

Supporting Information for:

A poly(pyridine-pyrrole) foldamer that binds isolated water molecules

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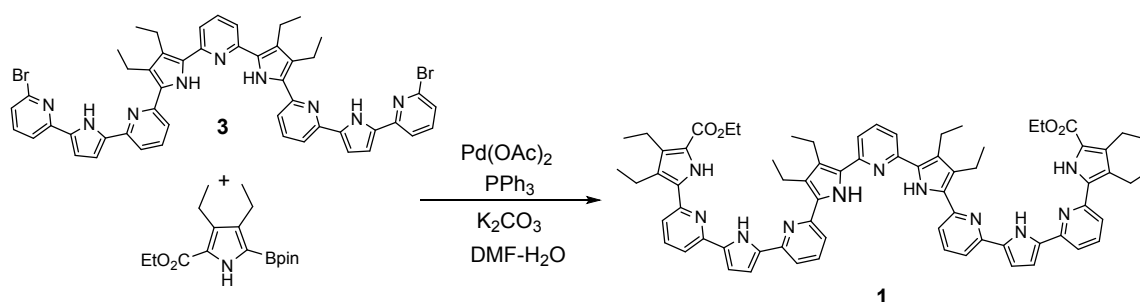
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I. Synthetic Experimental

General

All reagents and solvents were purchased from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was performed using commercial pre-coated silica gel plates containing a fluorescent indicator. Column chromatography was run using silica gel (0.040-0.063 mm). Mass spectra (MS) were taken using Bruker matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Autoflex speed). ¹H NMR, ¹³C NMR spectra were recorded on Bruker AV400 instruments. X-ray diffraction experiments were carried out on a Bruker D8 instrument. Further details of the structures and their refinement are given in a later section.



Scheme S1. Synthesis of foldamer **1**.

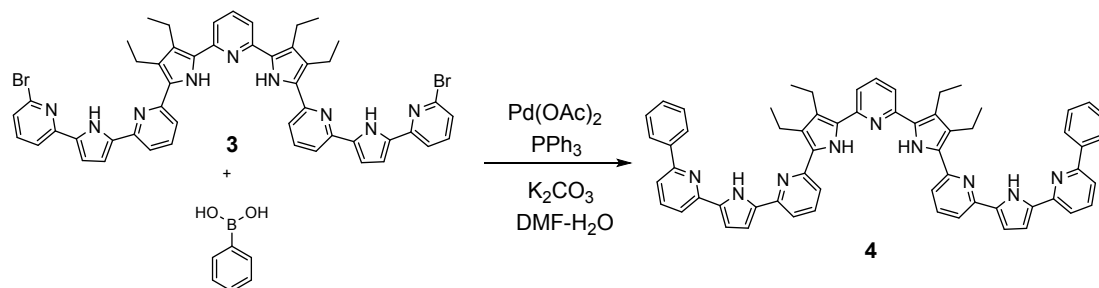
Compound **1** :

A mixture of **3**^{1,2} (92 mg, 0.1mmol), Pd(OAc)₂ (5 mg; 0.02mmol), PPh₃ (21 mg; 0.08mmol) and K₂CO₃ (69 mg; 0.5 mmol) was suspended in 10 mL DMF and 2 mL water under N₂. Pyrrolyl boron ester (77 mg; 0.24mmol) in DMF 2 mL was added at 70 °C via a syringe pump over the course of 0.5 h. The reaction was then allowed to proceed at the same temperature for another 5h. After the reaction mixture was cooled to rt, the organic layer was extracted with dichloromethane and washed with water three times. After removal of the solvent and other volatiles, the reaction mixture was purified by column chromatography over silica gel (hexanes/CH₂Cl₂, 3/1). **1** was obtained in the form of a bright yellow solid. Yield: 64%. HRMS (MALDI-TOF, [M]⁺) Calculated for C₇₁H₇₆N₁₁O₄: 1146.600. Found: 1146.608.

¹H NMR (400 MHz, CD₂Cl₂) δ = 10.61 (s, 2H, pyrrole NH), 10.33 (s, 2H, pyrrole NH), 9.60 (s, 2H, pyrrole NH), 7.59-7.55 (t, 1H, *J* = 8 Hz, pyridine H), 7.49-7.45 (t, 2H, *J* = 8 Hz, pyridine H), 7.28-7.24 (t, 2H, *J* = 8 Hz, pyridine H), 7.17-7.14 (t, 4H, *J* = 5 Hz, pyridine H), 7.07-7.01 (m, 4H,

pyridine H), 6.74-6.72 (d, 2H, $J = 8\text{Hz}$, pyridine H), 6.49-6.45 (m, 4H, pyrrole H), 3.76-3.71 (q, 4H, $J = 8\text{ Hz}$, CH₂), 2.68-2.53 (m, 16H, CH₂), 1.20-1.11 (m, 18H, CH₃), 1.06-1.03(t, 6H, $J = 8\text{ Hz}$, CH₃), 0.95-0.92(t, 6H, $J = 8\text{ Hz}$, CH₃).

¹³C NMR (100 MHz, CD₂Cl₂) $\delta = 161.0, 149.8, 149.7, 149.6, 149.1, 136.8, 136.7, 133.4, 132.8, 127.4, 126.3, 126.2, 118.7, 116.6, 116.4, 115.7, 115.7, 60.0, 18.8, 18.7, 18.5, 18.4, 16.2, 16.1, 15.8, 15.8, 14.1$.



Scheme S2. Synthesis of foldamer **4**.

Compound **4**

A mixture of **3** (92 mg, 0.1mmol), Pd(OAc)₂ (5 mg; 0.02 mmol), PPh₃ (21 mg; 0.08 mmol) and K₂CO₃ (69 mg; 0.5 mmol) was suspended in 10 mL DMF and 2 mL water under N₂. Phenylboronic acid (30 mg; 0.24mmol) in DMF 2 mL was added at 70 °C via a syringe pump over the course of 0.5 h. The reaction was then allowed to proceed at the same temperature for another 5h. After the reaction mixture was cooled to rt, the organic layer was extracted with dichloromethane and washed with water three times. After removal of the solvent and other volatiles, the reaction mixture was purified by column chromatography over silica gel (hexanes/CH₂Cl₂, 5/1). **4** was harvested in the form of a bright yellow solid. Yield: 57%. HRMS (MALDI-TOF, [M]⁺) Calculated for C₆₁H₅₄N₉: 912.442. Found: 912.447.

¹H NMR (400 MHz, CD₂Cl₂) $\delta = 10.48$ (s, 2H, pyrrole NH), 10.35 (s, 2H, pyrrole NH), 7.78-7.73 (m, 5H), 7.52-7.50 (t, 2H, $J = 4\text{ Hz}$), 7.42-7.40 (d, 2H, $J = 8\text{ Hz}$), 7.30-7.26 (m, 4H), 7.18-7.12 (m, 4H), 7.08(t, 2H, $J = 8\text{ Hz}$), 6.92-6.88 (t, 4H, $J = 8\text{ Hz}$), 6.75-6.73 (d, 2H, $J = 8\text{ Hz}$), 6.55-6.54 (m, 4H), 2.56-2.49 (m, 8H, CH₂), 1.17-1.13 (t, 6H, $J = 8\text{ Hz}$, CH₃), 1.07-1.03 (t, 6H, $J = 4\text{ Hz}$, CH₃).

¹³C NMR (100 MHz, CDCl₃) $\delta = 155.5, 150.4, 149.5, 149.2, 133.4, 133.1, 128.3, 128.1, 127.6, 126.6, 126.3, 126.0, 117.4, 117.3, 117.0, 116.4, 115.2, 110.1, 109.9, 17.8, 15.8, 15.7$.

