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Paper

Readily Functionalized AAA-DDD Triply Hydrogen-Bonded Motifs

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Herein we present a new readily functionalized AAA-DDD hydrogen bond array. The novel AAA monomeric unit (**3a-b**) was obtained from a two-step synthetic procedure starting with 2-aminonicotinaldehyde and via microwave radiation (overall yield of 52-66%). ^{1}H NMR and fluorescence spectroscopy confirmed the complexation event with a calculated association constant of 1.57 x 10^{7} M^{-1}. Likewise, the usefulness of this triple hydrogen bond motif into supramolecular polymerization was demonstrated through viscosity measurements in a crosslinked supramolecular alternating copolymer.

Introduction

Supramolecular polymerization represents a significant evolution in polymer science. Characterized by being a dynamic equilibrium, it allows to reversibly tune polymer's viscosity, aggregation, and morphology through the influence of external stimuli without compromising the chemical integrity of their components.[1] In this sense, there are good examples of this materials with a desired and controlled response towards temperature change,[2] pH,[3] competitive binders,[4] and light.[5] One of the best applications known is the creation of self-healing rubber.[6] Additionally, supramolecular polymer's synthesis is as complicated as the synthesis of their monomers; since the polymeric network is a result of the intermolecular interactions between these units. In other words, the polymerization step does not require any synthetic procedure such as cation/anion living polymerization, metal/radical catalysis, or polycondensation, as covalent polymers do.[1, 7]

From all intermolecular interactions employed in supramolecular polymerization, hydrogen bonds stand out due to their high directionality, and the strong binding achieved when several are used within an array.[7, 8] Self-complementary hydrogen-bonded arrays have gained high notoriety since their synthesis seem straightforward.[9] However, this approach may have two inconveniences: 1) intramolecular interactions that restrict polymer chain growth;[10] and, 2) to be limited to homopolymers.[11] Instead, the high fidelity in complementary hydrogen-bonded arrays has favoured the creation of alternating polymers and polymeric blends.[12] Likewise, complementary complexes with all hydrogen-bonded acceptor (A) and donor (D) sites arranged in an AAA-DDD way, exhibit high association constants.[13-16, 18]

In this sense, both Zimmerman and Leigh groups have developed notorious attempts to achieve complementary arrays readily accessible for supramolecular polymers. Zimmerman and coworkers reported the synthesis of an AAA monomer starting from (trimethoxy)methylbenzene, and malononitrile in pyridine, followed by an aminolysis, catalytic hydrogenation and a Friedländer reaction with acetophenone.[14] On the other hand, Leigh's AAA system started with 2,6-diamino-3,5-diiodopyridine and 2-formylphenyl boronic acid via double Suzuki coupling-cyclization-aromatization.[15] Later, this group applied Pd cross-coupling of 2-chloro-3-cyano-1,8-naphthyridine and 2-aminopyridine, followed by ring closure to afford another AAA system.[16]

In our previous work it is possible to find both coplanar[17] and helical[18] AAA-DDD arrays; however, these systems required several synthetic steps which defeat their usefulness in the construction of supramolecular polymers. Herein, we present some readily functionalized AAA-DDD triply hydrogen-bonded motifs, which can also be employed for the construction of supramolecular polymers.

Results and Discussion

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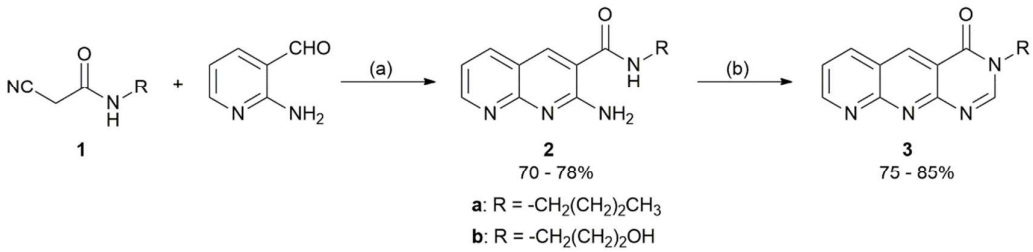

Scheme 1. Synthesis of AAA monomers. (a) EtOH, NaOH (cat), 80 °C for 1.5 h, CH_2Cl_2; (b) *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA), 100 °C for 2 h, EtOH.

The synthesis of the novel AAA systems presented in this work is a two-step procedure starting with the synthesis of 2-cyanoacetamide (**1**) from ethyl cyanoacetate (95-99%). The mixture of **1** and 2-amino-3-pyridinecarboxaldehyde under basic catalysis (10% NaOH) at 80 °C afforded 2-aminonaphthyridine-3-carboxamide (**2**) in good yields (70-83%). Intermediate **2** in 1,1-dimethoxy-N,N-dimehtylmethanamine (DMFDMA) was heated under microwave at 110 °C for 40 minutes at 150 psi to yield our desired AAA system (75-85%), Scheme 1. The DDD system employed (**4**) was prepared as reported by Wang and coworkers[17] from p-methoxybenzaldehyde and ethyl 2-amidinoacetate hydrochloride. The purity of all products was corroborated by ^{1}H NMR Spectroscopy and Liquid Chromatography-Mass Spectrometry.

