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Supplementary information for:

Templated Amplification of a Naphthalenediimide-based Receptor from a Donor-Acceptor Dynamic Combinatorial Library in Water

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Contents:

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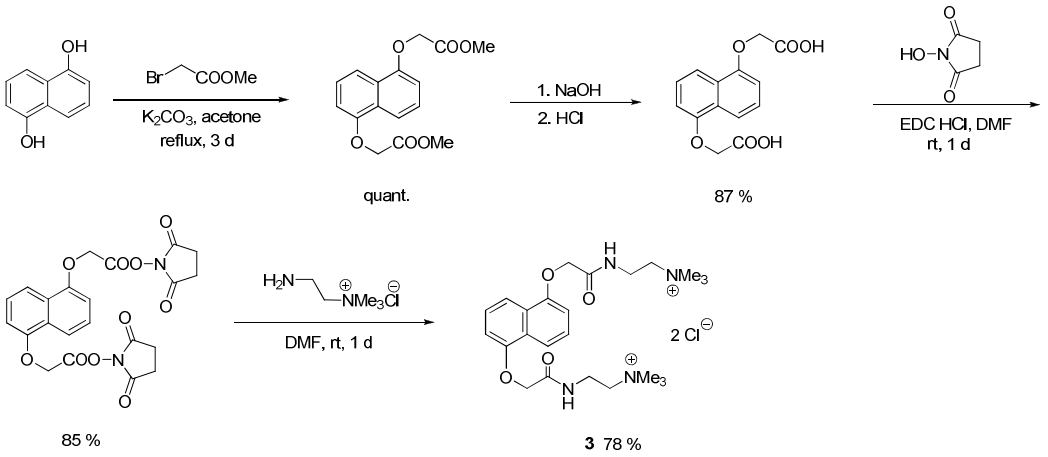
Synthesis

General: All solvents were of reagent grade and used without further purification. All commercially purchased materials (trifluoroacetic acid, triethylsilane, 1,5-dihydroxynaphthalene, methyl bromoactate, *N*-hydroxysuccinimide, *N*-(3-(dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl), 1,4,5,8-naphthalenetetracarboxylic dianhydride, triethylamine, (2-amino)ethyltrimethyl-ammonium chloride **4**, paraquat dichloride **5**, *N*-ethylquinolinium bromide **6**, *bis*(*N*-methylacridinium) nitrate **7**, and *N*-adamantylpyridinium bromide **8** were used as received. Trityl-protected precursor to **1**,[1] templates **2**[2] and model NDI **10**[1] were synthesised according to literature procedures. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-400 or Advance 500 TCI Cryo Spectrometers. All signals were internal referenced to solvent residue. All high-resolution (HR) electrospray ionisation (ESI) mass spectra were recorded on Waters LCT Premier XE instrument.

(2*R*,2'*R*)-2,2'-(1,3,6,8-Tetraoxobenzo[*lmn*][3,8]phenanthroline-2,7(1*H*,3*H*,6*H*,8*H*)-diyl)bis(3-mercaptopropanoic acid), 1: To a Schlenk flask charged with (2*R*,2'*R*)-2,2'-(1,3,6,8-tetraoxobenzo[*lmn*][3,8]phenanthroline-2,7-(1*H*,3*H*,6*H*,8*H*)-diyl)bis(3-(tritylthio)propanoic acid) (0.48 g, 0.5 mmol) was added degassed trifluoroacetic acid (5 ml, 65 mmol). The resulting solution was stirred under N_2 at room temperature for 1.5 hours, and triethylsilane (0.4 ml, 2.5 mmol) was added. The reaction mixture was stirred for a further 30 minutes and all the volatiles were removed *in vacuo*. The residue was re-dissolved in Et_2O (30 ml), filtered, and concentrated to *ca.* 5 ml. Hexane (40 ml) was added to the concentrated solution, and a yellow precipitate formed. The pale yellow solid was collected by filtration and dried *in vacuo*. Yield: 0.04 g, 16 %. M.p.: >250 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.20 (bs, 2 H, COOH), 8.77 (s, 4 H, ArH), 5.72 (dd, J = 5.2 Hz, 9.6 Hz, 2 H, α-H), 3.39-3.32 (m, 2 H, β-H), 3.25- 3.17 (m, 2 H, β-H), 2.70 (t, J = 9.0 Hz, 2 H, SH). ^{13}C{^{1}H} NMR (100.62 MHz, DMSO-d_6) δ (ppm): 208.0, 169.5, 162.3, 131.3, 126.0, 113.2, 56.0, 22.7. HRMS (ESI+) calcd. for: $C_{20}H_{14}N_2O_8S_2Na$ $[M+Na]^+$ (m/z): 497.0089, found: 497.0089.

[1] P. Pengo, G. D. Pantoş, S. Otto and J. K. M. Sanders, *J. Org. Chem*., 2006, **71**, 7063.
[2] D. G. Hamilton, J. E. Davies, L. Prodi and J. K. M. Sanders, *Chem. Eur. J.,* 1998, **4**, 608.

2,2'-(Naphthalene-1,5-diylbis(oxy))bis(*N*-(2-(trimethylammonium)ethyl) acetamide) dichloride, 3: The compound was synthesised according to the following scheme:



Dimethyl 2,2'-(naphthalene-1,5-diylbis(oxy))diacetate: To a solution of 1,5-dihydroxylnaphthalene (1.61 g, 10 mmol) in acetone (200 ml) was added finely grinded potassium carbonate (7 g, 50 mmol), and methyl bromoacetate (2 ml, 20 mmol). The mixture was heated to reflux for 1 day. The resulting solution was filtered, added Et_2O (100 ml), and washed successively with 1 M HCl (50 ml) and water (50 ml). Evaporation of solvents from the organic layer gave the product as yellow crystalline solid which was used in the next step without further purification. Yield: 3.06 g, quant. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.98 (d, J = 8.4 Hz, 2 H, ArH), 7.36 (t, J = 7.6 Hz, 2 H, ArH), 6.76 (d, J = 7.2 Hz, 2 H, ArH), 4.81 (s, 4 H, CH_2), 3.82 (s, 6 H, CH_3).

2,2'-(Naphthalene-1,5-diylbis(oxy))diacetic acid: To a solution of dimethyl 2,2'-(naphthalene-1,5-diylbis(oxy))diacetate (3.04 g, 10 mmol) in THF (150 ml) was added 0.5 M NaOH (200 ml). The mixture was stirred vigorously in room temperature for overnight, and poured to 1 M HCl (200 ml). The precipitate formed was collected by filtration, washed with Et_2O and dried. Yield: 2.40 g, 87 %. M.p.: >250 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.05 (bs, 2 H, COOH), 7.80 (d, J = 8.8 Hz, 2 H, ArH), 7.40 (t, J = 8.0 Hz, 2 H, ArH), 6.91 (d, J = 7.6 Hz, 2 H, ArH), 4.87 (s, 4 H, CH_2). ^{13}C{^{1}H} NMR (100.62 MHz, DMSO-d_6) δ (ppm): 170.0, 153.1, 125.9, 125.3, 114.3, 106.0, 64.9. HRMS (ESI+) calcd. for: $C_{14}H_{12}O_6Na$ $[M+Na]^+$ (m/z): 299.0532, found: 299.0527.

Bis(2,5-dioxopyrrolidin-1-yl)-2,2'-(naphthalene-1,5-diylbis(oxy))diacetate: A mixture of 2,2'-(naphthalene-1,5-diylbis(oxy))diacetic acid (0.41 g, 1.5 mmol) and *N*-hydroxylsuccinimide (0.70 g, 6.0 mmol) was dissolved in DMF (50 ml) and cooled with an ice bath. EDC·HCl (1.15 g, 6.0 mmol) was added to the solution, and the mixture was stirred in the melting ice bath for 15 min. Stirring was continued at room temperature for a further 1 day. The precipitate formed was collected by filtration and dried *in vacuo*. Yield: 0.60 g, 85 %. M.p.: 240-243 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.84 (d, J = 8.4 Hz, 2 H, ArH), 7.46 (t, J = 8.0 Hz, 2 H, ArH), 7.08 (d, J = 7.6 Hz, 2 H, ArH), 5.53 (s, 4 H, OCH_2), 2.84 (s, 8 H, $NC(O)CH_2$). ^{13}C{^{1}H} NMR (100.62 MHz, DMSO-d_6) δ (ppm): 169.9, 165.3, 152.4, 125.8, 125.6, 114.8, 106.8, 63.4, 25.5. HRMS (ESI+) calcd. for: $C_{22}H_{18}N_2O_{10}Na$ $[M+Na]^+$ (m/z): 493.0859, found: 493.0848.