II. NMR Spectral Studies

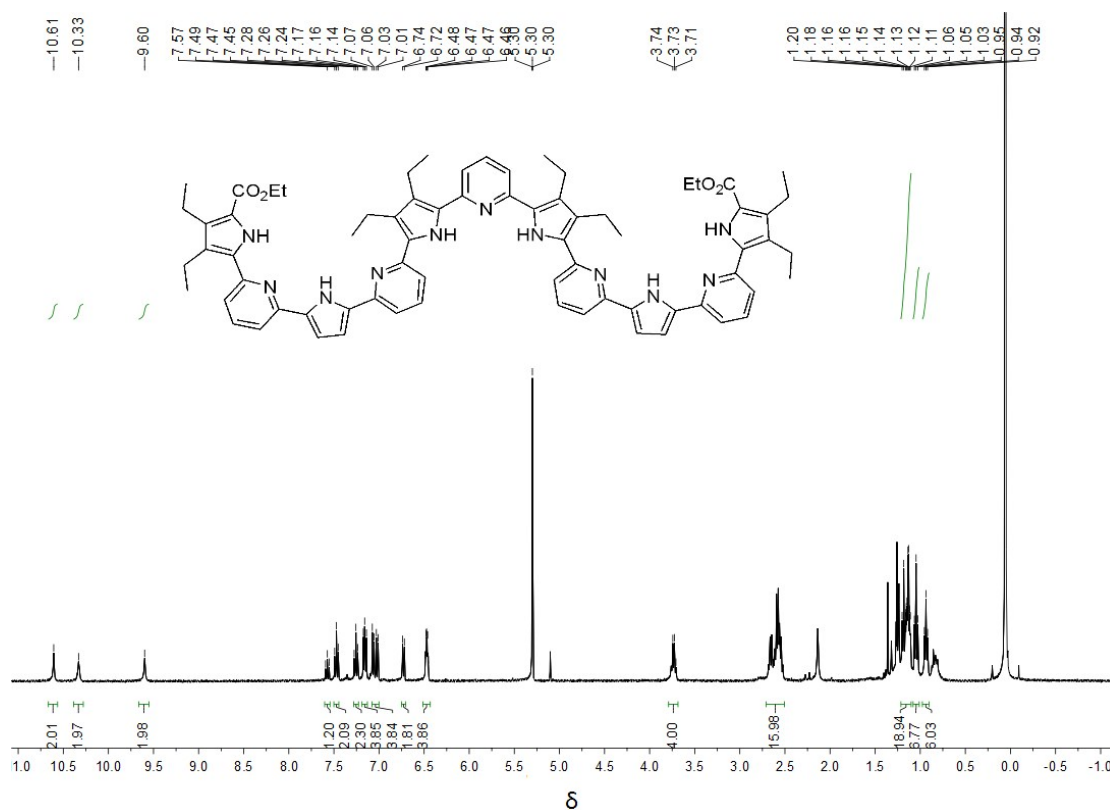


Figure S1. ^1H NMR spectrum of **1** recorded in CD_2Cl_2 at rt.

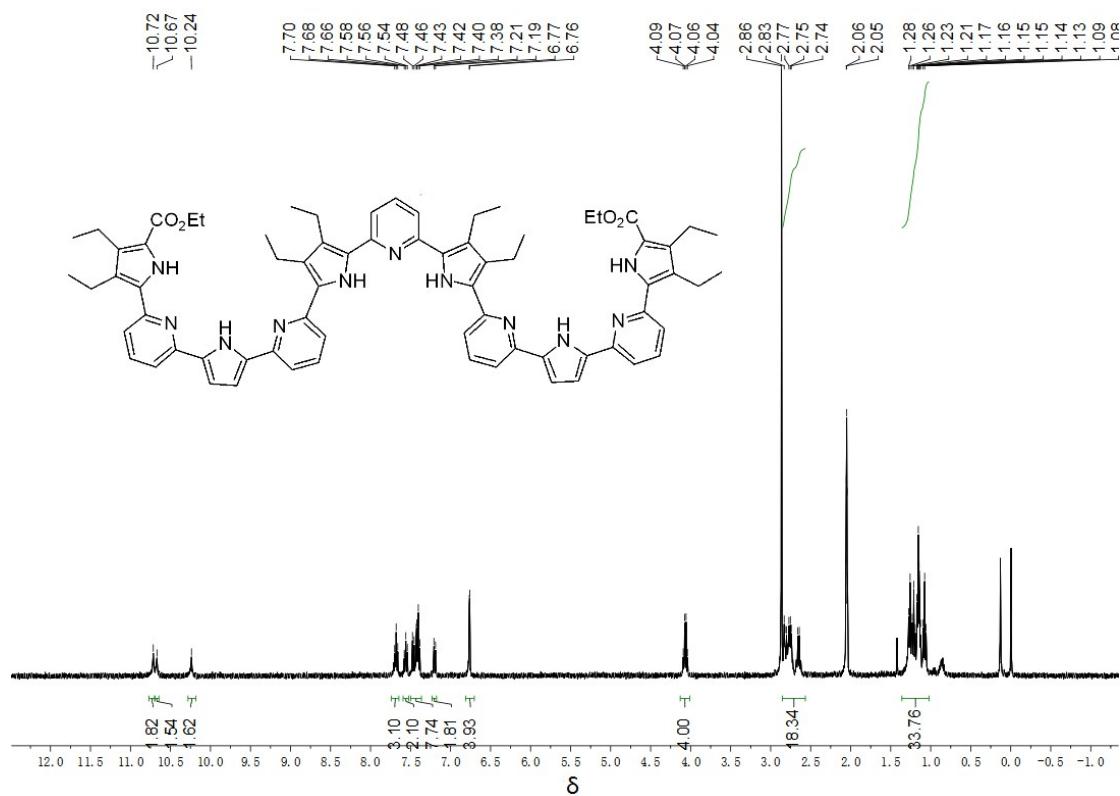


Figure S2. ^1H NMR spectrum of **1** recorded in $\text{acetone-}d_6$ at rt.

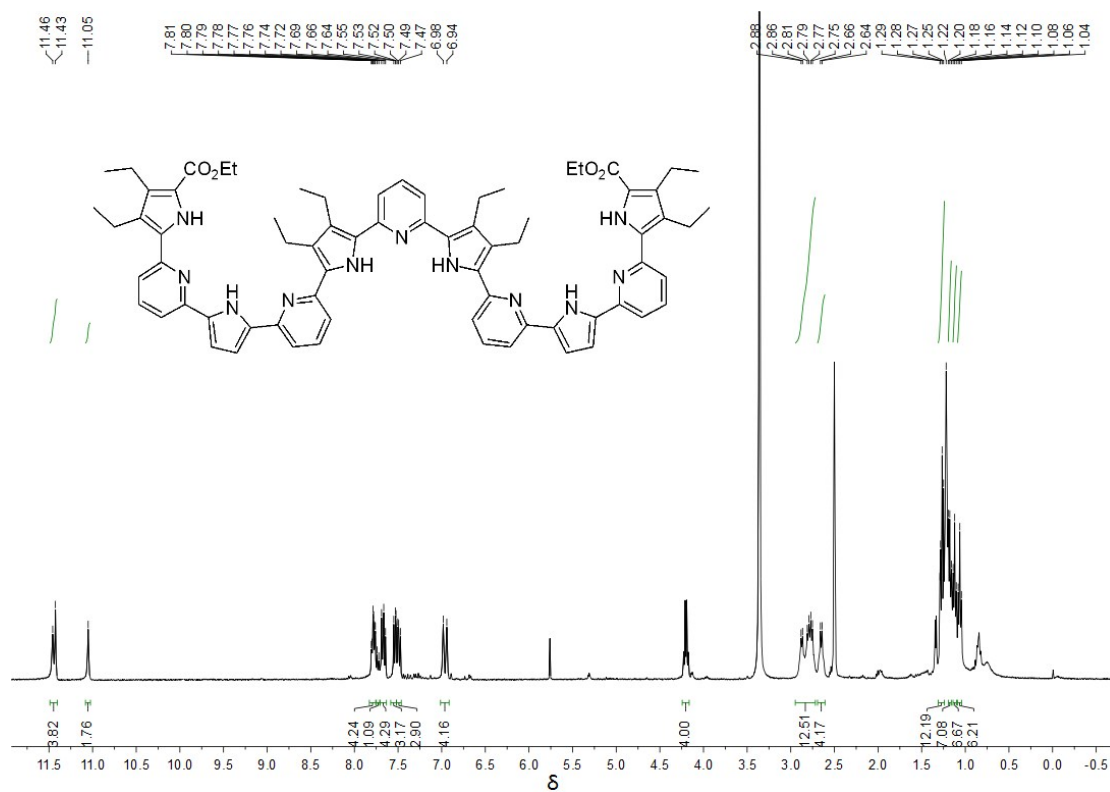


Figure S3. ¹H NMR spectrum of **1** recorded in DMSO-*d*₆ at rt.