Single crystal X-ray diffraction confirmed the AAA display in compound **3a**. Such crystal was obtained by slow evaporation from a saturated solution in chloroform. Compound **3a** belongs to the P 2_1/c space group (monoclinic) with four molecules per unit cell. Table S1 show all crystal parameters of this compound crystal structure. As expected, the naphthyridine backbone that holds the three hydrogen bonding acceptor sites can be considered planar since most significant deviation from the least square plane of all heavy atoms is no larger than 0.1 Å, Figure 1. Along the crystal lattice, two types of hydrogen contacts were observed: a bifurcated hydrogen contact between the oxygen atom with two C-H moieties (O1···H10A-C10 = 3.24 Å, ∠O···H-C = 159.9° and O1···H11A-C11 = 3.44 Å, ∠O···H-C = 140.4°); and, two N···H-C contacts between naphthyridine nitrogen atoms with aromatic C-H moieties (N1···H1A-C1 = 3.52 Å, ∠N···H-C = 145.8° and N3···H2A-C2 = 3.45 Å, ∠N···H-C = 139.8°). Likewise, π–π stacking between two symmetry-related molecules aligned in an antiparallel fashion was observed (the distance between least square planes of all heavy atoms is 3.48 Å), Figure S17.

As previously reported, compound **4** (DDD monomer) is present as two tautomeric forms in solution: 1,4-dihydro and 3,4-dihydro with a 52:48 ratio in $CDCl_3$ at 298 K, respectively.[17] This tautomer's distribution changed after the addition of **3a**; wherein the 1,4-dihydro tautomer was favoured up to a ratio greater than 99:1 when more than one equivalent was added, Figure 2. The downfield shifts of the N-H protons in **4** were in agreement with the formation of a hydrogen-bonded AAA-DDD array as designed. These changes were highly noted

Figure 1. Stick representation of the X-ray crystal structure of compound **3a**. Blue, grey, white and red correspond to nitrogen, carbon, hydrogen and oxygen atoms, respectively.

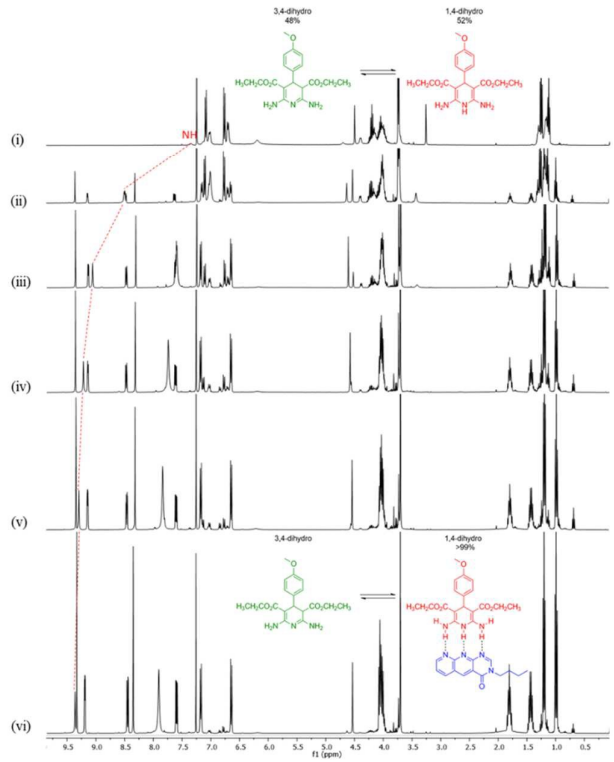

Figure 2. ^{1}H NMR spectra plot of DDD (compound **4**; 1,4-dihydro and 3,4-dihydro tautomers in red and green, respectively) with (i) 0 equivalents, (ii) 0.25 equivalents, (iii) 0.50 equivalents, (iv) 0.75 equivalents, (v) 1.0 equivalents, and (vi) 1.5 equivalents of AAA (compound **3a**).

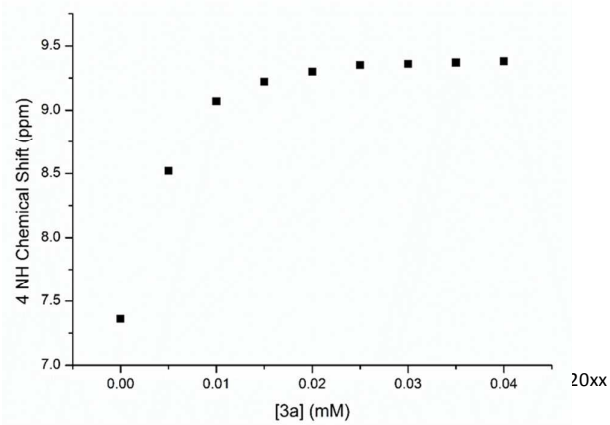

Figure 3. ^{1}H NMR titration isotherm of DDD compound **4** (host, 0.02 mM) and AAA compound **3a** (guest). Black squares correspond to the observed chemical shift at 0, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75 and 2.00 equivalents of AAA in solution.

