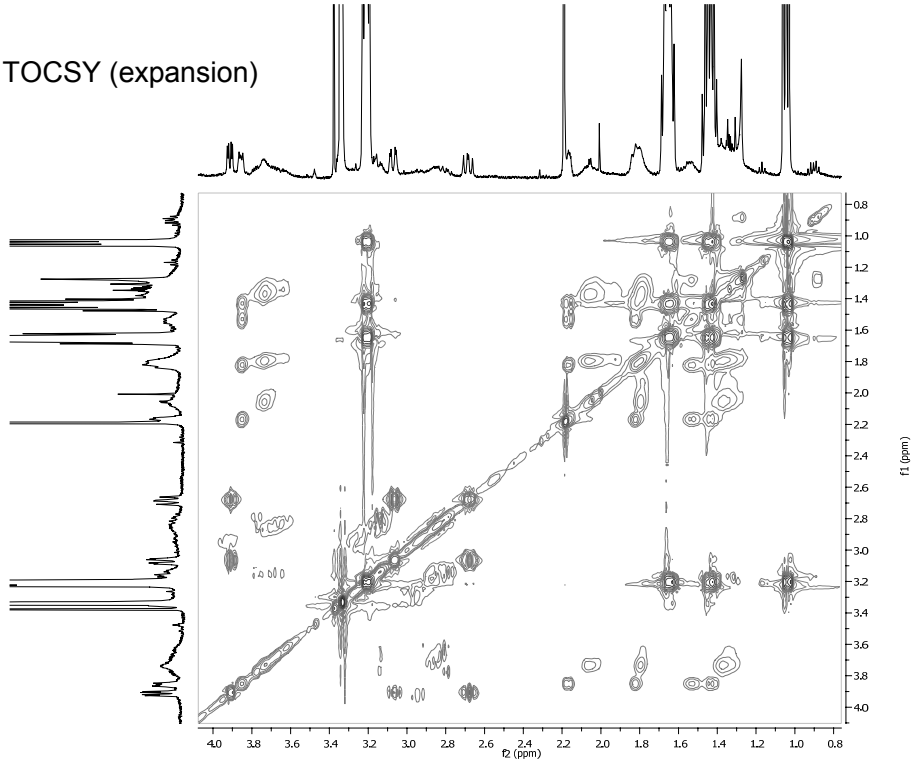


TOCSY spectrum (500 MHz, 1 : 1 $CDCl_3$: CD_3OD, 296 K) of the equilibrated mixture (**3a**+**4**+**5**)

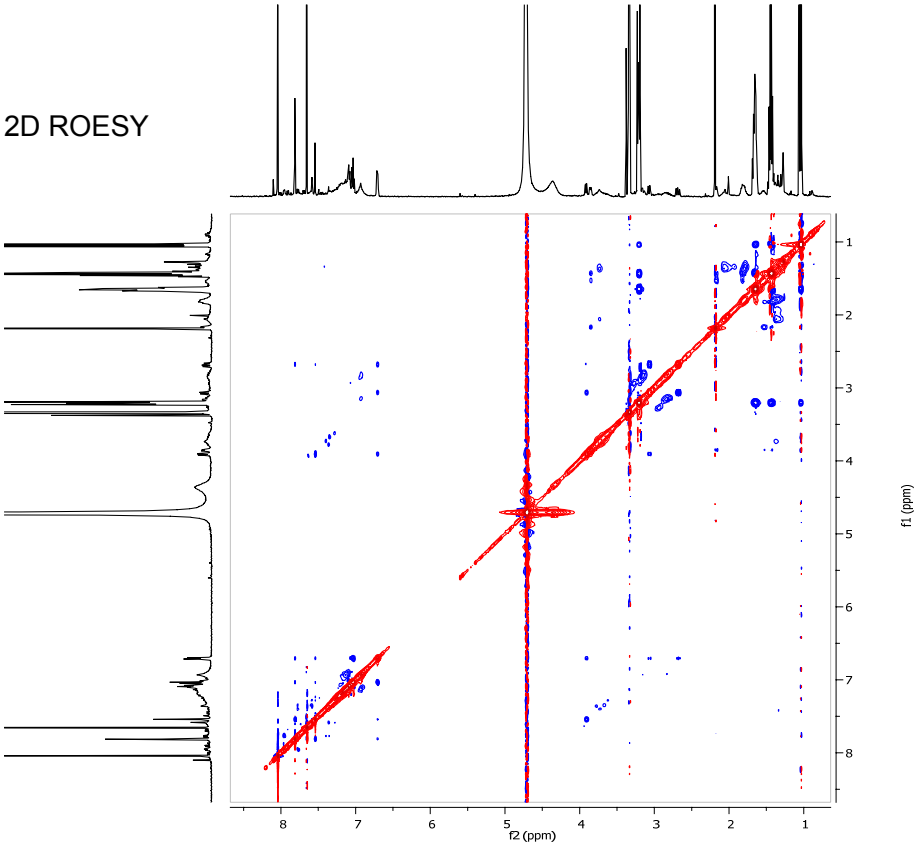
2D TOCSY

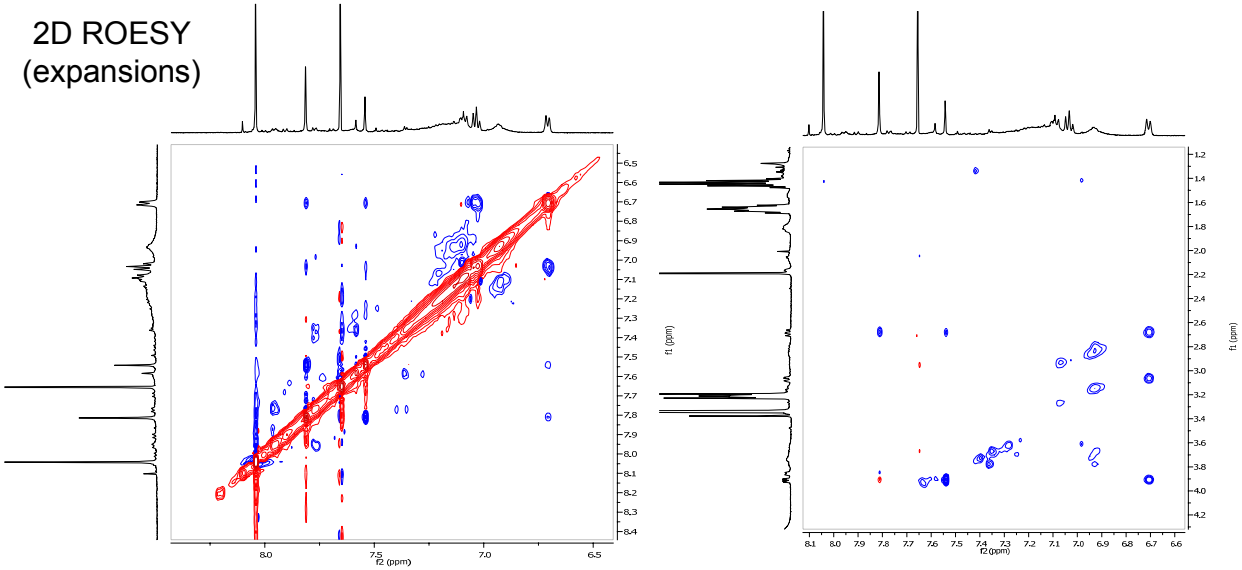


2D TOCSY (expansion)