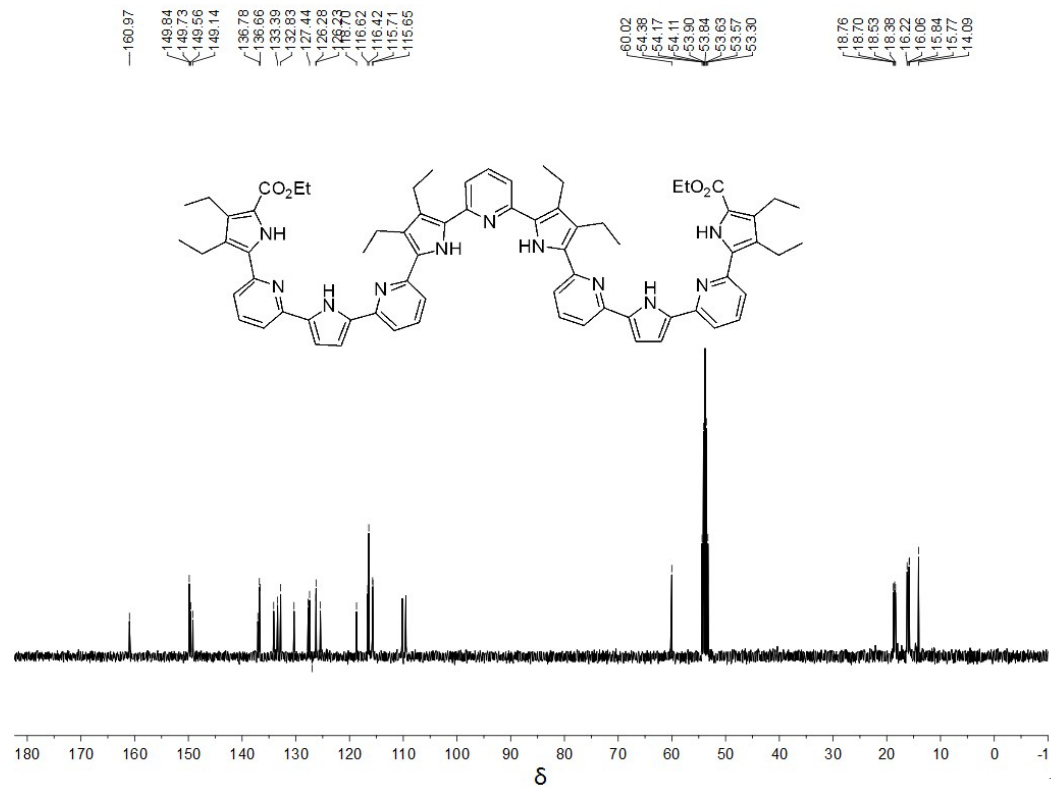


Figure S4. ¹³C NMR spectrum of **1** recorded in CD₂Cl₂ at rt.

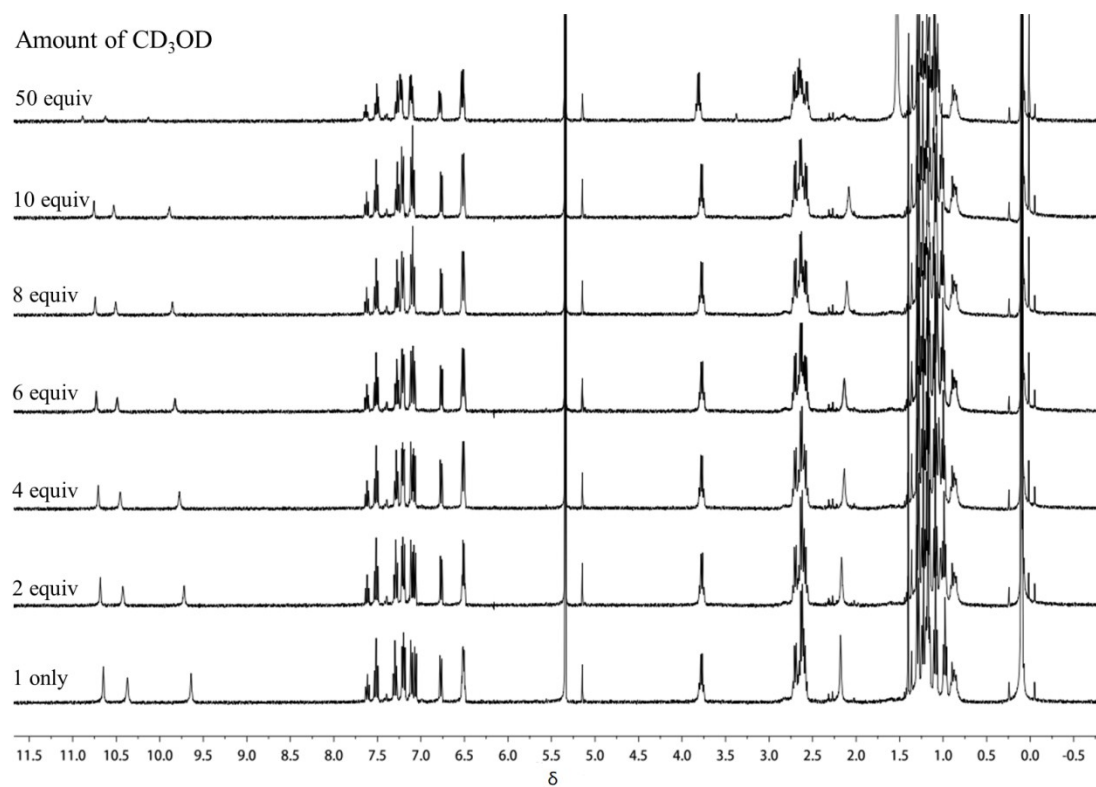


Figure S5. ¹H NMR spectra of **1** recorded upon the incremental addition of CD₃OD in CD₂Cl₂ at rt.

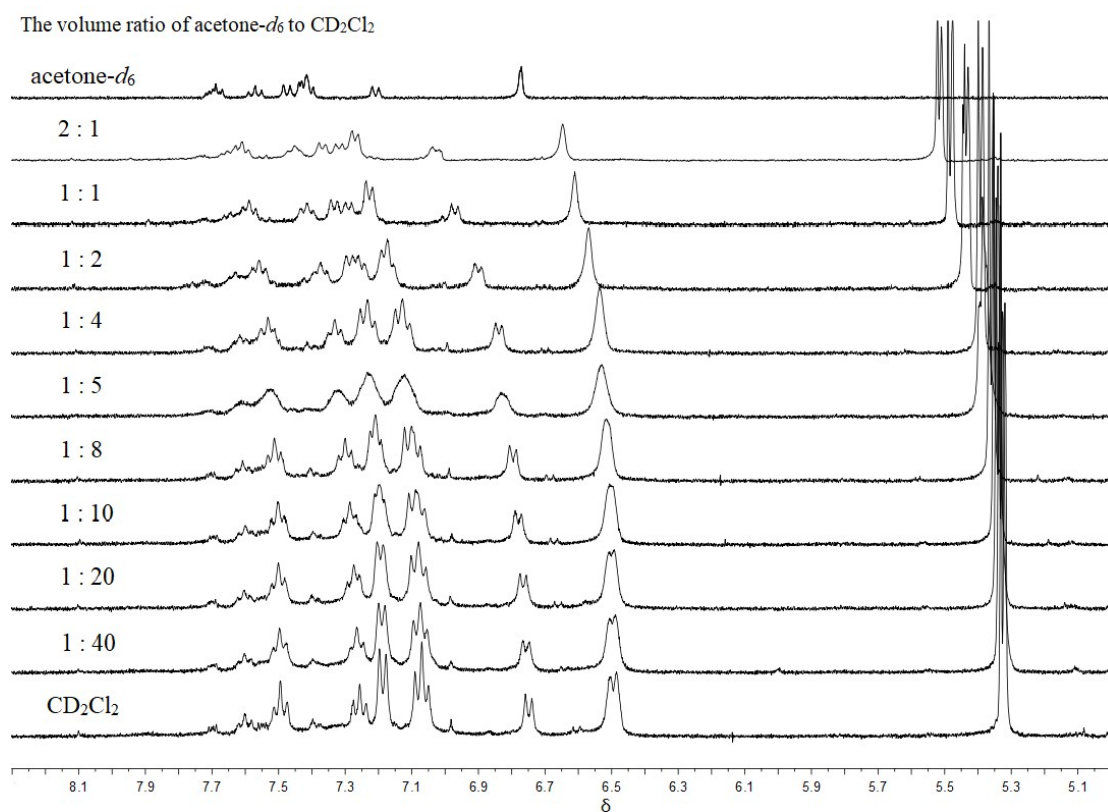


Figure S6. ¹H NMR spectra of **1** recorded upon the incremental addition of acetone-*d*₆ in CD₂Cl₂

at rt.