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before one equivalent of **3a** was added. After one equivalent of **3a**, changes in the chemical shifts were unnoticed. This observation indicated a highly stable complex which complexation constant was unable to be calculated via ^{1}H NMR titration, Figure 3.[20]

Fluorescence titration determined the association constant of the **3a·4** complex. Compound **3a** in solution showed a high-intensity fluorescence at 392 nm that decreased as **4** was added, Figure 4. The 1:1 molar ratio of **3a** and **4** in the complex structure was confirmed through a Job plot; wherein the average molar fraction of the guest (**4**) at the plot's maximum was 0.46 from three titration experiments, Figure S21. Likewise, the data obtained from the fluorescence titrations were submitted to an iterative fitting process with a 1:1 complexation model to calculate the **3a·4** association constant (K_a), as described in the following equation:

$$I = I_0 + \frac{I_{lim} - I_0}{2[\mathbf{3a}]}\left\{[\mathbf{3a}] + [\mathbf{4}] + \frac{1}{K_a} - [([\mathbf{3a}] + [\mathbf{4}] + 1/K_a)^2 - 4[\mathbf{3a}][\mathbf{4}]]^{1/2}\right\}$$

wherein: I_0 and I are the emission intensities of the complex at a selected wavelength in the absence and presence of **4**, respectively; and, I_{lim} is the limiting value of the emission intensity in the presence of an excess of 4.[22] The good correlation between the experimental data and the complexation model (r^2 values of 0.99, 0.99 and 0.99 from three parallel titration experiments) corroborated the expected 1:1 ratio for this complex structure, Figure 5. The association constant value obtained was 1.57 ± 0.48 x 10^7 M^{-1} in chloroform at room temperature; which corresponds to a binding energy (ΔG = 9.79 ± 0.21 kcal·mol^{-1}). According to Schneider and Sartorius' model (wherein the energetic contributions from primary and secondary hydrogen bond interactions are 1.9 and 0.7 kcal·mol^{-1}, respectively),[23] the AAA-DDD array herein presented should have a ΔG of -8.4 kcal·mol^{-1}. In other words, the AAA-DDD array presented was more stable than expected. Hence, there is a high likelihood of supramolecular polymerization using this system.

In order to demonstrate the application of our AAA-DDD in supramolecular polymerization, blocks **5** and **7** were synthesized, Figure 6. Monomer **5** comprised two AAA units at opposite sides linked by a linear aliphatic chain. Such compound was achieved by the condensation of compound **3b** with 1,6-diisocyanatohexane in the presence of dibutyltin dilaurate (DBTDL) as a catalyst, Scheme 2. On the other hand, **7** contained the DDD units, and it was characterized by a trifurcate structure. This monomer was synthesized starting

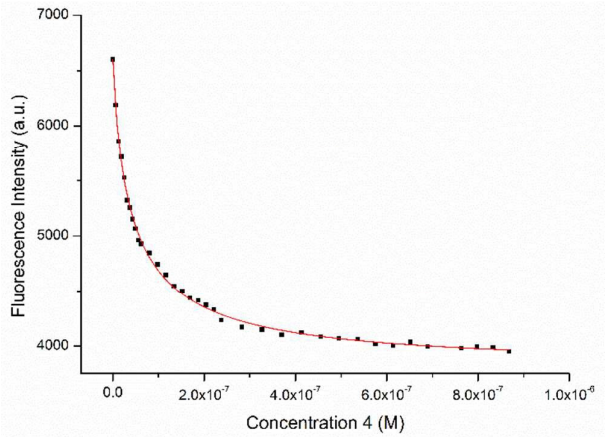

Figure 5. Change in fluorescence intensity of **3a** (5 x 10^{-7} M in chloroform) at 393 nm titrated with **4** (0, 2.5 x 10, 7.5 x 10, 20 x 15 µL of 5 x 10^{-6} M in chloroform). Black square marks correspond to the raw experimental data. Solid red line corresponds to the theoretical titration curve obtained fitting the data with a 1:1 binding model.