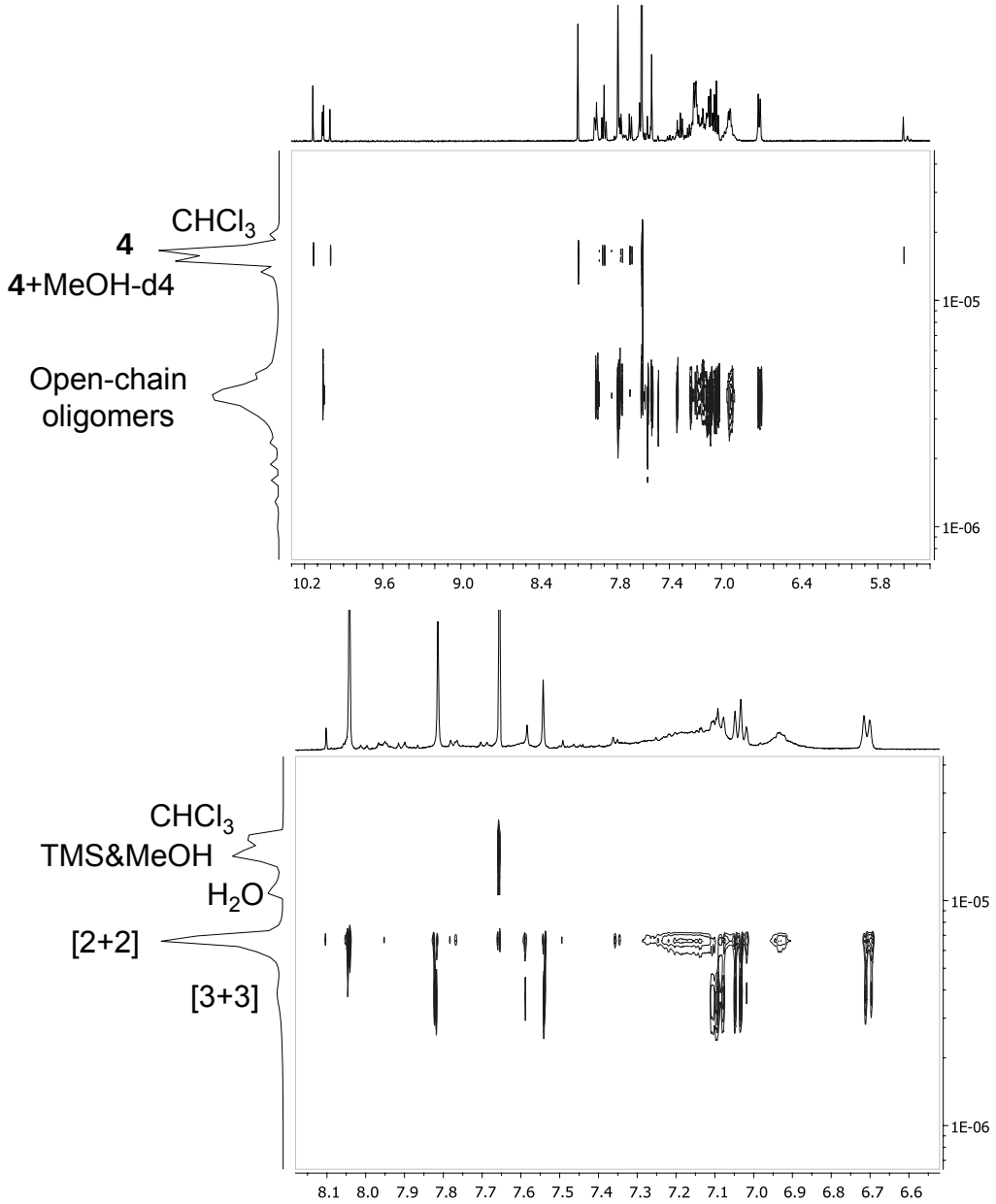


ROESY spectrum (500 MHz, 1 : 1 $CDCl_3$: CD_3OD, 296 K) of the equilibrated mixture (**3a**+**4**+**5**)





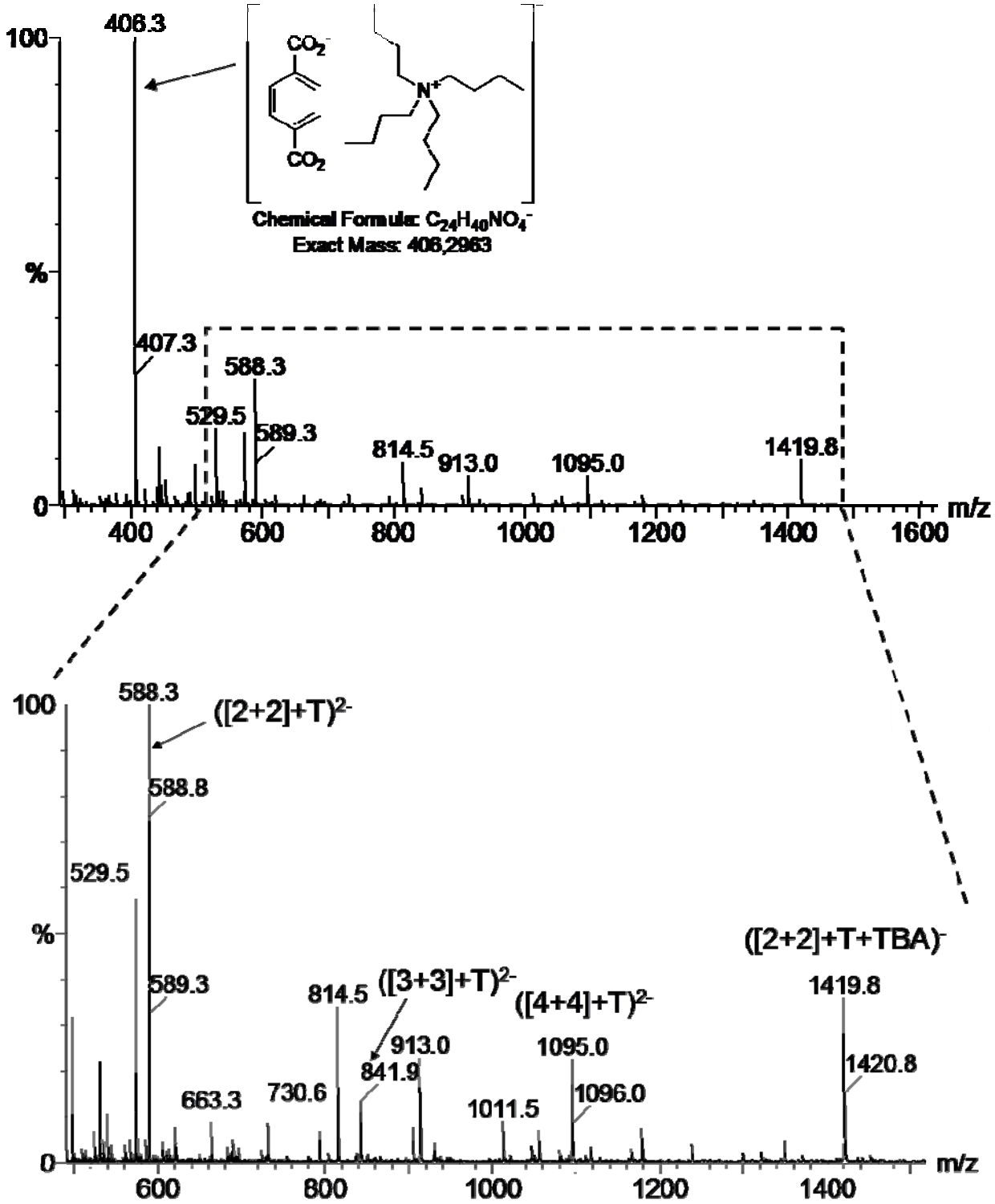
DOSY spectra (500 MHz, 1 : 1 $CDCl_3$: CD_3OD, 296 K) of the equilibrated (>48 h) reaction mixture of (**3a**+**4**) in the absence (up) and in the presence (down) of 0.5 equivalents of the template (**5**). The vertical trace shows the projection of the corresponding signals over the diffusion scale, therefore allowing a virtual separation of the protons for every species and rendering a semi-quantitative estimation of their proportion in the mixture. Also, an estimation of the molecular volumes by DOSY(1) and molecular modelling is shown in the table.