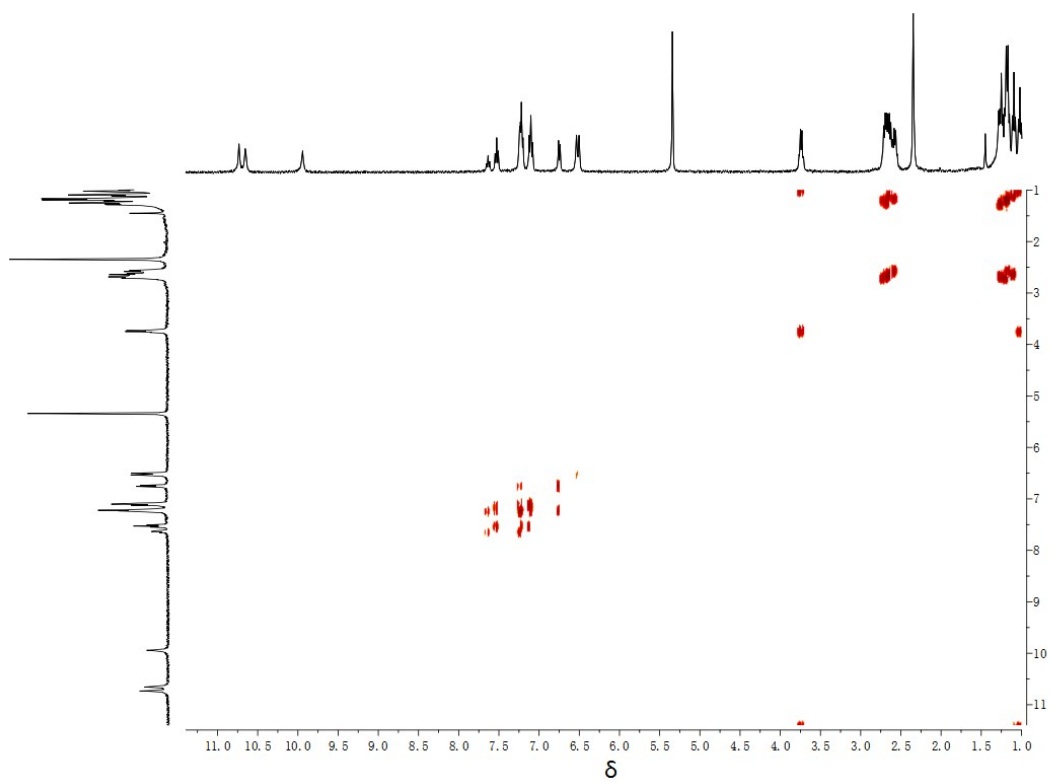


Figure S7. H-H COSY spectrum of **1** recorded in CD₂Cl₂ at rt.

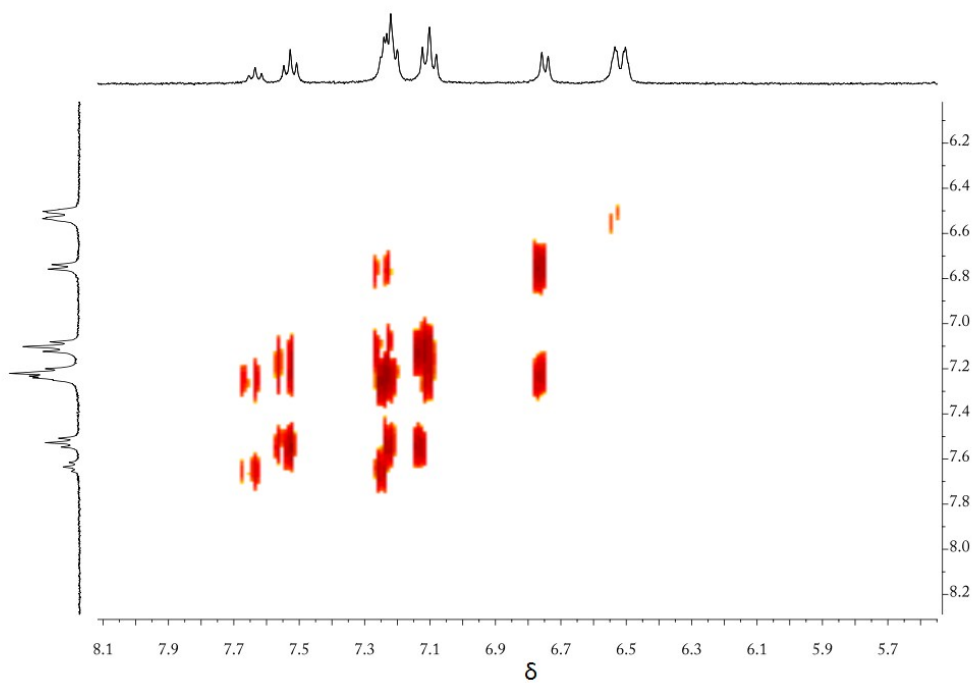


Figure S8. Partial H-H COSY spectrum of **1** recorded in CD₂Cl₂ at rt.

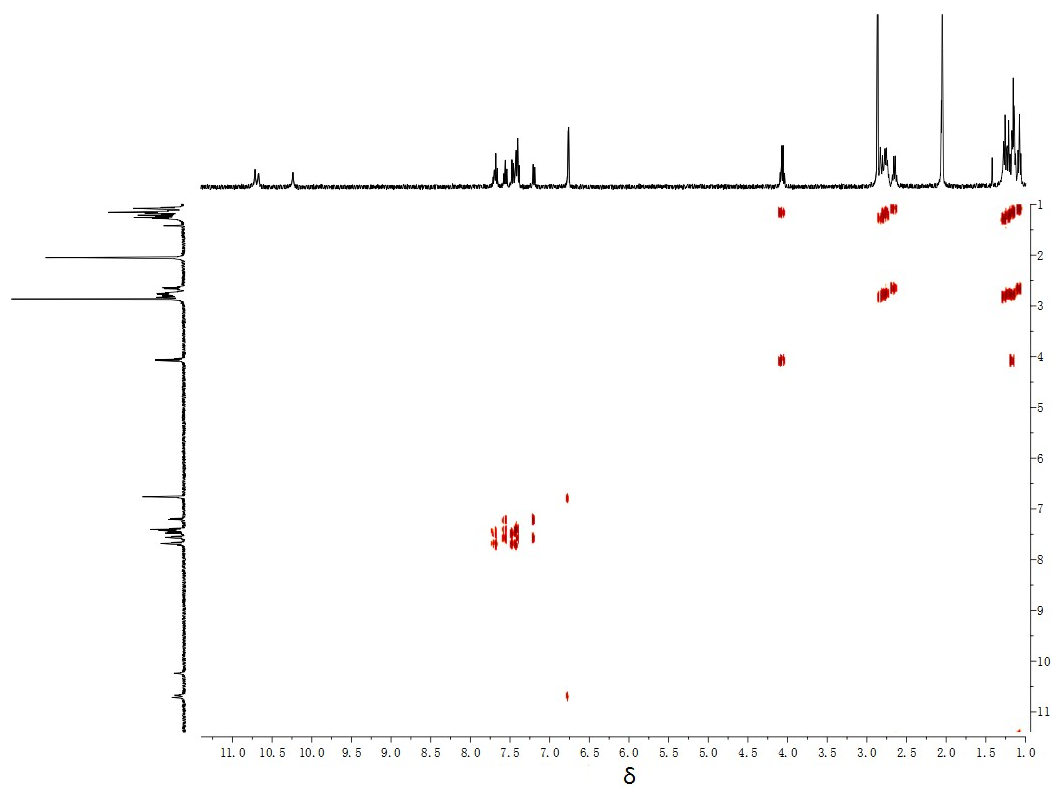


Figure S9. H-H COSY spectrum of **1** recorded in acetone-*d*₆ at rt.

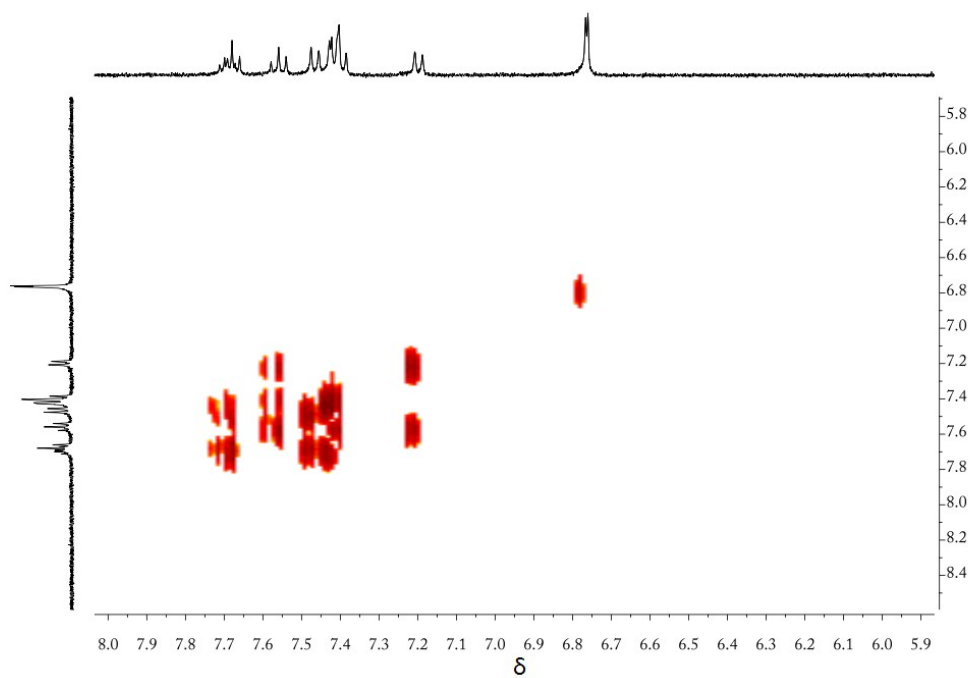


Figure S10. Partial H-H COSY spectrum of **1** recorded in acetone-*d*₆ at rt.