from benzene-1,3,5-tricarbonyl trichloride that provided a planar backbone wherefrom the DDD units were built. Synthesis of monomer **7** was achieved by a condensation reaction with 4-(2-hydroxyethoxy)benzaldehyde followed by the synthetic procedure employed in compound **4** with ethyl 2-amidinoacetate hydrochloride under basic conditions, Scheme 3. Based on the structural features of both blocks, the mixture of **5** and **7** was expected to arrange in a polymeric network as illustrated in Figure 6. The formation of such network was corroborated through viscosity measurements of equimolar mixtures of **5** and **7** in 1,2-dichloroethane at different concentrations, Figure 7. The double-logarithmic plot of specific viscosity *versus* concentration shows: 1) a relationship between both variables; and, 2) a sharp slope change from 1.02 when [**5**]+[**7**] < 0.036 mM to 3.00 when [**5**]+[**7**] >0.036 mM, Figure 8. Both features are distinctive of the formation of a supramolecular network.[24] Finally, a polymerization eye-naked proof was observed after adding **5** (37.5 mg) to a solution of **7** (50 mg in 0.5 mL of chloroform : methanol 10:1 v/v). The resulting mixture showed a red color, not observed in any of the

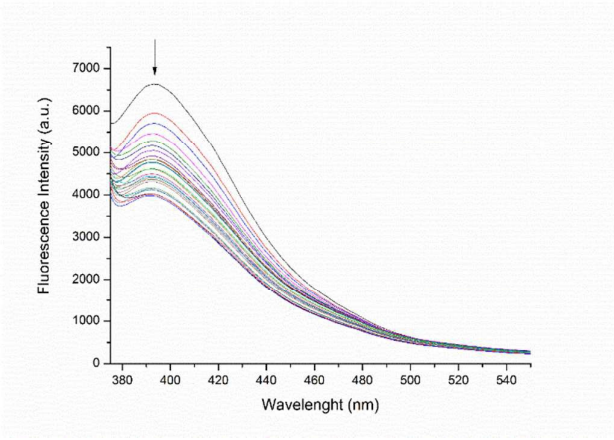

Figure 4. Fluorescence spectra of **3a** (5 x 10-7 M in chloroform) in the presence of **4** (0, 2.5 x 10, 7.5 x 10, 20 x 15 µL of 5 x 10-6 M in chloroform). Arrow indicates the decrease in the emission intensity as compound 4 is added.

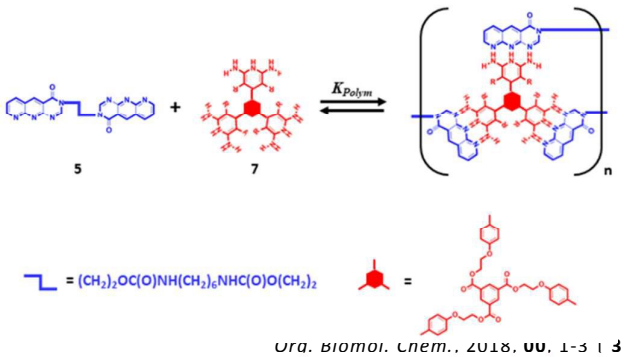

Figure 6. Structure of the polymeric network obtained by combining compound **5** (bifurcate AAA in blue color) and **7** (trifurcate DDD in red color).

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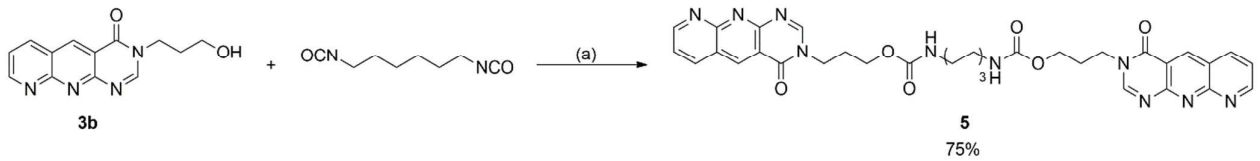
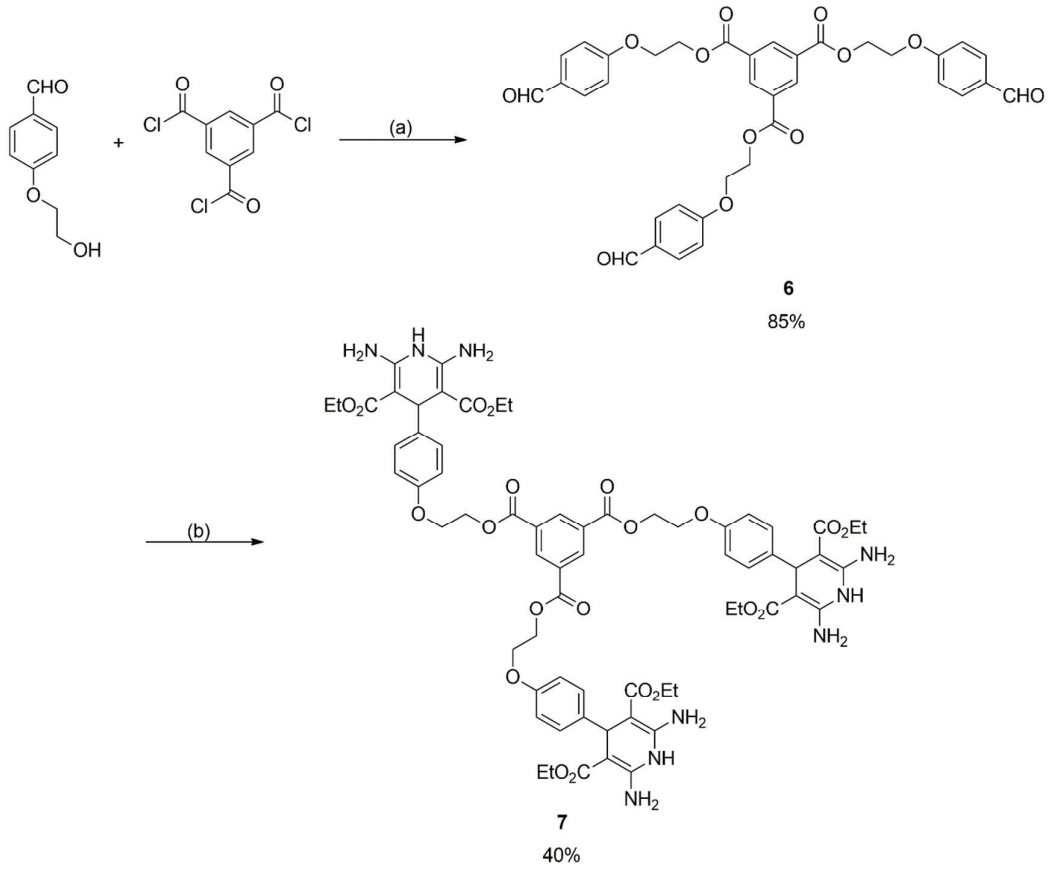