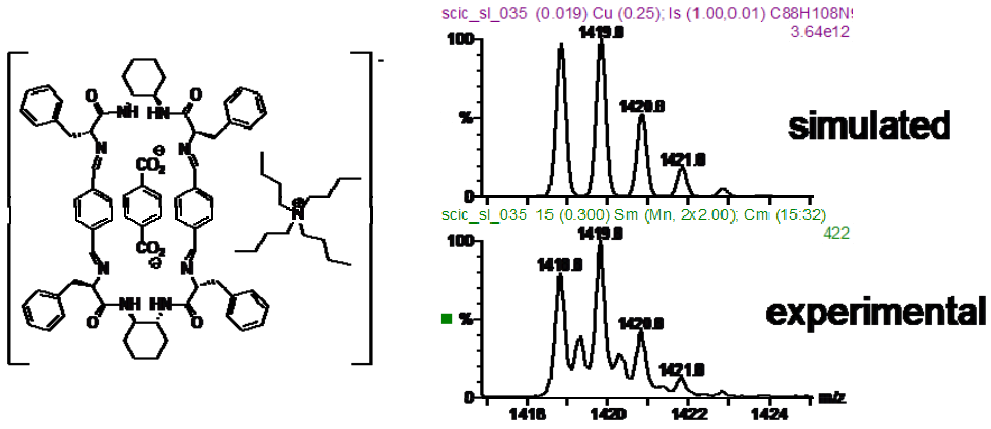
Compound	V calculated (Å^3)	D ($\times 10^{-6}$ cm$^2 \cdot$ s^{-1})	V by DOSY (Å^3)
TMS	120.4	16.7	-
4	140.4	16.5	124.4
CHO-C6H4-CH(OMe)OH	166.8	15.0	165.6
[2+2] + T + 2TBA	1864.0	6.58	1961.8

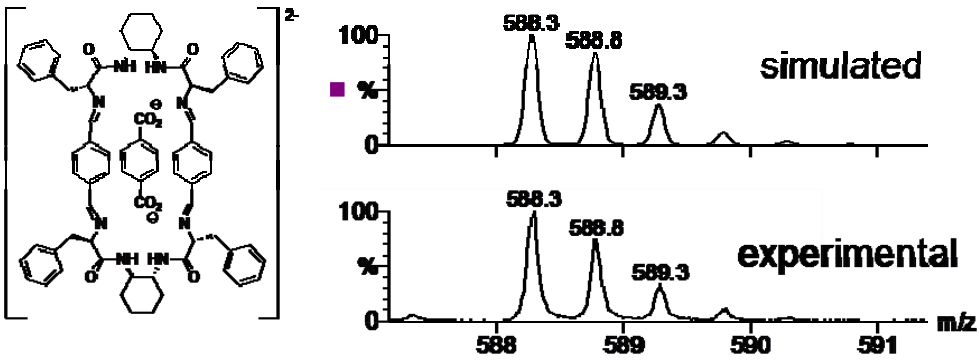
(1) Considering the Stokes-Einstein equation $D \propto (1/R)$, where D is the self-diffusion rate and R the molecular (hydrodynamic) radius, we used the approximation: $(V/V_{TMS}) \approx (R/R_{TMS})^3 \approx (D_{TMS}/D)^3$. For details, see: a) Crutchfield, C. A.; Harris, D. J. *Magn. Reson. Chem.* **45**, 463 (2007). b) Crutchfield, C. A.; Harris, D. J. *J. Magn. Reson.* **185**, 179 (2007),.

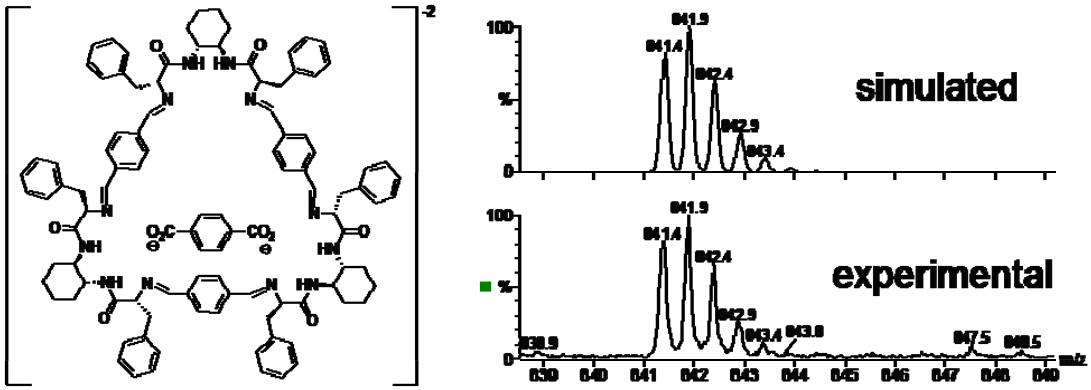
ESI-TOF mass spectrum (anion detection mode) of the templated reaction mixture (3a+4+5)