2,2'-(Naphthalene-1,5-diylbis(oxy))bis(*N*-(2-(trimethylammonium)ethyl) acetamide) dichloride, 3: To a suspension of bis(2,5-dioxopyrrolidin-1-yl)-2,2'-(naphthalene-1,5-diylbis(oxy))diacetate (0.26 g, 0.55 mmol) in dry DMF (50 ml) was added a solution of 2-aminoethyltrimethylammonium chloride (0.24 g, 1.38 mmol) and triethylamine (0.4 ml, 2.9 mmol) in the same solvent (20 ml). The solution was stirred under N_2 for 1 day, and the white precipitate formed was collected by filtration. Recrystallization of the white solid in MeOH gave the product as colourless crystals. Yield: 0.22 g, 78 %. M.p.: >250 °C (decomposed). ^{1}H NMR (400 MHz, D_2O) δ (ppm): 7.90 (d, J = 8.4 Hz, 2 H, ArH), 7.43 (t, J = 8.0 Hz, 2 H, ArH), 6.91 (d, J = 7.6 Hz, 2 H, ArH), 4.66 (s, 4 H, OCH_2), 3.71 (t, J = 6.4 Hz, 4 H, CH_2), 3.42 (t, J = 6.4 Hz, 4 H, CH_2), 3.03 (s, 18 H, NMe_3). ^{13}C{^{1}H} NMR (100.62 MHz, CD_3OD) δ (ppm): 172.3, 153.2, 126.5, 126.4, 115.6, 107.4, 67.6, 64.5, 53.7, 33.8. HRMS (ESI+) calcd. for: $C_{24}H_{38}N_4O_4Cl$ $[M-Cl]^+$ (m/z): 481.2555, found: 481.2576.

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2,2'-(1,3,6,8-Tetraoxobenzo[*lmn*][3,8]phenanthroline-2,7(1*H*,3*H*,6*H*,8*H*)-diyl)bis (*N*,*N*,*N*-trimethylethanaminium) dichloride, 9: A mixture of 1,4,5,8-naphthalenetetracarboxylic dianhydride (0.54 g, 2 mmol), (2-amino)ethyltrimethyl-ammonium chloride (0.70 g, 4 mmol) and triethylamine (1.1 ml, 8 mmol) in DMF (10 ml) was sonicated for 1 hour and heated in a microwave reactor at 140 °C for 5 minutes. Volatiles were removed by a rotary evaporator. The residue was re-dissolved in MeOH (150 ml), stirred with K_2CO_3 (1 g) for 10 minutes and filtered.

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Evaporation of solvent gave the product as dark brown solid. Yield: 1.0 g, quant. M.p.: >250 °C. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 8.80 (s, 4 H, ArH), 4.71 (t, *J* = 7.6 Hz, 4 H, CH_2), 3.75 (t, *J* = 7.6 Hz, 4 H, CH_2), 3.38 (s, 18 H, NMe_3). $^{13}C\{^{1}H\}$ NMR (100.62 MHz, CD_3OD) δ (ppm): 163.0, 130.6, 126.5, 62.5, 52.5, 33.9. HRMS (ESI+) calcd. for: $C_{24}H_{30}N_4O_4Cl$ $[M-Cl]^+$ (m/z): 473.1936, found: 473.1950.

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DCL Setup and Analysis

A typical analytical library was prepared in 1 ml scale by dissolving the building block in 10 mM NaOH to a 5 mM solution, followed by titration with 100 mM NaOH to pH 8.5. Where appropriate, a template solution in high concentration (25–100 mM) was added. The library was stirred at room temperature in a close capped vial for at least 5 days before analysis by HPLC/LCMS. The preparative library was set up in 5 ml scale in the same way as the analytical libraries. Template **3** (6.45 mg, 0.0125 mmol) was added to the library solution directly in the solid form, and the library was oxidised and equilibrated for 5 days before isolation.

HPLC analyses were carried out on Hewlett Packard 1050 or 1100 systems coupled to diode array or multiple wavelength UV–Vis detector and data processed using HP ChemStation software. Water for HPLC was either obtained from a Millipore water purification system or from Rathburn. THF and formic acid were from Romil and used without further purification. Analytical separations were achieved by injecting 5 µl aliquot of library solution onto the reverse phase Symmetry C_8 column (150 x 4.6 cm, 3 µm particle size) with isocratic elution of 40 % THF/water mixture (with 0.1 % formic acid in aqueous phase) at room temperature at room temperature with a flow rate of 1 ml/min. Semi–preparative separations were performed in the reverse phase SymmetryPrep C_{18} column (300 x 7.8 mm, 7 µm particle size) with isocratic elution of 40 % THF/water mixture (with 0.1 % formic acid in aquesous phase) at 40 °C with a flow rate of 2 ml/min. UV–Vis detector was set to 380 nm.

LCMS was carried out on an Agilent 1100 LC/MSD trap XCT system. Data were processed using ChemStation software. Mass spectra (negative ion mode) were acquired in ultra scan mode using a drying temperature of 350 °C, a nebuliser pressure of 55 psi, drying gas flow of 10 L/min, capillary voltage 4000 V, an ICC target of 200,000 ions, and a target mass of 1000.

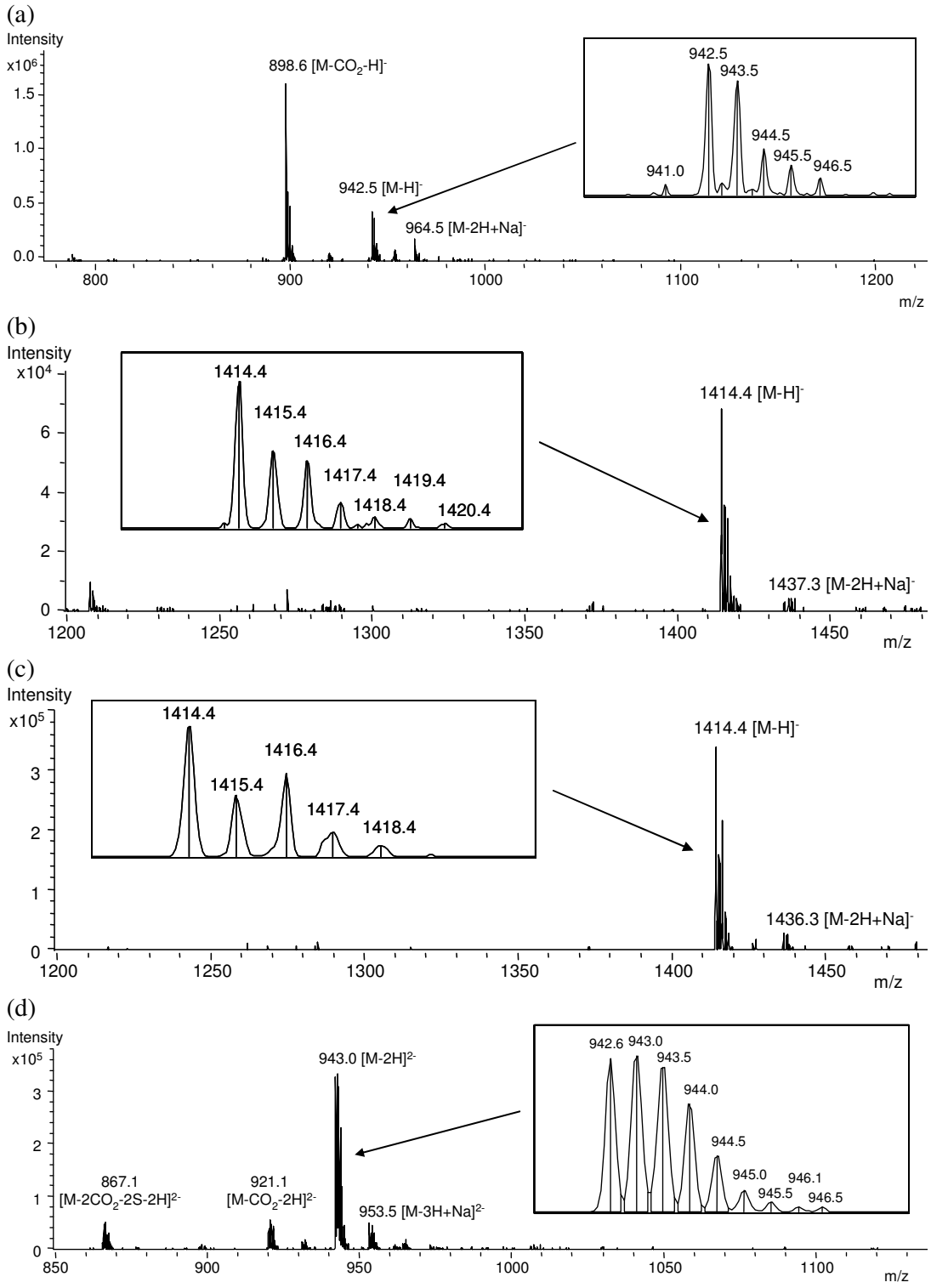
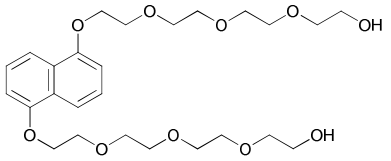


Figure S1. ESI mass spectra from LCMS analysis: (a) dimer $\mathbf{1}_2$ at retention time = 9.7 min; (b) & (c) trimers $\mathbf{1}_3$ at retention time = 19.8 and 23.3 min; (d) tetramer $\mathbf{1}_4$ at retention time = 35.8 min.

Table S1 DCL compositions in the presence of different templates.