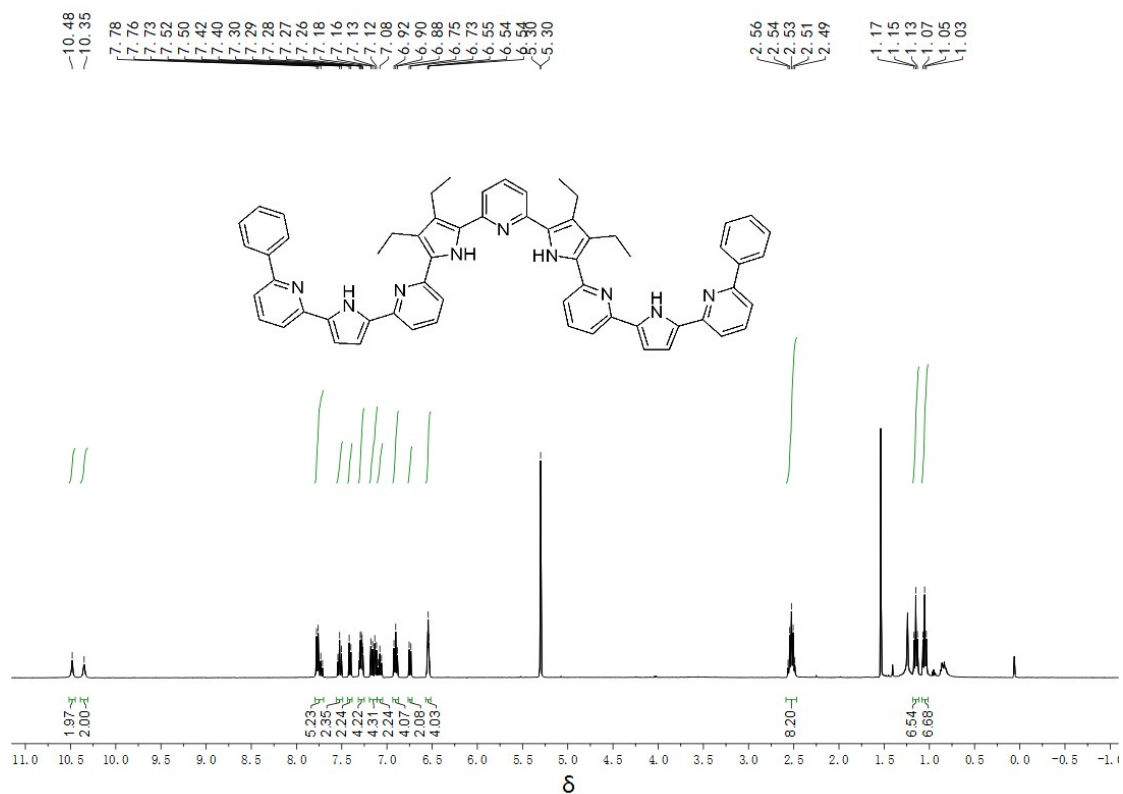


Figure S11. ¹H NMR spectrum of **4** recorded in CD₂Cl₂ at rt.

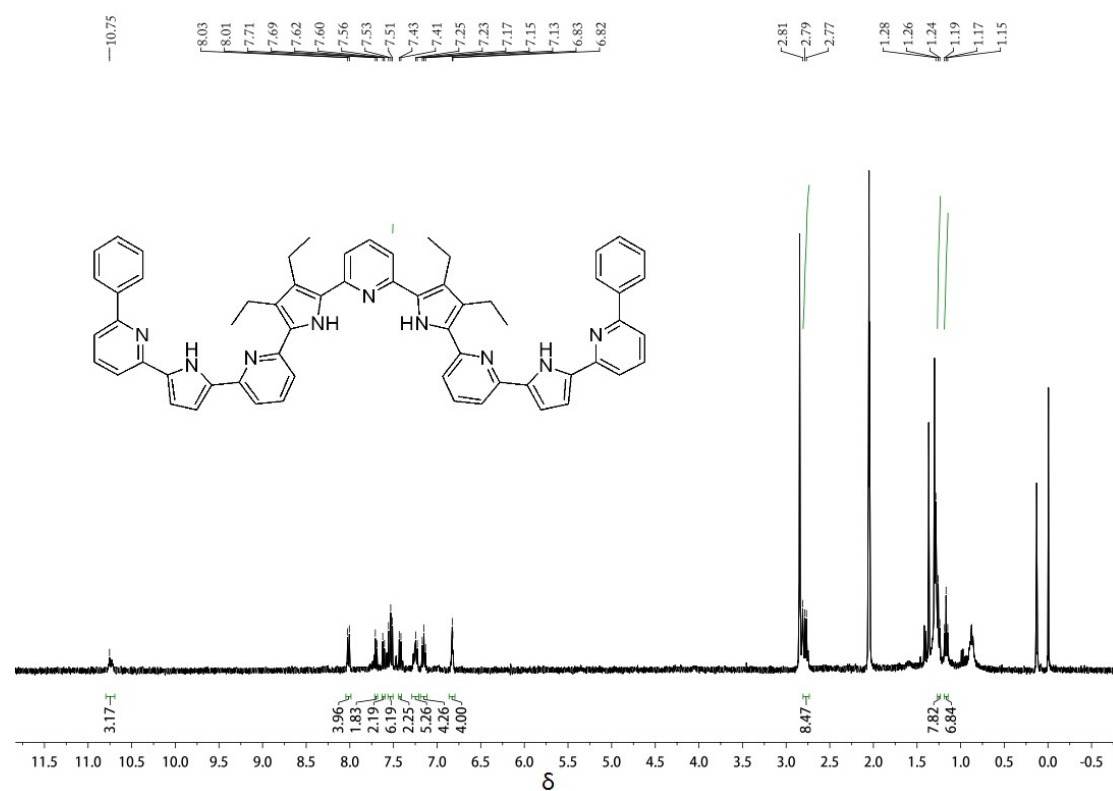


Figure S12. ¹H NMR spectrum of **4** recorded in acetone-*d*₆ at rt.