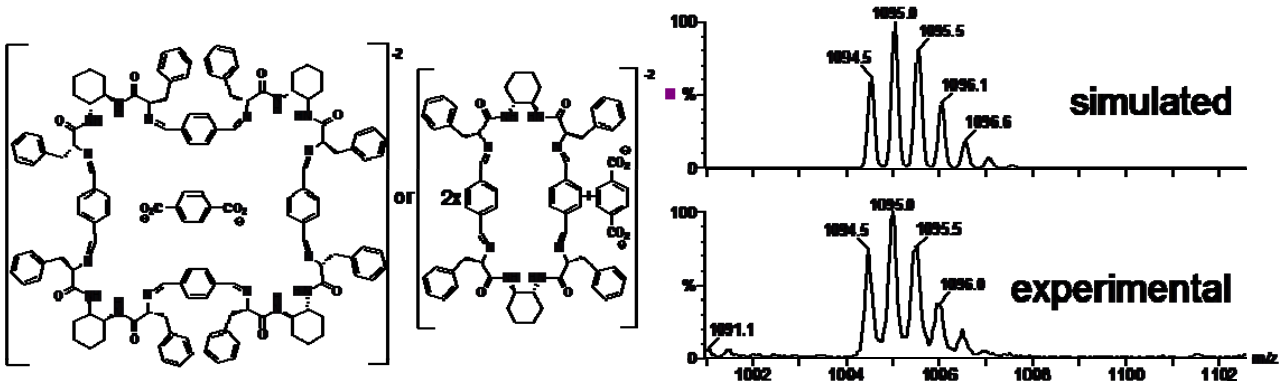


Simulated and experimental isotopic patterns for the mass peaks of the supramolecular complexes