Experiment	Components	Product		
		Dimer	Trimer[a]	Tetramer
1	**1** (5 mM)	52	34	14
2	**1** (5 mM) + **2** (2.5 mM)	39	49	12
3	**1** (5 mM) + **3** (2.5 mM)	8	12	80
4	**1** (5 mM) + **4** (2.5 mM)	49	36	15
5	**1** (5 mM) + **5** (2.5 mM)	22	17	61
6	**1** (5 mM) + **6** (2.5 mM)	43	27	30
7	**1** (5 mM) + **7** (2.5 mM)	54	16	30
8	**1** (5 mM) + **8** (2.5 mM)	61	22	16
9	**1** (5 mM) + **9** (2.5 mM)	49	36	15

[a] Reported as the sum of the two isomers.



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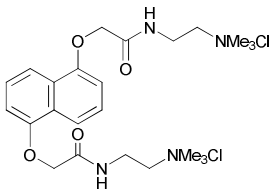

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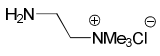

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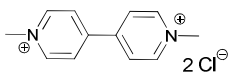

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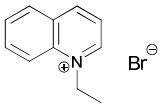

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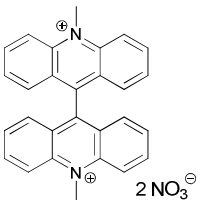

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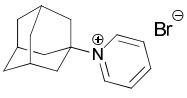

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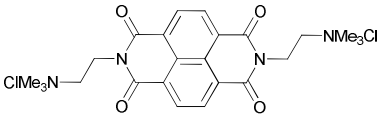

9

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DCLFit Calculations

A set of DCLs of **1** (0.5 mM) at different concentrations of **3** was produced and analysed. Peak areas in HPLC chromatograms were integrated and normalised. Concentrations of the oligomer were calculated from the normalised data assuming the extinction coefficients of the oligomers are multiples of that of **1**. Formation constants of dimer, trimer and tetramer were determined from four sets of untemplated libraries. Due to the variance in the total peak areas, the reported K_a values from *DCLFit* are for reference of the order of magnitude of the individual host–guest interaction. For fitting details, please refer to the corresponding reference.[3]

Experiment data of DCLs for fitting:

		[**3**] / mM									
		0	0	0	0	0.2	0.4	2	5	10	20
HPLC peak integrations	$\mathbf{1}_2$	618.2	538.3	538.9	499.6	180.1	97.8	39.0	51.6	69.9	114.7
	$\mathbf{1}_3$	188.6	163.3	172.3	139.9	164.4	117.8	62.8	68.6	85.8	111.0
	$\mathbf{1}_4$	9.7	28.8	15.7	14.5	240.6	385.0	332.1	386.4	322.9	215.6
	total	816.5	730.4	726.9	654.0	585.1	600.6	433.9	506.6	478.6	441.3
Percentage of library	$\mathbf{1}_2$	75.7	73.7	74.1	76.4	30.8	16.3	9.0	10.2	14.6	26.0
	$\mathbf{1}_3$	23.1	22.4	23.7	21.4	28.1	19.6	14.5	13.5	17.9	25.2
	$\mathbf{1}_4$	1.2	3.9	2.2	2.2	41.1	64.1	76.5	76.3	67.5	48.9
	total	100	100	100	100	100	100	100	100	100	100
Conc. / mM	$\mathbf{1}_2$	0.189	0.184	0.185	0.191	0.077	0.041	0.022	0.025	0.037	0.065
	$\mathbf{1}_3$	0.038	0.037	0.039	0.036	0.047	0.033	0.024	0.023	0.030	0.042
	$\mathbf{1}_4$	0.002	0.004	0.003	0.003	0.051	0.080	0.096	0.095	0.084	0.061

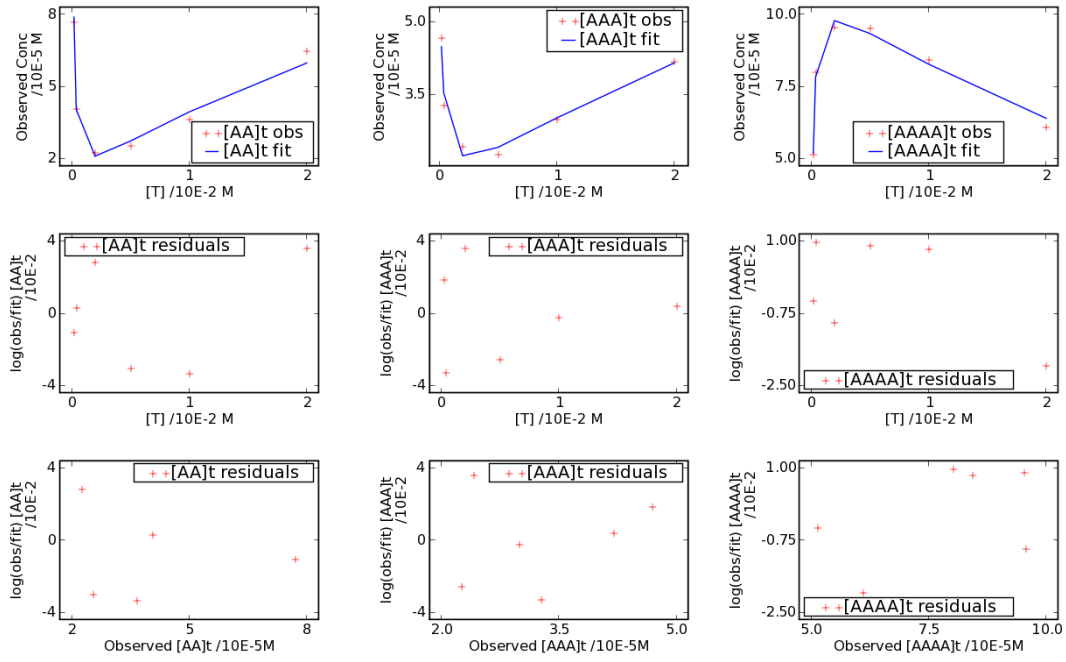

Figure S2. Fitting curves (blue traces) generated by *DCLFit* for dimer (top left), trimer (top middle) and tetramer (top right).

[3] R. F. Ludlow, J. Liu, H. Li, S. L. Roberts, J. K. M. Sanders and S. Otto, *Angew. Chem., Int. Ed.*, 2007, **46**, 5726.

The bootstrap method was done by repeating the fittings for 1000 times with varying weights (from 0 to 5) of the experimental input using the same fitting procedure. The consistency observed in the total binding constants of **3** to the same library member (dimer, trimer and tetramer bind to two, three and two templates respectively) indicates the reliability of the fitting model.

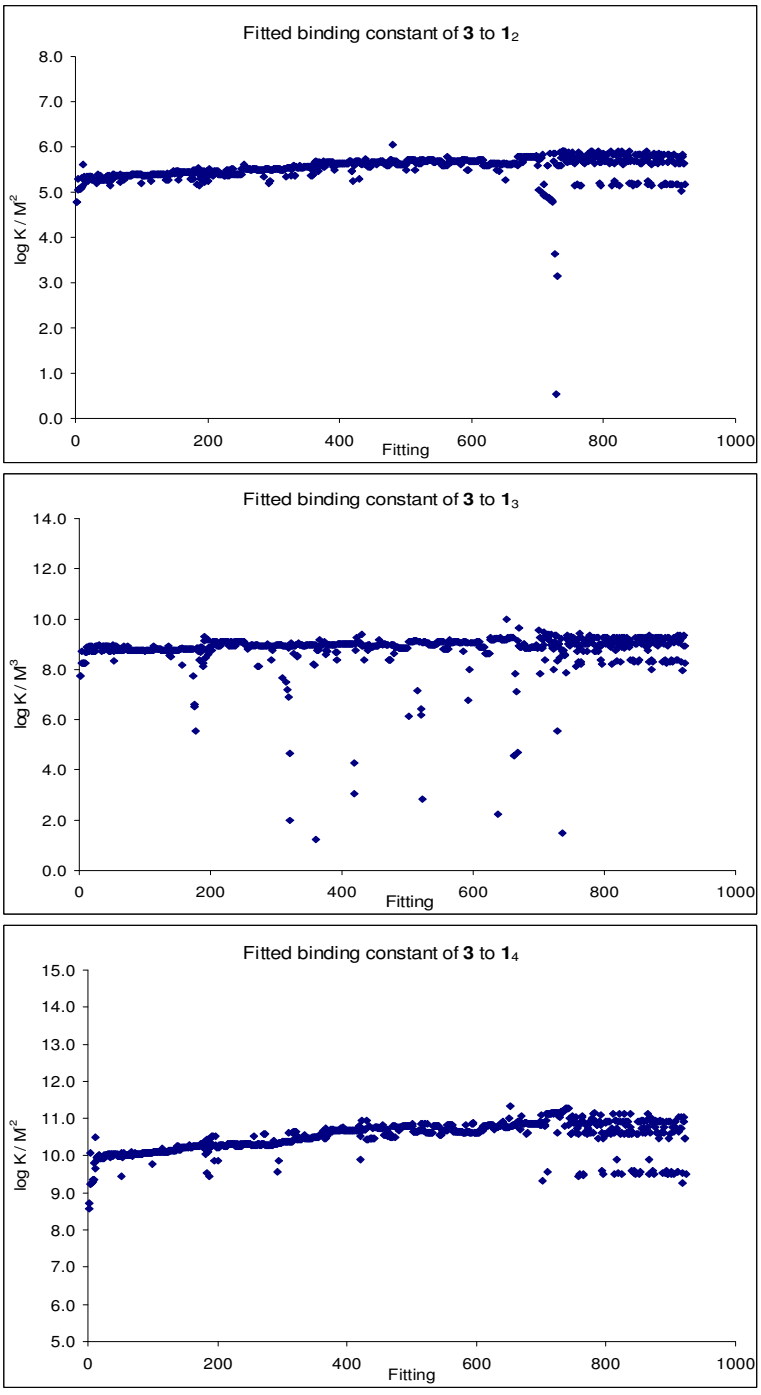

Figure S3. Distributions of products of fitted binding constants of dimer (top), trimer (middle) and tetramer (bottom) of 1000 fittings.

