Electronic Supplementary Material (ESI) for ChemComm.

Cage-like structures based on constrained cyclic arylopeptoids

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I-Chemicals and general experimental information

Chemicals: Rink acid resin (0.62 mmol/g loading) and 2-chlorotrityl resin (1.06 mmol/g loading) was obtained from Novabiochem, dichloromethane from Carlo Erba; 3-chloromethylbenzoylchloride, 2-chloromethylbenzoylchloride, TFA, DIPEA, 4-DMAP isopropyl and propargyl amines from TCI; DMSO from Acros. 1,4-bis(azidomethyl)benzene was synthetized according to literature procedures. 10 mL jacketed reactors were purchased from Kamush and thermo-regulated using a Lauda thermostat. Purification was performed on a Buchi Pure Chromatography system.

NMR was recorded on a Bruker AC-400 spectrometer, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C J-modulation or a Bruker AC-500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C.

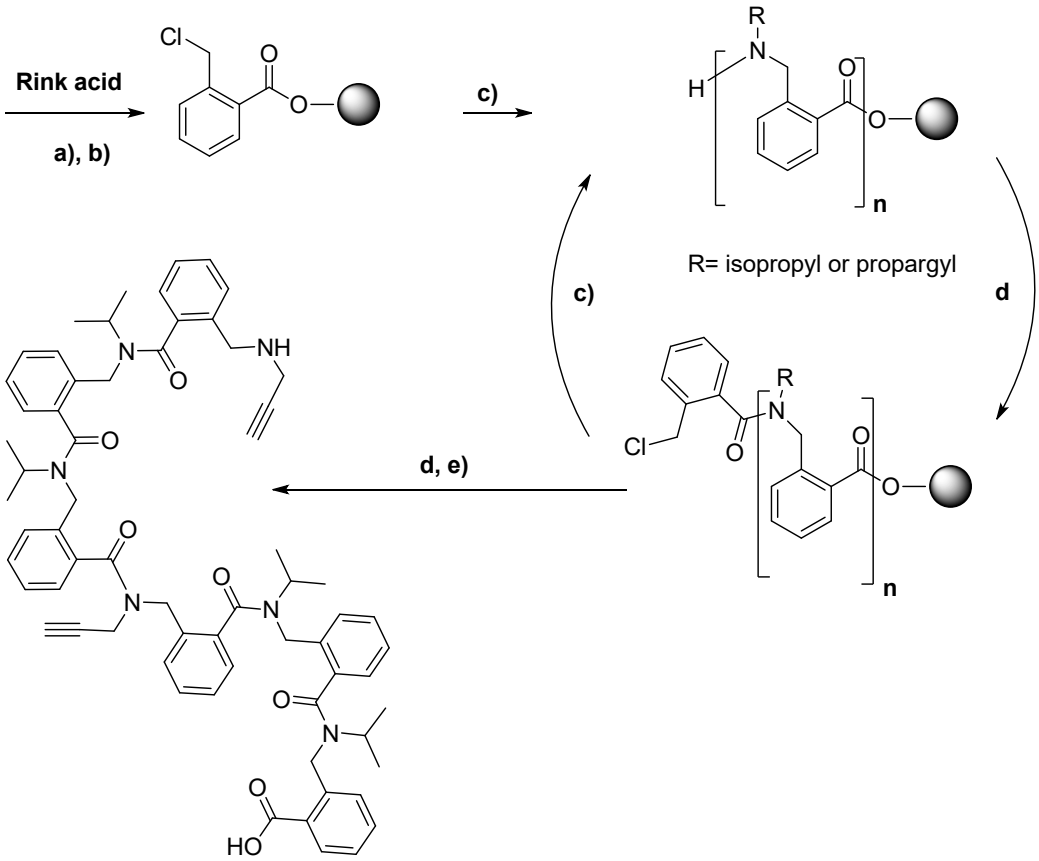
High-resolution mass spectra (HRMS) are recorded using electrospray ionization in positive mode (ESI+) on or a Q Exactive Quadrupole-Orbitrap Mass Spectrometer or on a Qtof-micro WATERS (3000V) spectrometer. Liquid chromatography mass spectroscopy (LC-MS) were recorded on a Q Exactive Quadrupole-Orbitrap Mass Spectrometer coupled to a UPLC Ultimate 3000 (Kinetex EVO C18; 1,7µm; 100mm x 2,1mm column with a flow rate of 0.45 ml.min-1 with the following gradient: a linear gradient of solvent B from 5% to 95% over 7.5 min (solvent A = H2O + 0.1% formic acid, solvent B = acetonitrile + 0.1% formic acid) equipped with a DAD UV/VIS 3000 RS detector) or on a Qtof-micro WATERS (3000V) with electrospray ionization coupled to a HPLC ALLIANCE WATERS system with a diode array detector (DAD) using a reverse-phase C18 Nucleosil column (100 mm x 2.1 mm, 5 µm pore size) with an H2O/acetonitrile gradient and a flow rate of 0.2 mL/min.

Analytical HPLC was recorded on a Hitachi liquid chromatograph (Oven 5310, 30°C; Pump 5160; DAD detector 5430) equipped with a C18 Acclaim column (4.6 mm×250 mm, 5µm, 120Å). Detection wavelength was 240nm or 280nm and flow rate 0.5mL/min. Gradient elution used (A) water/0.1% TFA; (B) methanol according Method A: (Solvents A/B: 0 to 5 minutes isocratic at 95/5; 5 to 25 minutes gradient to 5/95; 25 to 35 minutes isocratic at 5/95; 35 to 45 minutes gradient to 95/5; 45 to 50 minutes 95/5) or Method B (Solvents A/B: 0 to 5 minutes isocratic at 95/5; 5 to 10 minutes gradient to 75/25; 10 to 50 minutes gradient to 40/60; 50 to 65 minutes gradient to 5/95; 65 to 70 minutes isocratic at 5/95; 70 to 80 minutes gradient to 95/5).

II. General Procedures and compounds characterization

II.1. Linear arylopeptoids

II.1.a. Linear ortho-hexamer ***Ia***



a) Swelling, CH_2Cl_2; b) 2-chloromethyl benzoylchloride, DIPEA, DMAP; CH_2Cl_2; c) Isopropyl amine or propargyl amine, dmso; d) 2-chloromethyl benzoylchloride, DIPEA, CH_2Cl_2 ;e) Cleavage: TFA/CH_2Cl_2 (20:80).

Scheme S1. Solid-phase submonomer synthesis of **Ia** on Rink acid resin

1-For 100 mg of resin, swelling: 2 ml of CH_2Cl_2 at RT for 10 min

2- 2-chloromethylbenzoylchloride (3 equiv. per mmol loading), 4-DMAP (3 equiv. per mmol loading) DIPEA (3 equiv. per mmol loading) dissolved in 1 mL CH_2Cl_2 were added at RT, shaken 10 minutes. This step is repeated. The liquid was drained off, then the resin was washed with CH_2Cl_2 (5x2 ml), then with DMSO (5x2 ml).

3- Isopropyl amine (20 equiv per mmol loading) dissolved in 0.5 mL of DMSO were added. The reaction was shaken for 1h at RT. The liquid was drained off, then the resin was washed with DMSO (5x2 ml), then with CH_2CL_2 (5x2 ml).

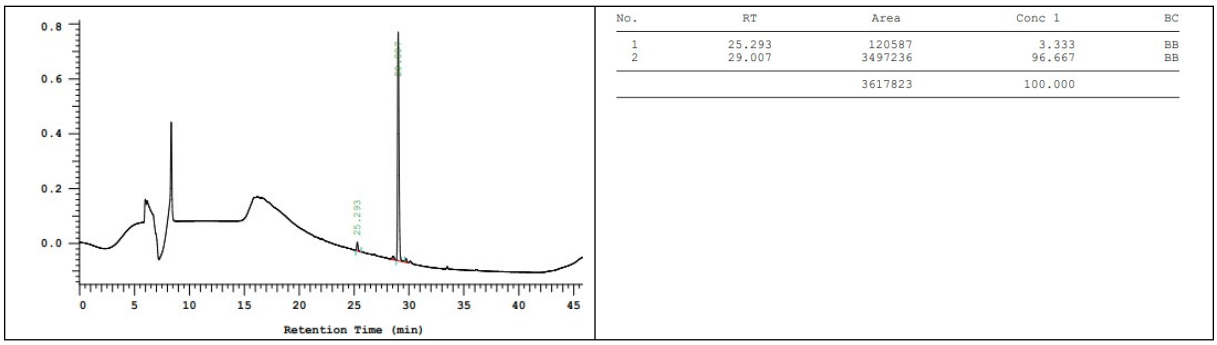
4- 2-chloromethylbenzoylchloride (3 equiv. per mmol loading), DIPEA (6 equiv. per mmol loading) dissolved in 1 mL CH_2Cl_2 were added at RT, shaken 10 minutes. The liquid was drained off, then the resin was washed with CH_2Cl_2 (5x2 ml), then with DMSO (5x2 ml).

5- Isopropyl amine or propargyl amine (20 equiv per mmol loading, 1M) dissolved in 0.5 mL of DMSO were added. The reaction was shaken for 1h at RT. The liquid was drained off, then the resin was washed with DMSO (5x2 ml), then with CH_2CL_2 (5x2 ml).

Steps 4 and 5 were repeated to grow the targeted arylopeptoid oligomer until the expected sequence length.

6-The arylopeptoid was cleaved from the resin by the addition of 1 ml of CH_2Cl_2/TFA (8:2) for 30 min at RT. The solution was collected and then the resin was washed with CH_2Cl_2 (5x2 ml). The solution was evaporated under reduced pressure. The product was purified on Buchi LC auctomatic C18 column (Water + 0.1% TFA/MeOH) affording 90% of product **Ia** (HPLC purity 96%).

HRMS (TOF MS ES+): *m/z* calcd for $C_{66}H_{73}N_6O_7$ $[M+H]^+$: 1061.55352; found: 1061.5520 (-1.43 ppm).



No.	RT	Area	Conc 1	BC
1	25.293	120587	3.333	BB
2	29.007	3497236	96.667	BB
		3617823	100.000	

Figure S1. HPLC chromatogram of the pure **Ia**.

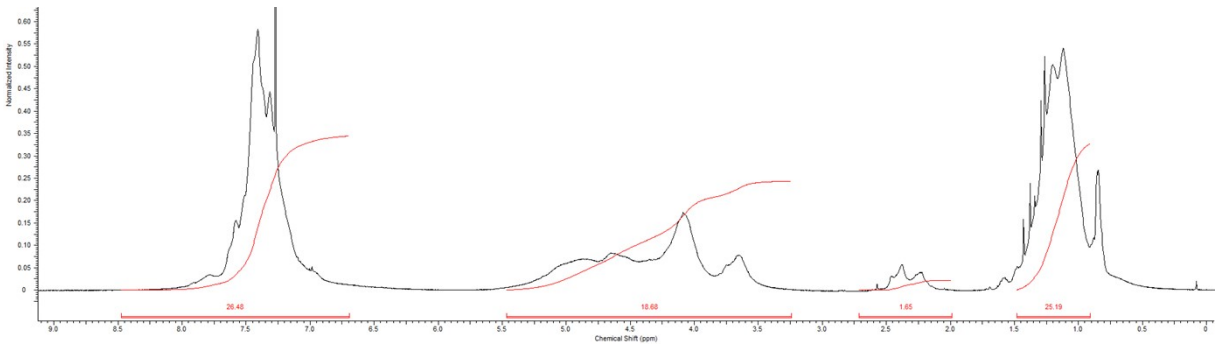


Figure S2. ^{1}H-NMR in $CDCl_3$ of the pure **Ia**.

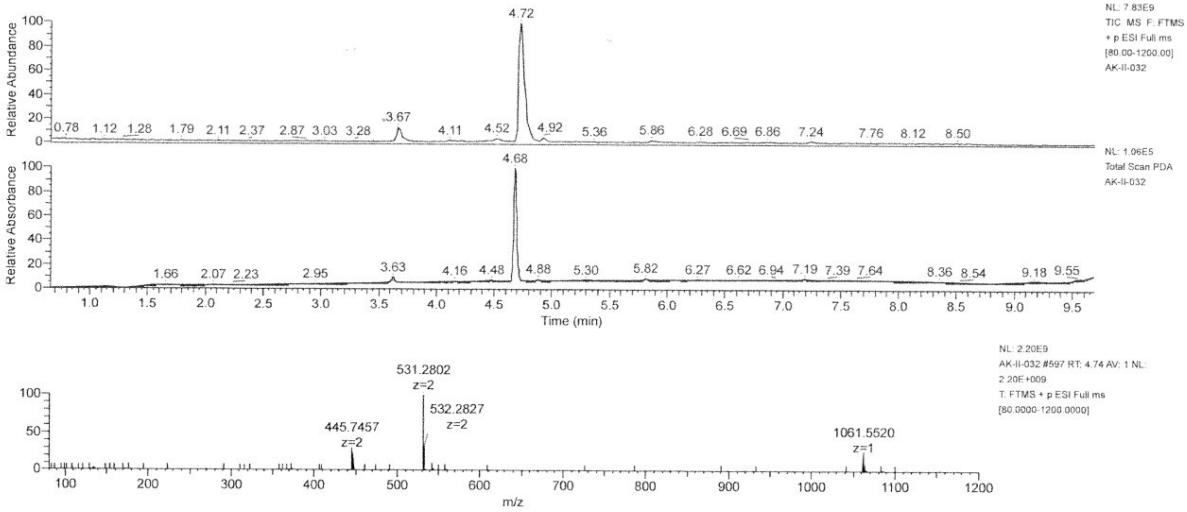


Figure S3. LCMS spectrum of the crude **Ia**.

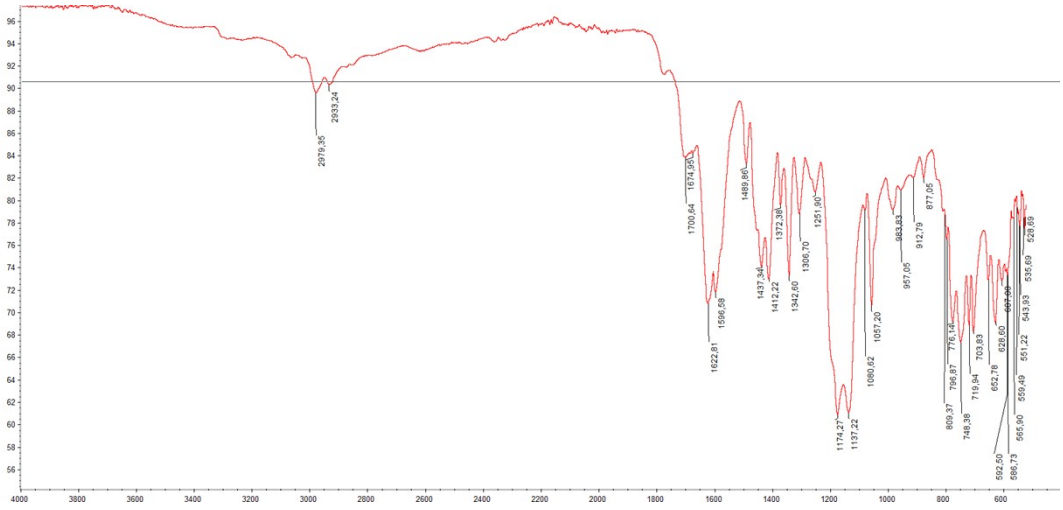
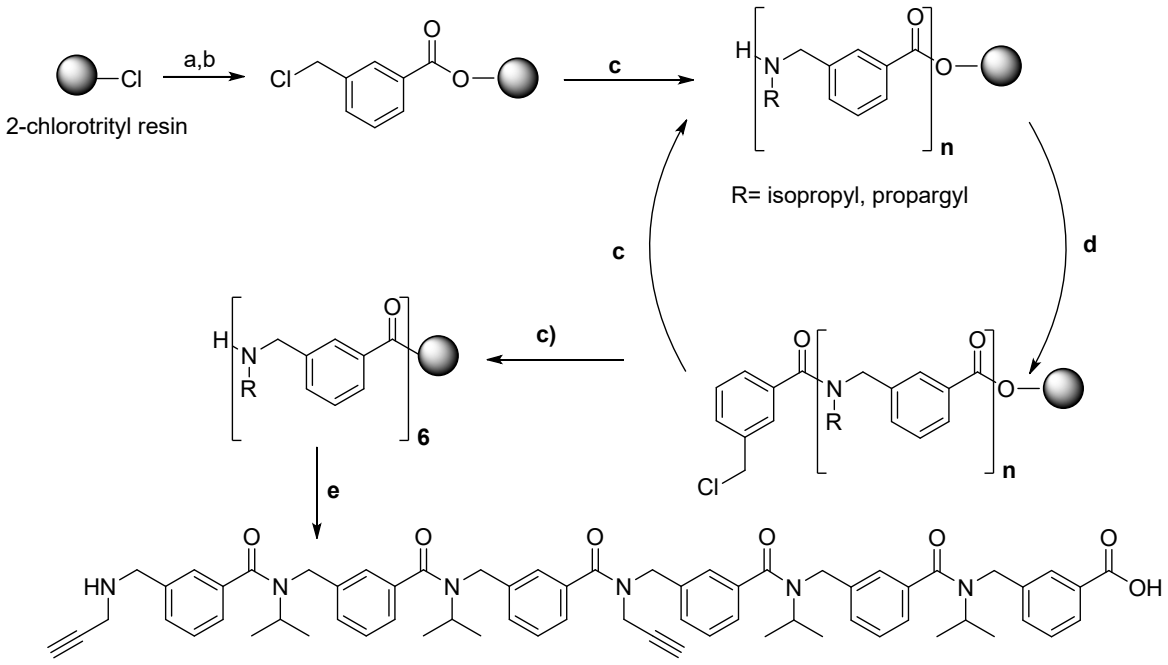


Figure S4. IR spectra of **Ia**.

*II.1.b. Linear meta-hexamer.**Ib***



a) Swelling, CH_2Cl_2; b) 3-chloromethyl benzoic acid, DIPEA, CH_2Cl_2; c) Isopropyl amine or propargyl amine, dmso, 50°C; d) 3-chloromethyl benzoiylchloride, DIPEA, CH_2Cl_2;e) Cleavage: TFA/CH_2Cl_2 (2:8).

Scheme S2. Synthesis of linear *meta*-arylopeptoid **Ib**

1-For 100 mg of resin, swelling: 2 ml of CH_2Cl_2 at RT for 10 min

2- 3-chloromethylbenzoic acid (1.2 equiv. per mmol loading), DIPEA (5 equiv. per mmol loading) dissolved in 1 mL CH_2Cl_2 were added at RT and shaken 40 minutes. This step is repeated. The liquid was drained off, then the resin was washed with CH_2Cl_2 (5x2 ml), then with DMSO (5x2 ml).

3- Isopropyl amine or propargyl amine (20 equiv per mmol loading, 1M) dissolved in 0.5 mL of DMSO were added. The reaction was shaken for 1h at 50°C. The liquid was drained off, then the resin was washed with DMSO (5x2 ml), then with CH_2CL_2 (5x2 ml).

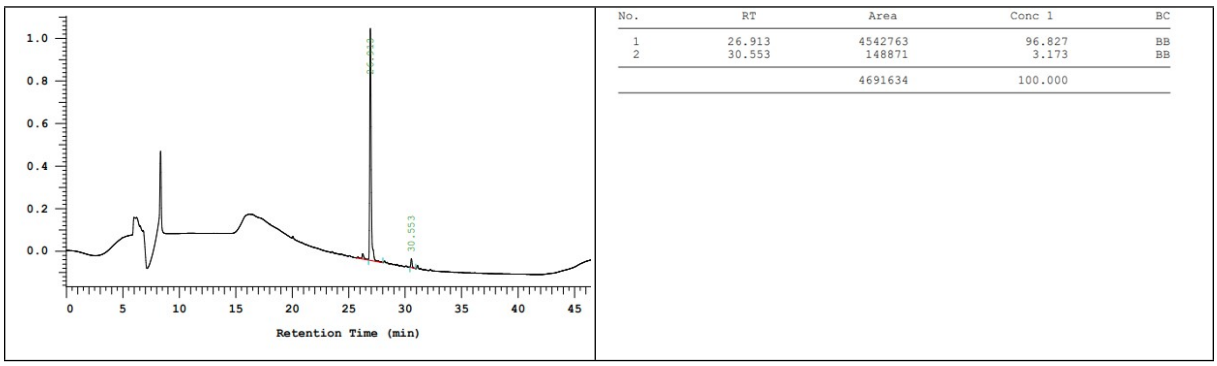
4- 3-chloromethylbenzoylchloride (3 equiv. per mmol loading), DIPEA (6 equiv. per mmol loading) dissolved in 1 mL CH_2Cl_2 were added at RT, shaken 10 minutes. The liquid was drawn down, then the resin was washed with CH_2Cl_2 (5x2 ml), then with DMSO (5x2 ml).

5- Isopropyl amine or propargyl amine (20 equiv per mmol loading) dissolved in 0.5 mL of DMSO were added. The reaction was shaken for 1h at 50°C. The liquid was drained off, then the resin was washed with DMSO (5x2 ml), then with CH_2CL_2 (5x2 ml).

Steps 4 and 5 were repeated to grow the targeted arylopeptoid oligomer until the expected sequence length.

6-The arylopeptoid was cleaved from the resin by the addition of 1 ml of CH_2Cl_2/TFA (8:2) for 30 min at RT. The solution was collected and then the resin was washed with CH_2Cl_2 (5x2 ml). The solution was evaporated under reduced pressure. The product was purified on LC Buchi C18 column (water +0.1%TFA/MeOH) affording 93% of product **Ib** (HPLC purity 96%).

HRMS (TOF MS ES+): *m/z* calcd for $C_{66}H_{73}N_6O_7$ $[M+H]^+$: 1061.55352; found: 1061.5536 (0.06 ppm).



No.	RT	Area	Conc 1	BC
1	26.913	4542763	96.827	BB
2	30.553	148871	3.173	BB
		4691634	100.000	

Figure S5. HPLC chromatogram of pure **Ib**.

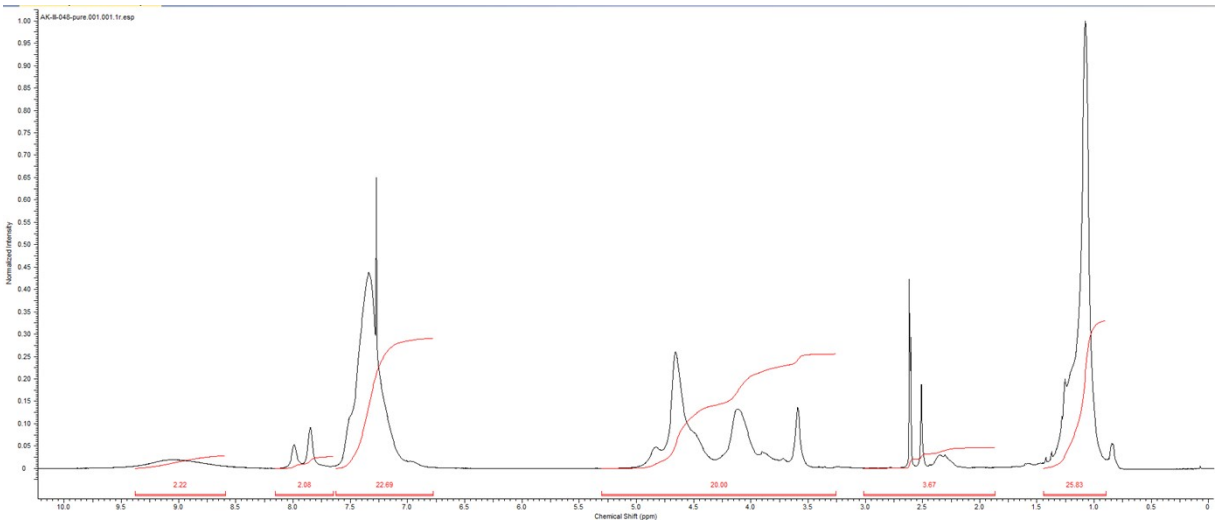


Figure S6. ^{1}H-NMR spectrum in $CDCl_3$ of pure **Ib**.