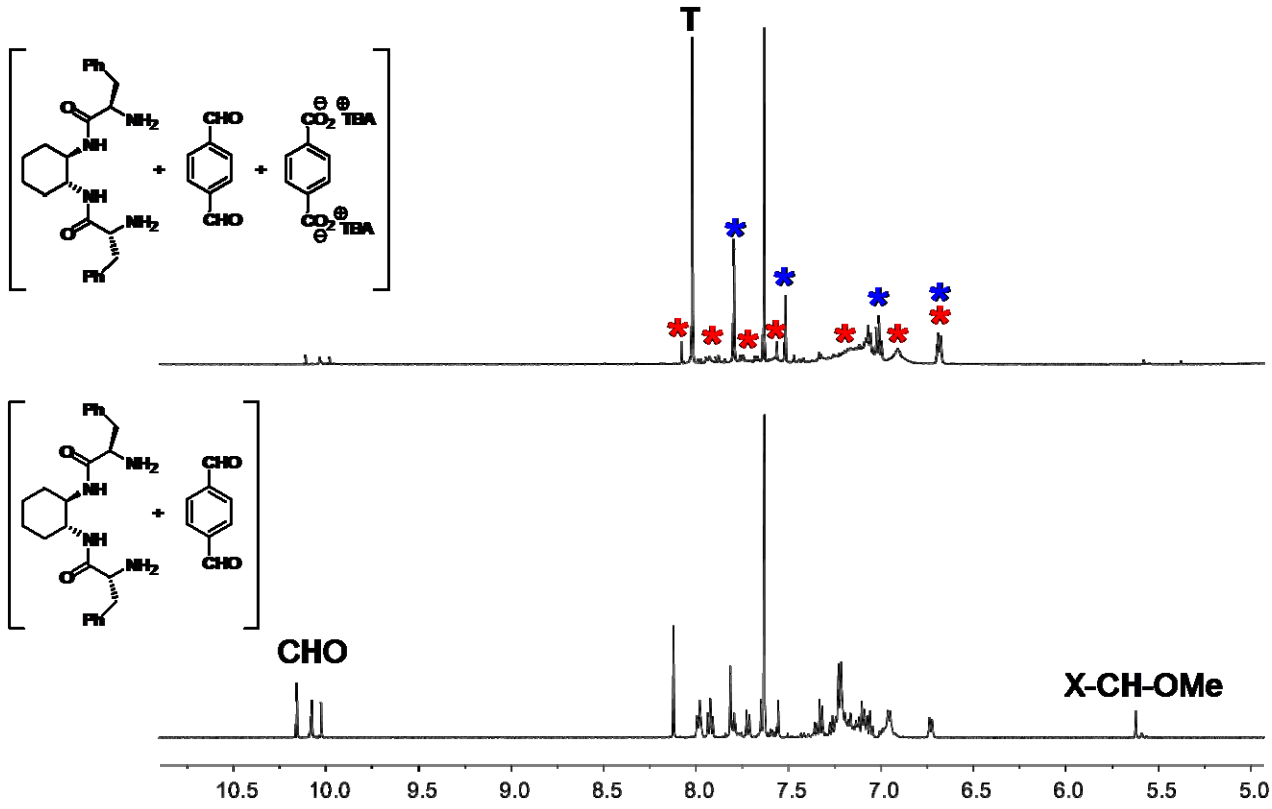




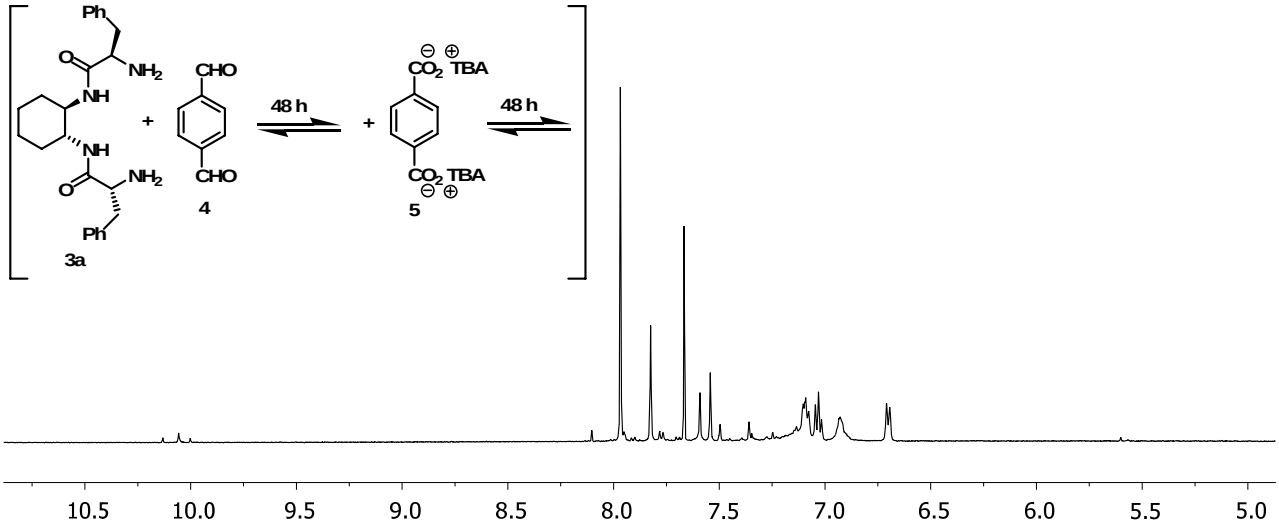


Additional NMR experiments to characterize the dynamic system

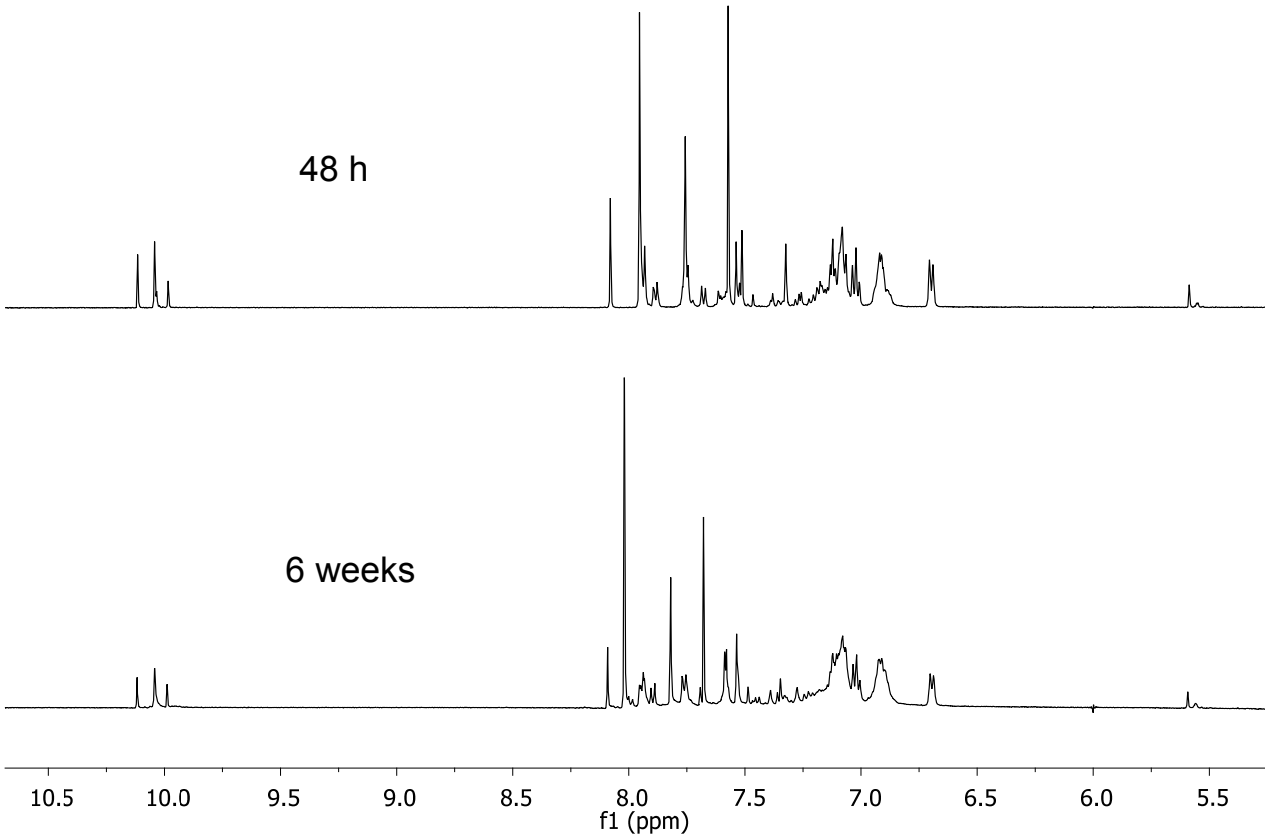
Detail of the partial ^{1}H NMR spectra of the equilibrated (>48 h) reaction mixture (**3a**+**4**) in the absence (lower trace) and in the presence (upper trace) of 0.5 equivalents of the template (**5**). The signals corresponding to the template (T), the [2+2] (red asterisk) and the [3+3] (blue asterisk) macrocycles have been highlighted.



Partial ^{1}H NMR spectrum obtained after the following reaction sequence: mixing (**3a** + **4**) and waiting for 48 hours to reach equilibrium, then adding 0.5 equivalents of the template **5** and waiting for 48 additional hours for the re-constitution.