Scheme 2. Synthesis of the bifunctional AAA monomeric unit **5**. (a) Dibutyltin dilaurate (DBTDL) cat., $CHCl_3$, 60 °C.



Scheme 3. Synthesis of the trifunctional DDD monomeric unit **7**. (a) Triethylamine (TEA), Ethyl acetate, 0 °C; (b) Ethyl-2-amidinoacetate hydrochloride, K_2CO_3, DMF. 85 °C, 12 h.

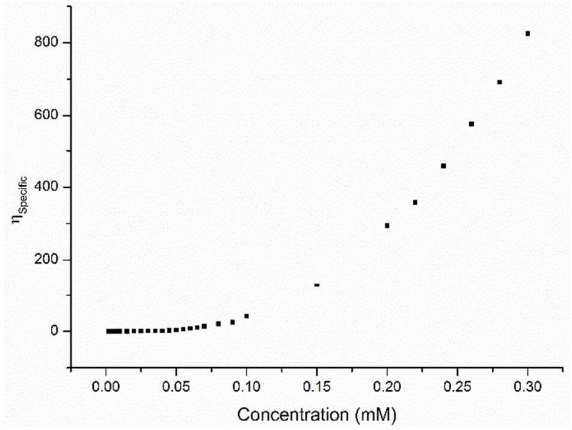


Figure 7. Specific viscosity of an equimolar mixture of **5** and **7** in 1,2-dichloroethane *versus* the concentration (298 K).

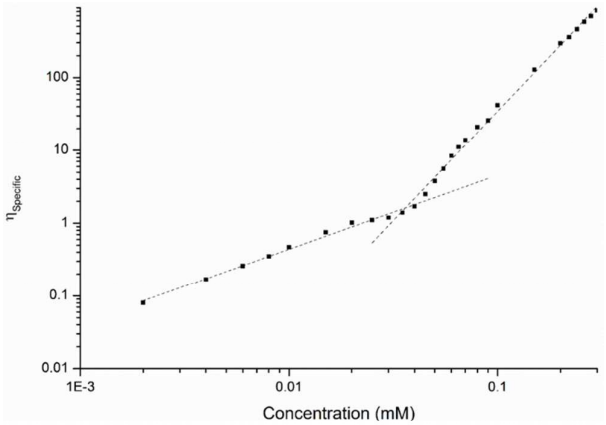


Figure 8. Double-logarithmic plot of the specific viscosity of an equimolar mixture of 5 and 7 in 1,2-dichloroethane versus its concentration (298 K). Black squares correspond to experimental data; dashed lines correspond to the linear fitting of the double logarithm when the total concentration was from 0.002 to 0.035 mM (calculated slope = 1.02), and from 0.040 to 0.30 mM (calculated slope = 3.00).

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Figure 9. From left to right: Compound **7** in chloroform: methanol solution (10:1 v/v). Compound **5**. Mixture of **5** and **7** in chloroform: methanol (10:1 v/v). High viscous polymer after evaporation of half volume of solvent.

previous solutions. Likewise, the resulting mixture displayed high viscosity after the solvent volume was reduced to one half Figure 9.