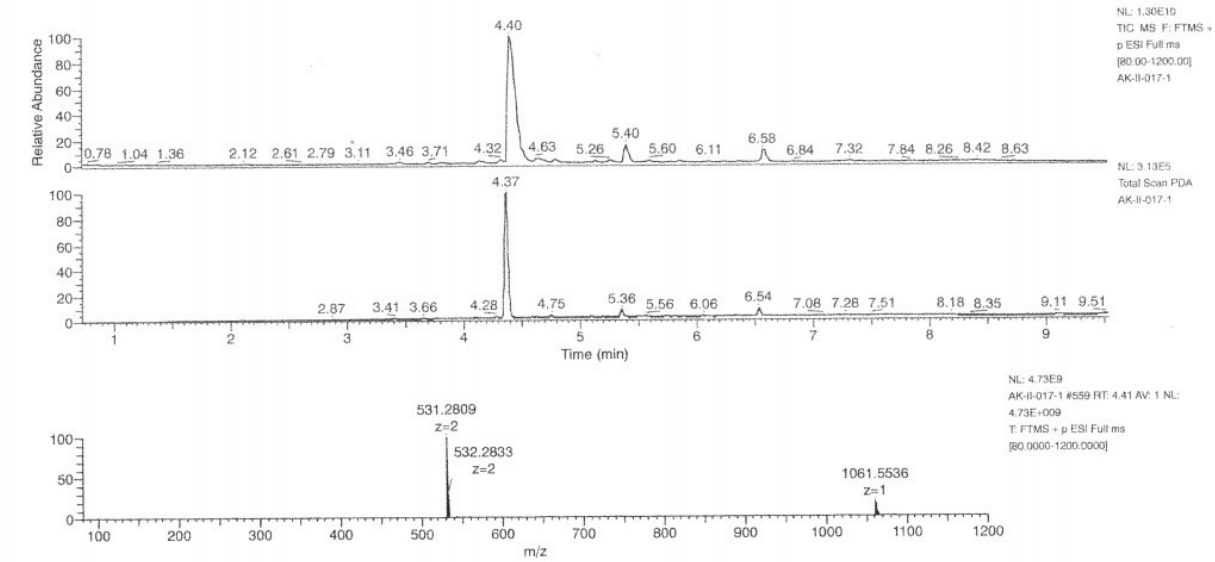


Figure S7. LCMS spectrum of the crude **Ib**.

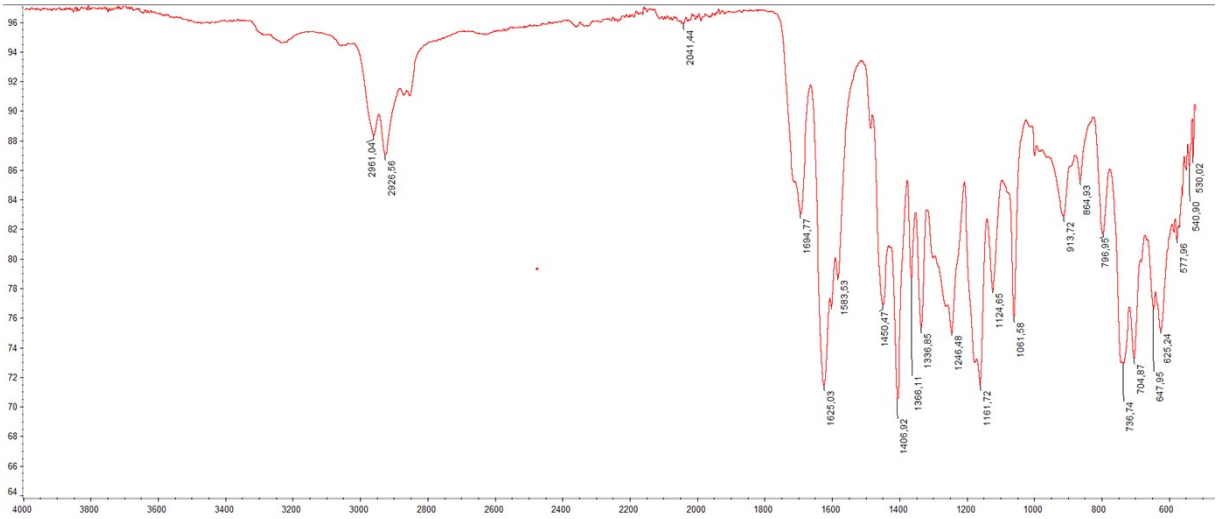
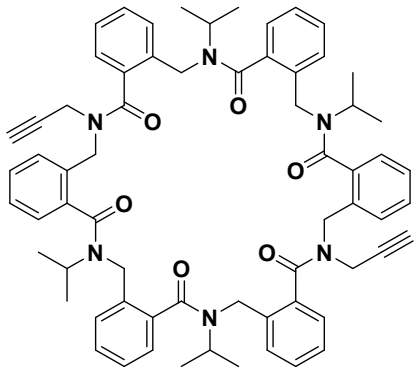


Figure S8. IR spectra of pure **Ib**.

II.2. Cyclisation

*II.2.a. ortho-cyclohexamer **IIa**.*

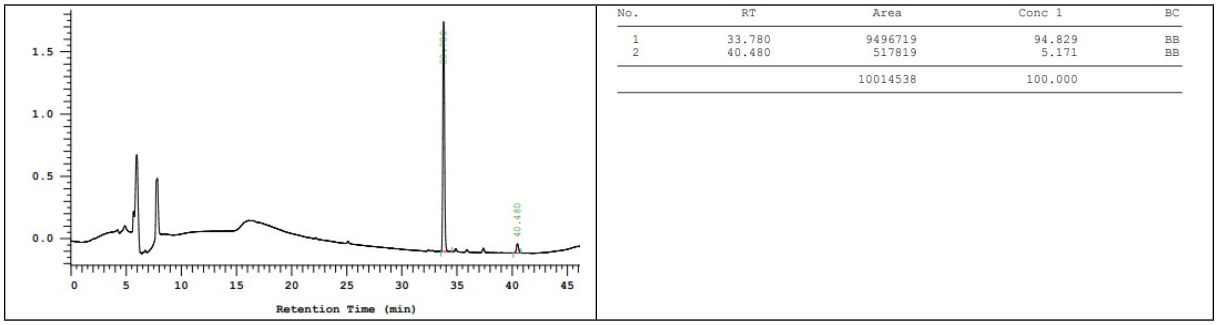


Chemical Formula: $C_{66}H_{70}N_6O_6$
Exact Mass: 1042,5357
Molecular Weight: 1043,3220

The *ortho*-hexamer **Ia** was dissolved in CH_2Cl_2 (5 mmol/L), then 5 equiv. of DIPEA was added followed by 1.2 equiv. of HATU. The reaction was stirred overnight at RT. The solvent was evaporated under reduced pressure and then the residue was evaporated with CH_2Cl_2 (2x20 ml). The residue is then

dissolved in EtOAc (20 ml), extracted with $NaHCO_3$ (2x10ml) then brine (1x10 ml). The organic layer was dried over $MgSO_4$, filtered then evaporated under reduced pressure. The product was purified on C18 column (Water + 0.1% TFA/ MeOH) affording macrocycle **IIa** in 70% yield (HPLC purity 95%).

HRMS (TOF MS ES+): *m/z* calcd for $C_{66}H_{71}N_6O_6$ $[M+H]^+$: 1043.54296; found: 1043.5422 (-0.69 ppm).



No.	RT	Area	Conc 1	BC
1	33.780	9496719	94.829	BB
2	40.480	517819	5.171	BB
		10014538	100.000	

Figure S9. HPLC chromatogram of the pure *ortho*-macrocycle (**IIa**).

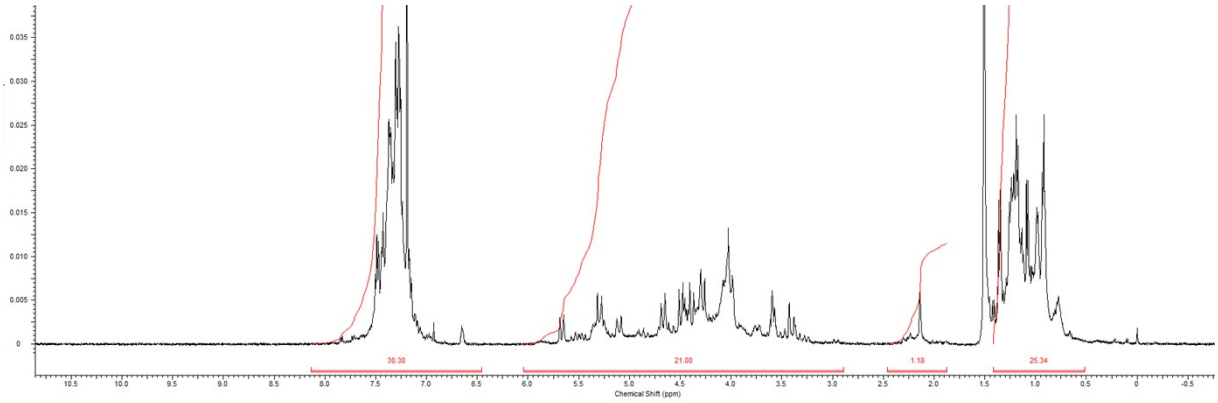


Figure S10. ^{1}H-NMR spectrum in $CDCl_3$ of pure *ortho*-macrocycle (**IIa**).

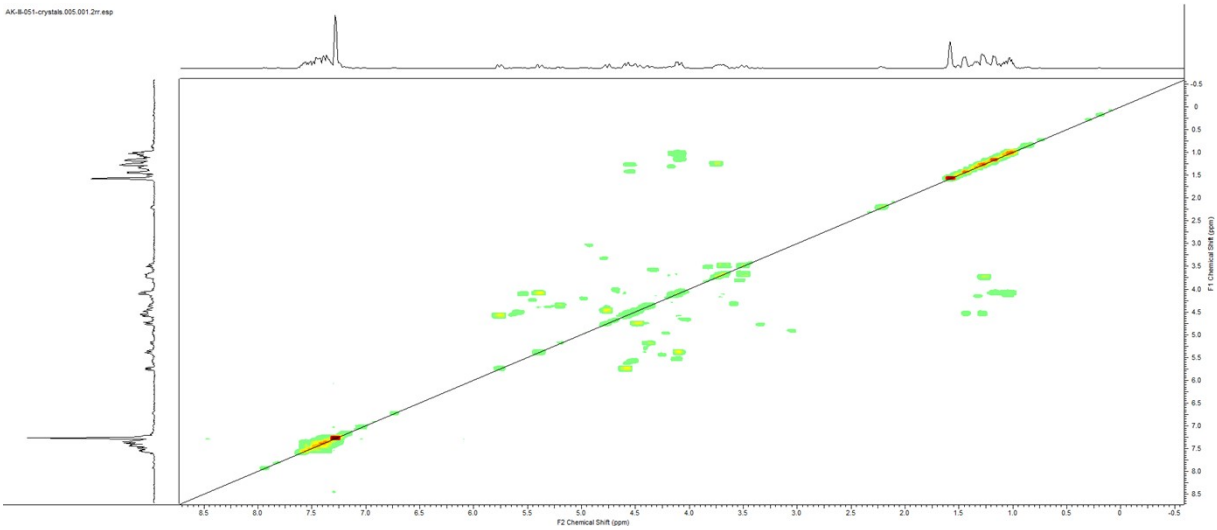


Figure S11. COSY spectrum in $CDCl_3$ of pure *ortho*-macrocycle (**IIa**).

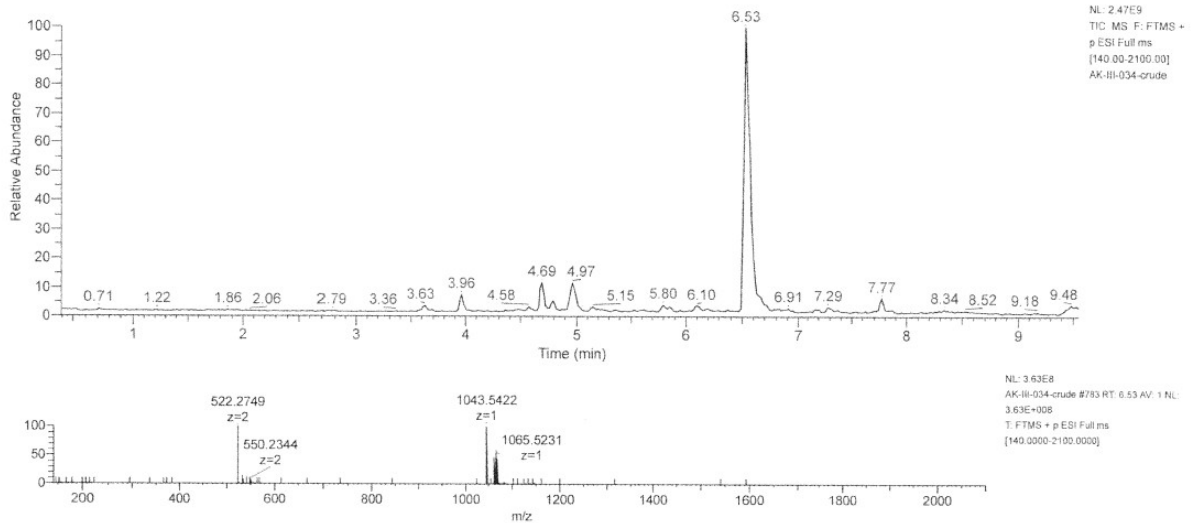


Figure S12. LCMS spectra of *ortho*-macrocycle (**IIa**).

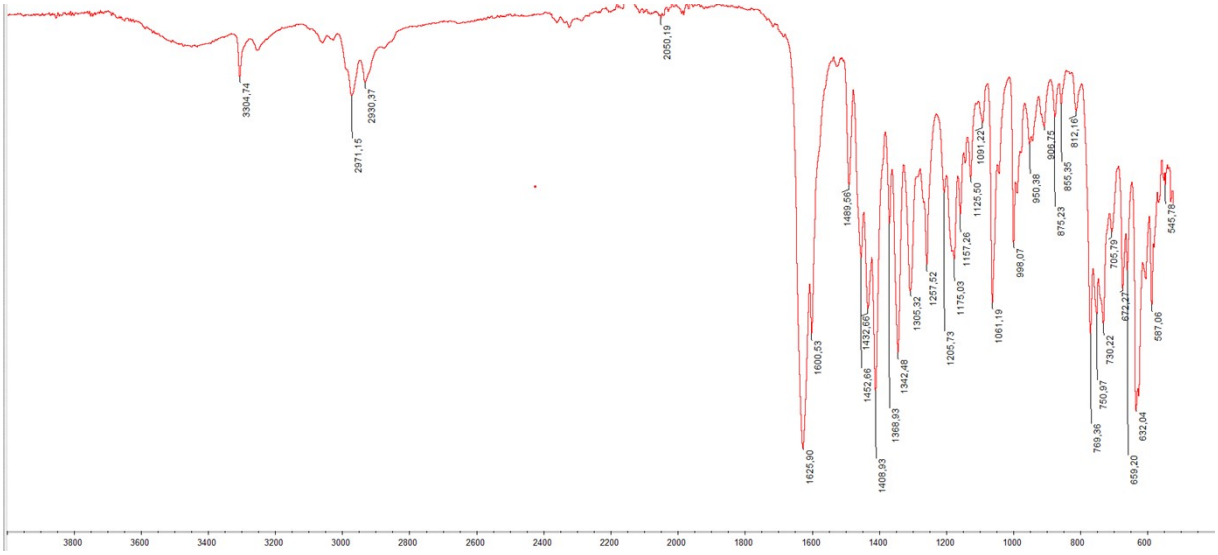
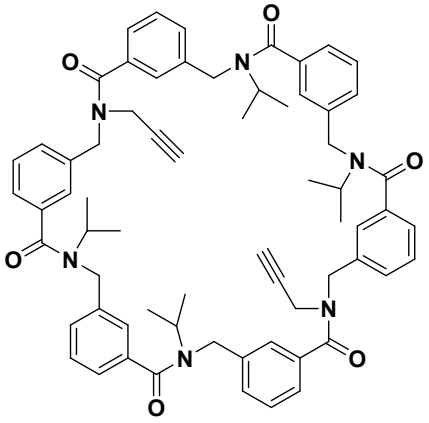


Figure S13. IR spectra of *ortho*-macrocycle (**IIa**).

*II.2.b. meta-cyclohexamer **IIb.***

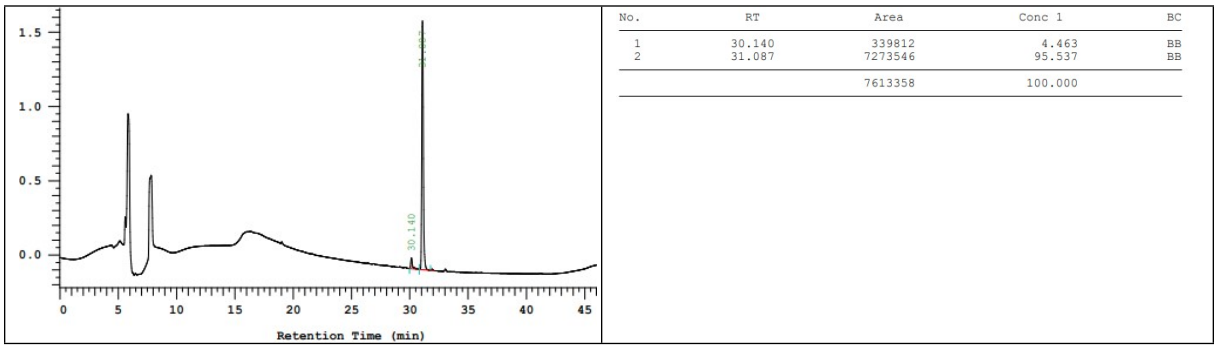


Chemical Formula: $C_{66}H_{70}N_6O_6$
Exact Mass: 1042,5357
Molecular Weight: 1043,3220

The *meta*-hexamer **Ib** was dissolved in CH_2Cl_2 (5 mmol/L), then 5 equiv. of DIPEA was added followed by 1.2 equiv. of HATU. The reaction was stirred overnight at RT. The solvent was evaporated under reduced pressure and then the residue was evaporated with CH_2Cl_2 (2x20 ml). The residue is then

dissolved in EtOAc (20 ml), extracted with $NaHCO_3$ (2x10 ml) then brine (1x10 ml). The organic layer was dried over $MgSO_4$, filtered then evaporated under reduced pressure. The product was purified on C18 column (Water + 0.1% TFA/ MeOH) affording macrocycle **IIb** in 81% yield (HPLC purity 95%).

HRMS (TOF MS ES+): *m/z* calcd for $C_{66}H_{71}N_6O_6$ $[M+H]^+$: 1043.54296; found: 1043.5427 (-0.23 ppm).



No.	RT	Area	Conc 1	BC
1	30.140	339812	4.463	BB
2	31.087	7273546	95.537	BB
		7613358	100.000	

Figure S14. HPLC of pure *meta*-macrocycle (**IIb**).

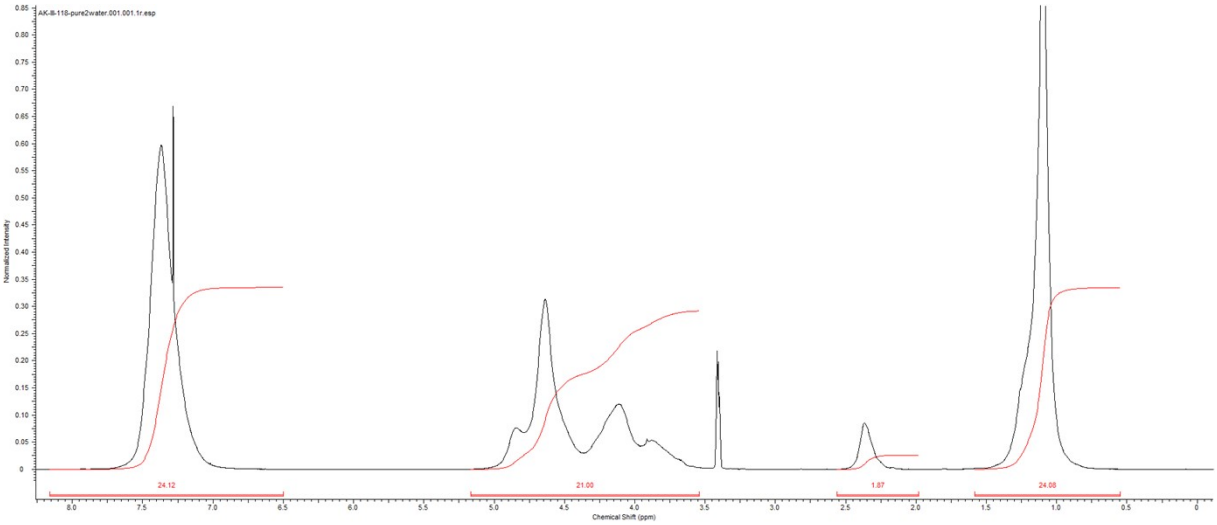


Figure S15. ^{1}H-NMR in $CDCl_3$ of pure *meta*-macrocycle (**IIb**).

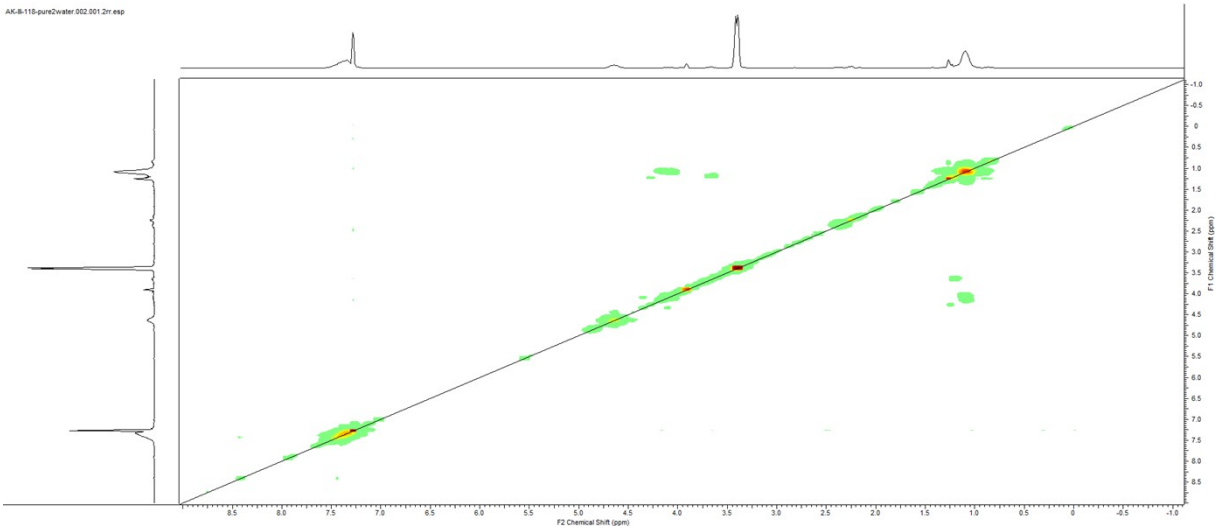


Figure S16. COSY spectra in $CDCl_3$ of pure *meta*-macrocycle (**IIb**).