NMR Analysis

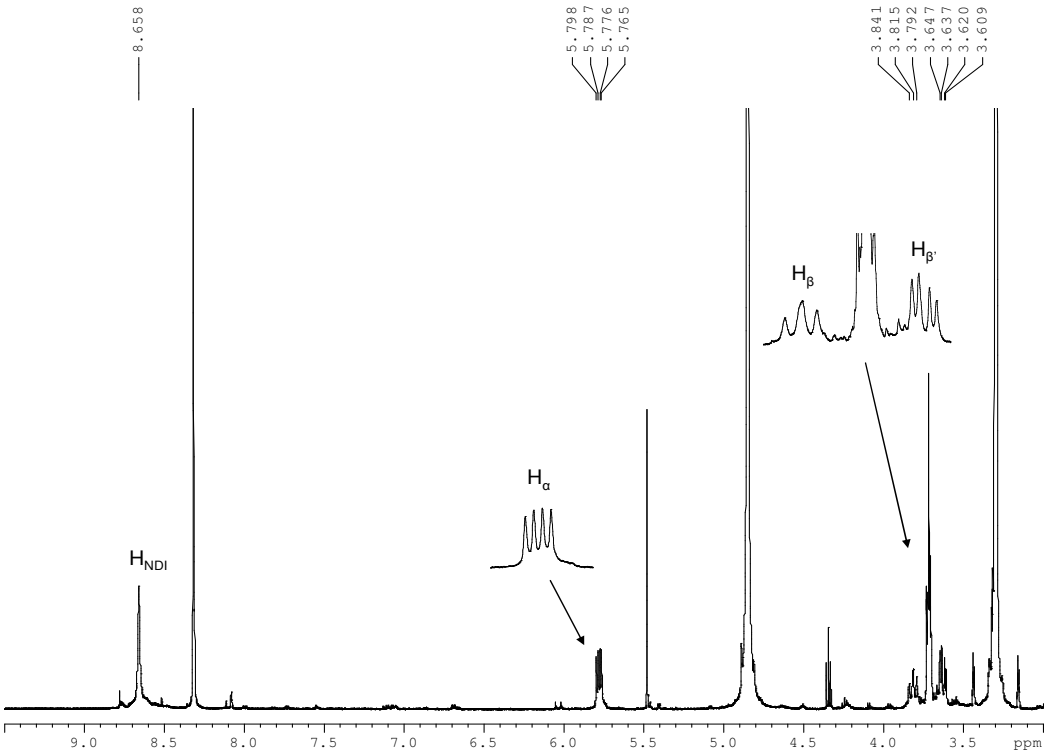

Figure S4. 500 MHz ^{1}H NMR spectrum of the dimer $\mathbf{1}_2$ in CD_3OD at room temperature.

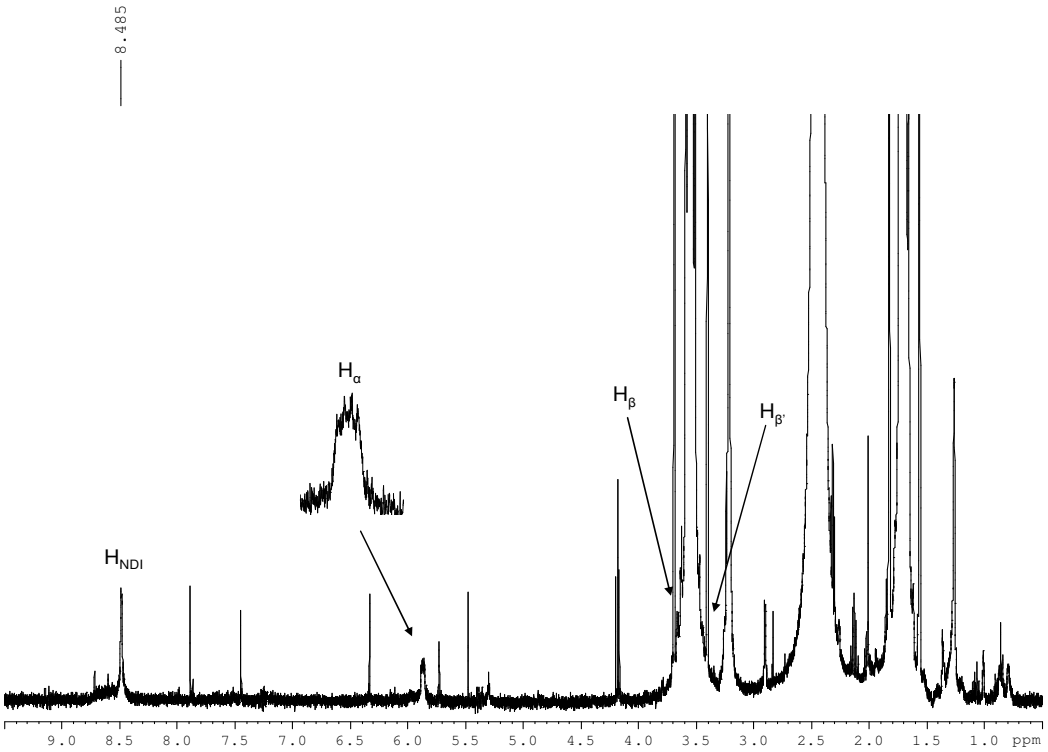

Figure S5. 500 MHz ^{1}H NMR spectrum of the trimer $\mathbf{1}_3$ in THF-d_6 at room temperature.

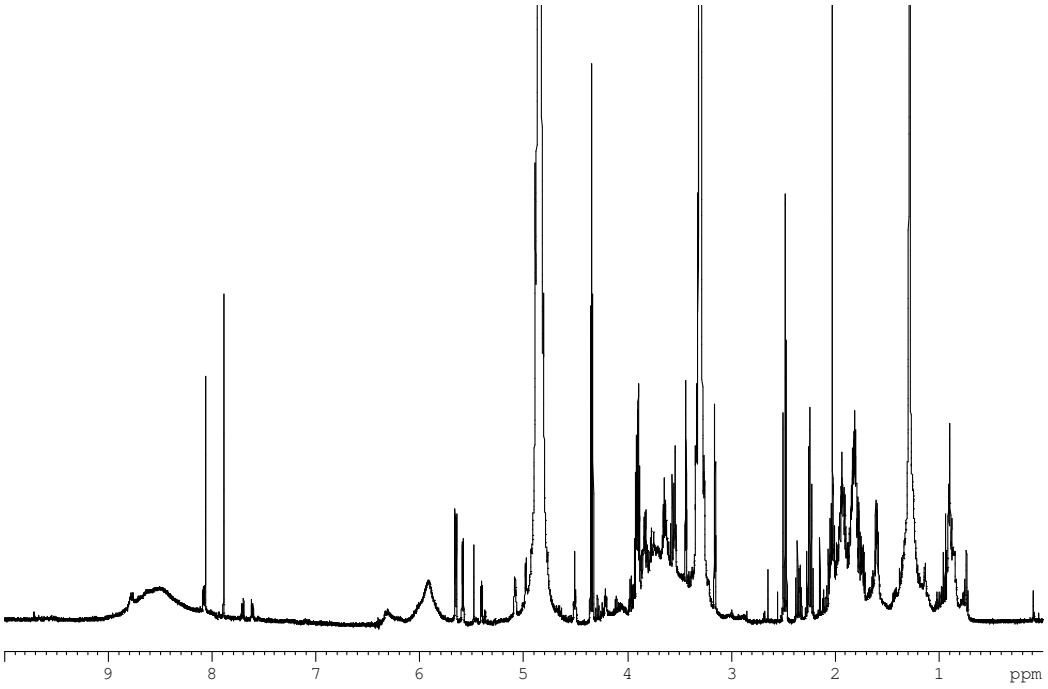

Figure S6. 500 MHz ^{1}H NMR spectrum of the tetramer $\mathbf{1}_4$ in CD_3OD at room temperature.