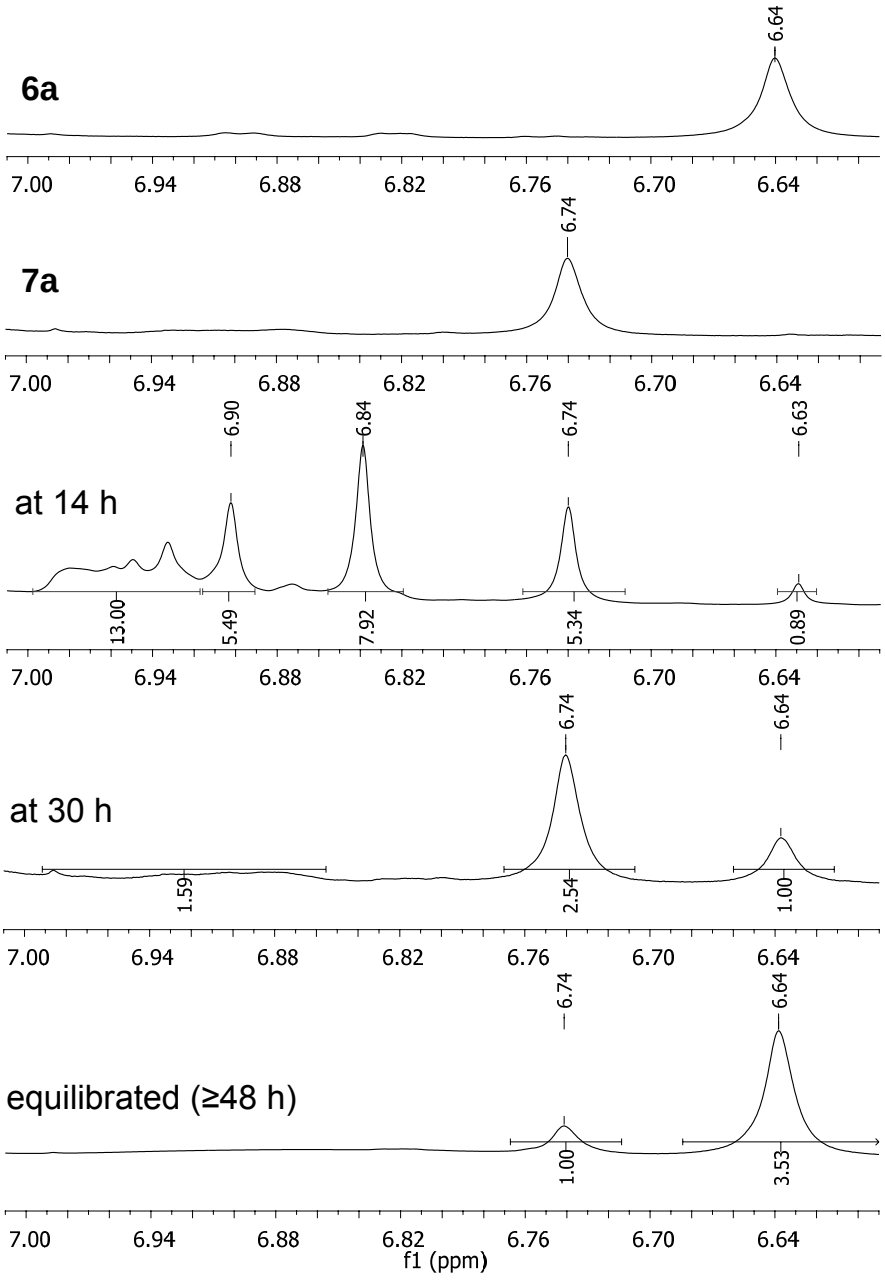


Partial ^{1}H NMR spectra of a mixture of (**3a** + **4** + 0.3 eq. of **5**) after 48 hours (upper trace) and after six weeks (lower trace) of equilibration time. The slight changes of the chemical shifts of some signals (especially for the template and residual chloroform peaks) are attributed to small changes in the solvent composition (initially 1 : 1 CD_3OD : $CDCl_3$) due to differential evaporation with time which leads to a slightly higher proportion of CD_3OD within the reaction mixture. The presence of open-chain oligomers even after 6 weeks is evident by the observation of the corresponding signals at ~10.05 ppm.



Analysis of the templated reaction with 3a before equilibration is reached

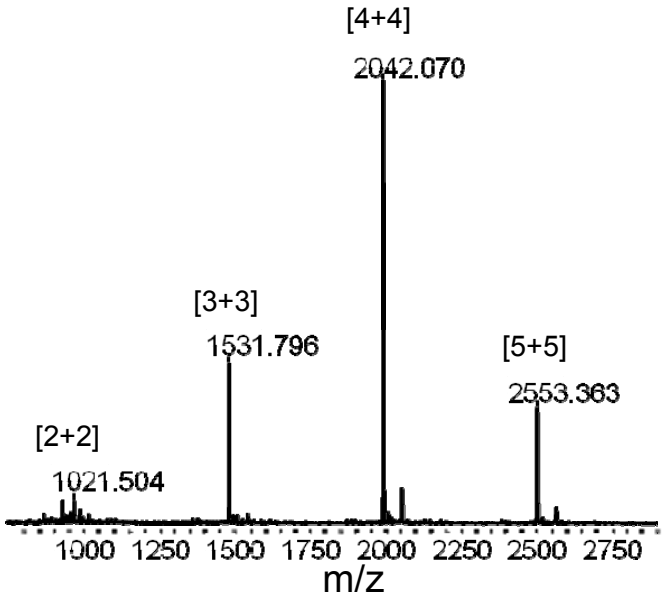
We have performed a series of reactions with **3a**, reducing the mixture before the time needed for equilibration. In this way, we could get definitive proofs for the proposed anion templated self-correction process, without the additional complication of the aggregation observed with Val. Following, the relevant ^{1}H NMR sub-spectra of the crude samples, reduced at different reaction times are shown, in addition to the corresponding sub-spectra of pure samples of **6a** and **7a**.



At short reaction times, most of the materials corresponded to open-chain oligomers (data not shown), which is in good agreement with the NMR data when we followed the equilibration process at the imine stage inside the NMR tube. However, after 14 hours, we observed several recognizable peaks in the ^{1}H NMR spectrum of the crude (after reduction, acidic hydrolysis and basic extraction). As previously stated, the most diagnostic proton signal, characteristic for the size of the cycle, is that corresponding to the *p*-phenylene proton. Thus, these protons resonate at 6.64 and 6.74 ppm for **6a** (first trace) and **7a** (second trace), respectively. The ^{1}H NMR spectrum of the crude reaction,

reduced after 14 hours of equilibration (third trace), showed a very small amount of **6a** (~2.8%) and a higher concentration of **7a** (~15.2%). Some additional peaks at 6.84 ppm and 6.91 ppm were assigned to the [4+4] (~23.2%) and [5+5] (~17.5%) macrocycles, respectively. This tentative assignation was further confirmed by the MALDI-TOF mass spectrum of the same sample (also shown below). Finally, a broad group of signals at ~6.92-7.00 ppm can be ascribed to open chain compounds, rendering the rest of the material (~40%).
The reaction reduced after 30 hours of equilibration (fourth trace) showed an increase of the peaks corresponding to the trimer and to the dimer, being the trimer the major compound and still with a detectable amount of larger oligomers. Finally, the crude of the reaction reduced after equilibration (48 h, lower fifth trace) showed the peaks for the [2+2] and [3+3] compounds in a relative proportion according to the observed imines and also with the isolated yields of **6a** and **7a**.

Besides, the MALDI-TOF spectrum of the reaction stopped at 14 h shows the peaks corresponding to the $[M+H]^+$ species of the macrocyclic amines: [2+2] (**6a**), [3+3] (**7a**), [4+4] and [5+5] at *m/z* = 1021.504, 1531.796, 2042.070 and 2553.363, respectively. This is in good agreement with our initial tentative assignation of the ^{1}H NMR spectra of the mixture.



These results strongly support our hypothesis that larger macrocycles are initially formed and then, the dynamic system is able to self-correct amplifying the best-fitted macrocyclic-anion complex. The complication of our system arises from the fact that the formation of the cycles from the open chain oligomers and the reorganization of the larger macrocycles towards the best fitted system are not sequential processes. Thus, for the Phe derivative, dynamic correction occurs in parallel with the cyclization, since we already observed the dimeric species when still ~40% of the materials had not cyclized. This experiment also confirms that in the case of the Val derivative, aggregation is affecting either the kinetic or the thermodynamic situation of the dynamic network, trapping the larger macrocycles once they are formed.