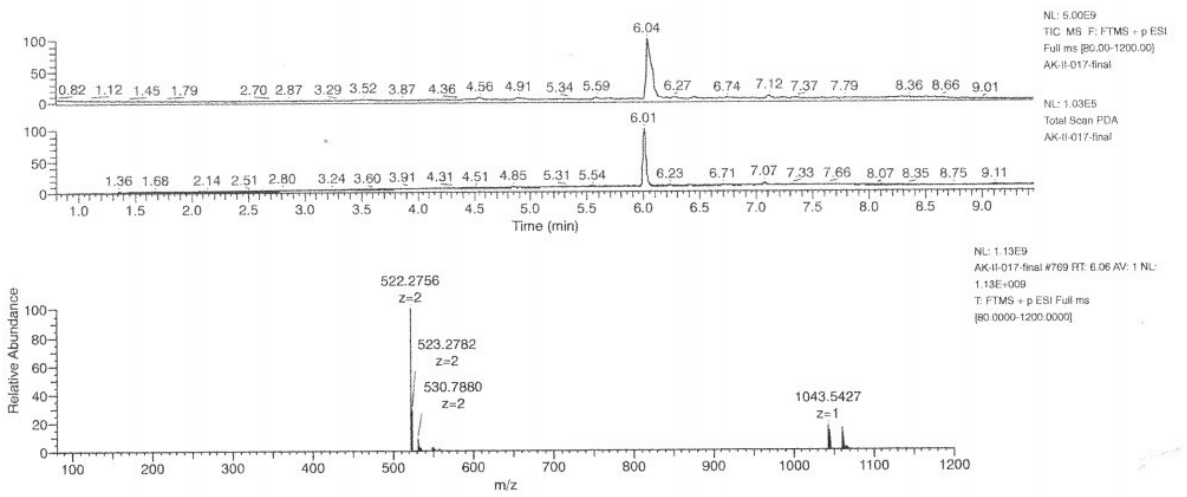


Figure S17. LCMS spectrum of the crude *meta*-macrocycle (**IIb**).

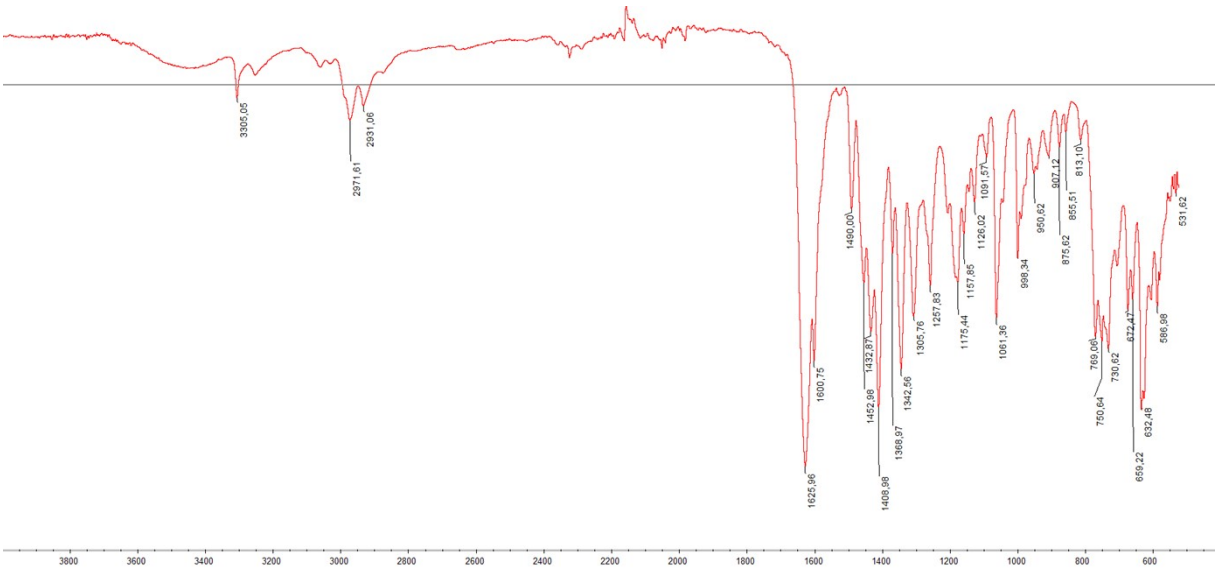


Figure S18. IR spectra of *meta*-macrocycle (**IIb**).

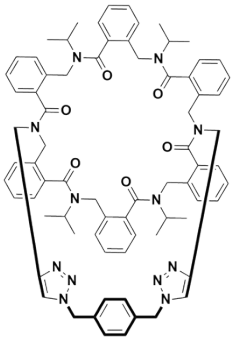
II.3. CuAAC reactions

High dilution procedure: Macrocycle **IIa** or **IIb** (1.0 equiv.) was dissolved in methanol (C = 1.0 mM). 1,4-bis(azidomethyl) benzene (1.1 equiv.) and catalyst **III** (10 mol-% per alkyne) were added. The reaction was stirred for 2 days at room temperature and the solvent was evaporated under reduced pressure.

High concentration procedure for ortho series: Macrocycle **IIa** (1.0 equiv.) was dissolved in methanol/CH_2Cl_2 (1/1) at concentration of 0.1 M. 1,4-bis(azidomethyl) benzene (1.1 equiv.) and catalyst **III** (10 mol-% per alkyne) were added. The reaction was stirred for 2 days at room temperature and the solvent was evaporated under reduced pressure.

High concentration procedure for meta series: Macrocycle **IIb** was dissolved in methanol (C = 0.1 M). 1,4-bis(azidomethyl) benzene (1.1 equiv.) and catalyst **III** (10 mol-% per alkyne) were added. The reaction was stirred for 2 days at room temperature and the solvent was evaporated under reduced pressure.

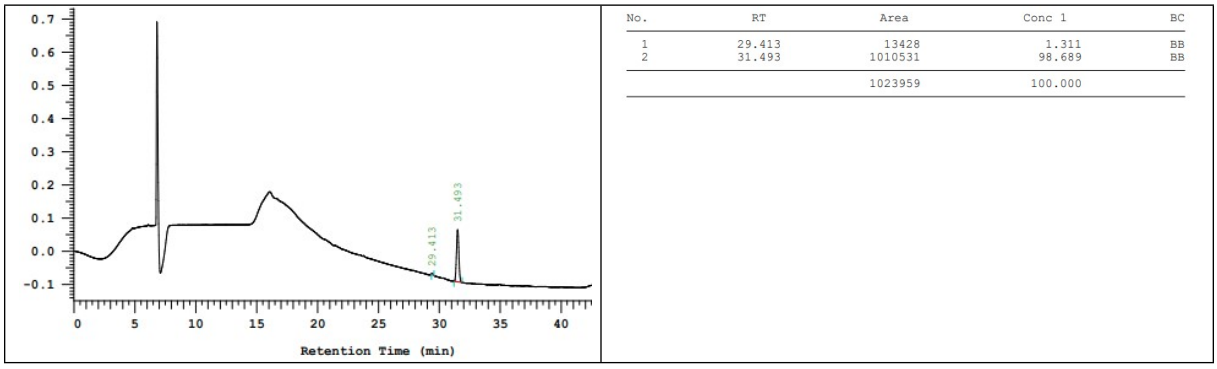
II.3.a. *Compound **IVa**.*



High dilution procedure performed on 95 mg (0.09 mmol) of macrocycle **IIa**. HRMS of the crude indicates the presence of crown-like **IVa** as major compound and tube-like **Va** as traces. The product **IVa** was purified by column chromatography (EtOAc/MeOH 90:10 then CH_2Cl_2/MeOH 95:5 to 70:30) followed by C18 purification (MeOH/H_2O + 0.1%TFA) furnishing **IVa** (86 mg, 78%, 98% HPLC purity).

High concentration procedure performed on 50 mg (0.045 mmol) of **Ia**. HRMS of the crude also indicates the presence of crown-like **IVa** as major compound and tube-like **Va** as traces. The product **IVa** was purified by column chromatography (EtOAc/MeOH 90:10 then CH_2Cl_2/MeOH 95:5 to 70:30) followed by C18 purification (MeOH/H_2O + 0.1%TFA) furnishing **IVa** (40 mg, 76 %, 98% HPLC purity).

HRMS (TOF MS ES+): *m/z* calcd for $C_{74}H_{79}N_{12}O_6$ $[M+H]^+$: 1231.624; found: 1231.6248 (0.61 ppm)



No.	RT	Area	Conc 1	BC
1	29.413	13428	1.311	BB
2	31.493	1010531	98.689	BB
		1023959	100.000	

Figure S19. HPLC of the pure *ortho* compound **IVa**.

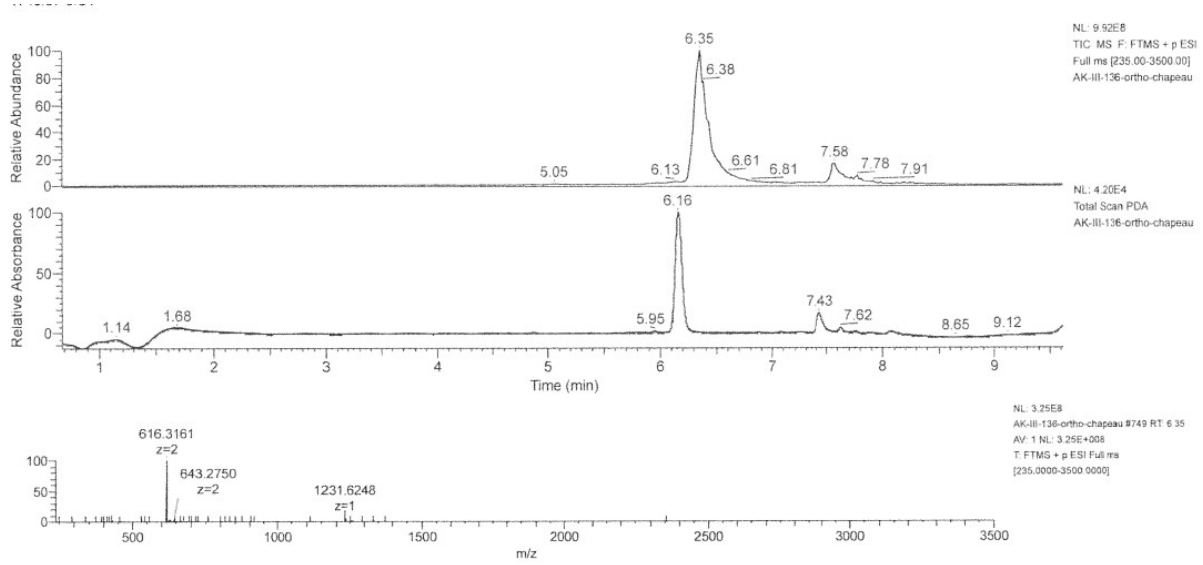


Figure S20. LC-MS spectra of the pure *ortho* compound **IVa**.

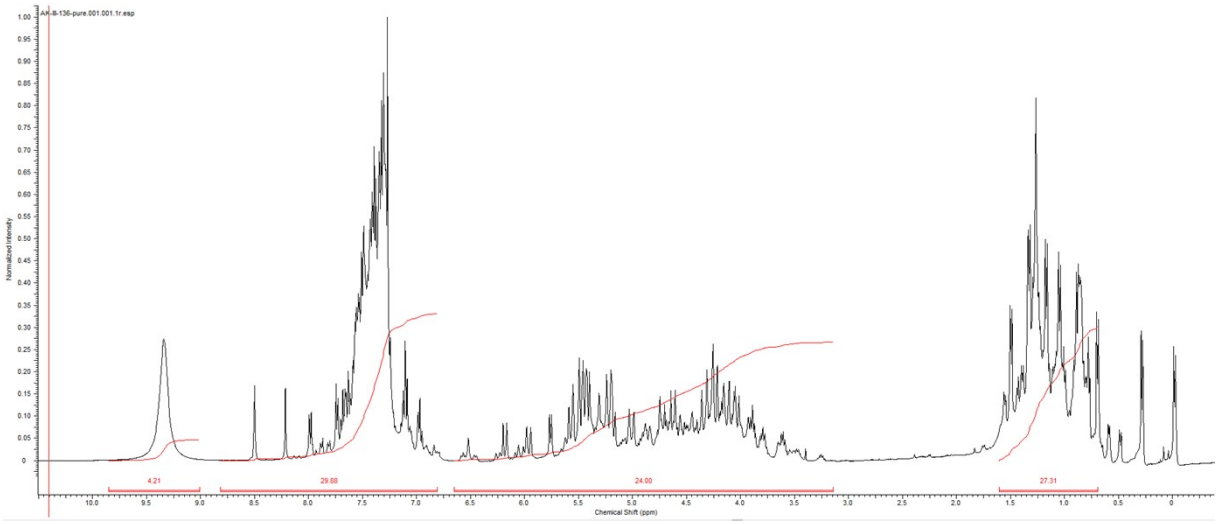


Figure S21. ^{1}H-NMR in $CDCl_3$ of the pure *ortho* compound **IVa**.

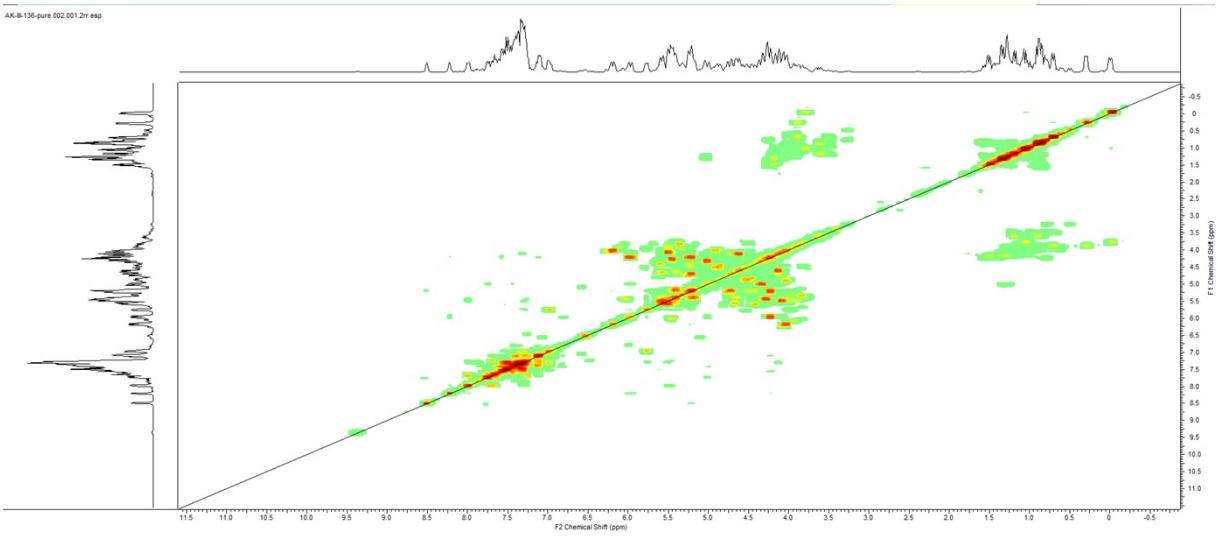


Figure S22. COSY spectra in $CDCl_3$ of the pure *ortho* compound **IVa**.

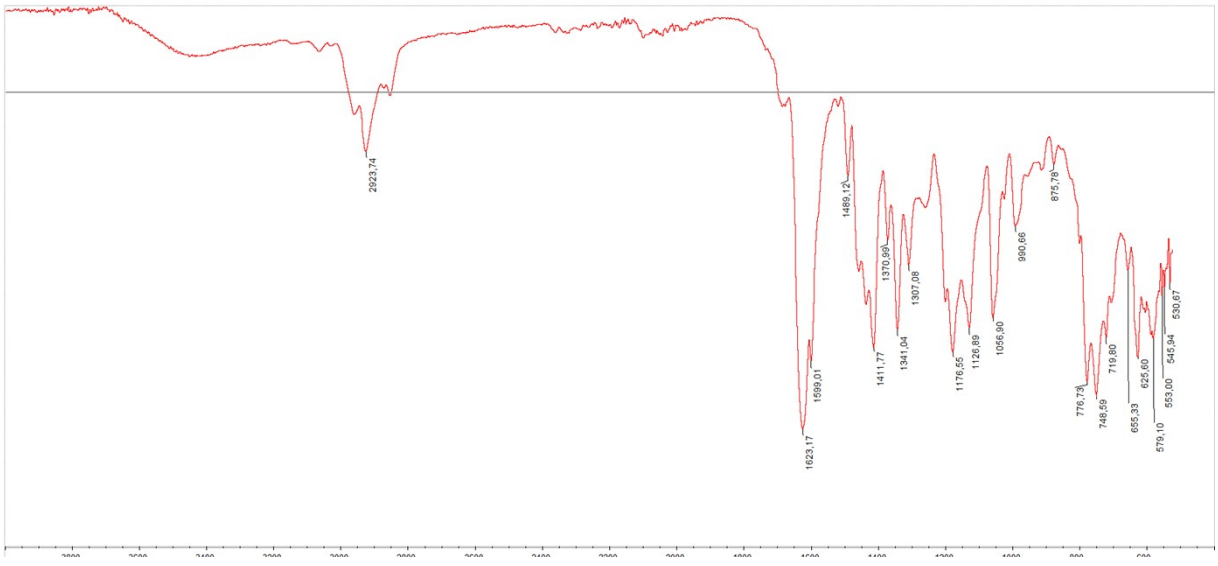
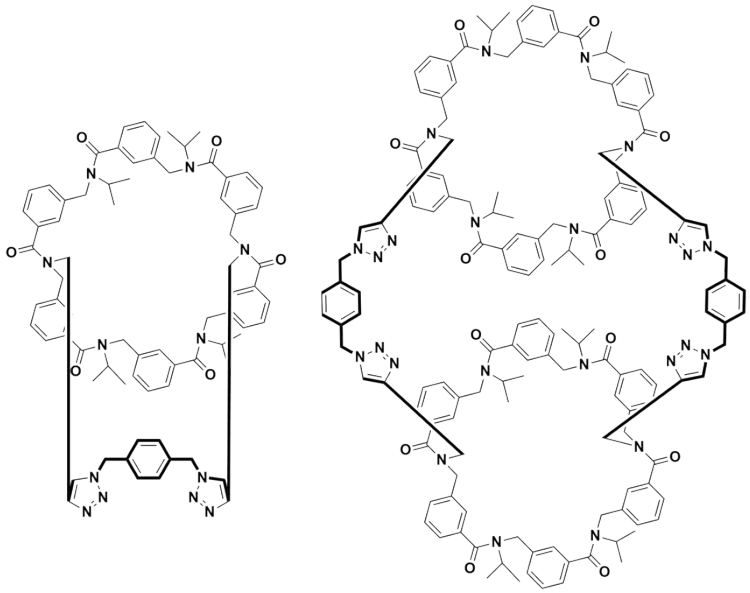


Figure S23. IR spectra of *ortho* compound **IVa**.

*II.3.b. Compounds **IVb** and **Vb**.*



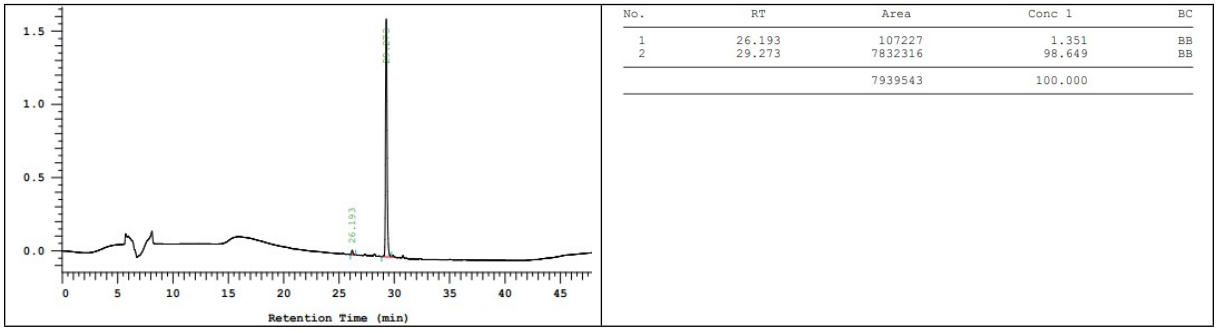
High dilution procedure performed on 200 mg (0.19 mmol) of macrocycle **IIb** furnishing 103 mg of cupola-like compound **IVb** (44 % yield, 98% HPLC purity) and 88 mg of tube-like compound **Vb** (37% yield, 98.5% HPLC purity).

High concentration procedure performed on 100 mg (0.1 mmol) of **IIb** furnishing 48 mg of cupola-like compound **IVb** (39 % yield, 98% purity) and 50 mg of tube-like compound **Vb** (41 % yield, 98% purity).

Purification procedure: The products were purified by column chromatography (EtOAc/MeOH 90:10 then CH_2Cl_2/MeOH 95:5 to 70:30) affording mixture of cupola-like **IVb** and tube-like **Vb.** Further C18 purification (MeOH/H_2O + 0.1%TFA) was performed for separation of **IVb** and **Vb.**

Compound **IVb:**

HRMS (TOF MS ES+): *m/z* calcd for $C_{74}H_{79}N_{12}O_6$ $[M+H]^+$: 1231.624; found: 1231.6257 (1.4 ppm).



No.	RT	Area	Conc 1	BC
1	26.193	107227	1.351	BB
2	29.273	7832316	98.649	BB
		7939543	100.000	

Figure S24. HPLC chromatogram of the pure *meta* compound **IVb**.