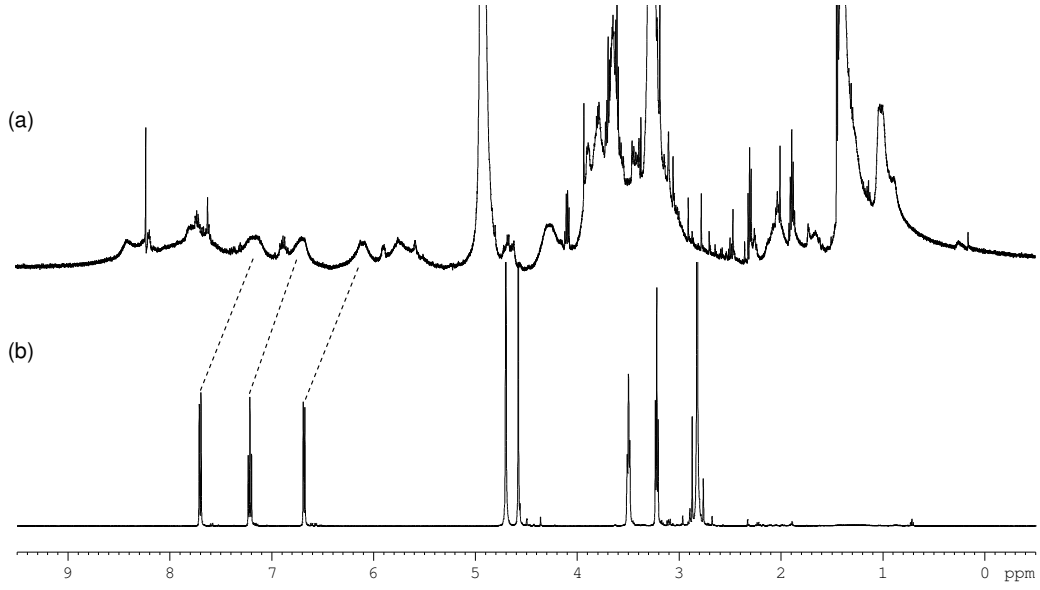

Figure S7. 500 MHz ^{1}H NMR spectrum of (a) the tetramer-guest complex $(\mathbf{1}_4)\cdot\mathbf{3}$ in D_2O/NaOD and (b) the free guest **3** in D_2O at room temperature.

UV–Vis Titration

UV–Vis spectra were recorded using Cary 400 UV Spectrometer at room temperature. Isolated sample of the tetramer $\mathbf{1}_4$ was dissolved in pH 8.5 borate buffer to solutions of 3.6×10^{-4} M and 1.1×10^{-5} M. Stock solutions of model NDI compound **10** were made up in the same buffer in concentration of 2.000×10^{-3} M (1.03 mg in 1.347 ml) for titration with **2**, or 5.020×10^{-3} M (3.95 mg in 2.060 ml) for titration with **3**. The stock solution of **10** at 2.000×10^{-3} M was diluted 10 and 20 times, yielding 2.000×10^{-4} M and 1.000×10^{4} M solutions respectively; while the stock solution of **10** at 5.020×10^{-3} M was diluted 50 times to a 1.004×10^{4} M solution. Stock solutions of the guests were prepared by mixing equal volume (1.000 ml : 1.000 ml) of a 2.000×10^{-3} M solution of **2** (3.97 mg in 3.872 ml) with solution of **10** at 2.000×10^{-4} M, or by dissolving 10 equivalents of **3** in 1.500 ml of $\mathbf{1}_4$ at 3.6×10^{-4} M and 1.1×10^{-5} M, and diluted solution of **10** at 1.004×10^{4} M respectively.

Procedure of the binding studies involved making sequential additions of guest **2** or **3** using Eppendorf pipettes to a 1.500 ml or 0.150 ml aliquots of the tetramer solutions and stock solution of **10** in a spectrometric cell (b = 1 cm for $\mathbf{1}_4$ at 1.1×10^{-5} M and **10** at 1.004×10^{4} M; b = 0.1 cm for $\mathbf{1}_4$ at 3.6×10^{-4} M). UV–Vis spectra were then combined to produce plots that showed the changes in the spectral features as a function of changes in the concentration of **2** and **3**.

Binding constant was calculated using equation 4.5 of Connors[4] where [L] = [**2**] or [**3**]. The resulting equation, of the form, $y = B \times K_a \times x/(1+K_a+x)$, was computer fit using the Origin version 7 software package, where x = [**2**] or [**3**], y = ΔA, B = $\Delta\varepsilon \times b$, K_a = binding constant. The change in absorbance, ΔA, was calculated at a λ = 400 nm where the spectral change was maximal.

For the construction of Job plot, a stock solution of **10** was prepared as described for the K_a determination. Stock solution of **3** was prepared by dissolving 10 equivalents of the compound (0.6 mg, in 1.178 ml) in the same solvent, and diluted 10 times. Sequential additions of the diluted solution of **3** using Eppendorf pipettes to a 1.500 ml aliquot of the stock solution of **10** was taken place in a spectrometric cell. UV–Vis spectra were then combined from which a Job plot can be constructed, where the molar fraction of **3** was plotted as a function of $\Delta A \times$ [**10**].

[4] K. A. Connors, *Binding Constants*, John Wiley & Sons: New York, 1987, 148.

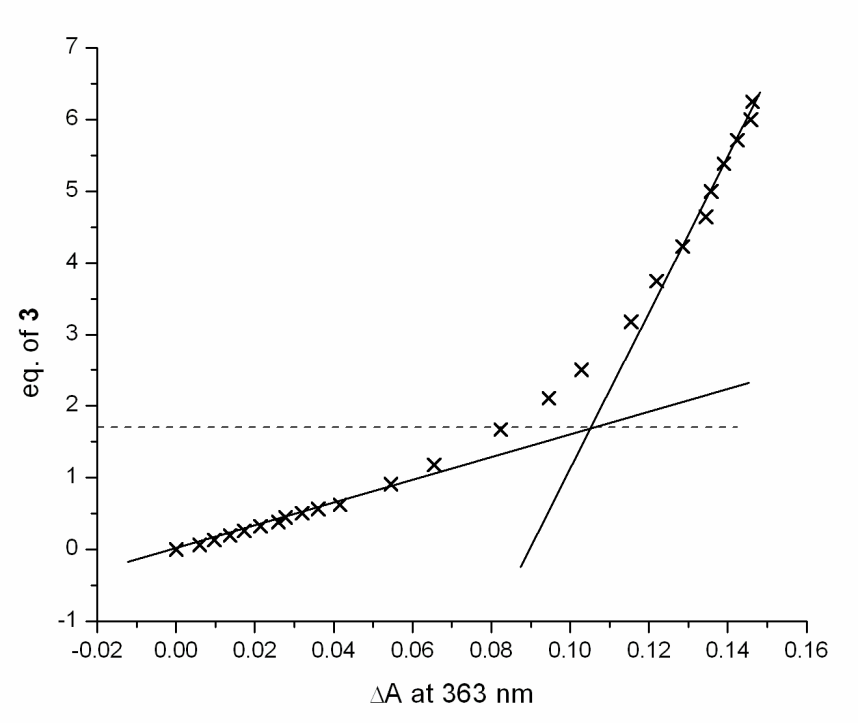

Figure S8. Mole ratio plot of titration of **3** to $\mathbf{1}_4$ at 1.1 x 10^{-5} M.

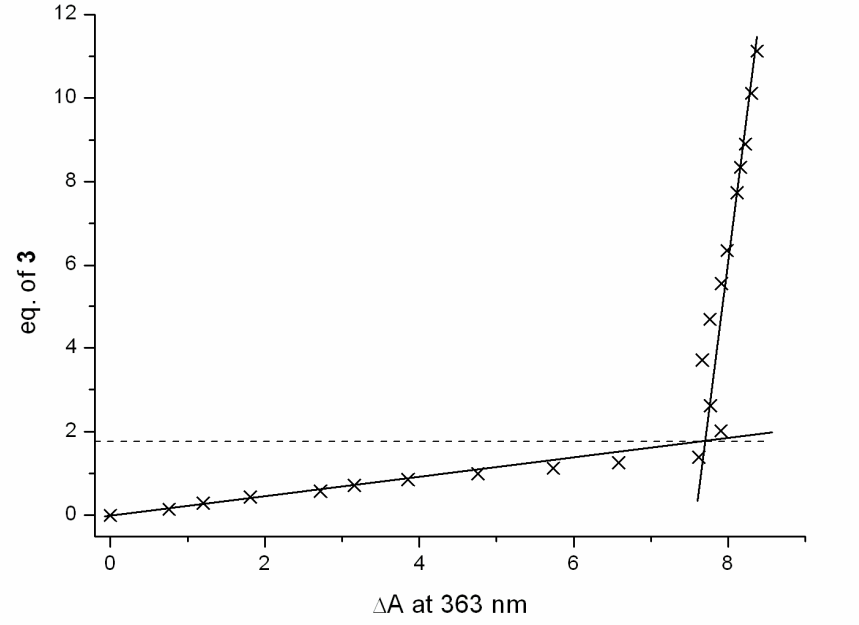

Figure S9. Mole ratio plot of titration of **3** to $\mathbf{1}_4$ at 3.6 x 10^{-4} M

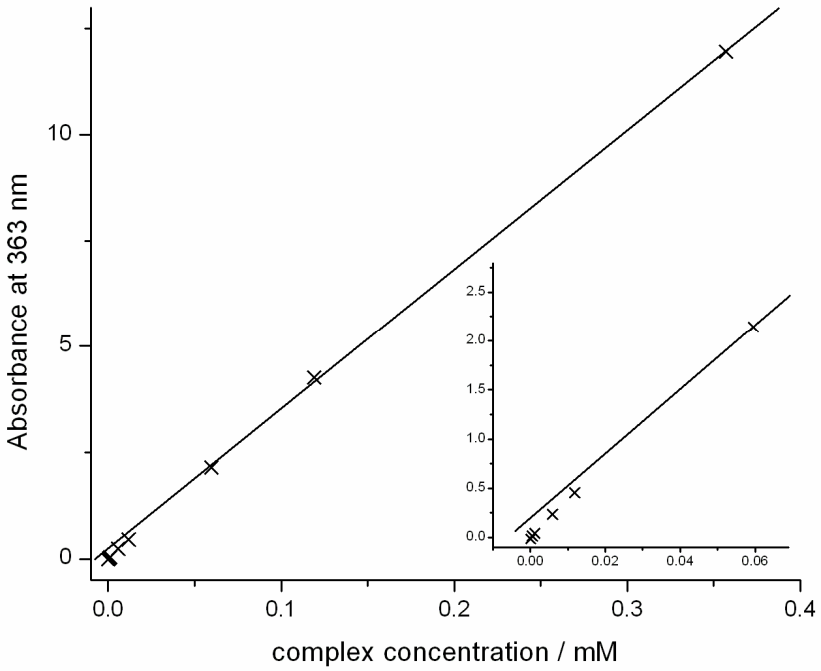

Figure S10. Concentration dependence of absorption coefficient at 363 nm of a *ca.* 10:1 mixture of **3** to $\mathbf{1}_4$ complex solution.