Crystallographic data

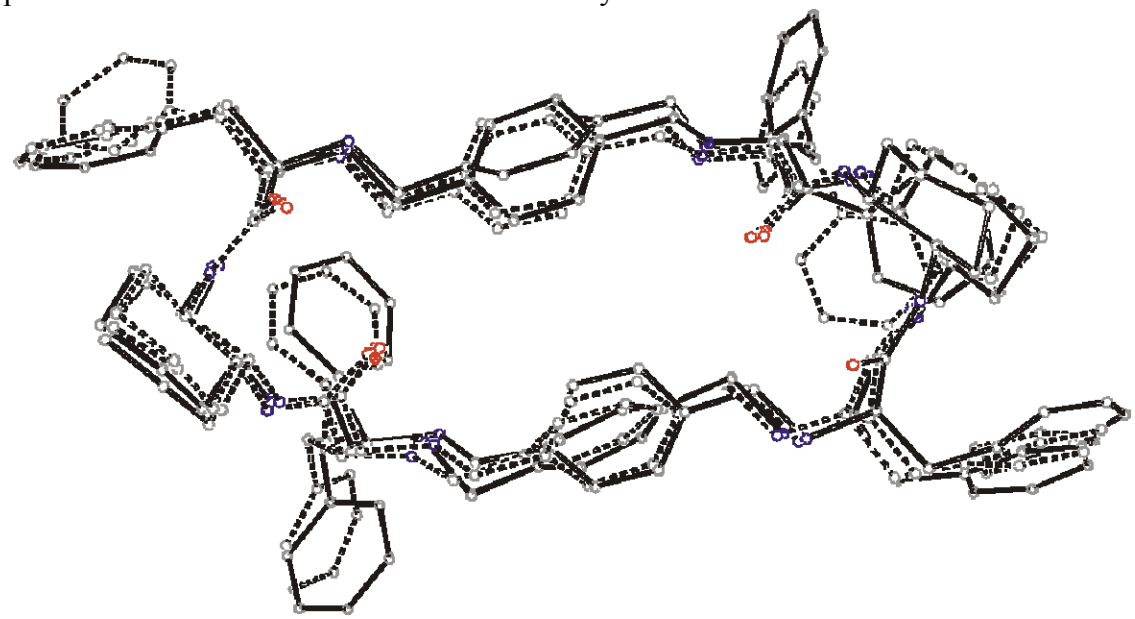
Crystals of **6a** were grown by dissolving the compound in MeOH, adding a slight excess of aqueous concentrated $HClO_4$ and after the very slow evaporation of the MeOH/water solution, giving rise to colorless needles.
Data were collected on a STOE-IPDS-II two-circle diffractometer employing graphite-monochromated MoKα radiation (0.71073 Å). Data reduction was performed with the X-Area software(2). An empirical absorption correction was performed using the MULABS(3) option in PLATON. (4) The structure was solved by direct methods with SHELXS-90(5) and refined by full-matrix least-squares techniques with SHELXL-97.(5) All non-H atoms were refined with anisotropic displacement parameters. Hydrogens bonded to C were included at calculated positions and allowed to ride on their parent atoms. Several restraints were applied to keep geometric parameters and displacement parameters in reasonable ranges.

Table 1. Crystal data and structure refinement for nacho2.

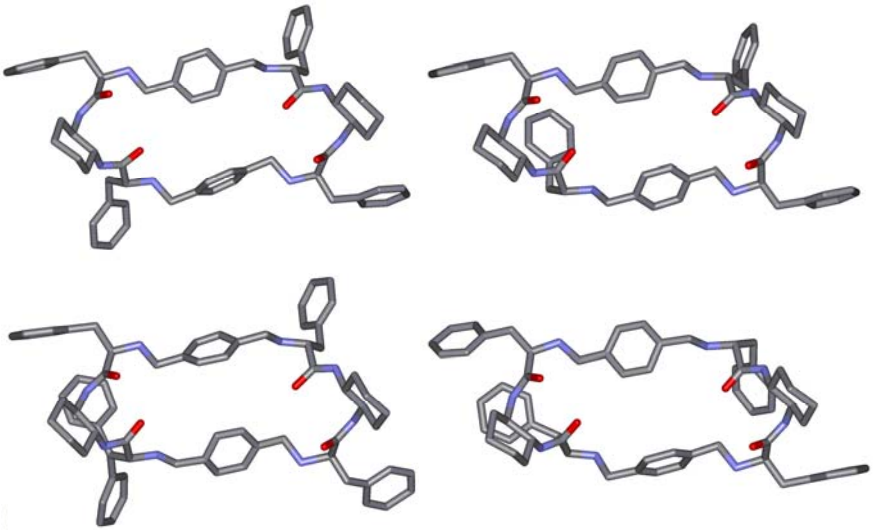
Identification code	**6a**	
Empirical formula	$4[C_{64}H_{80}N_8O_4]^{+} \cdot 16ClO_4^{-} \cdot 32H_2O \cdot 7CH_3OH$	
Formula weight	811.68	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 20.1702(9) Å	α= 90°.
	b = 20.6243(8) Å	β= 100.750(4)°.
	c = 40.444(2) Å	γ = 90°.
Volume	16529.3(13) $Å^3$	
Z	16	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.225 mm^{-1}	
F(000)	6876	
Crystal size	0.36 x 0.32 x 0.29 mm^3	
Theta range for data collection	2.04 to 25.29°.	
Index ranges	-23<=h<=23, -24<=k<=24, -43<=l<=48	
Reflections collected	118072	
Independent reflections	57893 [R(int) = 0.1760]	
Completeness to theta = 25.00°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9375 and 0.9233	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	57893 / 223 / 3701	
Goodness-of-fit on F^2	1.368	
Final R indices [I>2sigma(I)]	R1 = 0.1585, wR2 = 0.3857	
R indices (all data)	R1 = 0.2131, wR2 = 0.4405	
Absolute structure parameter	-0.02(10)	
Largest diff. peak and hole	1.792 and -0.905 e.$Å^{-3}$	

(2) *X-Area. Area-Detector Control and Integration Software*, Stoe & Cie, Darmstadt, Germany (2001)
(3) R. H. Blessing, *Acta Crystallogr., Sect. A*, **51**, 33-3 (1995).
(4) A. L. Spek, *J. Appl. Crystallogr.,* , 3**6**, 7–13, (2003).
(5) G. M. Sheldrick, *Acta Crystallogr., Sect. A*, **64**, 112–122 (2008).

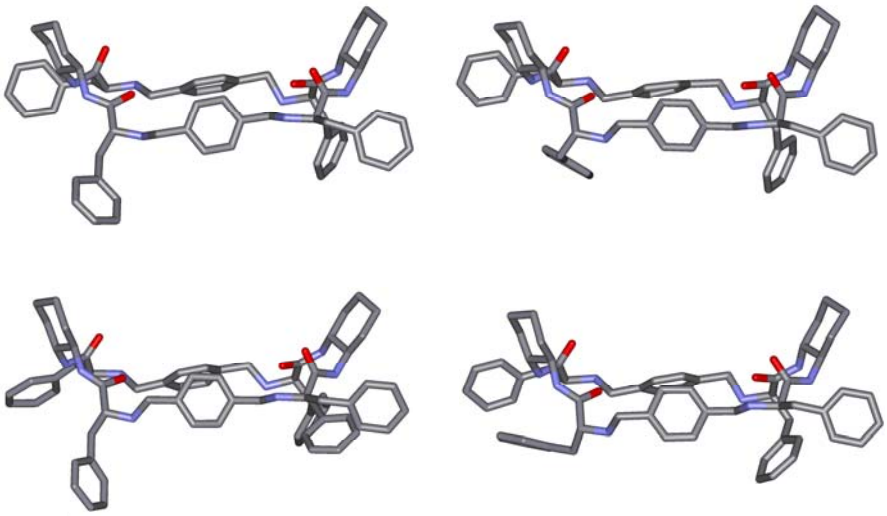
Superposition of the four conformers found in the crystal cell