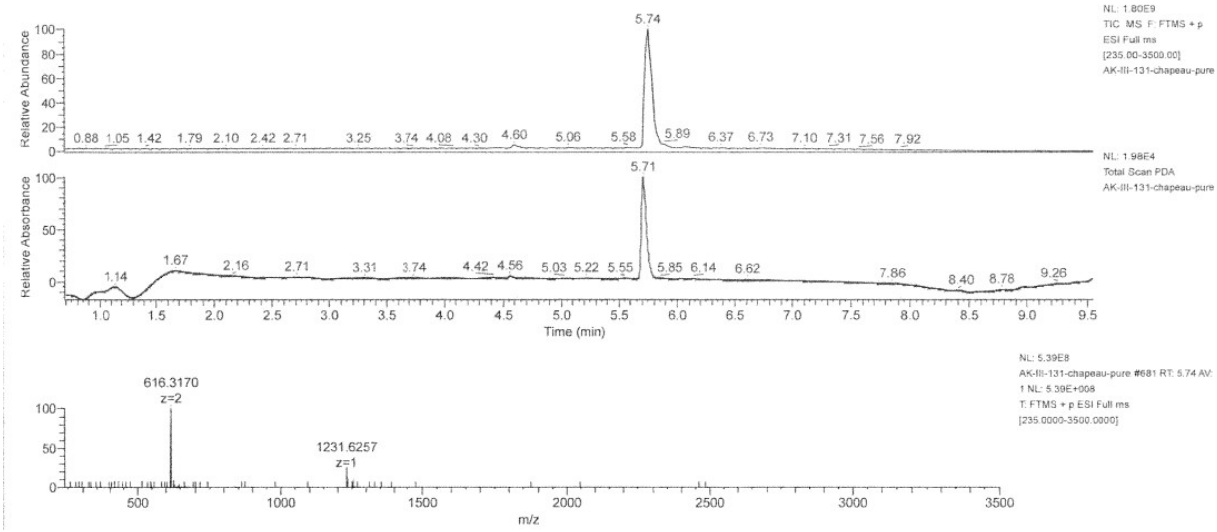


Figure S25. LCMS spectrum of crude *meta* compound **IVb**.

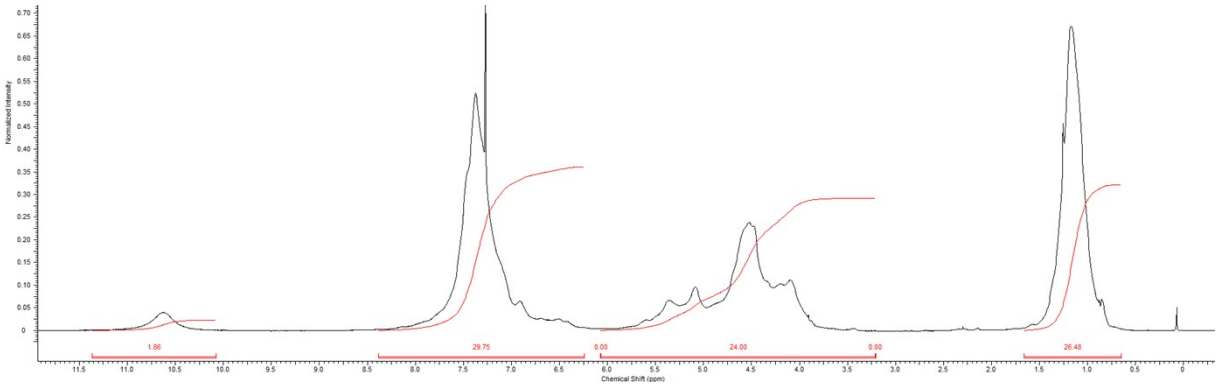


Figure S26. ^{1}H-NMR spectra in $CDCl_3$ of the pure *meta* compound **IVb**.

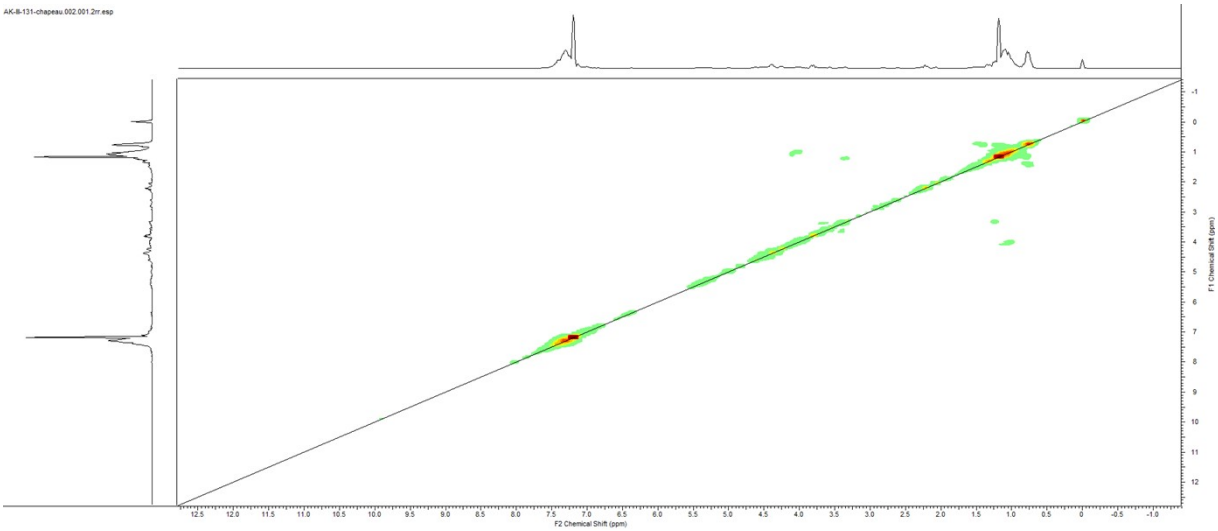


Figure S27. COSY spectra in $CDCl_3$ of the pure *meta* compound **IVb**.

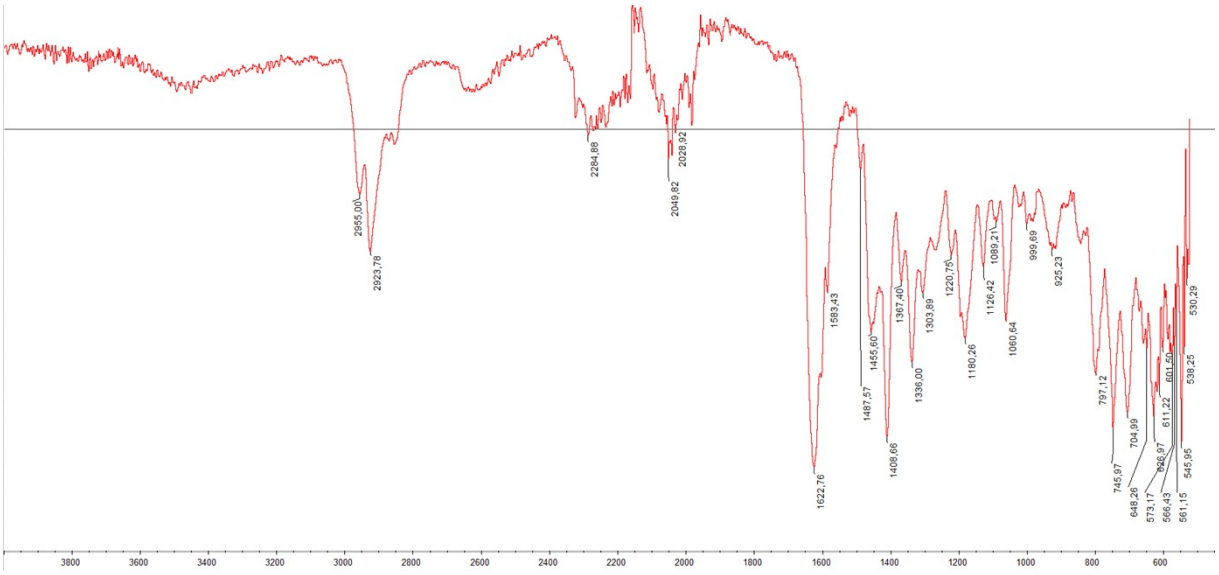


Figure S28. Infra-red of *meta* compound **IVb**.

Compound **Vb:**

HRMS (TOF MS ES+): *m/z* calcd for $C_{148}H_{158}N_{24}O_{12}$ $[M+2H]^{2+}$: 1231.624; found: 1231.6252 (1.01 ppm).

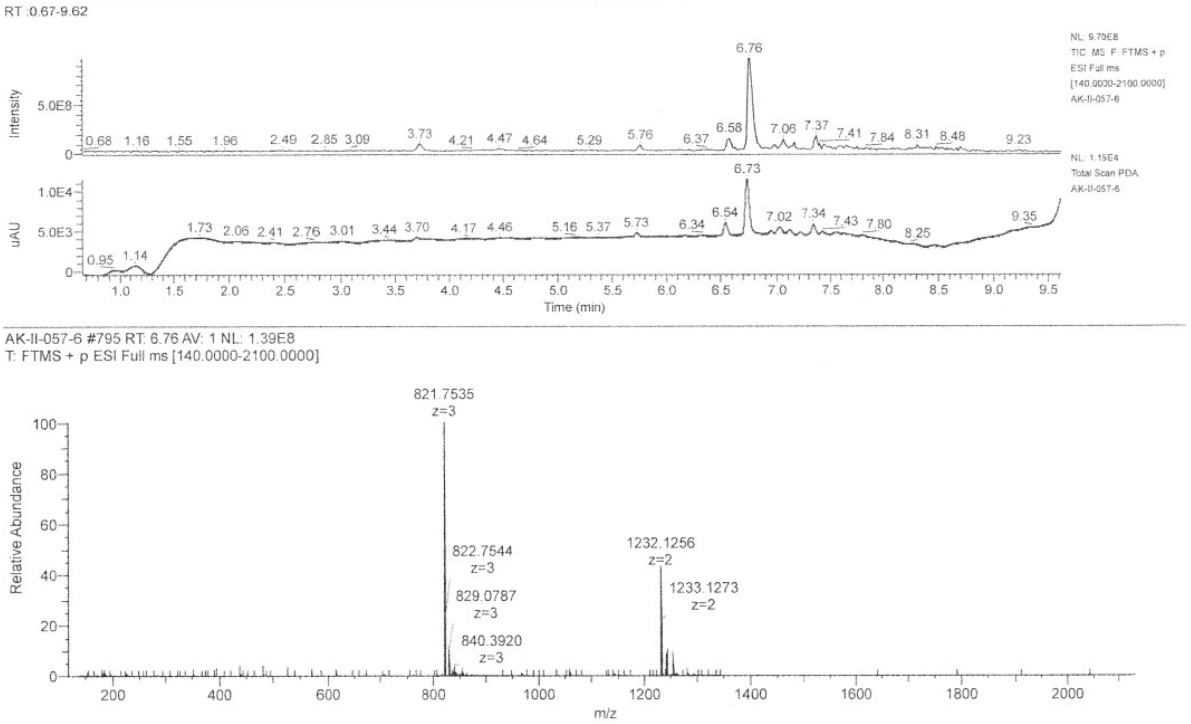


Figure S29. LCMS spectra of the pure *meta* compound **Vb.**

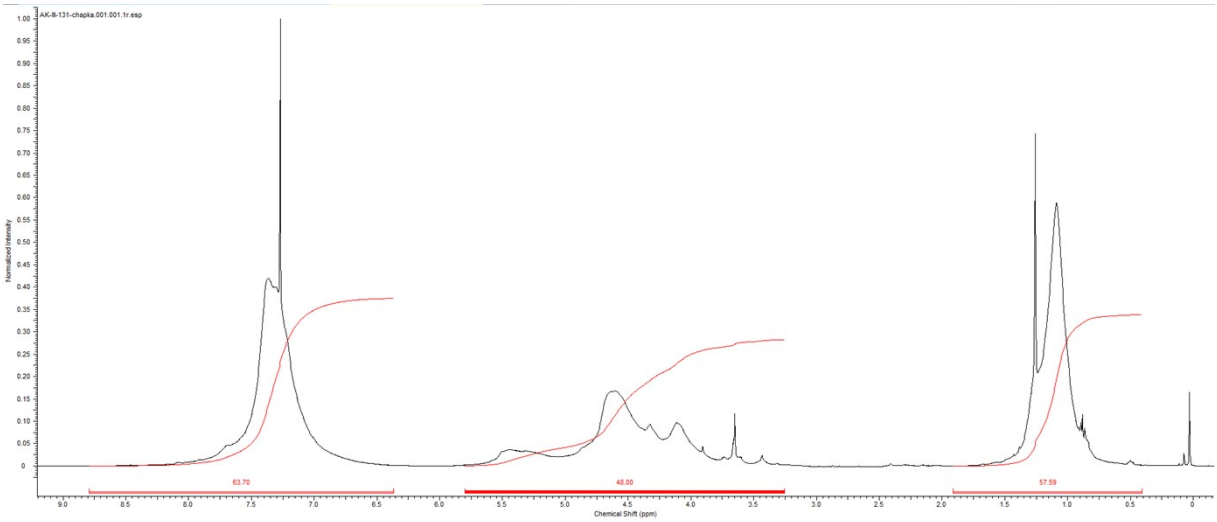


Figure S30. ^{1}H-NMR spectra in $CDCl_3$ of the pure *meta* compound **Vb**.

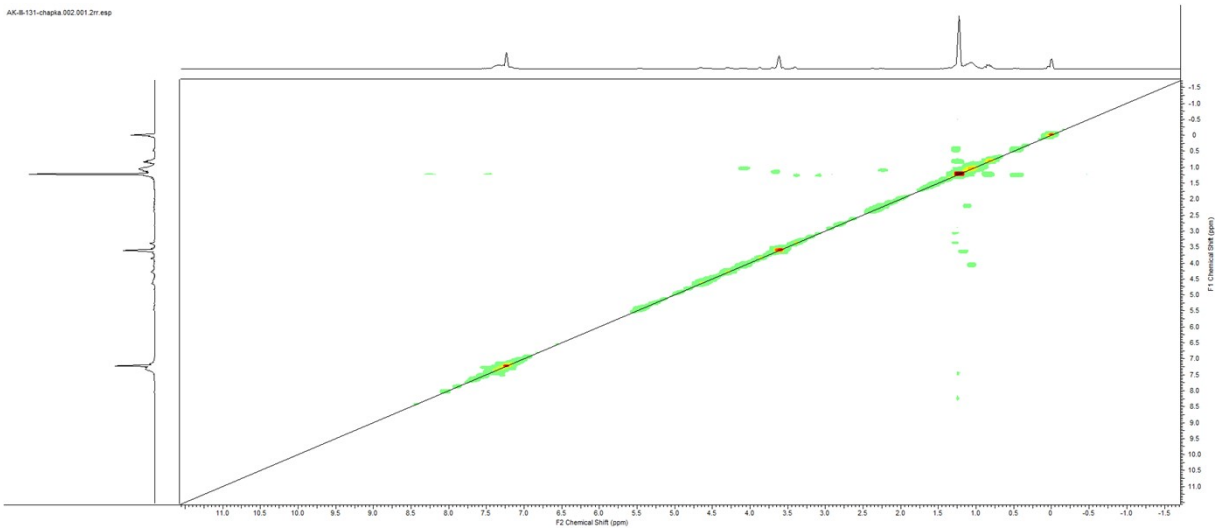


Figure S31. COSY in $CDCl_3$ of the pure *meta* compound **Vb**.

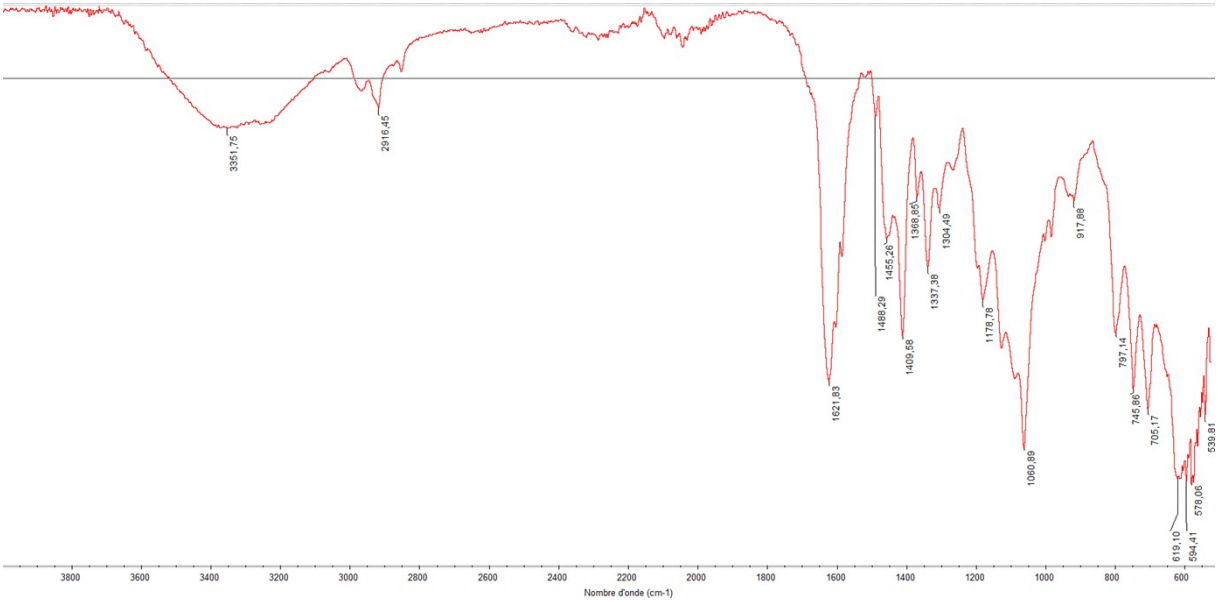
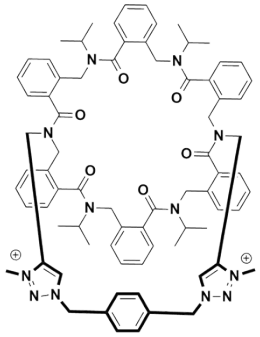


Figure S32. IR spectra of pure *meta* compound **Vb**.

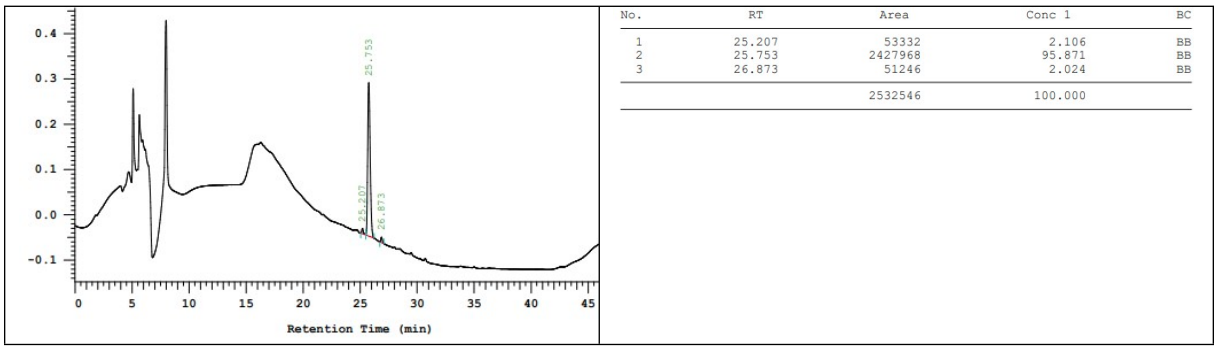
II.4. Triazolium formation

The methylation of cupola-like compounds I**Va** and I**Vb** was performed in ace pressure tube in pure MeI at 70°C for 24 hours and produced the double methylated products **VIa** and **VIb** in quantitative yields.

*II.4.a. ortho cupola-like **bis**-triazolium **VIa**.*



HRMS (TOF MS ES+): *m/z* calcd for $C_{76}H_{84}N_{12}O_6$ $[M]^{2+}$: 630.33129; found: 630.3325 (1.95 ppm).



No.	RT	Area	Conc 1	BC
1	25.207	53332	2.106	BB
2	25.753	2427968	95.871	BB
3	26.873	51246	2.024	BB
		2532546	100.000	

Figure S33. HPLC spectra of the crude *ortho* bis-triazolium compound **VIa**.

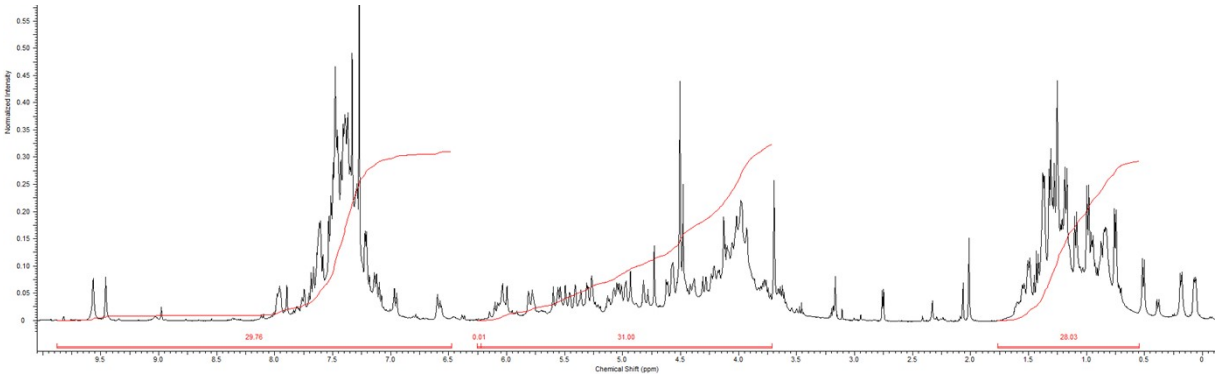


Figure S34. ^{1}H-NMR spectra in $CDCl_3$ of the crude *ortho* bis-triazolium compound **VIa**.

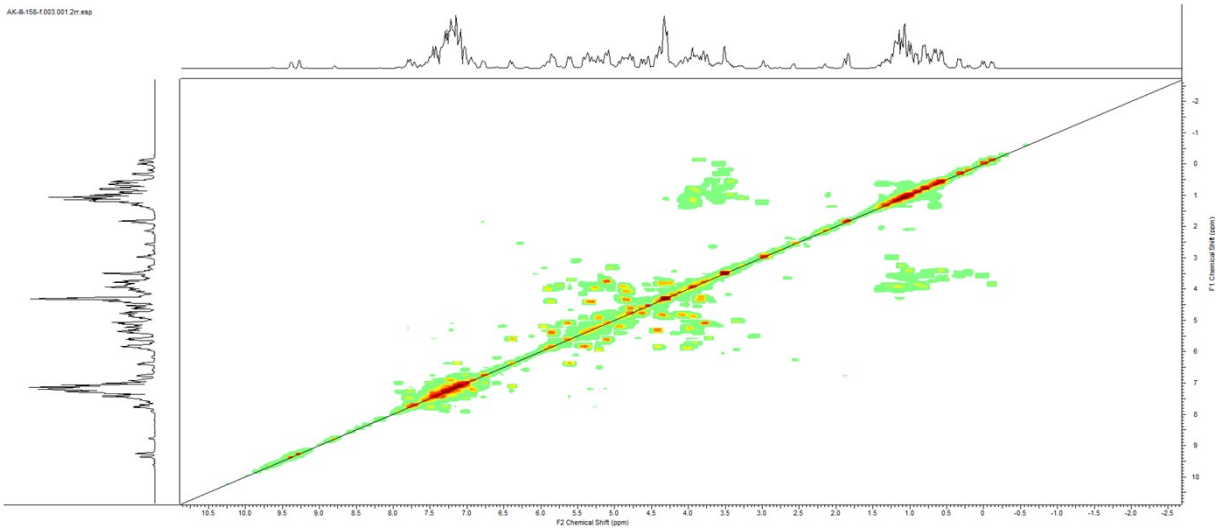


Figure S35. COSY spectra in $CDCl_3$ of the crude *ortho* bis-triazolium compound **VIa**.