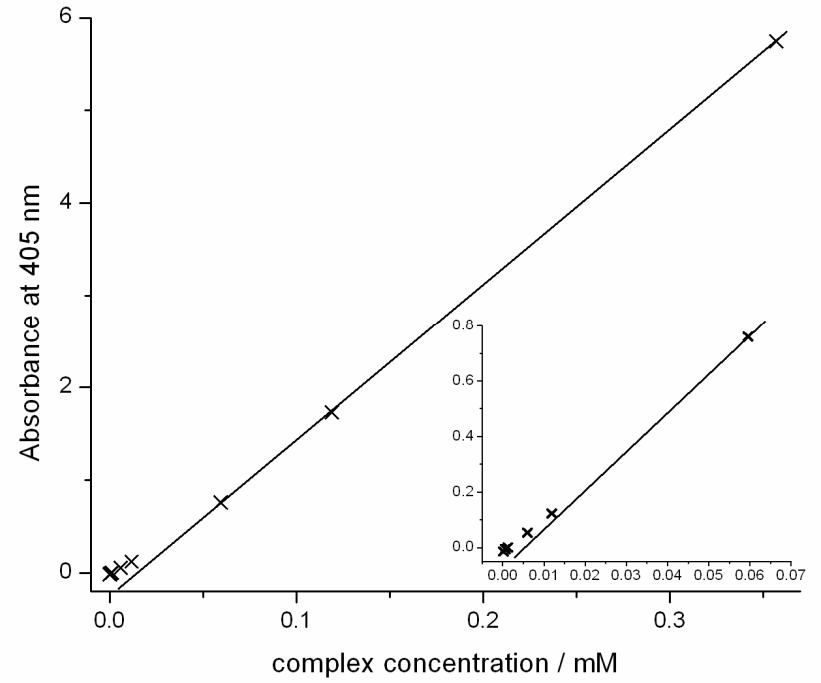

Figure S11. Concentration dependence of absorption coefficient at 405 nm of a *ca.* 10:1 mixture of **3** to $\mathbf{1}_4$ complex solution.

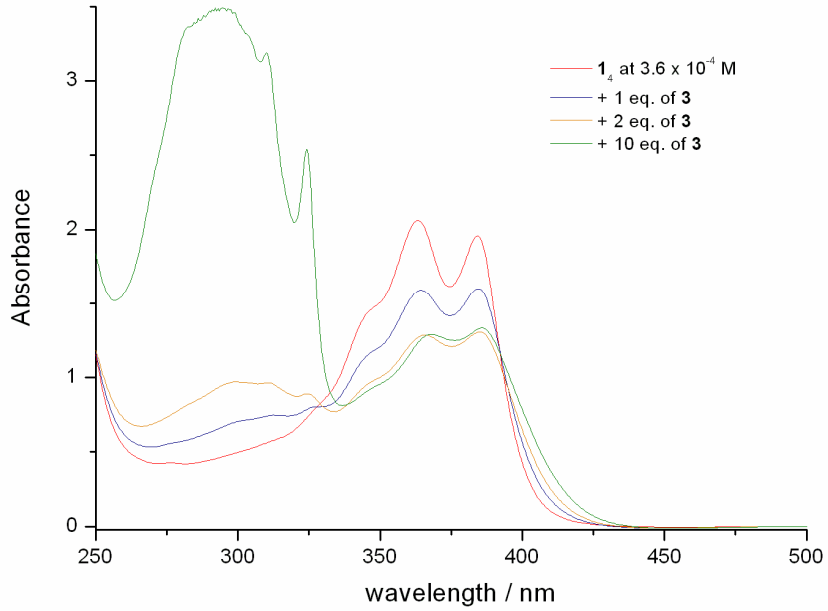

Figure S12. UV–Vis spectra of $\mathbf{1}_4$ in the presence of different equivalent of **3**.

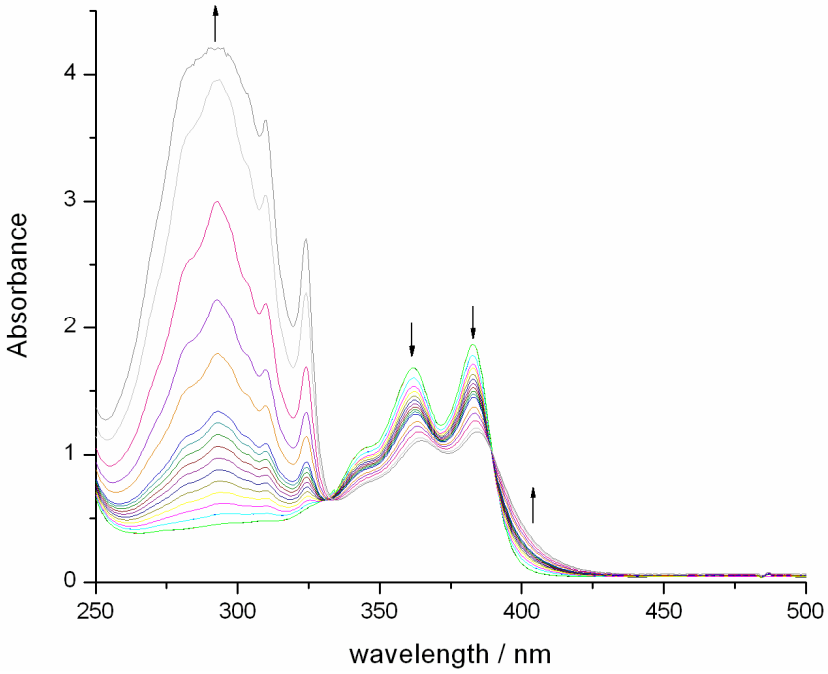

Figure S13. Change in UV–Vis spectra of **10** at increasing concentration of **3**.

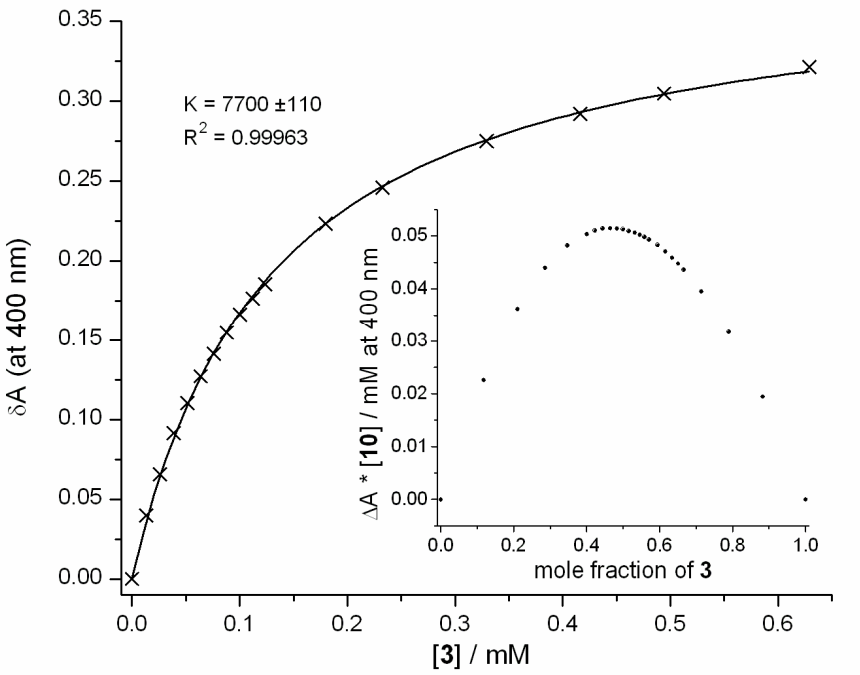

Figure S14 Fitting of UV–Vis titration curve and the Job plot (inset) of binding between **3** and **10**.