Conclusions

A new readily functionalized AAA monomer was synthesized from 2-aminonicotinaldehyde in two steps with the aid of microwave synthesis. Single crystal X-ray structure confirmed the disposition of its acceptor sites and the planarity of its backbone. The molecular recognition between this new AAA system with a known DDD unit was studied by ^{1}H NMR and fluorescence titrations; wherein the association constant obtained was 1.57 ± 0.48 x107 M^{-1} in chloroform at room temperature (ΔG = 9.79 ± 0.21 kcal·mol^{-1}). Integration of these binding units into a supramolecular polymer was assessed through the synthesis of block units **5** and **7**. The dependency of the mixture's viscosity corroborated the formation of a supramolecular network.

Acknowledgment

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Conflict of Interest

There are no conflicts to declare.

Experimental

Reagents and Apparatus

All chemical and solvents were of reagent grade, purchased from commercial sources and used directly without any further purification. Microwave-assisted reactions were carried out in a Discover SP 909155 (CEM Corporation). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded using AscendTM 400 MHz spectrometer (Bruker). ^{1}H and ^{13}C NMR spectra were referenced relative to tetramethylsilane (TMS) using the residual non-deuterated NMR solvent signal. UV-Vis absorption spectra were obtained on a ZF-I UV-Visible spectrometer (Shanghai Gu Village electro-optical instrument) and a UV-spectrophotometer Agilent 8401. Fluorescent Spectrometer F-700 (Hitachi High Technologies) was used to acquire fluorescence spectra. Mass spectra were recorded using electron impact ionization on a MALDI-TOF Mass spectrometer SYNAPT G2 (Waters Corporation). X-Ray diffraction data were collected on Bruker APEX-II CCD diffractometer using monochromatic Mo-Kα radiation (λ = 0.71073 Å). Viscosity measurements were carried out with a micro-Ubbelohde dilution viscometer at 298 K.

Synthesis

***N*-butyl-2-cyanoacetamide, 1a**. In a 50 mL round bottom flask *n*-butylamine (293 mg, 3.99 mmol) and ethyl cyanoacetate (453 mg, 4.00 mmol) were added and dissolved in anhydrous ethanol under Argon atmosphere. The reaction mixture was heated up to 80 °C for 3 hours. After the mixture was cooled down to room temperature, the solvent was removed under reduced pressure. The product was obtained after recrystallization with cold dichloromethane. Solid was filtered and rinsed with cold ethanol. Yield = 533 mg, 95%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.18 (bs, 1H), 3.58 (s, 2H), 3.06 (m, 2H), 1.42-1.35 (m, 2H), 1.32-1.33 (m, 2H), 0.87 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 162.3, 116.7, 39.2, 31.3, 25.7, 19.9, 14.0.

2-cyano-*N*-(3-hydroxypropyl)acetamide, 1b. Synthetic procedure as performed by Proença and Costa.[19] Yield = 610 mg, 99%.

2-amino-*N*-butyl-1,8-naphthyridine-3-carboxamide, 2a. Synthetic procedure as reported by Domling and coworkers.[20] A mixture of *N*-butyl-2-cyanoacetamide **1a** (421 mg, 3.00 mmol), 2-amino-3-pyridinecarbaldehyde (366 mg, 3.00 mmol) and NaOH (12 mg, 0.3 mmol) were dissolved in absolute ethanol. The reaction mixture was heated to 80 °C until starting material consumption. The product desired precipitated as a yellow solid once reaction mixture is cooled down to 0 °C. The solid was filtered and washed at least three times with cold dichloromethane. Yield = 610 mg, 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.78 (dd, 1H, *J* = 4.4, 2.0 Hz), 8.76 (bs, 1H), 8.41 (s, 1H), 8.14 (dd, 1H, *J* = 7.9, 2.1 Hz) 7.43 (bs, 2H), 7.22 (dd, 1H, *J* = 7.8, 4.4 Hz), 3.28 (td, 2H, *J* = 7.0, 5.5 Hz), 1.53 (m, 2H), 1.36 (m, 2H), 0.91 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 167.2, 159.1, 157.2, 154.5, 138.8, 137.9, 118.4, 116.6, 116.4, 39.3, 31.5, 20.1, 14.2.