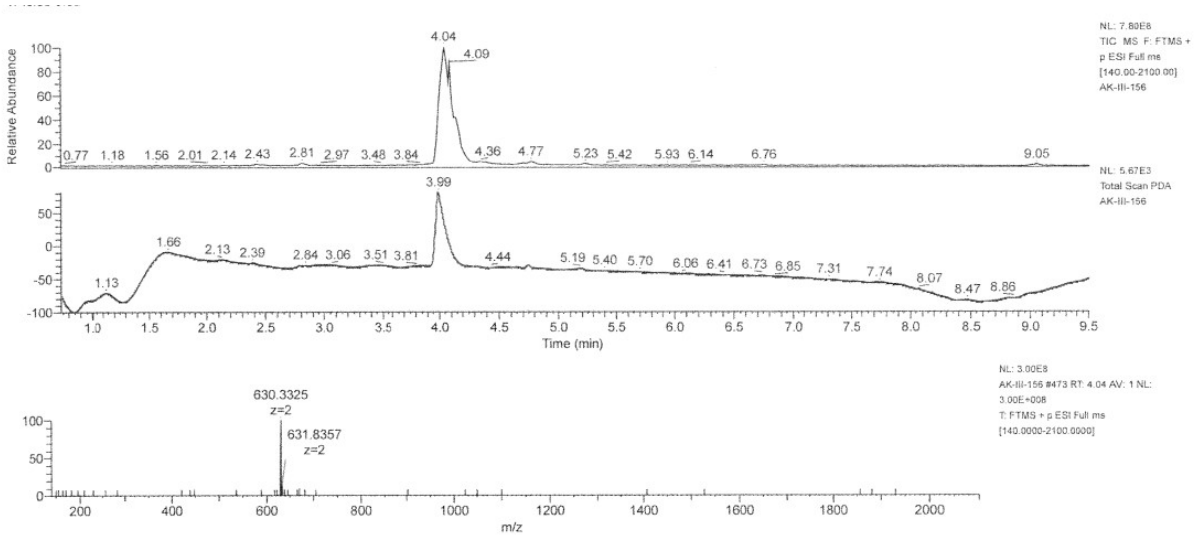
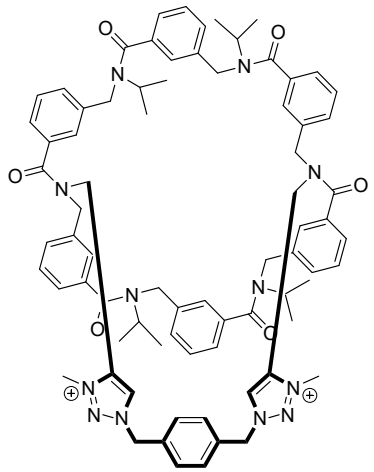


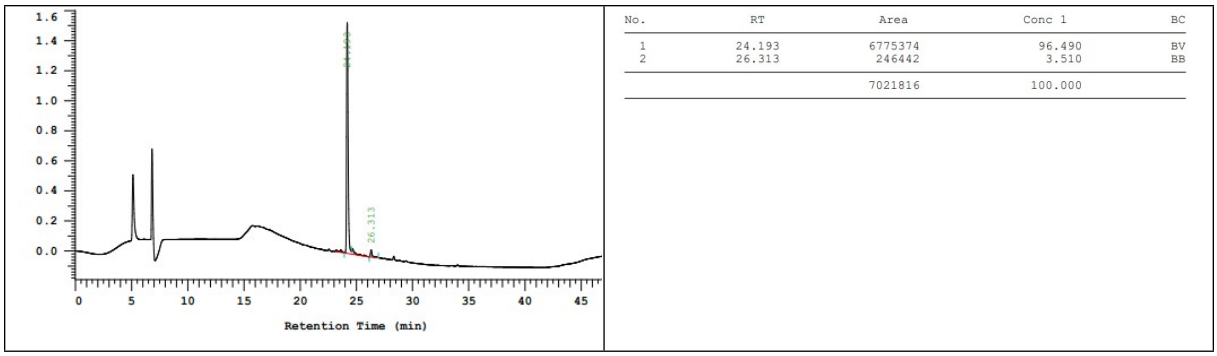
Figure S36. LCMS of the crude *ortho* bis-triazolium compound **VIa**.

*II.4.b. Meta cupola-like triazolium **VIb**.*



m_{crude} = 40 mg (HPLC purity 96%), isolated yield 98%

HRMS (TOF MS ES+): *m/z* calcd for $C_{82}H_{90}N_{12}O_6$ $[M]^{2+}$: 669.35477; found: 669.3538 (-1.41 ppm).



No.	RT	Area	Conc 1	BC
1	24.193	6775374	96.490	BV
2	26.313	246442	3.510	BB
		7021816	100.000	

Figure S37. HPLC chromatogram of *meta* bis-triazolium compound **VIb**.

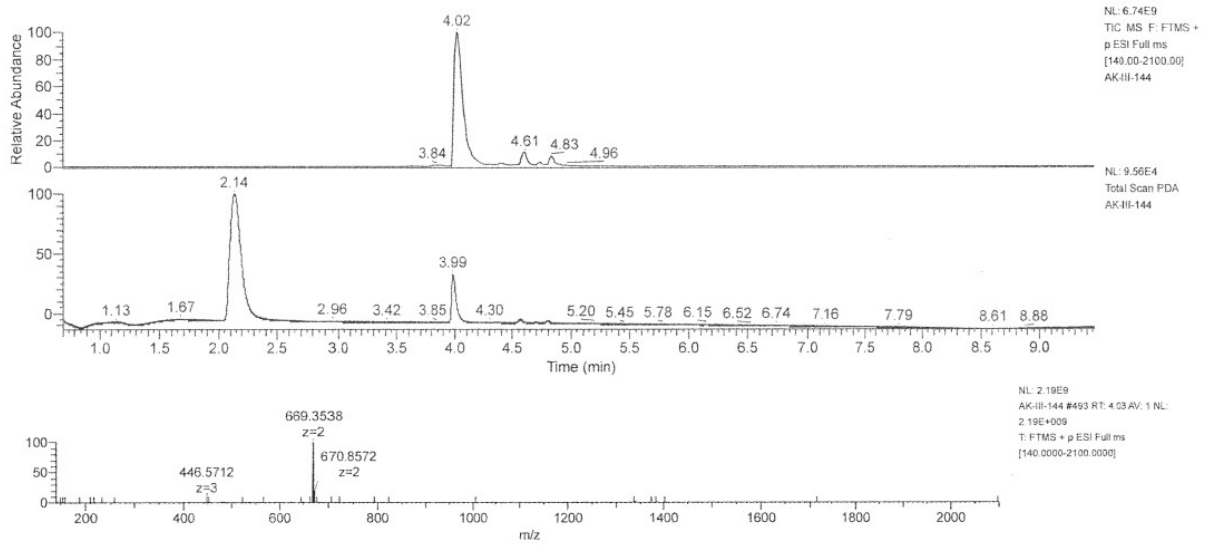


Figure S38. LCMS spectrum of *meta* bis-triazolium compound **VIb**.

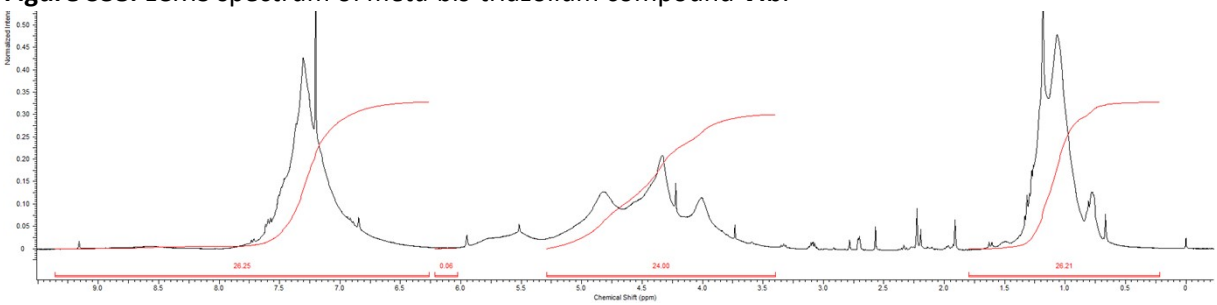


Figure S39. ^{1}H-NMR in $CDCl_3$ of the pure *meta* bis-triazolium compound **VIb**.

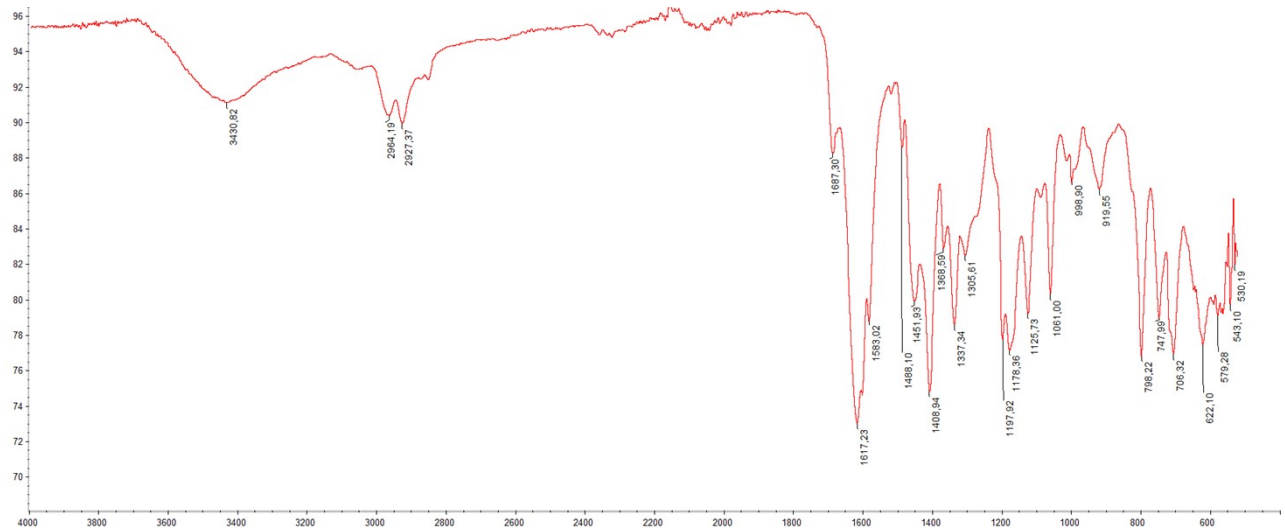


Figure S40. IR spectra of *meta* bis-triazolium compound **VIb**.

III-Conformational studies

III.1. NMR study

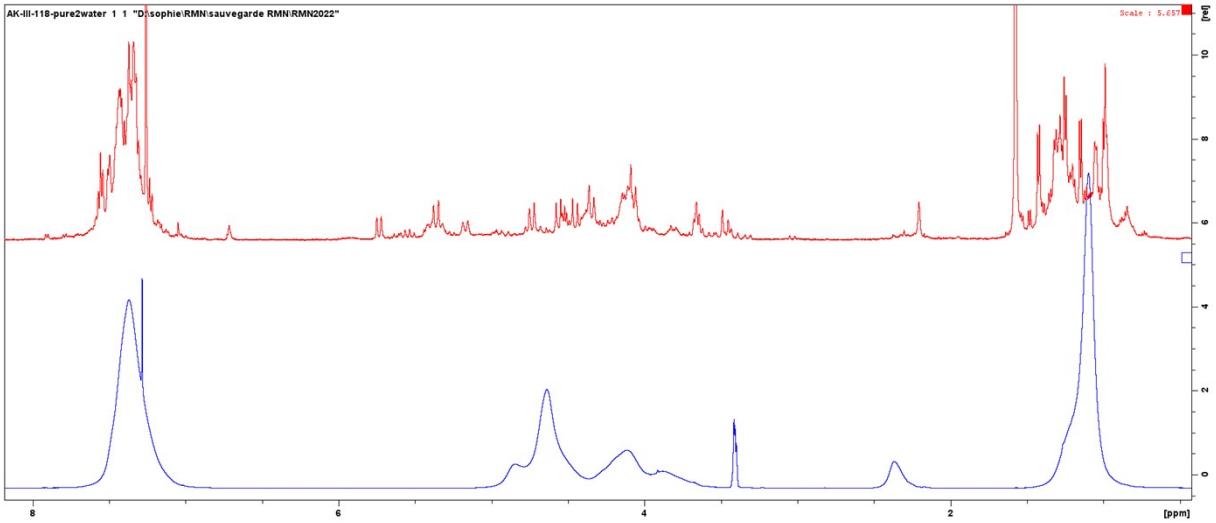


Figure S41. Comparison of ^{1}H NMR spectra of **IIa** (red curve) and **IIb** (blue curve) in $CDCl_3$ at 298 K.

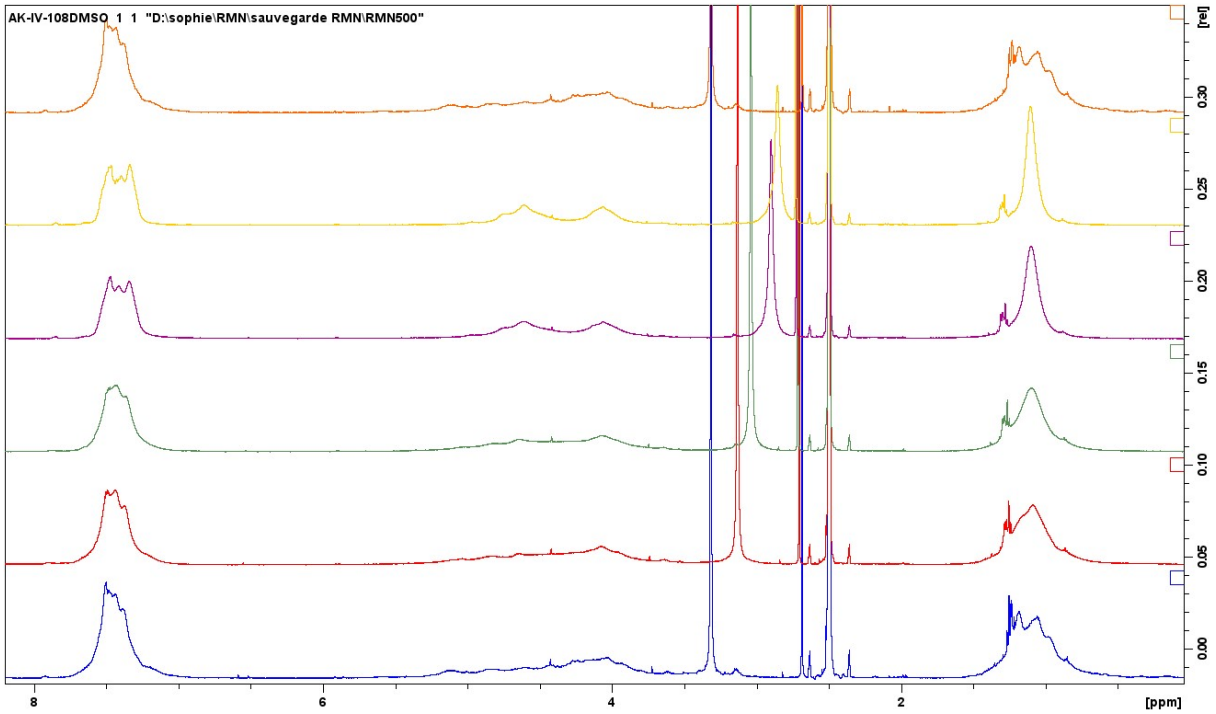


Figure S42. Variable temperature study of macrocycle **IIa** in DMSO (2.7 mg in 0.6 mL): 298 K (blue curve), 338 K (red curve), 358 K (green curve), 388 K (purple curve), 398 K (yellow curve), back to 298 K (orange curve).

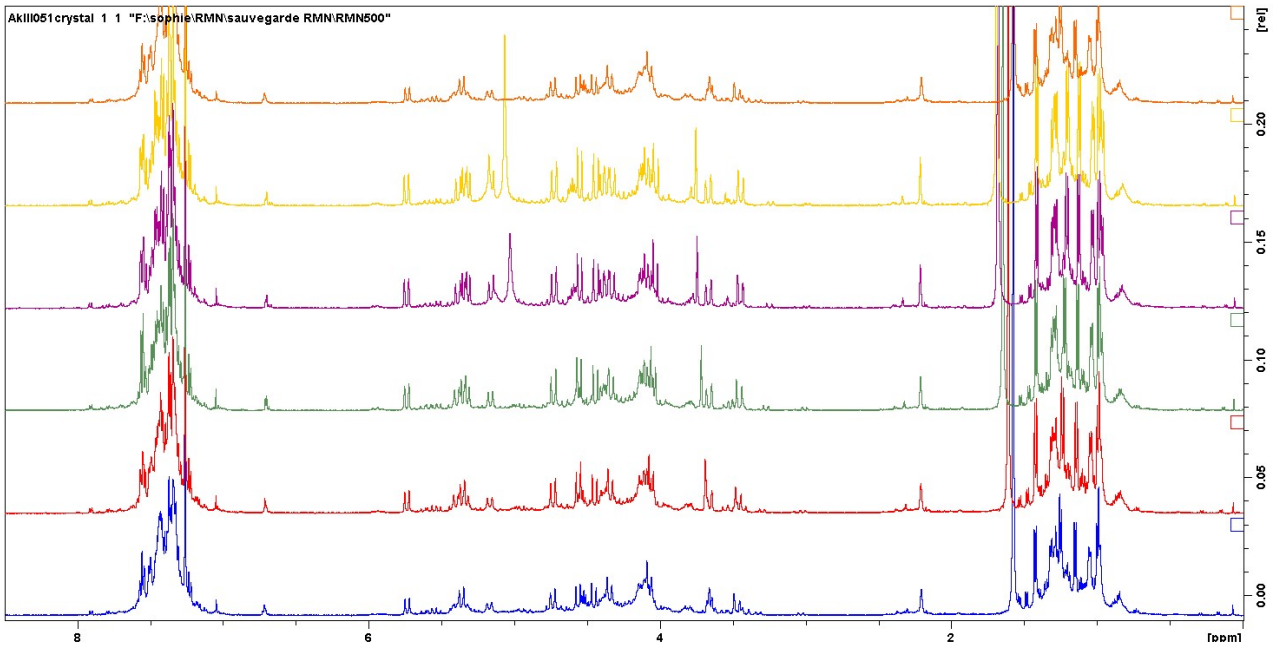


Figure S43. VT study of macrocycle **IIa** in $CDCl_3$ (5 mg in 0.6 mL): 298 K (blue curve), 288K (red curve), 278 K (green curve), 268 K (purple curve), 265 K (yellow curve), back to 298 K (orange curve).

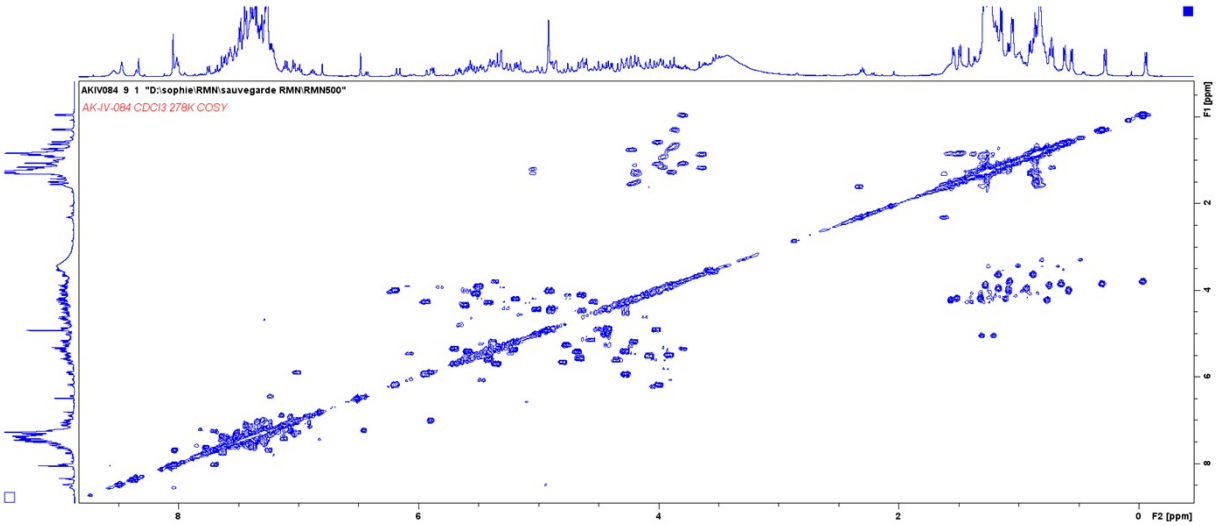


Figure S44. COSY experiment of *ortho* bicyclic compound **IVa** in $CDCl_3$ (8-10 mM) at 278 K.

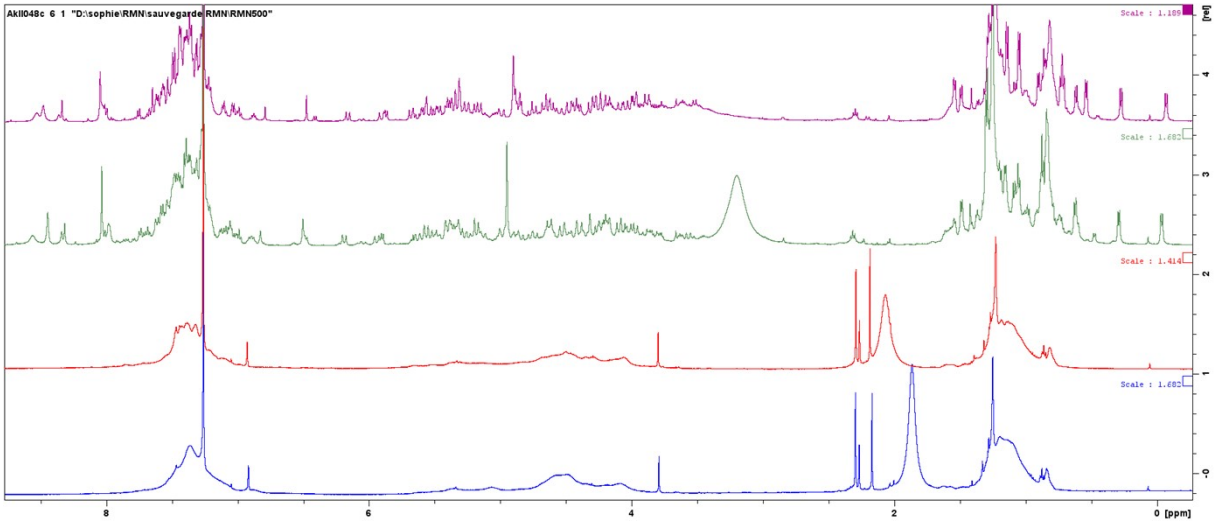


Figure S45. Comparison of ^{1}H NMR spectra of *ortho* bicyclic compound **IVa** in $CDCl_3$ at 298 K (green curve) and at 268 K (purple curve) and *meta* bicyclic compound **IVb** in $CDCl_3$ at 298 K (blue curve) and at 268 K (red curve).