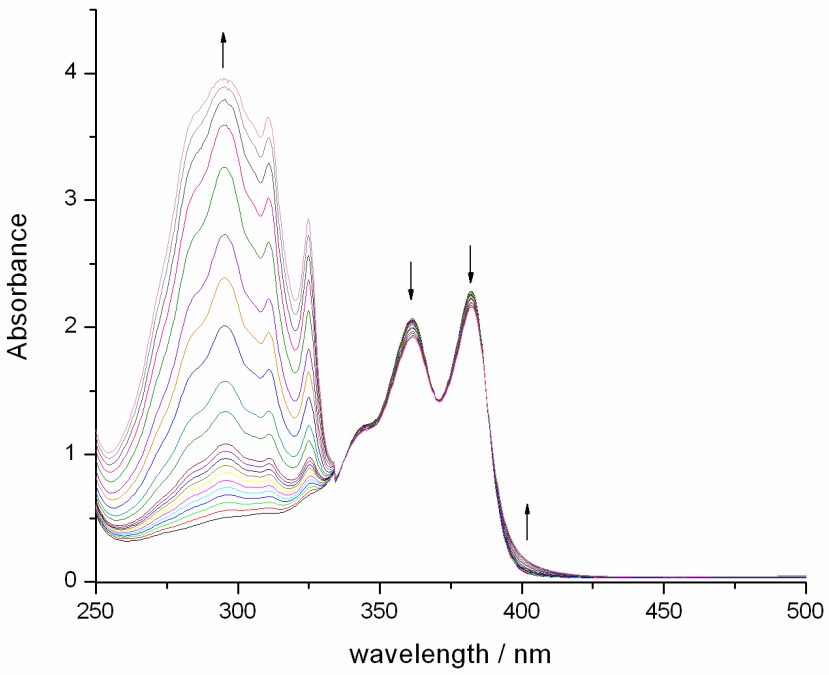

Figure S15. Change in UV–Vis spectra of **10** at increasing concentration of **2**.

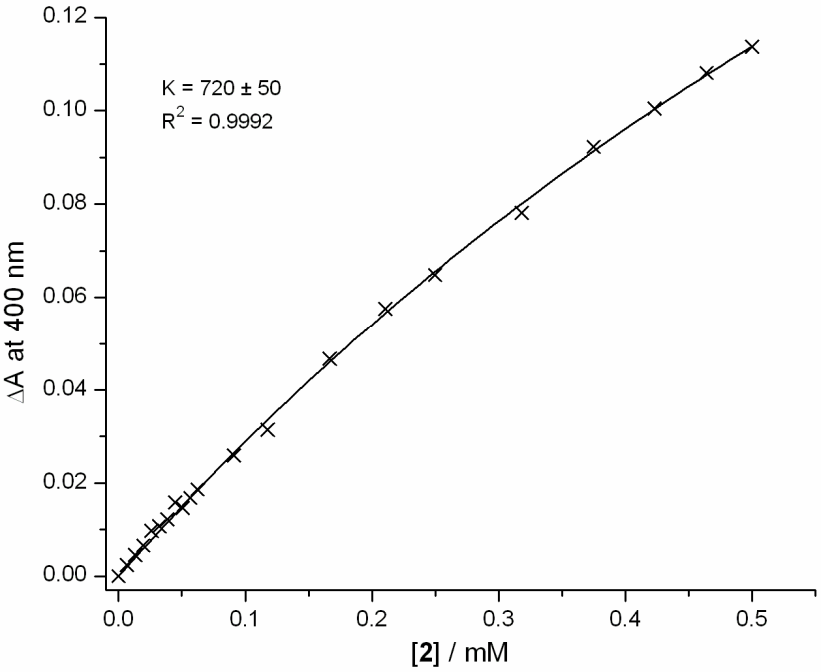

Figure S16. Fitting of the UV–Vis titration curve of binding between of **10** and **2**.

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X-ray Diffraction Analysis

Compound	**3** · 3.25 H_2O	**3·10** · 6 H_2O
Empirical formula	$C_{24}H_{44.50}Cl_2N_4O_{7.25}$	$C_{42}H_{58}N_6O_{18}$
Formula weight	576.04	934.94
Temperature / K	180(2)	180(2)
Wavelength / Å	0.71073	0.71073
Crystal system	Triclinic	Triclinic
Space group	P-1	P-1
Unit cell dimension		
a / Å α / degree	10.5572(3) 73.187(2)	8.3691(1) 85.201(1)
b / Å β / degree	11.3888(3) 82.840(2)	8.4678(2) 75.792(1)
c / Å γ / degree	13.1194(3) 83.681(2)	15.9082(3) 83.444(1)
Volume / $Å^3$	1493.64(7)	1083.94(4)
Z	2	1
Density (calcd) / Mgm^{-3}	1.281	1.432
Absorption coeff. / mm^{-1}	0.264	0.113
F(000)	617	496
Crystal size / mm^3	0.23 x 0.14 x 0.12	0.46 x 0.18 x 0.16
θ range for data collection	3.57 to 32.00°	3.67 to 34.96°
Index ranges	-15<=h<=15 -15<=k<=16 -17<=l<=19	-12<=h<=13 -13<=k<=13 -24<=l<=25
Reflections collected	22846	17034
Independent reflections	10174 [R(int) = 0.0413]	9240 [R(int) = 0.0763]
Completeness to θ	θ = 32.00°, 98.1 %	θ = 34.96°, 97.0 %
Absorption correction	Semi-empirical from equivalent	Semi-empirical from equivalent
Max and min transmission	0.972 and 0.911	0.998 and 0.522
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/ restraints / parameters	10174 / 12 / 369	9240 / 9 / 321
Goodness-of-fit on F^2	1.082	1.033
Final R indices [I>2σ(I)]	R1 = 0.0617, wR2 = 0.1166	R1 = 0.0583, wR2 = 0.1470
R indices (all data)	R1 = 0.1045, wR2 = 0.1356	R1 = 0.0744, wR2 = 0.1618
Largest diff. peak and hole	0.352 and -0.309 e.$Å^{-3}$	0.478 and -0.334 e.$Å^{-3}$

Diffractometer: *Nonius Kappa CCD* area detector. **Data Collection**: Collect (Collect: Data collection software, R. Hooft, Nonius B. V., 1998). **Structure Refinement**: SHELXL97 (G. M. Sheldrick (1997), University of Göttingen, Germany). **Special Details**: The water hydrogen atoms were located and their position satisfactorily refined, except for the forth water solvate of **3** · 3.25 H_2O, which was assigned occupancy 0.25 for the refinement, are doubtful, but they are in reasonable hydrogen-bond making positions. Solvent O4W atom is refined istropically.

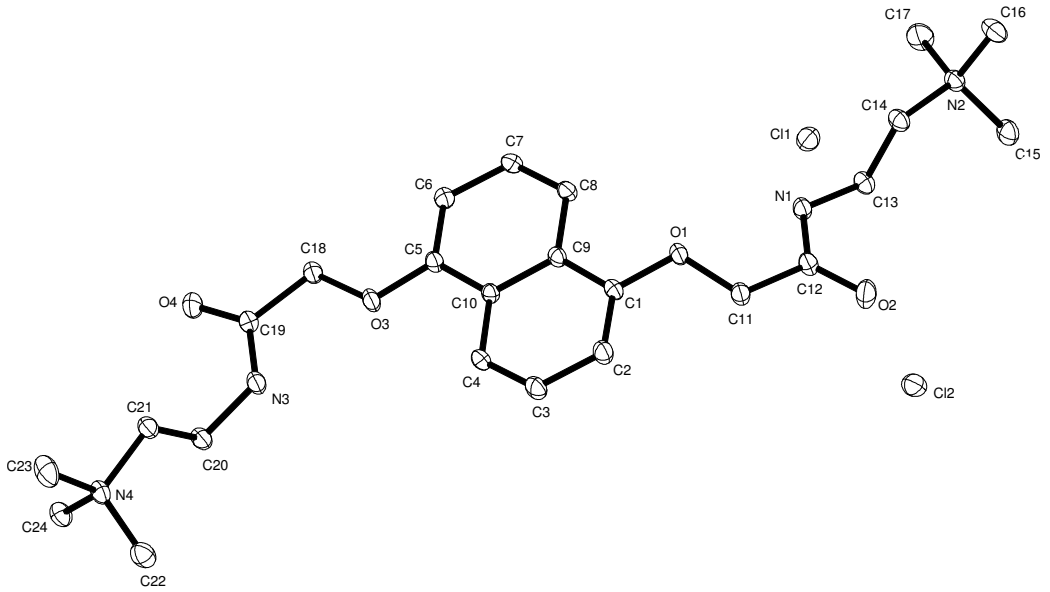


Figure S17. Molecular structure of **3** with atom labelling scheme. Thermal ellipsoids are drawn in 30 % probability level. Hydrogen atoms and solvent molecules are omitted for clarity.