2-amino-*N*-(3-hydroxypropyl)-1,8-naphthyridine-3-carboxamide, 2b. In a round bottom flask 2-cyano-*N*-(3-hydroxypropyl)acetamide **1b** (1.25 g, 8.8 mmol) and 2-amino-3-pyridinecarbaldehyde (976 mg, 8.0 mmol) were dissolved in 20 mL of absolute ethanol. Once dissolved, piperidine (7 mL) was added and the reaction mixture was heated to 80 °C for 5 h. Reaction completion was monitored by thin layer chromatography. After completion, the reaction mixture was cooled down to room temperature and the precipitate was vacuum filtered to yield a pale-yellow powder. Product was purified by washing at least two times with ethyl acetate and absolute ethanol. Yield = 1.38 g, 70%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.78 (dd, 1H, *J* = 4.4, 2.0 Hz), 8.76 (bs, 1H), 8.41 (s, 1H), 8.12 (dd, 1H, *J* = 7.9, 2.1 Hz), 7.44 (bs, 2H), 7.22

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(dd, 1H, *J* = 7.8, 4.4 Hz), 4.51 (t, 1H), 3.50 (m, 2H), 3.34 (m, 2H), 1.71 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm)δ 167.25, 159.03, 157.19, 154.48, 138.83, 137.96, 118.43, 116.59, 116.36, 59.02, 37.05, 32.63.

3-butylpyrimido[4,5-b][1,8]naphthyridin-4(3*H*)-one, 3a. In a 35 mL microwave reaction tube 2-amino-N-butyl-1,8-naphthyridine-3-carboxamide **2a** (488 mg, 2.00 mmol) and 2.5 mL of *N,N*-dimethylformamide dimethyl acetal (DMFDMA) were mixed and heated to 110 °C for 40-45 minutes at 150 psi. Once the reaction mixture cooled down to room temperature 5 mL of ethanol was added. The product, that precipitated as pale yellow solid, was filtered and rinsed with ethanol. Yield = 432 mg, 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.45 (s, 1H), 9.26 (dd, 1H, *J* = 4.2, 2.1 Hz), 8.76 (dd, 2H, *J* = 8.2, 2.0 Hz), 8.73 (s, 1H), 7.70 (dd, 1H, *J* = 8.2, 4.1 Hz), 4.01 (t, 2H, *J* = 7.3 Hz), 1.72 (m, 2H), 1.35 (m, 2H), 0.93 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.2, 158.3, 157.9, 157.6, 153.4, 141.4, 139.3, 122.8, 121.7, 117.3, 46.3, 31.1, 19.8, 14.0.

3-(3-hydroxypropyl)pyrimido[4,5-b][1,8]naphthyridin-4(3*H*)-one, 3b. Synthetic procedure as performed for compound **3a**. Yield = 625 mg, 75%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.45 (s, 1H), 9.26 (dd, 1H, *J* = 4.2, 2.0 Hz), 8.76 (dd, 1H, *J* = 8.2, 2.0 Hz), 8.67 (s, 1H), 7.70 (dd, 1H, *J* = 8.2, 4.1Hz), 4.65 (t, 1H, *J* = 5.0 Hz), 4.09 (t, 2H, *J* = 7.0 Hz), 3.50 (q, 2H, *J* = 5.5 Hz), 1.89 (p, 2H, *J* = 6.5 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.8, 157.9, 157.5, 157.2, 153.2, 140.9, 138.9, 122.3, 121.3, 117.0, 57.9, 43.9, 31.2.

Diethyl 2,6-diamino-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate, 4. Synthetic procedure as reported by Wang and coworkers.[17] *p*-methoxybenzaldehyde (1.50 g, 11.02 mmol), ethyl 2-amidinoacetate hydrochloride (3.8 g, 22.80 mmol), K_2CO_3 (3.34 g, 24.17 mmol) and 6 mL of DMF were added to a 50 mL round bottom flask under Argon. The reaction mixture was heated to 80 °C for 14 h. After completion, the reaction mixture was poured into distilled water (50 mL) and then extracted with ethyl acetate (4 x 50 mL). The organic phase was dried over Na_2SO_4 and solvent was removed under reduced pressure. The product (white solid) was isolated by flash chromatography using ethyl acetate : petroleum ether (3:1) as eluent. The product exhibited 1,4-dihydro (52%) and 3,4-dihydro (48%) tautomeric forms in $CDCl_3$, and thus, some hydrogen atoms in the structure could not be integrated as integer numbers in the ^{1}H NMR spectrum. Yield = 3.58 g, 90%. HRMS (MALDI): m/z calcd for $C_{18}H_{22}N_3O_5$ [M+H$^+$]: 360.1554; found: 362.1553. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.10 (dd, 2H, *J* = 28.7, 8.4 Hz), 6.77 (dd, 2H, *J* = 25.0, 8.5 Hz), 6.18 (s, 0.67H), 4.53 (s, 0.61H), 4.43 (d, 0.49H, *J* = 6.9 Hz), 4.29-3.98 (m, 4H), 3.77 (t, 3H, *J* = 6.9 Hz), 3.26 (d, 0.59H, *J* = 1.4 Hz), 1.24 ppm (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 169.5 162.8, 158.2, 136.4, 128.3, 114.0, 61.2, 57.8, 55.4, 51.0, 15.2, 14.5.