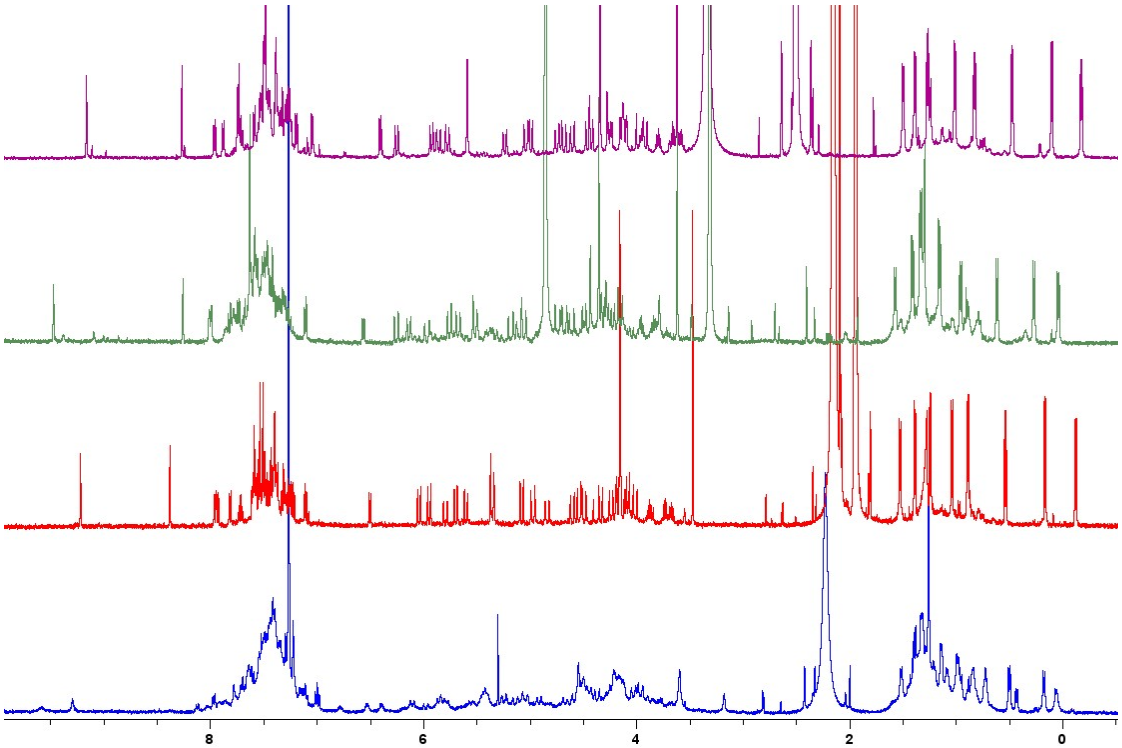


Figure S46. Comparison of ^{1}H NMR spectra of the *ortho* bis-triazolium bicyclic compound **VIa** at 298 K in various solvants: $CDCl_3$ (blue curve), CD_3CN (red curve), CD_3OD (green curve) and DMSO-d_6 (purple curve).

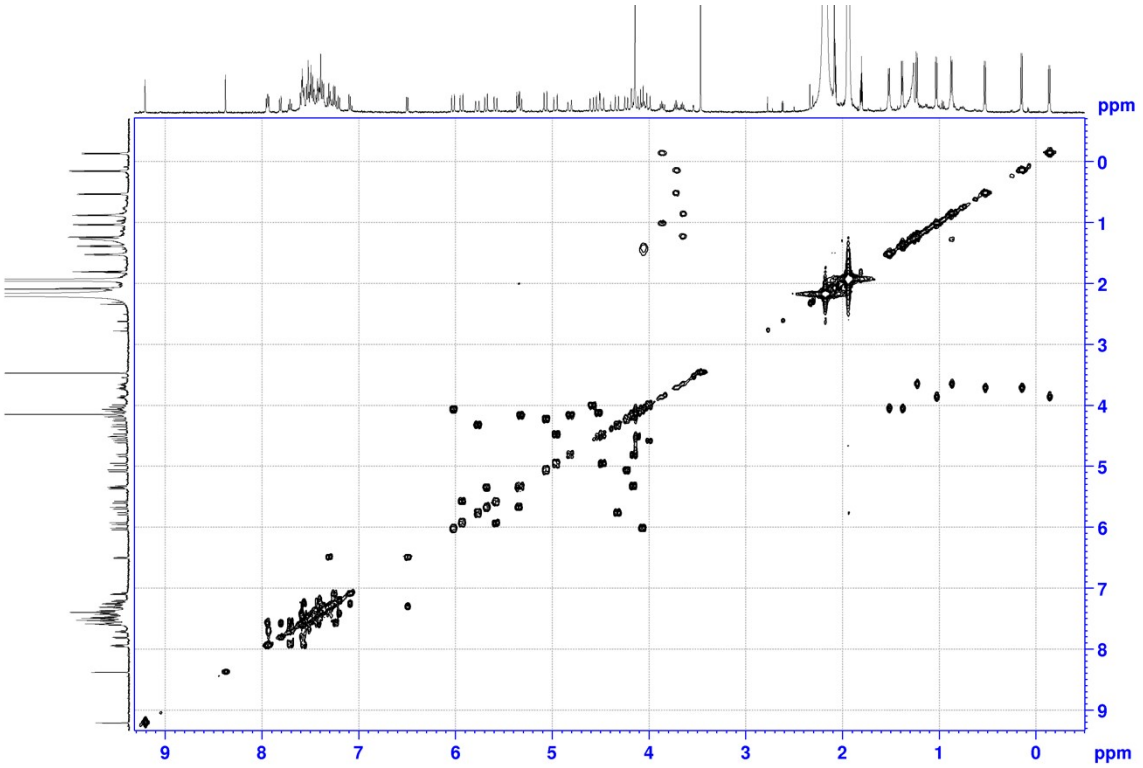


Figure S47. COSY NMR spectra of the *ortho* bis-triazolium bicyclic compound **VIa** (2 mM) in CD_3CN at 288K.

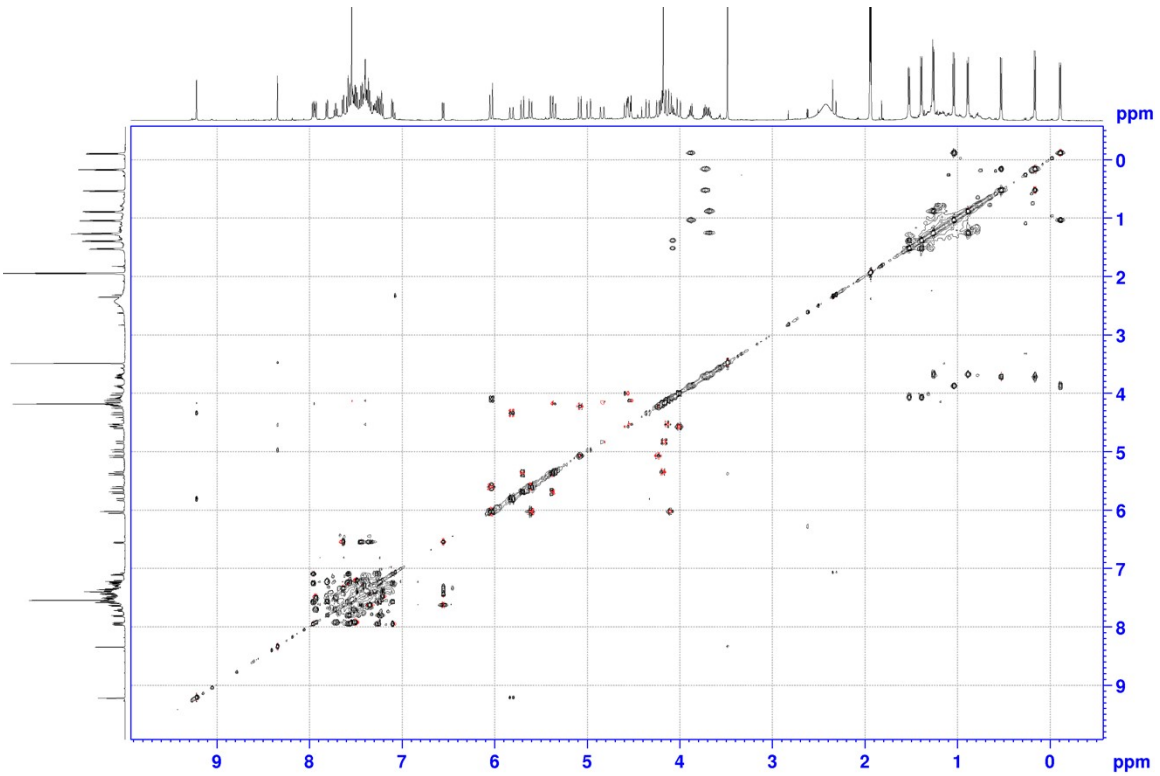


Figure S48. TOCSY NMR spectra of the *ortho* bis-triazolium bicyclic compound **VIa** (20 mM) in CD_3CN at 298K.

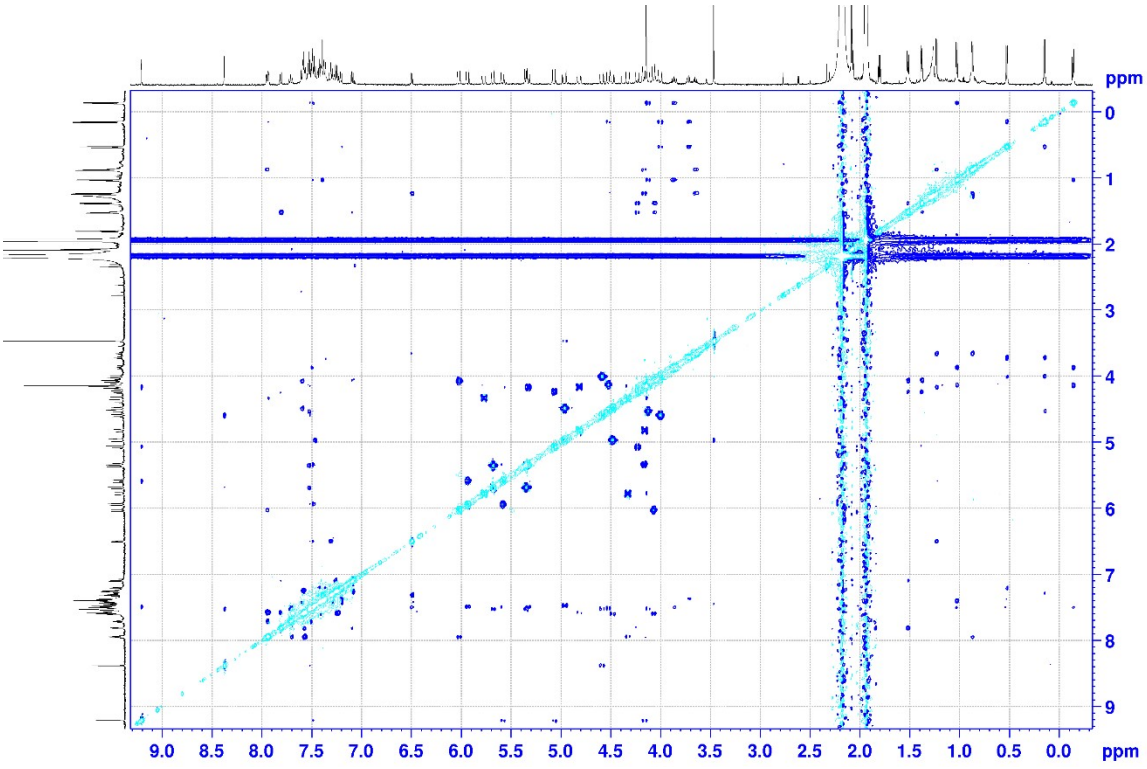


Figure S49. NOESY NMR spectra of the *ortho* bis-triazolium bicyclic compound **VIa** (2 mM) in CD_3CN at 288K (d8=500).

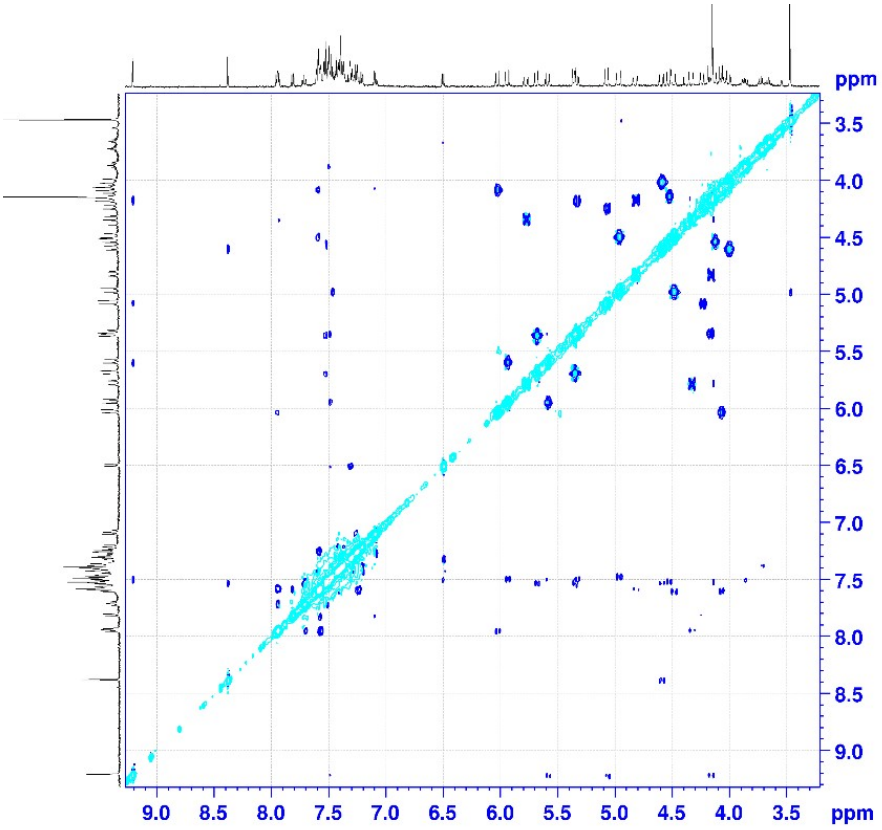


Figure S50. NOESY NMR spectra (3-9.5 ppm region) of the *ortho* bis-triazolium bicyclic compound **VIa** (2 mM) in CD_3CN at 288K (d8=500).

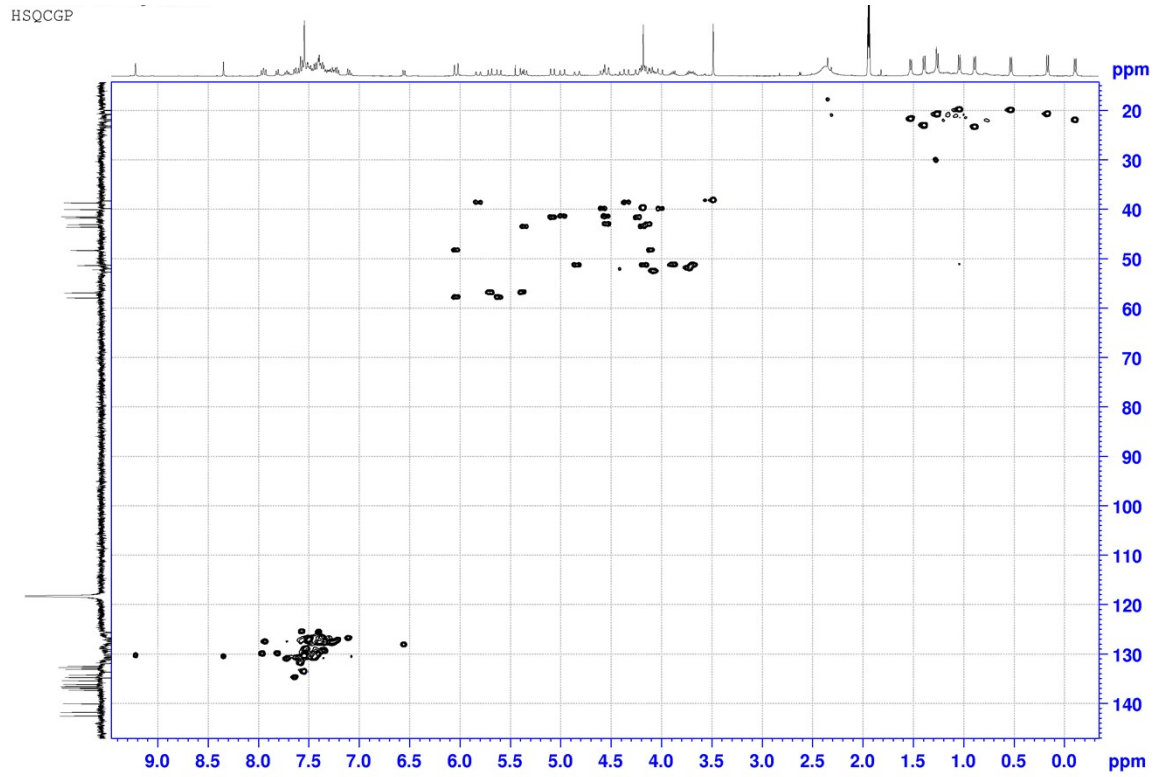


Figure S51. HSQC NMR spectra of the *ortho* bis-triazolium bicyclic compound **VIa** (20 mM) in CD_3CN at 298K.

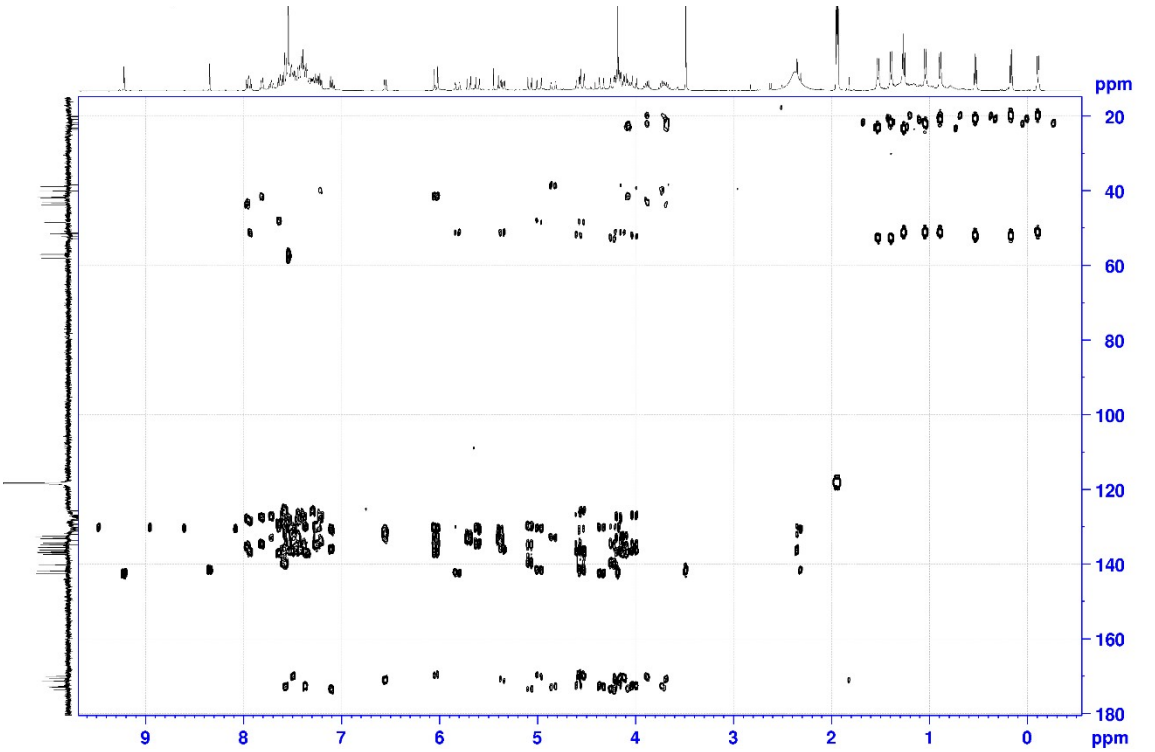
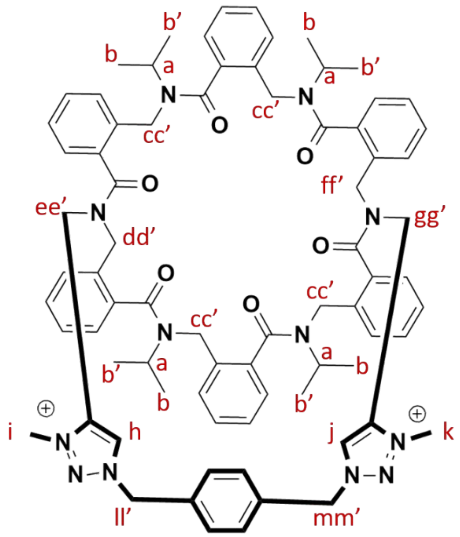


Figure S52. HMBC NMR spectra of the *ortho* bis-triazolium bicyclic compound **VIa** (20 mM) in CD_3CN at 298K.



Protons number	Ha (CH)	Hb (CH_3)	b' (CH_3)	c,c' ABsystem (CH_2)
Residue 1	3.87 (hept, *J* = 7.5 Hz	-0.14 (d, *J* = 7.5 Hz)	1.03 (d, *J* = 7.5Hz)	4.12 (d, *J* = 15.9 Hz) 4.53 (d, *J* = 15.9 Hz)
Residue 2	3.72 (hept, *J* = 6.5 Hz)	0.15 (d, *J* = 6.5 Hz)	0.53 (d, *J* = 6.5 Hz)	4.00 (d, *J* = 17.7 Hz) 4.59 (d, *J* = 17.7 Hz)
Residue 3	3.66 (hept, *J* = 6.5 Hz)	0.87 (d, *J* = 6.5 Hz)	1.23 (d, *J* = 6.5 Hz)	4.16 (d, *J* = 16,0 Hz) 5.34(d, *J* = 16.0 Hz)
Residue 4	4.06 (m)	1.38 (d, *J* = 6.8 Hz)	1.52 (d, *J* = 6.4 Hz)	4.23 (d, *J* = 14.9 Hz) 5.07(d, *J* = 14.9 Hz)
	d,d' ABsystem (CH_2)	e,e' ABsystem (CH_2)	f,f' ABsystem (CH_2)	g,g' ABsystem (CH_2) (CH_2)
Residue 5	4.07 (d, *J* = 14 Hz) 6.03 (d, *J* = 14 Hz)	4.48 (d, *J* = 18.6 Hz) 4.97 (d, *J* = 18.6 Hz)		
Residue 6			4.16 (d, *J* = 18.5 Hz) 4.82 (d, *J* = 18.5 Hz)	4.33 (d, *J* = 17.5 Hz) 5.77 (d, *J* = 17.5 Hz)
Triazolium	Hh (CH)	Hi (CH_3)	Hj (CH)	Hk(CH_3)
Triazolium 1	8.38 (s)	3.47 (s)		
Triazolium 2			9.21 (s)	4.14 (s)
Linker	l,l' ABsystem (CH_2)	m,m' ABsystem (CH_2)		
	5.35 (d, *J* = 14 Hz) 5.69 (d, *J* = 14 Hz)	5.58 (d, *J* = 14.5 Hz) 5.92 (d, *J* = 14.5 Hz)		

Table S1. H^1 NMR signals attribution of bis-triazolium bicyclic compound **VIa** in CD_3CN at 298K.