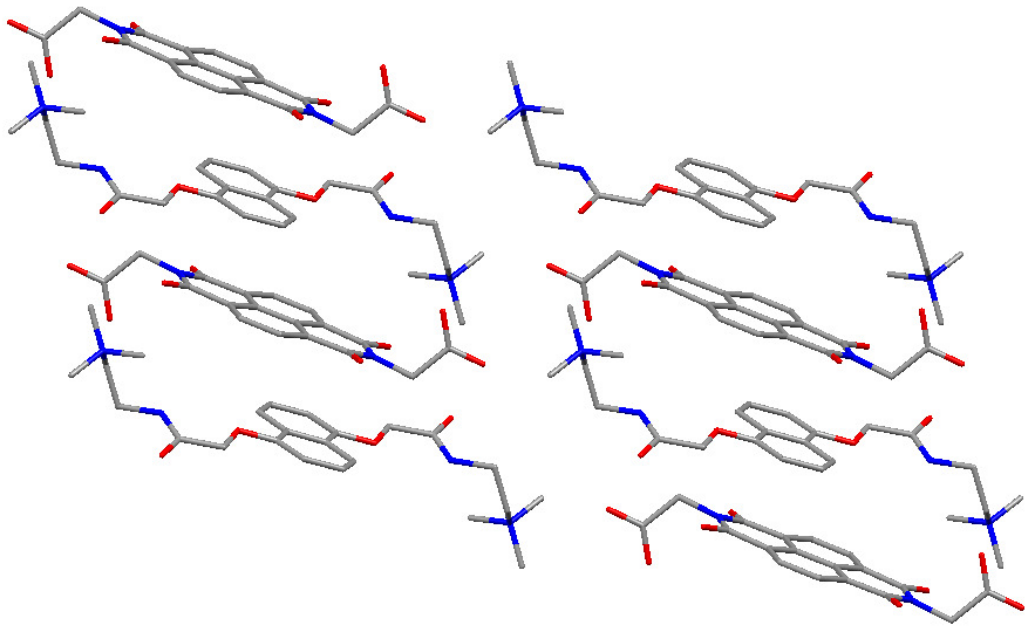
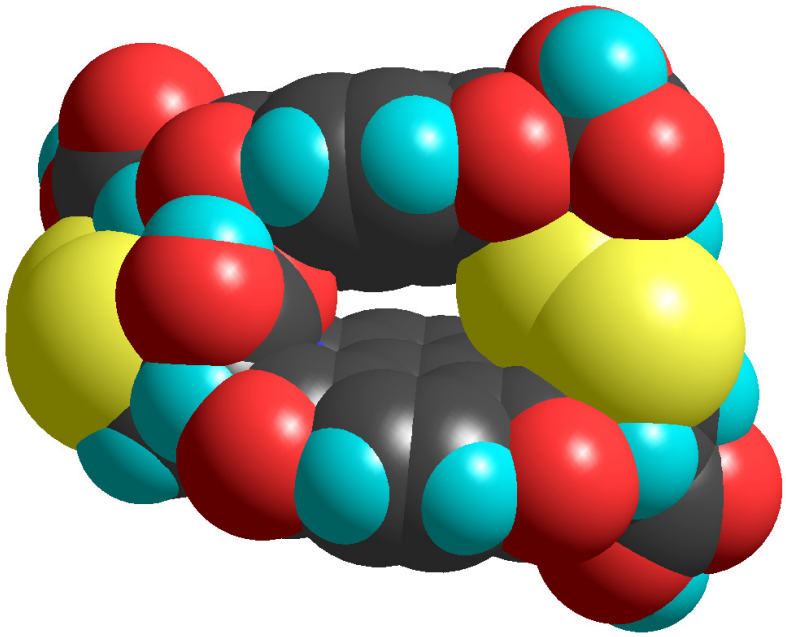


Figure S18. Crystal packing of co-crystal **3**·**10**, viewed along the *b* axis on the crystal. Hydrogen atoms and solvent molecules are omitted for clarity.

Molecular Modelling

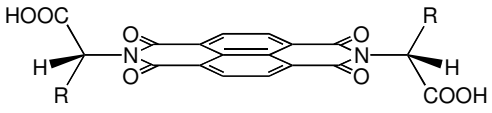
Dimer:

Space filling model for $\mathbf{1}_2$ obtained by geometry optimisation of a dimer structure with HyperChem v 8.01, Semi-empirical method, AM1, convergence criterion 0.01 kcal/mol•Å.

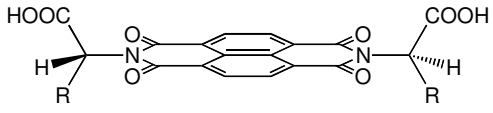


Trimer:

For the $\mathbf{1}_3$ species the following conformers are possible, with respect to the orientation of the carboxylic groups (see Figures below): all-syn, syn-syn-anti, syn-anti-anti, and all anti.



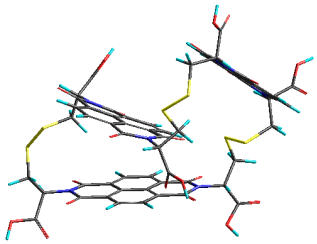
"Anti"



"Syn"

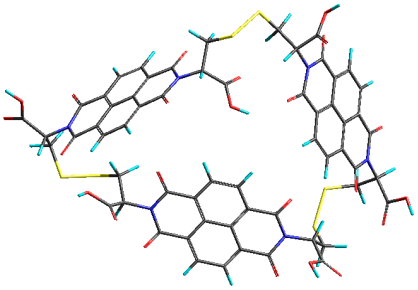
To calculate the relative energies of these conformers molecular modeling was done using HyperChem v 8.01, Semi-empirical method, AM1, convergence criterion 0.01 kcal/mol•Å.

Optimised structures:



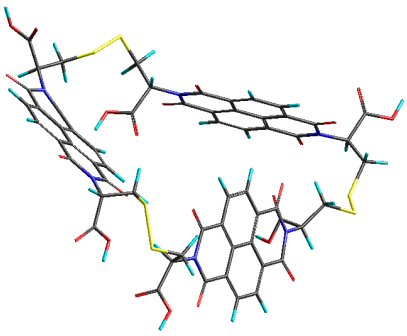
E = -421418.90 kcal/mol

"SynSynAnti – folded"



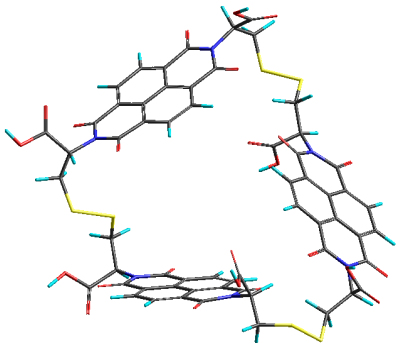
E = -421417.30 kcal/mol

"SynSynAnti – open"



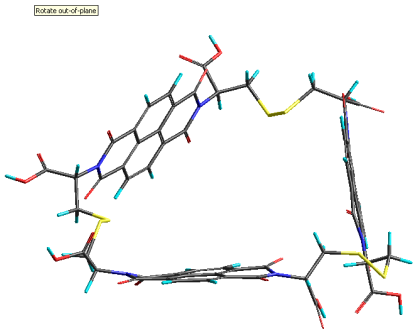
E = -421407.94 kcal/mol

"All anti"



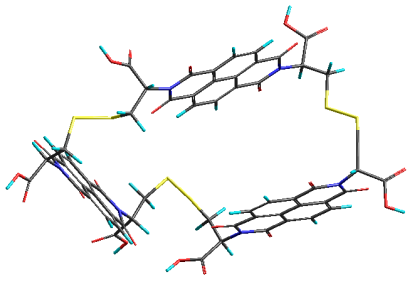
E = -421402.89 kcal/mol

"SynAntiAnti"



E = -421401.65 kcal/mol

"SynSynAnti – open2"



E = -420754.65 kcal/mol

"All syn"

Table S2. Energetic, electronic and geometric parameters calculated with Hyperchem 8.01 (MM+, followed by AM1, in both cases a 0.01 kcal/mol·Å was used as convergence criterion)[a]

	Conformation	ΔE[b] (kcal/mol)	E_{hydr} (kcal/mol)	V ($Å^3$)	μ (D)	A_{WAS}[c] ($Å^2$)	δ_{min}[d]	R_t[e]
1	**S**yn**S**yn**A**nti - folded	0	-43.06	2891.5	2.54	1193.91	-0.35185	15.09
2	**S**yn**S**yn**A**nti - open	1.6	-34.84	2785.5	2.76	1045.05	-0.36514	12.37
3	All anti	10.9	-39.23	2814.6	5.47	1072.72	-0.37119	10.69
4	**S**yn**A**nti**A**nti	16.0	-39.35	2858.8	4.92	1114.73	-0.36049	11.89
5	**S**yn**S**yn**A**nti – open2	17.1	-41.68	2895.1	4.41	1156.05	-0.35863	12.96
6	All syn	664.2	-40.98	2904.2	4.82	1189.69	-0.35736	13.22

[a] single molecule in vacuum, no solvent model was used
[b] relative energie of formation with respect to the SynSynAnti – folded conformation
[c] A_{was} represents the solvent accessible area calculated with the QSAR module
[d] δ_{min} represents the partial charge on the most charged atom in the molecule
[e] The estimated retention times were calculated using QSRR methods.[5] The equation used was:
$R_t = k_1 - 0.7723 \cdot \mu + 7.5117 \cdot \delta_{min} + 0.0165 \cdot A_{was}$
The values reported in the table represent the increments for each conformer to a regression coefficient k_1.

From this modelling data we can conclude that with the exception of the "All syn" conformations, the $\mathbf{1}_3$ conformers have similar energies of formation and therefore can all be formed in the thermodynamically controlled DCC conditions. The molecular descriptors (E_{hydr}, V, μ, A_{WAS}) and the R_t, calculated using the unmodified equation from ref. 5, support the initial premise of existence of trimer conformations with different HPLC retention times.

[5] T. Baczek and R. Kaliszan, *J. Chromatogr. A,* 2003, **987**, 29.