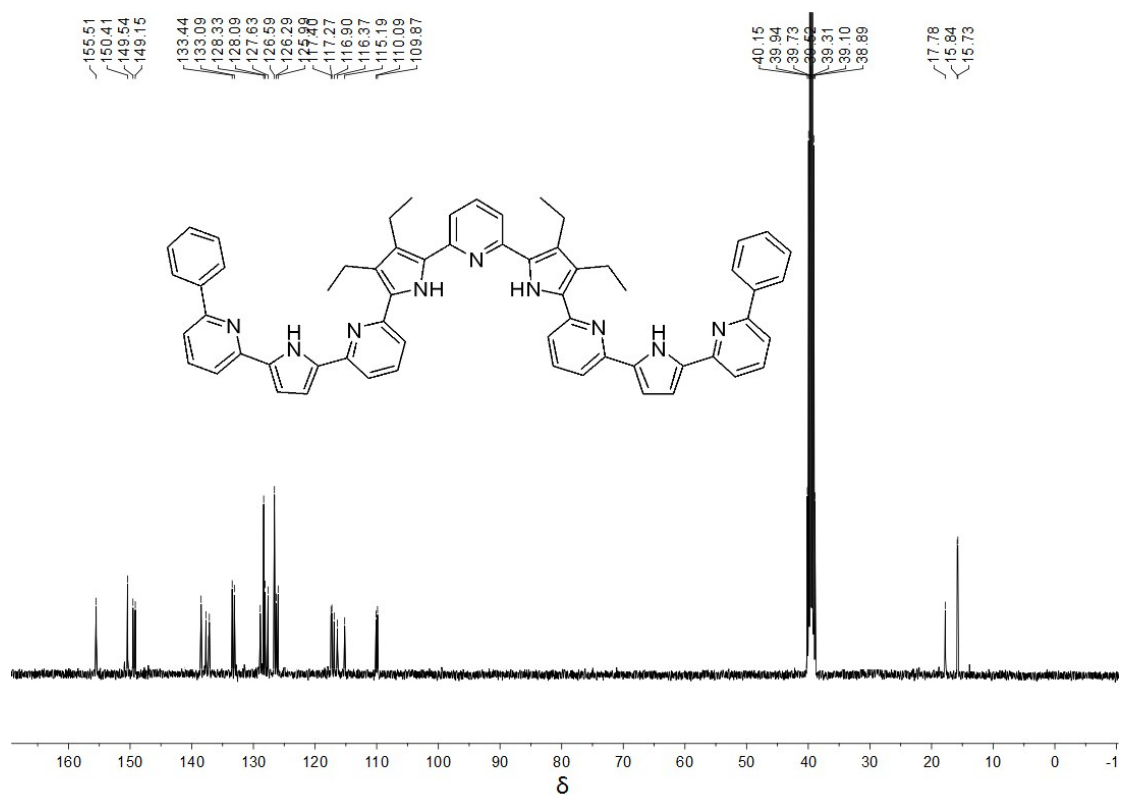


Figure S13. ^{13}C NMR spectrum of **4** recorded in $\text{DMSO-}d_6$ at rt.

III. X-ray Experimental

Single-crystal X-ray diffraction data were collected on a Bruker-D8 X-ray diffractometer equipped with a low temperature device and a fine-focus sealed-tube X-ray source (graphite monochromated Cu-K α radiation, $\lambda = 1.54184 \text{ \AA}$). Suitable single crystals were mounted in oil on glass fibers and placed in the nitrogen cold stream for data collections.

Compound 1:

Single crystals suitable for X-ray diffraction analysis were grown by vapor diffusion of hexanes to a DCM solution of compound **1**. The solvents used were not further purified or dried before use. A light yellow BLOCK-like specimen of C₁₄₆H₁₆₆Cl₄N₂₂O₁₂, approximate dimensions 0.230 mm x 0.155 mm x 0.147 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The total exposure time was 25.99 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm.³ The integration of the data using a triclinic unit cell yielded a total of 153259 reflections to a maximum θ angle of 79.42° (0.78 Å resolution), of which 24496 were independent (average redundancy 6.256, completeness = 99.9%, $R_{\text{int}} = 5.96\%$, $R_{\text{sig}} = 3.77\%$) and 19650 (80.22%) were greater than $2\sigma(F^2)$. The final cell constants of $a = 15.372(3) \text{ \AA}$, $b = 21.287(4) \text{ \AA}$, $c = 21.861(4) \text{ \AA}$, $\alpha = 96.32(3)^\circ$, $\beta = 103.33(3)^\circ$, $\gamma = 95.65(3)^\circ$, volume = 6861(3) Å³, are based upon the refinement of the XYZ-centroids of 9806 reflections above $20 \sigma(I)$ with $5.522^\circ < 2\theta < 134.16^\circ$. Data were corrected for absorption effects using the Multi-Scan method (SADABS).³ The ratio of minimum to maximum apparent transmission was 0.905. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.749 and 0.828.

The structure was solved and refined using the Bruker SHELXTL Software Package,⁴ using the space group $P\bar{1}$, with $Z = 2$ for the formula unit, C₁₄₆H₁₆₆Cl₄N₂₂O₁₂. The final anisotropic full-matrix least-squares refinement on F^2 with 1964 variables converged at $R1 = 8.36\%$, for the observed data and $wR2 = 21.10\%$ for all data. The goodness-of-fit was 1.089. The largest peak in the final difference electron density synthesis was 1.707 e/Å³ and the largest hole was -0.872 e/Å³ with an RMS deviation of 0.069 e/Å³. On the basis of the final model, the calculated density was 1.240 g/cm³ and $F(000)$, 2720 e⁻.

Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms

on carbon and nitrogen were calculated in ideal positions with isotropic displacement parameters set to $1.2 \times U_{eq}$ of the attached atom ($1.5 \times U_{eq}$ for methyl hydrogen atoms). Hydrogen atoms on water were found from the electron density map, and the model of water was restrained by DFIX command.

The unit cell contains a large region of highly disordered solvent molecules, which could not be modeled as satisfactory discrete atomic sites, and therefore PLATON/SQUEEZE⁵ was employed to remove these electron densities.

The SQUEEZE results are given as follows:

loop_

```

_platon_squeeze_void_nr
_platon_squeeze_void_average_x
_platon_squeeze_void_average_y
_platon_squeeze_void_average_z
_platon_squeeze_void_volume
_platon_squeeze_void_count_electrons
_platon_squeeze_void_content
  1 -0.020  0.031  0.247      30      0 ''
  2 -0.029  0.437  0.795      34      2 ''
  3  0.000  0.500  0.500     172     51 ''
  4  0.028  0.563  0.205      34      2 ''
  5  0.020  0.968  0.753      30      0 ''
_platon_squeeze_void_probe_radius          1.20
_platon_squeeze_details                    ?

```

55 electrons / unit cell were removed by SQUEEZE. Since $Z = 2$, each asymmetric unit contains 27.5 electrons in the region of highly disordered solvent. These electron densities were tentatively modeled as $0.5C_2H_4Cl_2$ (50 e-) per asymmetric unit.

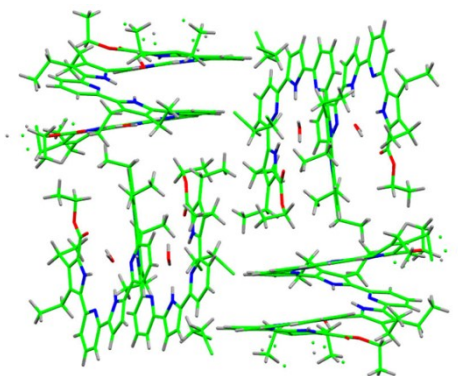


Figure S14. Single crystal structure of foldamer **1**.

Table S1. Crystal data for 1.

Empirical Formula		$C_{146}H_{166}Cl_4N_{22}O_{12}$
Formula Weight		2562.80
Temperature		150K
Crystal Color, Habit		light yellow block
Crystal Dimensions		0.147 X 0.155 X 0.230 mm
Crystal System		Triclinic
Space Group		<i>P</i> -1
	<i>a</i> /Å	15.372(3)
	<i>b</i> /Å	21.287(4)
	<i>c</i> /Å	21.861(4)
Lattice Parameters	<i>α</i> /deg	96.32(3)
	<i>β</i> /deg	103.33(3)
	<i>γ</i> /deg	95.65(3)
	<i>V</i> /Å ³	6861(3)
Z Value		2
<i>F</i> ₀₀₀		2720.0
No. of Reflections Measure	Total:	153259
	Unique:	24496 (<i>R</i> _{int} = 0.0596)
<i>R</i> 1; <i>wR</i> 2 (refined on <i>F</i> ² , all data)		0.0980; 0.2249
Goodness of Fit Indicator (GOF)		1.008
<i>R</i> 1; <i>wR</i> 2 (refined on <i>F</i> , <i>I</i> > 2σ(<i>I</i>))		0.0836; 0.2110

Compound 4:

Single crystals suitable for X-ray diffraction analysis were grown by vapor diffusion of hexanes to a DCM solution of compound **4**. A light gold Prism-like specimen of $C_{62}H_{55}ClN_9$, approximate dimensions 0.132 mm x 0.195 mm x 0.203 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The total exposure time was 10.81 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm.³ The integration of the data using a monoclinic unit cell yielded a total of 109737 reflections to a maximum θ angle of 79.45° (0.78 \AA resolution), of which 10816 were independent (average redundancy 10.146, completeness = 99.5%, $R_{\text{int}} = 6.15\%$, $R_{\text{sig}} = 3.33\%$) and 9358 (86.52%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a} = 20.4193(10) \text{ \AA}$, $\underline{b} = 9.8047(5) \text{ \AA}$, $\underline{c} = 26.0036(12) \text{ \AA}$, $\beta = 105.963(2)^\circ$, volume = $5005.3(4) \text{ \AA}^3$, are based upon the refinement of the XYZ-centroids of 9867 reflections above $20 \sigma(I)$ with $4.501^\circ < 2\theta < 158.4^\circ$. Data were corrected for absorption effects using the Multi-Scan method (SADABS).³ The ratio of minimum to maximum apparent transmission was 0.851. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8120 and 0.8720.

