Electronic Supplementary Information (ESI)

Supramolecular gel formation regulated by water content in organic solvents: self-assembly mechanism and biomedical applications

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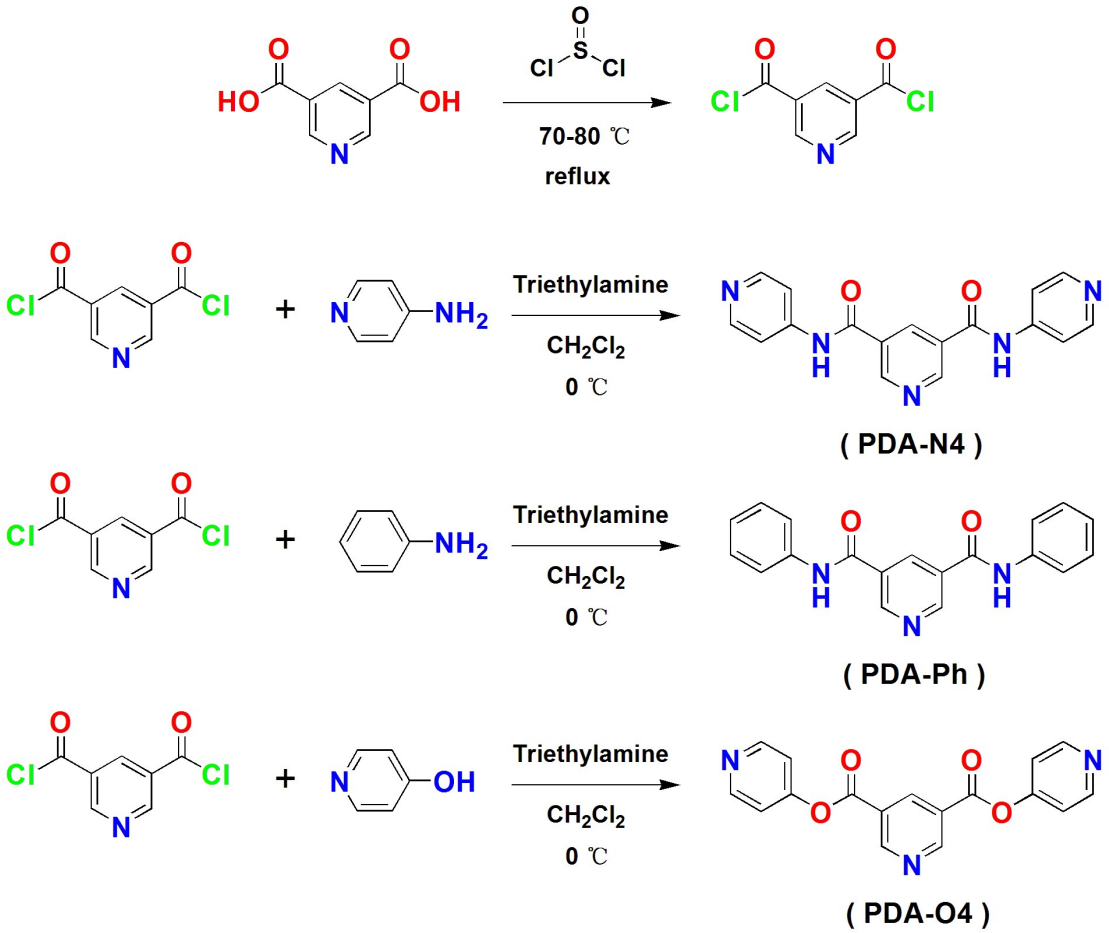
1. Synthesis of compounds



Scheme S1. Synthetic route for PDA-N4, PDA-Ph and PDA-O4

The pyridylamide derivative, PDA-N4, was prepared according to the literature method.[1,2] Other compounds (PDA-Ph and PDA-O4) were obtained similar to the PDA-N4 (Scheme S1). They were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and LC-MS, respectively.

In a typical experiment, 3,5-pyridinedicarboxylic acid (7.1945 g, 43.05 mmol) was added into $SOCl_2$ (24 mL) in the presence of N,N-dimethylformamide (DMF, 0.1 mL), and then was stirred for 0.5 h at room temperature. The mixture was refluxed at 75-80℃ for 6 h until all solid have been dissolved and reacted. Subsequently, the solvent was removed by reduced pressure distillation, and the remaining material was dried under vacuum. The corresponding acyl chloride was obtained as a solid at room temperature. Next, a freshly distilled THF (15mL) containing 3,5-pyridin-dicarbonyl dichloride (15 mmol, 3.075 g) was added dropwise to the THF solution (30 mL) of 4-

pyridylamine (30 mmol, 2.820g) and distilled triethylamine (43.1 mmol, 6 mL) at 0℃ with continuous stirring. After stirring for 7h, the white precipitate was filtered and washed with THF for four times. The crude product was recrystallized from a mixed solvent of DMSO (100 mL) and H_2O (200 mL), washed with H_2O and dried at 80℃ under vacuum (3.390 g, 70.8%).