2-(4-oxopyrimido[4,5-b][1,8]naphthyridin-3(4*H*)-yl)ethyl-3-(4-oxopyrimido[4,5-b][1,8]naphthyridin-3(4*H*)-yl)propyl)hexane-1,6-diyldicarbamate, 5. In a 100 mL round bottom flask compound **3b** (740 mg, 2.75 mmol) and 1,6-diisocyanatohexane (210 mg, 1.25 mmol) were dissolved in 50 mL of chloroform. Dibutyltin dilaurate (10 drops) was added and the reaction mixture was heated to 60 °C until starting material consumption was corroborated by thin layer chromatography. Solvent was removed under reduced pressure and the product was isolated by flash chromatography with ethyl acetate : methanol (8:1 v/v) mixture as eluent. Yield = 632mg, 76%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.42 (s, 2H), 9.26 (dd, 2H, *J* = 4.1, 2.1 Hz), 8.74 (d, 2H, *J* = 8.3 Hz), 8.67 (s, 2H), 7.69 (ddd, 2H, *J* = 8.2, 4.2, 1.7 Hz), 7.08 (m, 2H), 4.05 (m, 8H), 2.91 (d, 4H, *J* = 6.6 Hz), 2.05 (d, 4H, *J* = 6.6 Hz), 1.32-1.15 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.34, 158.37, 157.77, 157.61, 156.52, 153.40, 141.33, 139.35, 122.78, 121.75, 117.46, 61.56, 44.19, 30.47, 29.77, 28.47, 26.35. mp =211.4 °C.

Tris(2-(4-formylphenoxy)ethyl)benzene-1,3,5-tricarboxylate, 6. A mixture of triethylamine (404 mg, 4.0 mmol) and 4-(2-hydroxyethoxy)benzaldehyde (548 mg, 3.3 mmol) in 8 mL of ethyl acetate was prepared in a 25 mL round bottom flask and cooled down to 0 °C. A solution of benzene-1,3,5-tricarbonyl trichloride (265 mg, 1 mmol) in ethyl acetate was added dropwise to the reaction mixture. Starting material consumption was monitored by thin layer chromatography. After reaction completion, the reaction mixture was filtered. The solvent was removed from the filtrate under reduced pressure, and the crude was submitted to flash chromatography with petroleum ether : ethyl acetate (4:1 v/v) as eluent. The product is a yellow powder. Yield = 226 mg, 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.87 (s, 3H), 8.70-8.60 (m, 3H), 7.85 (dd, 6H, *J* = 9.1, 2.2 Hz), 7.18 (d, 6H, *J* = 8.7 Hz), 4.72 (dd, 6H, *J* = 5.2, 3.3 Hz), 4.51 (dd, 6H, *J* = 5.1, 3.6 Hz).

Tris(2-(4-(2,6-diamino-3,5-bis(ethoxycarbonyl)-1,4-dihydropyridin-4-yl)phenoxy)ethyl)benzene-1,3,5-tricarboxylate, 7. Compound **6** (327 mg, 0.5 mmol), ethyl 2-amidinoacetate hydrochloride (1.25 g, 7.5 mmol) and potassium carbonate (1.04 g, 7.5 mmol) were dissolved in 8 mL of DMF. The reaction mixture was heated to 85 °C for 12 h. After completion, the reaction mixture was poured in 20 mL of distilled water and liquid-liquid extraction with ethyl acetate (5 x 20 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by flash chromatography with ethyl acetate : methanol (10:1 v/v) as eluent. Yield = 266 mg, 40%. ESI-HRMS: Calc. for $C_{66}H_{75}N_9O_{21}$: 1329.51, Found [M+H$^+$]: 1330.55. ^{1}H NMR (400 MHz, DMSO-d_6) 8.68 (s, 3H), 8.37 (s, 2H), 7.95 (s, 1H), 7.03 (d, 6H, *J* = 7.6 Hz), 6.98-6.82 (m, 9H), 6.76 (d, 3H, *J* = 7.8 Hz), 4.65 (s, 6H), 4.28 (d, 6H, *J* = 13.1 Hz), 3.90 (d, 12H, *J* = 6.9 Hz), 2.89 (s, 2H), 2.73 (s, 2H) 1.34-0.89 (m, 18H); ^{13}C NMR(100MHz, DMSO-d_6) δ (ppm) 168.77, 164.53, 156.12, 151.80, 143.87, 134.19, 131.47, 128.58, 114.71, 113.88, 79.49, 66.01, 58.32, 35.86, 14.93. mp = 74.4 °C.

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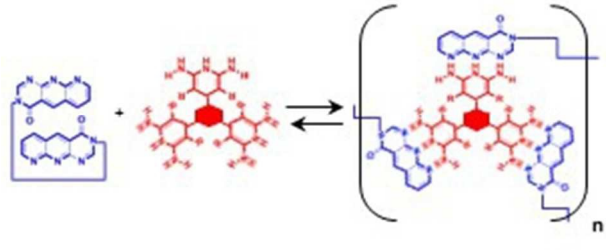

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