The structure was solved and refined using the Bruker SHELXTL Software Package,⁴ using the space group $P2_1/c$, with $Z = 4$ for the formula unit, $C_{62}H_{55}ClN_9$. The final anisotropic full-matrix least-squares refinement on F^2 with 669 variables converged at $R1 = 4.17\%$, for the observed data and $wR2 = 10.84\%$ for all data. The goodness-of-fit was 1.023. The largest peak in the final difference electron density synthesis was $0.225 \text{ e}/\text{\AA}^3$ and the largest hole was $-0.508 \text{ e}/\text{\AA}^3$ with an RMS deviation of $0.047 \text{ e}/\text{\AA}^3$. On the basis of the final model, the calculated density was $1.276 \text{ g}/\text{cm}^3$ and $F(000)$, 2028 e⁻.

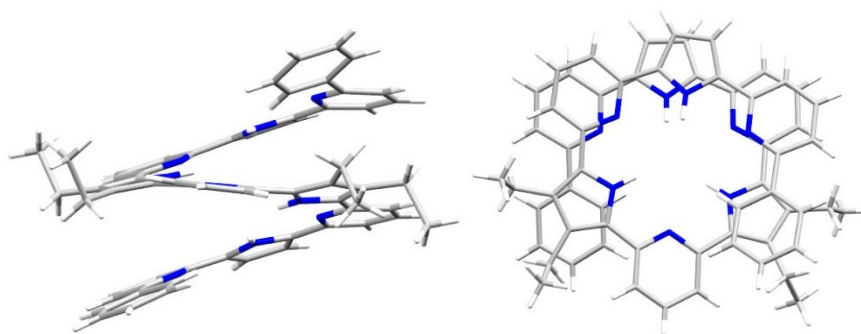


Figure S15. Views of the single crystal structure of foldamer **4**.

Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms on carbon and nitrogen were calculated in ideal positions with isotropic displacement parameters set to $1.2 \times U_{\text{eq}}$ of the attached atom ($1.5 \times U_{\text{eq}}$ for methyl hydrogen atoms).

Table S2. Crystal data for 4.

Empirical Formula		$\text{C}_{62}\text{H}_{55}\text{ClN}_9$
Formula Weight		961.60
Temperature		100K
Crystal Color, Habit		light gold Prism
Crystal Dimensions		0.132 X 0.195 X 0.203 mm
Crystal System		monoclinic
Space Group		$P 1 21/c 1$
	$a/\text{\AA}$	20.4193(10)
	$b/\text{\AA}$	9.8047(5)
	$c/\text{\AA}$	26.0036(12)
Lattice Parameters	α/deg	90
	β/deg	105.963(2)
	γ/deg	90
	$V/\text{\AA}^3$	5005.3(4)
Z Value		4
F_{000}		2028
No. of Reflections Measure	Total:	109737
	Unique:	10816 ($R_{\text{int}} = 0.0615$)
$R1; wR2$ (refined on F^2 , all data)		0.0499; 0.1003
Goodness of Fit Indicator (GOF)		1.023
$R1; wR2$ (refined on $F, I > 2\sigma(I)$)		0.0417; 0.1003

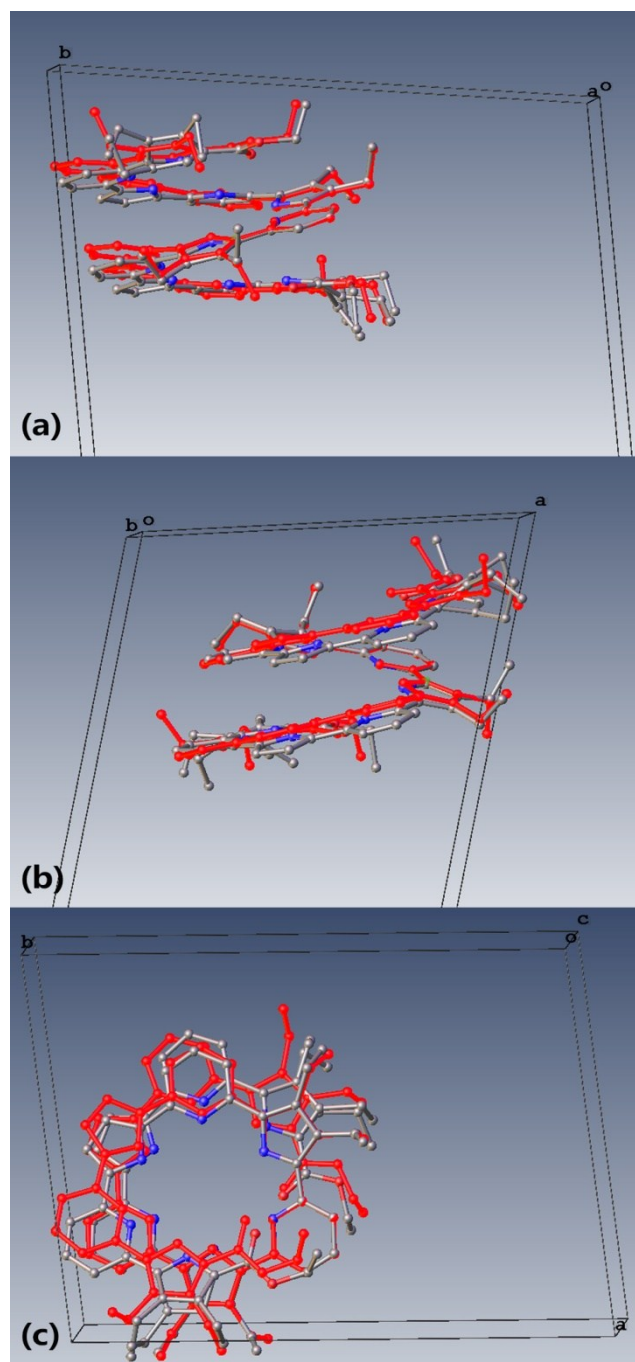


Figure S16. Overlay images of the two conformers of foldamer 1. Red: conformer A; silver: conformer B. Note: the middle pyridine rings (F rings) of conformers A and B were exactly superposed.