***N,N′*-di(pyridin-4-yl)-pyridine-3,5-dicarboxamide (PDA-N4):**

^{1}H NMR (400MHz, DMSO-*d*6, δ_H): 9.30 (2H, d, *J* = 2.1 Hz), 8.83 (1H, t, *J* = 2.1 Hz), 8.59–8.44 (2 H, m), 7.79 (2H, dd, *J* = 4.8 Hz, 1.5 Hz). ^{13}C NMR (100MHz, DMSO-*d6*, δ_C): 164.93, 152.22, 149.94, 146.92, 135.69, 129.89, 114.68. IR (KBr): 3240, 3157, 3070, 1680, 1594, 1515, 1419, 1335, 1230, 1253, 1208, 1107, 1059, 1031, 1000, 924, 886, 830, 730, 582, 539 cm^{-1}. LC-MS $[M+H]^+$ calculated for $C_{17}H_{13}N_5O_2$: m/z 319.11; found: 320.12

N,N′-di(phenyl)-pyridine-3,5-dicarboxamide (PDA-Ph):

Yield >75％

^{1}H NMR (400MHz, DMSO-*d*6, δ_H): 10.64 (2H, s), 9.28 (2H, s), 8.87 (1 H, d, *J* = 1.2 Hz), 7.82 (4H, d, *J* = 8.3 Hz), 7.40 (4H, t, *J* = 7.9 Hz), 7.15 (2H, t, *J* = 7.4 Hz). ^{13}C NMR (100MHz, DMSO-*d*6, δ_C): 163.93, 151.48, 139.18, 135.21, 130.70, 129.24, 124.65, 120.87. IR (KBr): 3461, 3263, 3062, 1670, 1645, 1599, 1549, 1499, 1447, 1336, 1268, 1027, 883, 760, 743, 691, 584, 507 cm^{-1}. LC-MS $[M+H]^+$ calculated for $C_{19}H_{15}N_3O_2$: m/z 317.12; found: 318.12.

***N,N′*-di(pyridin-4-yl)-pyridine-3,5-dicarbomethoxy (PDA-O4):**

Yield >80％

^{1}H NMR (400MHz, DMSO-*d*6, δ_H): 9.21 (2H, d, *J* = 2.1 Hz), 8.64 (1H, t, *J* = 2.1 Hz), 7.88 (4H, d, *J* = 7.4 Hz), 6.43 (4H, d, *J* = 7.3 Hz). ^{13}C NMR (100MHz, DMSO-*d6*, δ_C): 176.54, 166.27, 153.72, 140.27, 137.73, 127.73, 116.33. IR (KBr): 3068, 1713, 1636, 1517, 1476, 1397, 1333, 1278, 1189, 1036, 848, 751, 704, 547 cm^{-1}. LC-MS $[M+H]^+$ calculated for $C_{17}H_{11}N_3O_4$: m/z 321.29; found: 322.30.

Table S1. Solubility of PDA-N4, PDA-Ph and PDA-O4 in various solvents

	Solvents	Compounds		
		PDA-N4	**PDA-Ph**	**PDA-O4**
1	DMSO	S	S	S
2	DMF	S	S	S
3	Methanol	S	P	S
4	Ethanol	S	P	S
5	Benzene	I	I	I
6	CCl_4	I	I	I
7	THF	I	S	P
8	1,4-Dioxane	S	S	P
9	H_2O	I	I	P

* S = solution; I = insoluble; P = precipitate.

Table S2. Gelation properties of PDA-N4, PDA-Ph and PDA-O4 in DMSO-H_2O mixed solvents

DMSO/H_2O (v/v)		Compounds		
		PDA-N4	**PDA-Ph**	**PDA-O4**
1	10/90	G	P	P
2	20/80	G	P	S
3	30/70	G	P	S
4	40/60	G	P	S
5	50/50	G	P	S
6	60/40	TS	P	S
7	70/30	S	P	S
8	80/20	S	S	S
9	90/10	S	S	S

* G = gel; C = crystal; S = solution; TS = turbid solution; P = precipitate; Gelator concentration: 15 $mg \cdot mL^{-1}$.