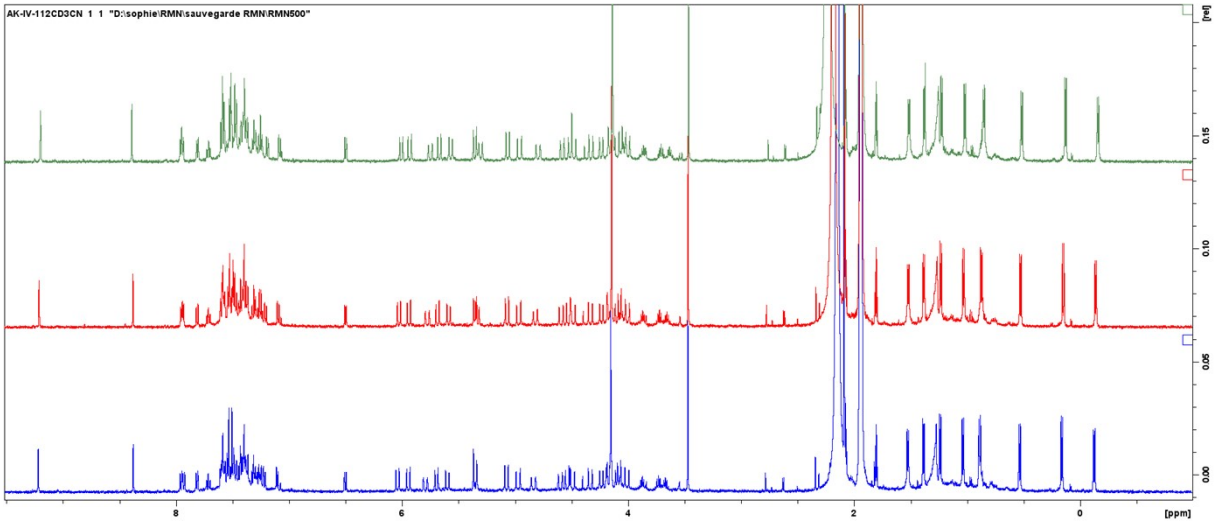


Figure S53. Variable temperature NMR spectra of the *ortho* bis-triazolium bicyclic compound **VIa** (2 mM) in CD3CN: 298K (blue curve), 288K (red curve) and 273K (green curve).

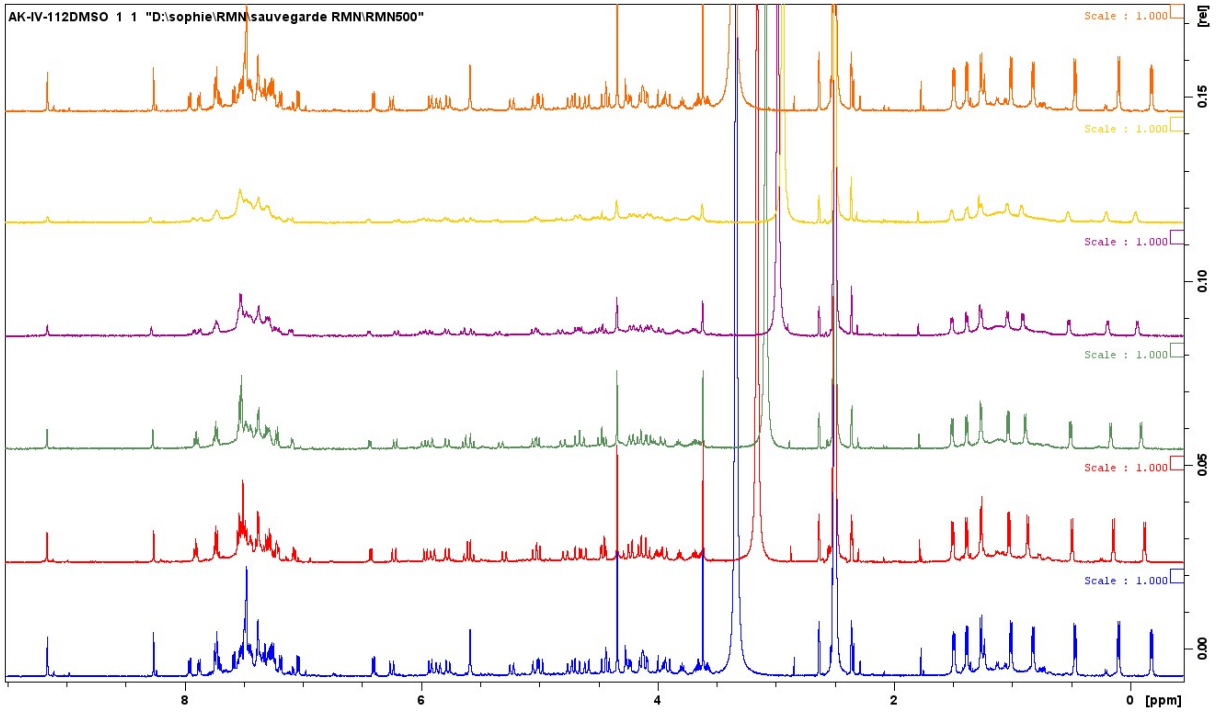


Figure S54. Variable temperature NMR of the *ortho* bis-triazolium bicyclic compound **VIa** (3 mM) in DMSO-d_6: 298K (blue curve), 338K (red curve), 358K (green curve), 378K (purple curve), 388K (Yellow curve) and back to 298K (orange curve).

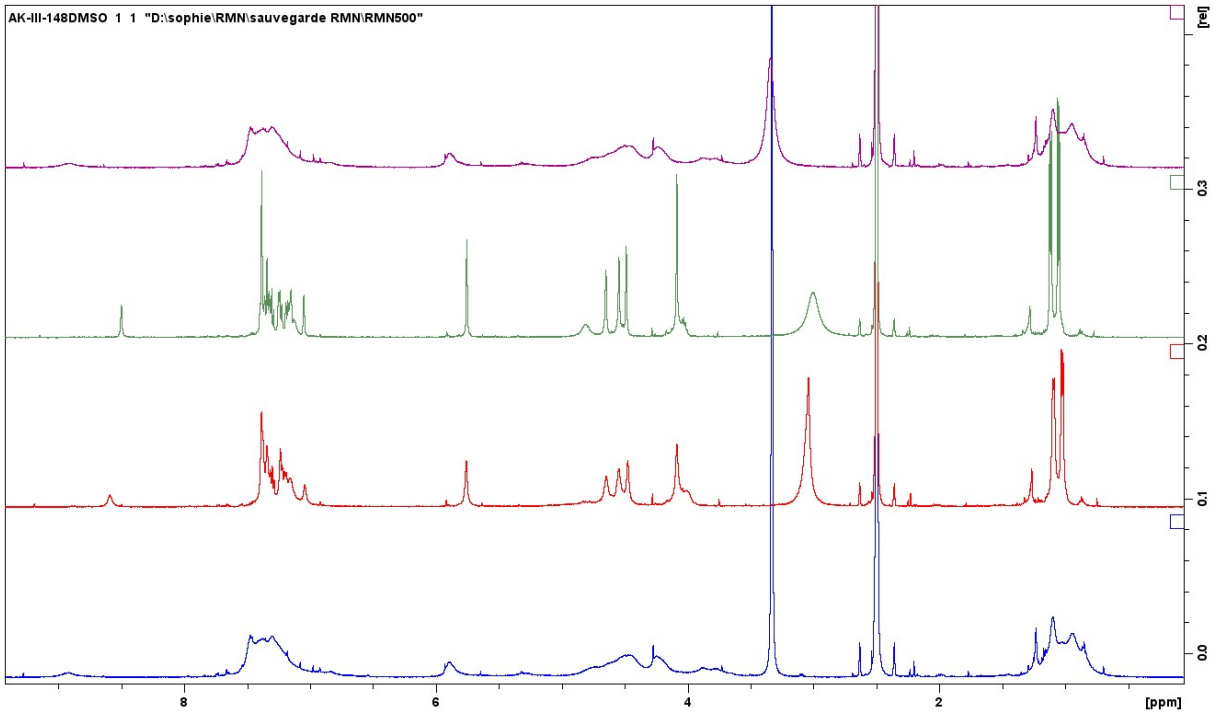


Figure S55. Variable temperature NMR of the *meta* bis-triazolium bicyclic compound **VIb** (3 mM) in DMSO-d_6: 298 K (blue curve), 358 K (red curve), 388 K (green curve) and back to 298 K (purple curve).

III.2. Computational study

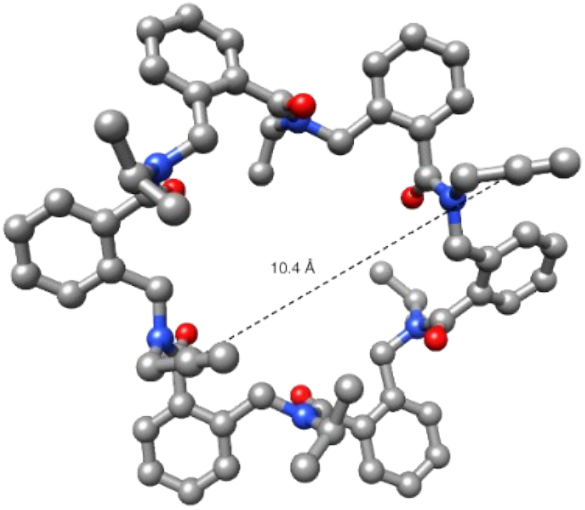
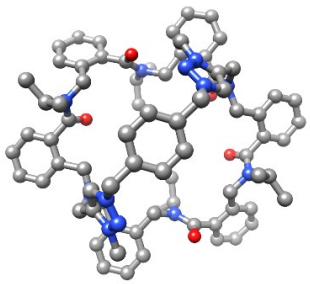


Figure S56. Model structure of *ortho*-arylopeptoid macrocycle **IIa** with all amides in the trans conformation and the two propargyl groups on the same side of the ring.

Computational study of bicyclic bis-triazolium **VIa** using Conformer-Rotamer Ensemble Sampling Tool (CREST) [1]

We first built a possible structure, without a priori, of the bicyclic system with Chimera software. This structure has been geometrically optimized with Gaussian 16[2] at DFT level of theory, using the B3LYPas a hybrid functional and 6-31g as a basis for the description of the electrons and acetonitrile as solvent in SCRF model (Table S2).[3,4] It was not necessary to do an optimization with a more precise electronic basis because only a geometrically valid starting system was needed. the rest of the conformational research being done by semi-empirical methods. CREST program is used using the conformer search module of ChimeraX software.[5] The charge is set to +2 to respect the two triazoliums and the six amide bonds are constrained in the *trans* conformation. The APLB implicit solvent model was used with the dielectric constant of acetonitrile (37,5). Energy threshold for energy and RMSD was set by default to 6 kcal and 0.125. There is no protonation screening. We used the method GFN2-xTB[6] with no empirical dispersion and with the default integration grid. 198 solutions proposed by CREST have energy in a 6 kcal window (Fig. S57). Structures of the 10 lowest energy solutions are represented in Figure 58.



Atom	X	Y	Z
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C	4.43800	-2.80500	0.03800
H	3.39500	-2.46700	0.04600
H	4.60100	-3.34300	0.98100
C	6.20500	-1.37600	1.22800
H	6.66700	-0.39400	1.06100
C	7.32600	-2.42000	1.34800

H	6.93800	-3.41100	1.60800
H	8.01700	-2.11500	2.14100
H	7.90000	-2.50400	0.42000
C	5.37600	-1.29500	2.52200
H	4.87000	-2.24100	2.74500
H	4.61400	-0.51200	2.45100
H	6.03200	-1.06300	3.36800
C	4.66100	-3.77800	-1.11500
C	3.59000	-4.54000	-1.63300
C	3.83500	-5.53600	-2.59600
H	3.00700	-6.13100	-2.97400
C	5.12500	-5.76100	-3.08000
H	5.30000	-6.53300	-3.82300
C	6.18300	-4.97900	-2.60300
H	7.19000	-5.13200	-2.98000
C	5.94700	-4.00400	-1.62900
H	6.77700	-3.40900	-1.26300
C	2.19400	-4.37400	-1.10300
O	1.96000	-4.59700	0.12000
N	1.17800	-4.06000	-1.97000
C	-0.18300	-3.94100	-1.42000
H	-0.10200	-3.50100	-0.41400
H	-0.74000	-3.23000	-2.03900
C	1.37100	-3.66100	-3.40200
H	2.43400	-3.82200	-3.62000
C	0.53800	-4.55000	-4.33400
H	-0.53800	-4.42300	-4.16300
H	0.78400	-5.60900	-4.20500
H	0.74300	-4.27600	-5.37500
C	1.07300	-2.16500	-3.60100
H	0.03000	-1.91600	-3.37700
H	1.25300	-1.89900	-4.64900
H	1.73300	-1.55500	-2.97800
C	-0.98300	-5.23700	-1.34300
C	-2.36200	-5.17400	-1.03200
C	-3.12500	-6.35200	-0.96300
H	-4.19100	-6.29300	-0.75700
C	-2.52800	-7.59700	-1.17800
H	-3.12600	-8.50100	-1.12800
C	-1.15900	-7.66600	-1.45900
H	-0.68300	-8.62900	-1.61900
C	-0.39800	-6.49400	-1.53800
H	0.66100	-6.56100	-1.76400
C	-3.03700	-3.83900	-0.89000
O	-3.10300	-3.05600	-1.86900
N	-3.57900	-3.46500	0.32600
C	-4.23400	-2.13800	0.40200
H	-3.63100	-1.44000	-0.19100
H	-4.19100	-1.80300	1.44700
C	-3.51700	-4.28400	1.55200
H	-3.28000	-5.31400	1.27500
H	-4.50900	-4.30800	2.02500

C	-5.67500	-2.10000	-0.09100
C	-6.21700	-0.88500	-0.56800
H	-7.95900	0.09800	-1.37900
C	-7.55500	-0.83400	-0.99300
C	-8.36500	-1.97100	-0.93700
H	-9.39700	-1.91900	-1.27000
C	-7.83400	-3.17400	-0.46000
H	-8.45200	-4.06600	-0.41600
C	-6.50100	-3.23200	-0.04000
H	-6.10100	-4.17700	0.31200
C	-5.34800	0.32900	-0.78200
O	-4.60300	0.38100	-1.79900
N	-5.37500	1.36300	0.12000
C	-4.45600	2.48800	-0.13600
H	-4.23900	2.98900	0.81600
H	-3.50800	2.05800	-0.49700
C	-6.15400	1.33600	1.39500
H	-6.71300	0.39100	1.38000
C	-5.21900	1.31300	2.61800
H	-4.70800	2.27100	2.76500
H	-4.46000	0.52900	2.52200
H	-5.80600	1.11300	3.52100
C	-7.16100	2.49400	1.47100
H	-7.88200	2.45100	0.64900
H	-6.66000	3.46800	1.44200
H	-7.71600	2.43100	2.41400
C	-4.93100	3.52600	-1.14600
C	-4.05200	4.57600	-1.49500
C	-4.47000	5.58500	-2.37600
H	-3.79100	6.39800	-2.62200
C	-5.74500	5.54000	-2.94900
H	-6.06000	6.32300	-3.63300
C	-6.60100	4.47800	-2.64400
H	-7.58600	4.42200	-3.09800
C	-6.19300	3.48100	-1.74900
H	-6.86600	2.66500	-1.51200
C	-2.68800	4.65200	-0.85900
O	-2.56800	5.12100	0.30800
N	-1.59500	4.20000	-1.55500
C	-0.29800	4.17400	-0.84500
H	0.21200	3.24600	-1.11800
H	-0.52700	4.13300	0.22900
C	-1.65100	3.65400	-2.95100
H	-2.68200	3.80600	-3.28900
C	-1.36100	2.14400	-2.97600
H	-0.34500	1.91800	-2.63400
H	-1.44600	1.78000	-4.00600
H	-2.08100	1.58800	-2.36500
C	-0.71800	4.42800	-3.89900
H	-0.90900	4.10900	-4.93000
H	0.33600	4.23000	-3.67400
H	-0.89400	5.50600	-3.83600

C	0.59600	5.37500	-1.11800
C	1.98100	5.21900	-1.34100
C	2.78500	6.34500	-1.59800
H	3.84100	6.21700	-1.82000
C	2.23000	7.62800	-1.59800
H	2.85800	8.48900	-1.80400
C	0.86400	7.79100	-1.33800
H	0.42600	8.78500	-1.32500
C	0.05900	6.67300	-1.10300
H	-1.00000	6.80200	-0.89900
C	2.57400	3.84300	-1.43900
O	2.27400	3.09200	-2.39900
N	3.42100	3.38700	-0.44500
C	3.92200	2.00100	-0.55900
H	3.75100	1.49700	0.40200
H	3.29200	1.49200	-1.29900
C	3.87300	4.19500	0.70600
H	4.94400	3.99600	0.86000
H	3.79200	5.25900	0.46600
C	5.38300	1.85400	-0.97000
C	5.94500	0.55600	-1.03900
H	7.69900	-0.60800	-1.51000
C	7.28200	0.39200	-1.43500
C	8.07200	1.50000	-1.75700
H	9.10400	1.35900	-2.06300
C	7.51700	2.78100	-1.70100
H	8.11500	3.64900	-1.96200
C	6.18200	2.95200	-1.31300
H	5.76200	3.95200	-1.29800
C	5.07100	-0.66400	-0.91200
O	4.13100	-0.81700	-1.74000
C	1.98100	-0.09800	5.25600
C	1.50900	1.22200	5.21500
C	0.12600	1.46300	5.21500
C	-0.77300	0.39600	5.28700
C	-0.30000	-0.92400	5.35800
C	1.08200	-1.16600	5.32700
C	2.48800	2.37400	5.27100
C	-1.27000	-2.06700	5.56000
N	-1.56000	-2.84300	4.32300
N	2.59400	3.13500	3.99600
C	-2.71300	-2.85300	3.58700
C	-2.53100	-3.79700	2.58300
N	-1.24400	-4.27200	2.77400
N	-0.64900	-3.70200	3.83600
N	2.26500	4.74100	2.63900
N	1.90100	4.27400	3.84600
C	3.38200	2.87000	2.91000
C	3.17700	3.91100	2.01100
H	3.05000	-0.29500	5.26000
H	-0.25100	2.48200	5.18800
H	-1.84000	0.59400	5.31500

H	1.45900	-2.18300	5.38500
H	2.19100	3.10700	6.03200
H	3.50000	2.02700	5.51000
H	-2.24100	-1.70600	5.91900
H	-0.88200	-2.78600	6.29200
H	-3.57300	-2.25700	3.84600
H	4.04200	2.01700	2.86000
C	-0.49100	-5.29500	2.02400
H	-1.18300	-5.86500	1.40500
H	0.26600	-4.81900	1.38600
H	-0.01000	-5.96500	2.74100
C	1.69500	6.02800	2.19900
H	2.24300	6.39000	1.32800
H	0.64200	5.89100	1.93900
H	1.78800	6.75000	3.01500

Table S2. Starting point for CREST: Representation (H atom are removed for clarity) and xyz file of the optimized structure of bicyclic bis-triazolium **VIa**.