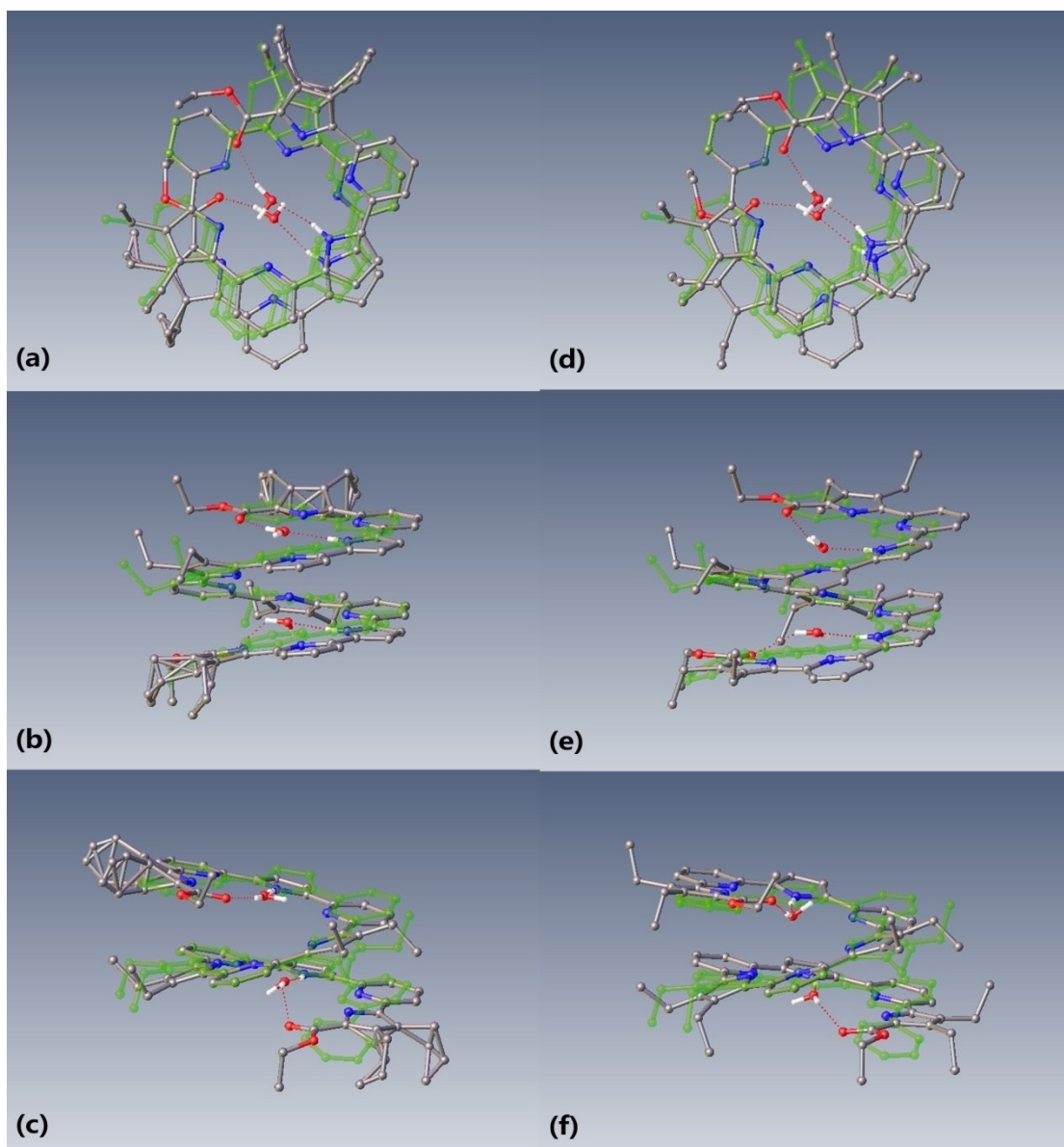


Figure S17. Overlay images of foldamers **1** (green) and **4** (silver). a)-c): foldamer **4** and conformer B; d)-f): foldamer **4** and conformer A. Note: the middle pyridine rings (F rings) on foldamers **1** and **4** were exactly superposed.

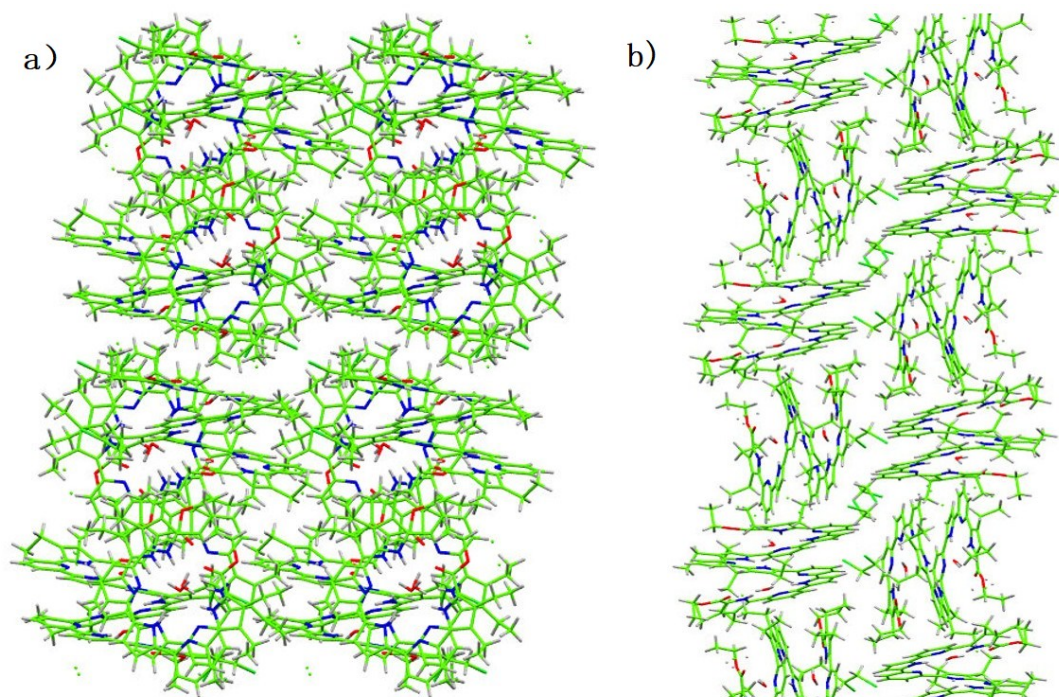


Figure S18. Crystal packing of foldamer 1. Note: solvent molecules were removed for clarity.

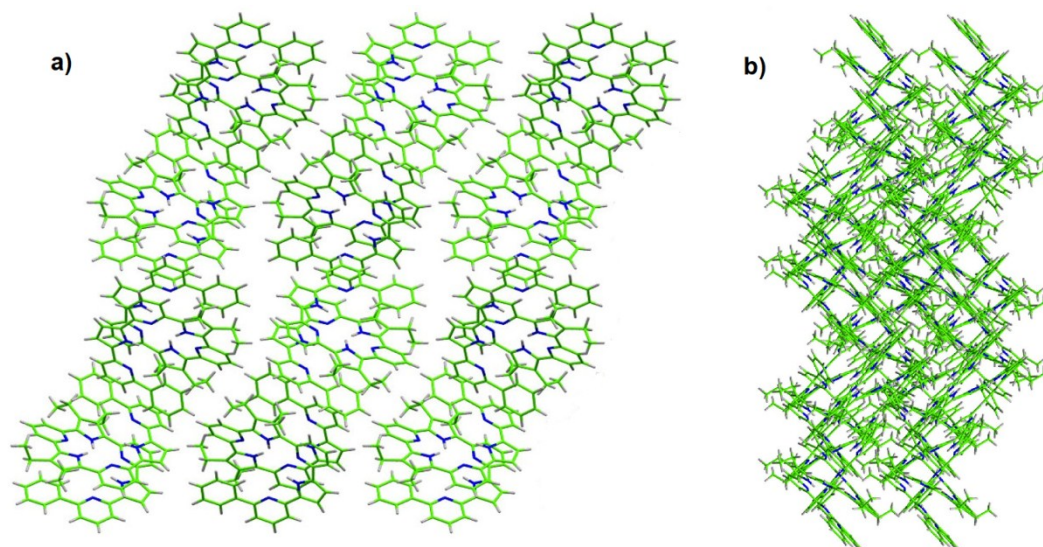


Figure S19. Crystal packing of foldamer 4. Note: solvent molecules were removed for clarity.

IV. Mass Spectrum

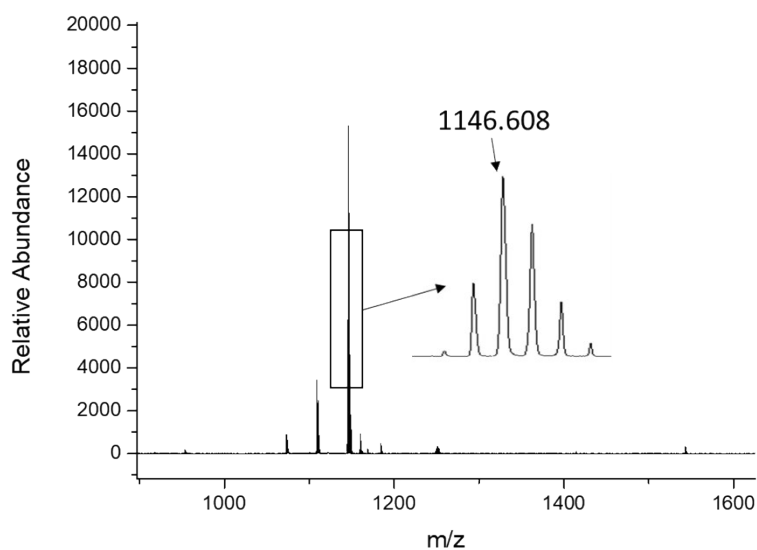


Figure S20. High resolution MALDI-TOF spectrum of foldamer 1.

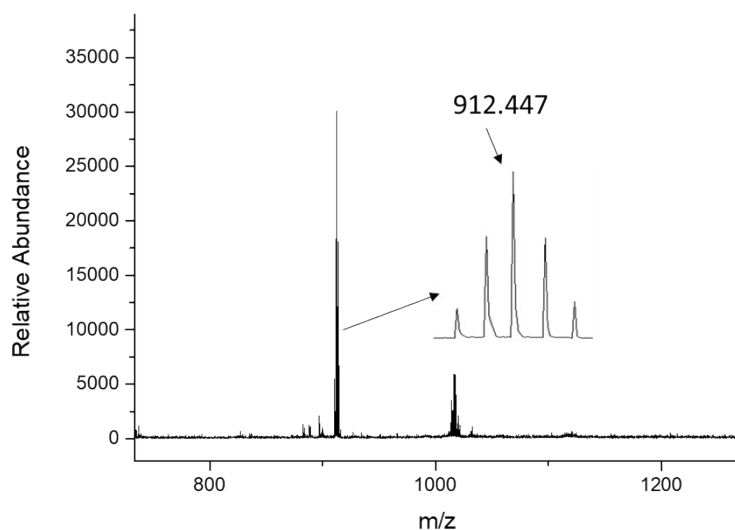


Figure S21. High resolution MALDI-TOF spectrum of foldamer 4.

V. References

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