Table S3. Gel-crystal transition of PDA-N4 in DMSO-H_2O mixed solvents upon aging time extension (90Day)

DMSO/H_2O	**C_{PDA-N4}**	**States**							
(v/v)	**mg·mL^{-1}**	**1D**	**2D**	**5D**	**10D**	**15D**	**30D**	**60D**	**90D**
50/50	6	S	S	S	S	S	S	S	S
	9	S	S	S	S	S	S	S	S
	13	TS	TS	TS+C	TS+C	C	C	C	C
	15	G	G	G	G+C	G+C	C	C	C
	20	G	G	G	G	G+C	G+C	C	C
20/80	6	S	S	S	S	S	S	S	S
	10	TS	TS	TS	TS	TS	TS	TS	TS
	11	G	G	G	G	G	G	G	G
	15	G	G	G	G	G	G	G	G
	20	G	G	G	G	G	G	G	G
10/90	6	S	S	S	S	S	S	S	S
	7	TS	TS	TS	TS	TS	TS	TS	TS
	9	G	G	G	G	G	G	G	G
	12	G	G	G	G	G	G	G	G
	15	G	G	G	G	G	G	G	G
	20	G	G	G	G	G	G	G	G

* G = gel; C = crystal; S = solution; TS = turbid solution.

Table S4. Gelation properties of PDA-N4, PDA-Ph and PDA-O4 in DMF-H_2O mixed solvents

DMF/H_2O (v/v)		Compounds		
		PDA-N4	PDA-Ph	PDA-O4
1	10/90	G	P	S
2	20/80	G	P	S
3	30/70	G	P	S
4	40/60	G	P	S
5	50/50	G	P	S
6	60/40	TS	P	S
7	70/30	TS	P	S
8	80/20	S	S	S
9	90/10	S	S	S

* G = gel; C = crystal; S = solution; TS = turbid solution; P = precipitate; Gelator concentration: 15 $mg \cdot mL^{-1}$.

Table S5. Gelation properties of PDA-N4, PDA-Ph and PDA-O4 in methanol-H_2O mixed solvents

Methanol/H_2O (v/v)		Compounds		
		PDA-N4	PDA-Ph	PDA-O4
1	10/90	P	P	S
2	20/80	P	P	S
3	30/70	P	P	S
4	40/60	P	P	S
5	50/50	P	P	S
6	60/40	P	P	S
7	70/30	S	P	S
8	80/20	S	P	S
9	90/10	S	P	S

* P = precipitate; S = solution; P = precipitate; Gelator concentration: 15 mg·mL^{-1}.

Table S6. Gelation properties of PDA-N4, PDA-Ph and PDA-O4 in ethanol-H_2O mixed solvents

Ethanol/H_2O (v/v)		**Compounds**		
		PDA-N4	**PDA-Ph**	**PDA-O4**
1	10/90	P	P	S
2	20/80	P	P	S
3	30/70	P	P	S
4	40/60	P	P	S
5	50/50	P	P	S
6	60/40	P	P	S
7	70/30	P	P	S
8	80/20	S	P	S
9	90/10	S	P	S

* P = precipitate; S = solution; Gelator concentration: 15 mg·mL^{-1}.

Table S7. Gelation properties of PDA-N4, PDA-Ph and PDA-O4 in 1, 4-dioxane-H_2O mixed solvents

1, 4-dioxane/H_2O (v/v)		**Compounds**		
		PDA-N4	**PDA-Ph**	**PDA-O4**
1	10/90	P	P	S
2	20/80	P	P	S
3	30/70	P	P	S
4	40/60	P	P	S
5	50/50	P	P	S
6	60/40	S	P	S
7	70/30	S	P	S
8	80/20	S	P	S
9	90/10	S	P	S

* P = precipitate; S = solution; Gelator concentration: 15 mg·mL^{-1}.