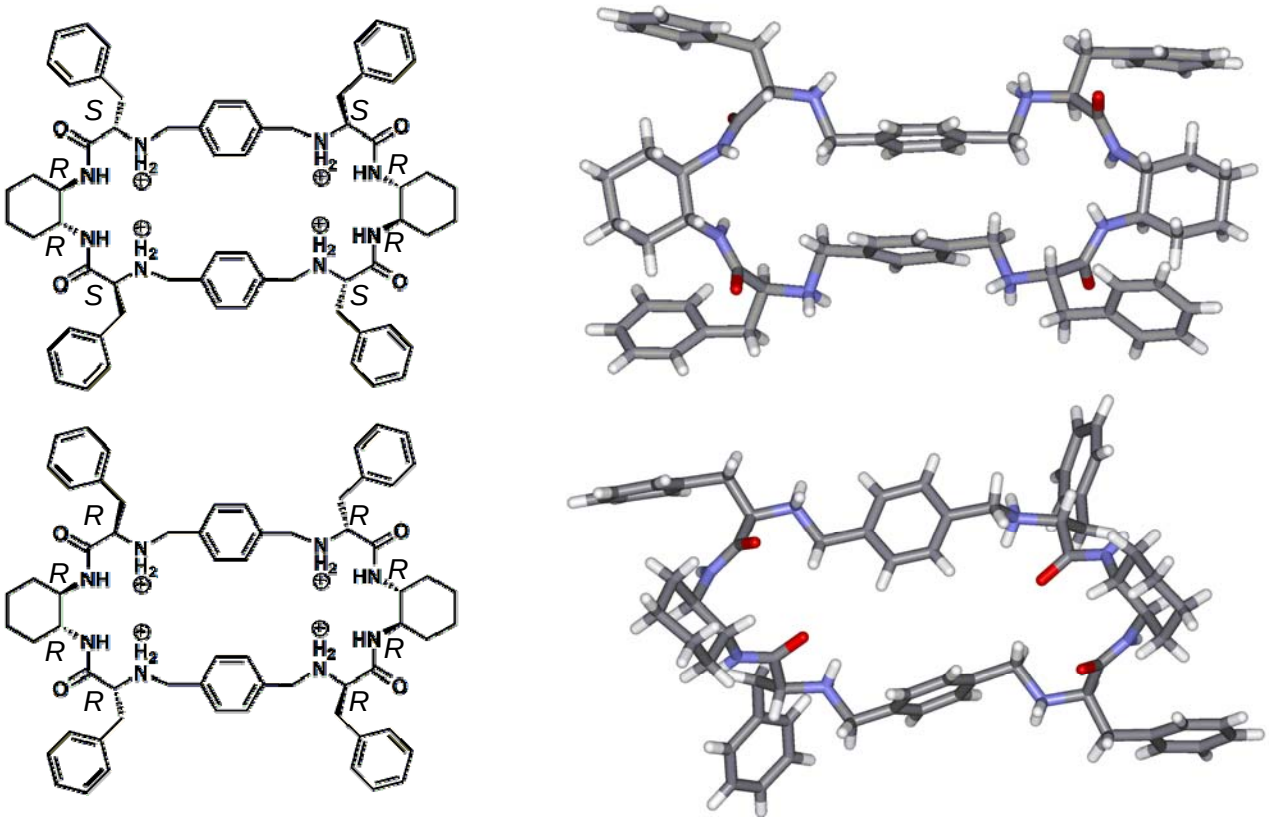
Upper view of the conformers found in the solid state



Side view of the conformers found in the solid state



Comparison between the crystal structures of the *match* (up, from reference 9a of the manuscript) and the *mismatch* (down) isomers. For the *match* isomer, the macrocycle shows a conformation with almost D_2 symmetry. The cyclohexane moiety adopts a chair conformation with the amide substituents in equatorial positions. All the amide NH groups are *trans* with respect to the methynes of the chiral centers of the cyclohexane rings and in *anti* one to each other within every pseudopeptidic moiety. The benzyl sidechains are in pseudoequatorial positions and point away from the macrocyclic ring. The aromatic rings of the backbone *p*-phenylene groups are perpendicular to the macrocyclic main plane and very close to each other. The strained non-symmetrical (disordered) conformation of the *mismatch* (down) isomer is evident from this comparison, as explained in the manuscript. Just compare the whole macrocyclic shape, the disposition of the *p*-phenylene groups, that of the benzylic side chains and, especially, the *syn* conformation of the cyclohexanebis(amide) moieties.

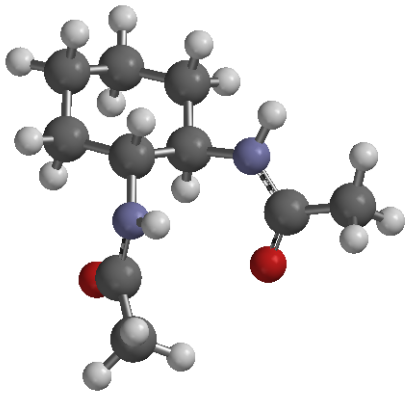


Molecular modelling

All the theoretical calculations were performed using Spartan '06 program. The optimized geometries for the corresponding minima (Fig. 3 of the manuscript) were obtained as follows. A stochastic conformational search was applied (Monte Carlo Search followed by MMFF force field minimization) without restrictions to each compound or supramolecular complex. More than 100 conformers were obtained in this way (ca. 10 kcal/mol cut off). The obtained structures were ordered by their energies and analyzed. The Boltzmann distribution at 298 K and the molecular volumes were also calculated with Spartan '06. The DFT calculations on the cyclohexne-1,2-bis(acetamide) conformers were also performed with Spartan '06 program at the B3LYP//6-31+G*, using the standard parameters from the software. Following, the optimized geometries for the *trans*/*trans* and the *cis*/*trans* conformations can be found, as well as their corresponding computed energies. They show that the *cis*/*trans* conformer is about 6.4 kcal/mol less stable. We also optimized the corresponding supramolecular complex with the *cis*/*trans* bis(amide) and formiate to evaluate the stabilization effect of the carboxylate-amide interaction. This interaction leads to the following stabilization energy:

$$E_{\text{interaction}} = E_{\text{complex amide-carboxylate}} - [E_{cis/trans\ \text{amide}} + E_{\text{formiate}}] = -38.66\ \text{kcal/mol}$$

Therefore, the anion-amide interaction compensates, by far, the conformational destabilization.



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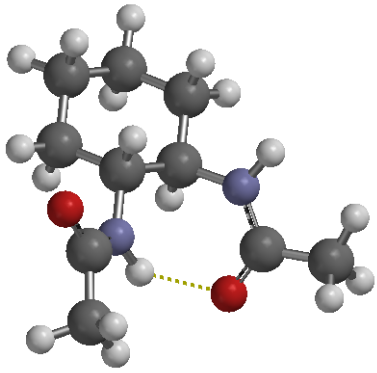
E = -651.928612 a.u.



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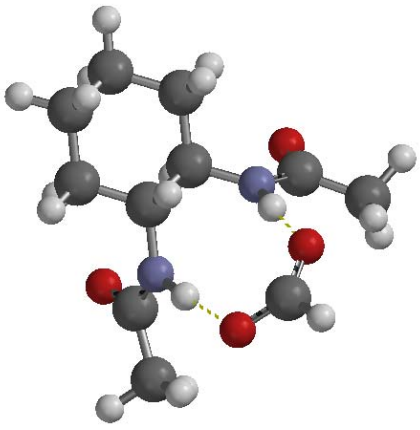

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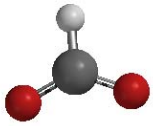

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