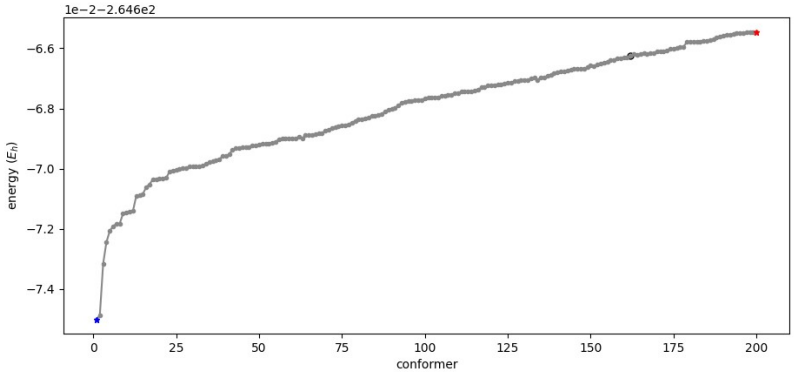


Figure S57. Energies of the 198 conformers proposed by CREST

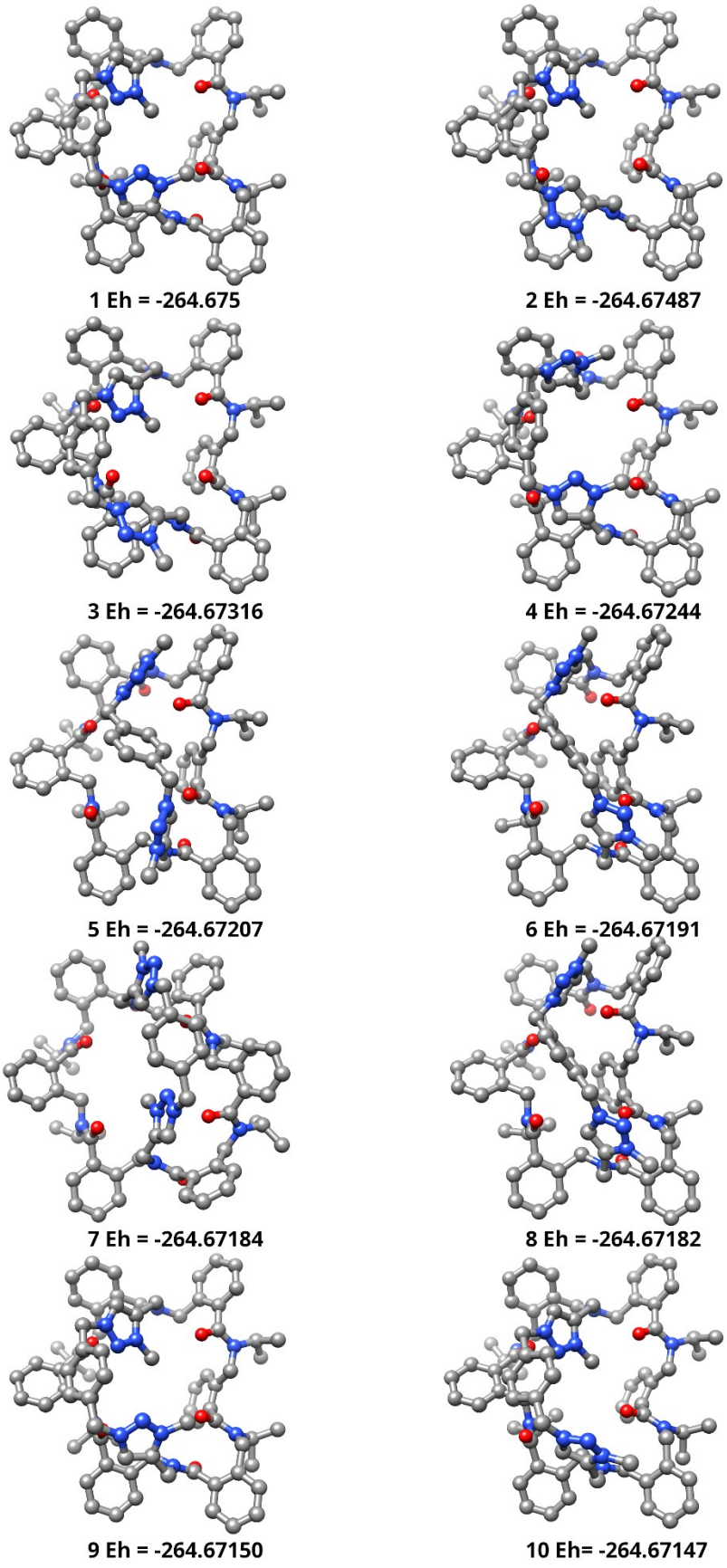


Figure S58. Structures of the 10 lowest energy solutions obtained by CREST

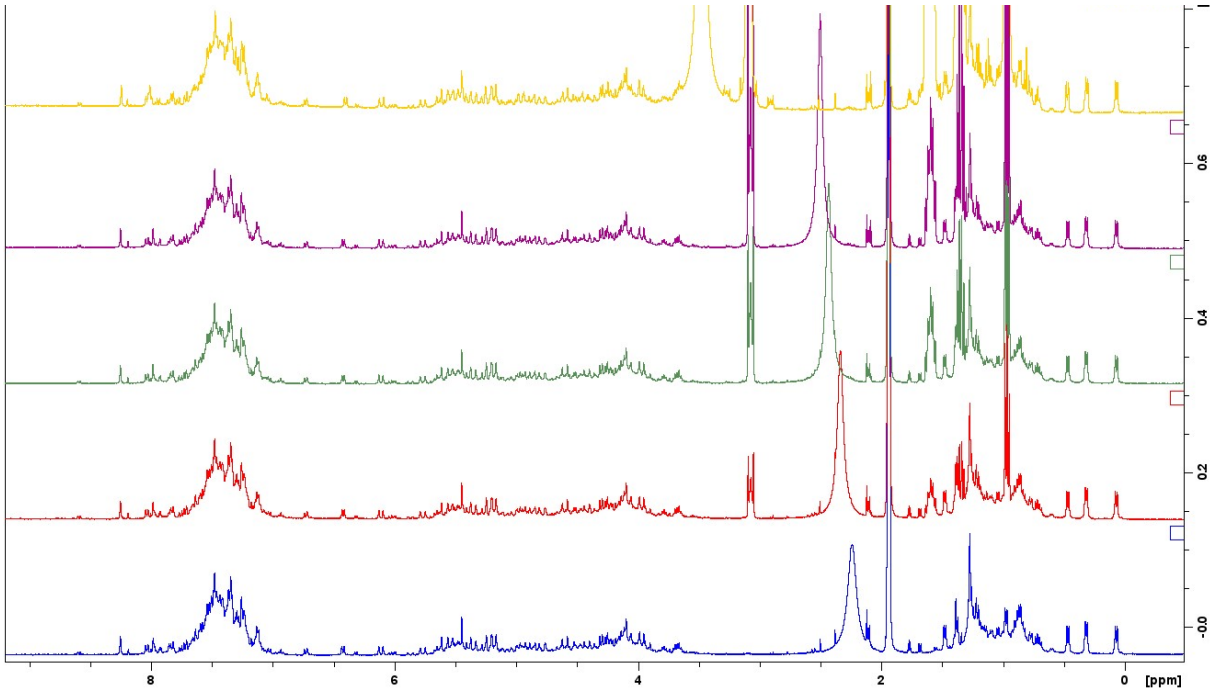


Figure S59. ^{1}H NMR of the *ortho* bis-triazole bicyclic compound **IVa** (3 mM) in CD_3CN at 298 K (blue curve), upon addition of $TBAHSO_4$: ≈ 0.25 equiv. (red curve), ≈ 0.70 equiv. (green curve), ≈ 1.05 equiv. (purple curve) and ≈ 6.0 equiv. (yellow curve).

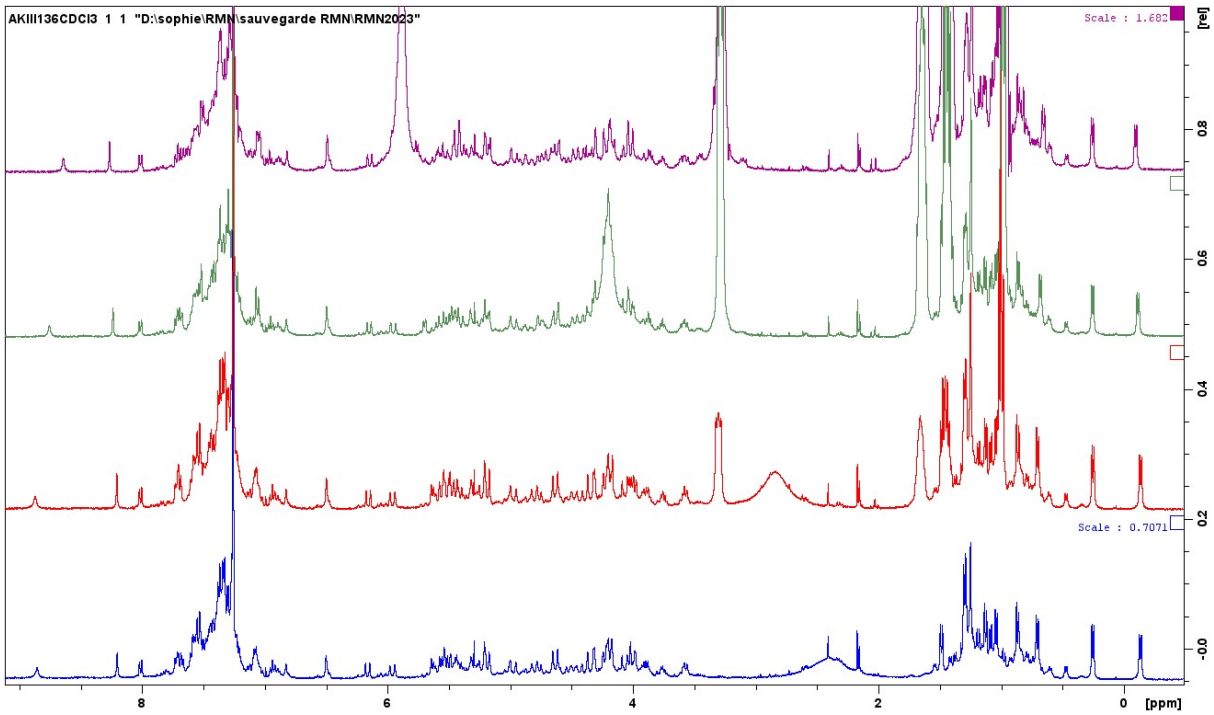


Figure S60. ^{1}H NMR of the *ortho* bis-triazole bicyclic compound **IVa** (3 mM) in $CDCl_3$ at 298 K (blue curve), upon addition of $TBAHSO_4$: ≈ 0.5 equiv. (red curve), ≈ 2.5 equiv. (green curve) and ≈ 9 equiv. (purple curve).

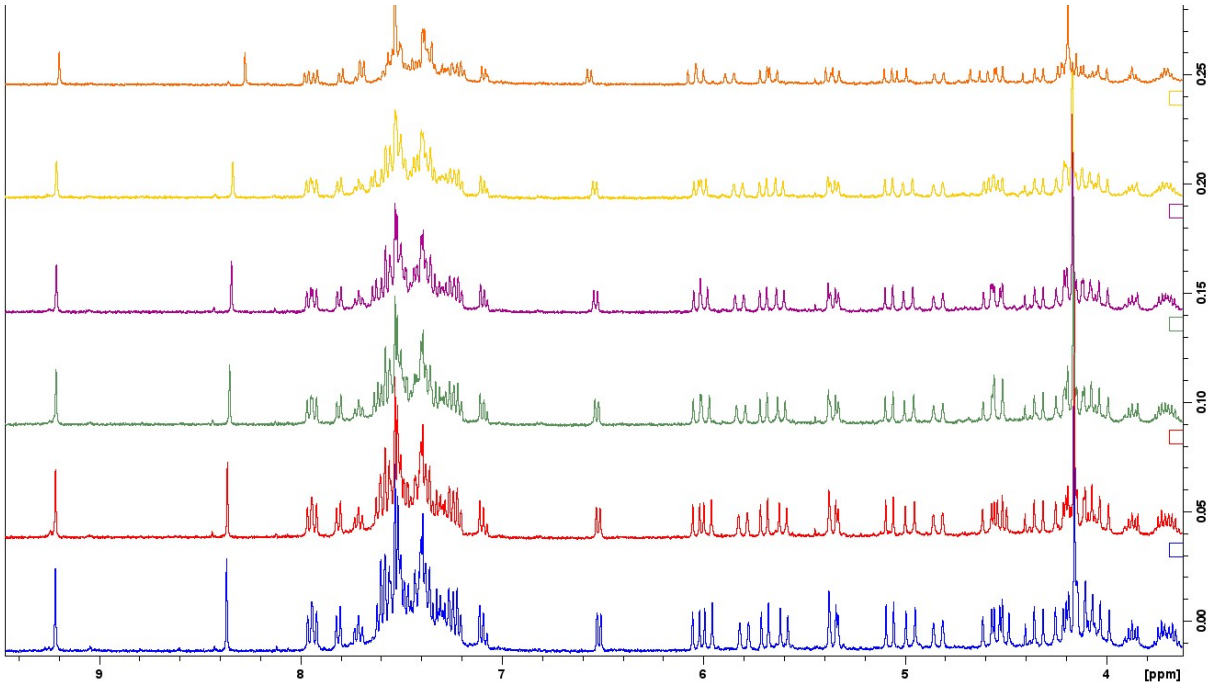


Figure S61. ^{1}H NMR of the *ortho* bis-triazolium bicyclic compound **VIa** in CD_3CN at 298 K (blue curve), upon addition of $TBAHSO_4$: ≈ 1.5 equiv. (red curve), ≈ 3 equiv. (green curve), ≈ 5.3 equiv. (purple curve), ≈ 6 equiv. (yellow curve) and ≈ 20 equiv. (orange curve).

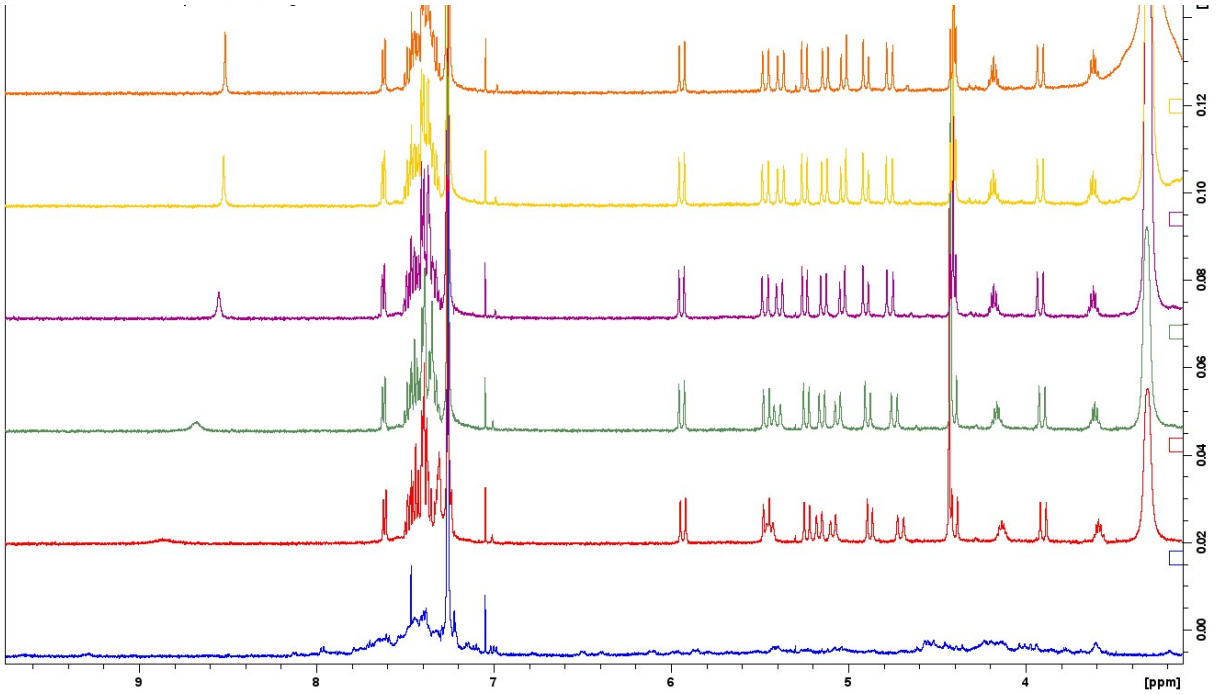


Figure S62. ^{1}H NMR of the *ortho* bis-triazolium bicyclic compound **VIa** (3 mM) in $CDCl_3$ at 298 K (blue curve), upon addition of $TBAHSO_4$: ≈ 1.9 equiv. (red curve), ≈ 2.4 equiv. (green curve), ≈ 5 equiv. (purple curve), ≈ 6.5 equiv. (yellow curve) and ≈ 8 equiv. (orange curve).

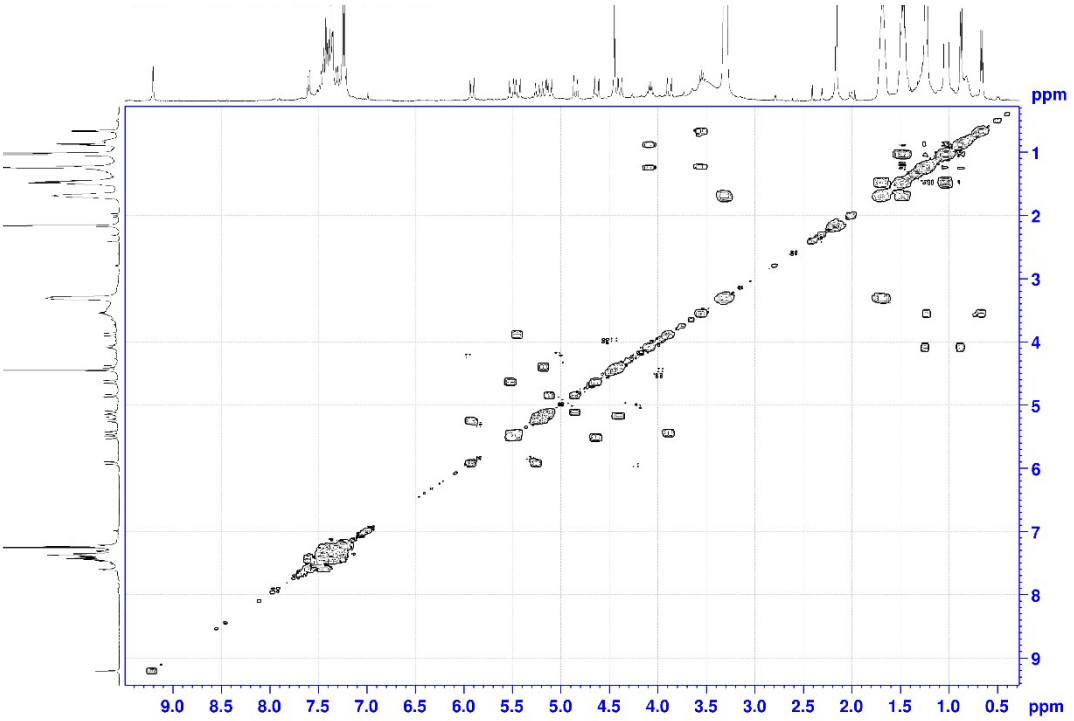


Figure S63. COSY NMR spectra of the *ortho* bis-triazolium bicyclic compound **VIa** + 2.25 equiv. $TBAHSO_4$ in $CDCl_3$ (3 mM) at 298K.

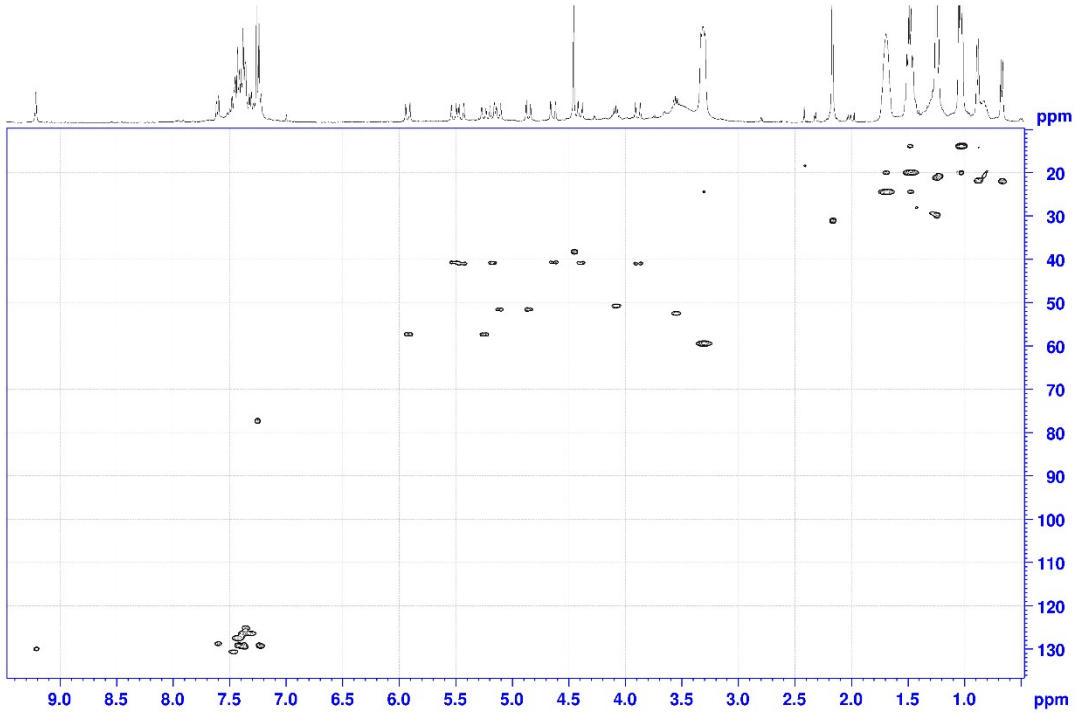


Figure S64. HSQC NMR spectra of the *ortho* bis-triazolium bicyclic compound **VIa** + 2.25 equiv. $TBAHSO_4$ in $CDCl_3$ (3 mM) at 298K.

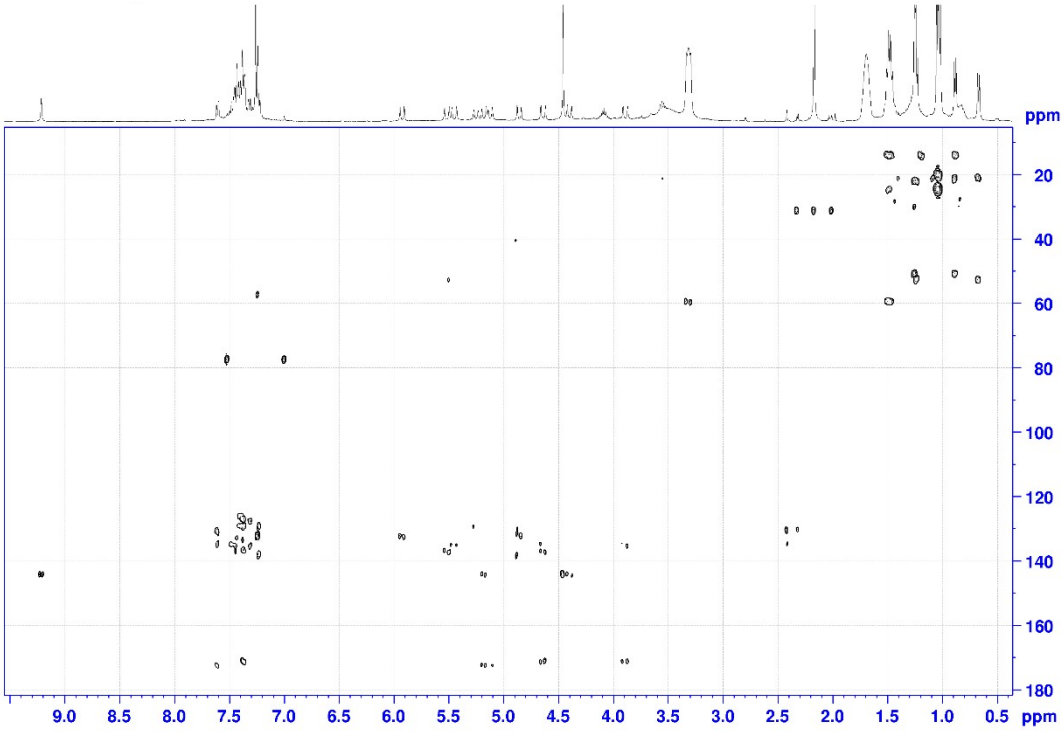
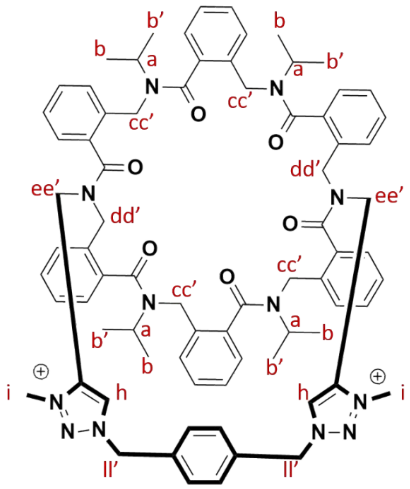


Figure S65. HMBC NMR spectra of the *ortho* bis-triazolium bicyclic compound **VIa** + 2.25 equiv. $TBAHSO_4$ in $CDCl_3$ (3 mM) at 298K.



Protons number	Ha (CH)	Hb (CH_3)	b' (CH_3)	c,c' ABsystem (CH_2)
Residue 1,3	3.55 (hept, *J* = 6.6 Hz	0.67 (d, *J* = 6.6 Hz)	1.23 (d, *J* = 6.6Hz)	4.63 (d, *J* = 17.3 Hz) 5.52 (d, *J* = 17.3 Hz)
Residue 2,4	4.08 (hept, *J* = 6.6 Hz)	0.88 (d, *J* = 6.6 Hz)	1.25 (d, *J* = 6.6 Hz)	3.88 (d, *J* = 17.1 Hz) 5.45 (d, *J* = 17.1 Hz)
	d,d' ABsystem (CH_2)	e,e' ABsystem (CH_2)		
Residue 5,6	4.85 (d, *J* = 14.9 Hz) 5.12 (d, *J* = 14.9 Hz)	4.39 (d, *J* = 15.5 Hz) 5.17 (d, *J* = 15.5 Hz)		
Triazolium	Hh (CH)	Hi (CH_3)	Hj (CH)	Hk(CH_3)
Triazolium 1,2	9.21 (s)	4.46 (s)		
Linker	l,l' ABsystem (CH_2)			
	5.25 (d, *J* = 15.2 Hz) 5.92 (d, *J* = 15.2 Hz)			

Table S3. H^1 NMR signals attribution of bicyclic bis-triazolium compound **VIa** + $TBAHSO_4$ in CD_3CN at 298K.

V. References:

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