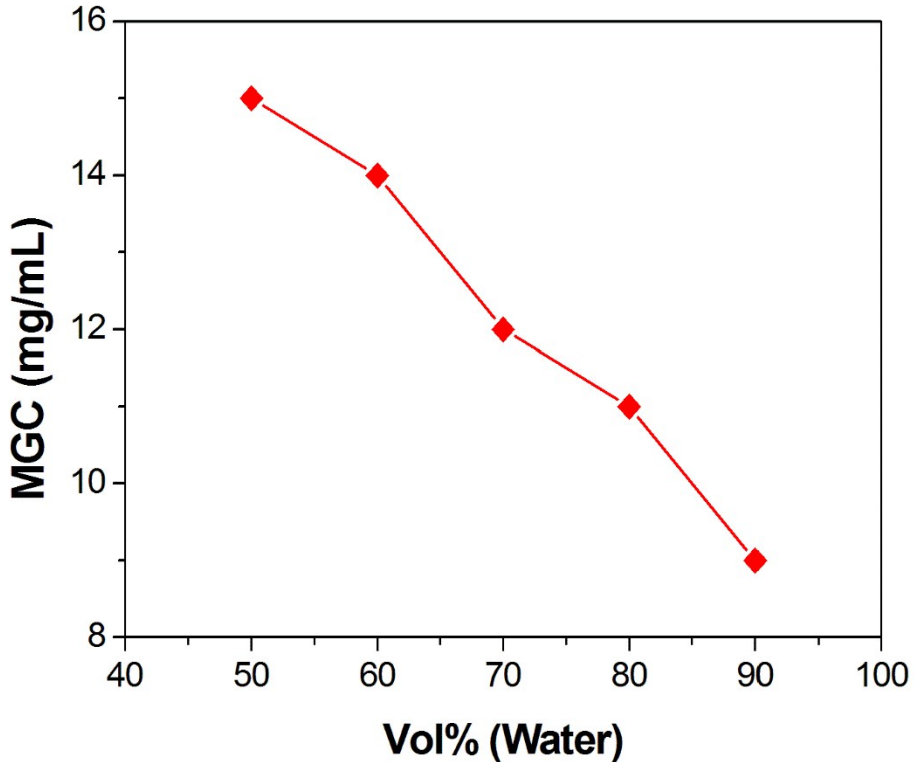


Figure S1. MGC variation of PDA-N4 with the water content in mixed solution

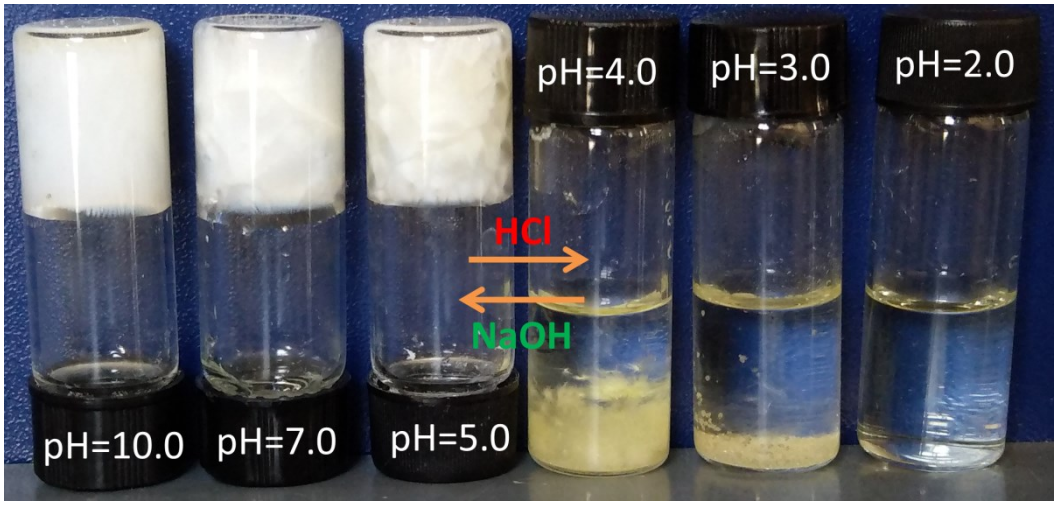


Figure S2. Gelation behavior of PDA-N4 under various pH conditions (V_{DMSO} : V_{H2O} = 1 : 1; $c_{PDA\text{-}N4}$ = 15mg·mL^{-1})

Table S8. Crystal data and structure refinement for PDA-N4

Compound	**PDA-N4**
Formula	$C_{17}H_{15}N_5O_3$
F.w.	337.34
T (K)	100 (2)
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	14.6401(3)
b (Å)	8.4503(2)
c (Å)	13.3398(3)
α (°)	90
β (°)	112.159(3)
γ (°)	90
V (Å^3)	1528.42(7)
Z	4
Dc (g/cm^3)	1.466
μ (mm^{-1})	0.868
R_{int}	0.0938
GOF	1.207
$R1$, $wR2$ [$I > 2\sigma(I)$]	0.1837, 0.4051
$R1$, $wR2$ (all data)	0.1897, 0.4077

Table S9. Hydrogen bond geometry (Å and °) for PDA-N4 crystal

D-H···A	d(D-H)	d(H···A)	d(D···A)	< (DHA)
O(2)-H(2B)···N(2)$^{\#1}$	0.85	2.01	2.7596	146
N(3)-H(3)···O(2)	0.86	1.99	2.8082	160
N(6)-H(6)···N(5)$^{\#2}$	0.86	2.08	2.9327	169

#1 1-x,1/2+y,1/2-z; #2 -x,1-y,-z.

Table S10. Selected bond lengths (Å) and angles (º) for PDA-N4 crystal

O1—C11	1.228(7)	C10—C23	1.376(9)
N2—C24	1.329(8)	C10—C15	1.400(8)
N2—C19	1.348(7)	C11—C18	1.499(8)
N3—C14	1.361(9)	C12—C17	1.405(8)
N3—C15	1.397(8)	C13—C18	1.399(8)
N4—C21	1.334(9)	C13—C16	1.413(8)
N4—C20	1.356(7)	C14—C16	1.482(9)
N5—C22	1.339(7)	C15—C25	1.405(10)
N5—C23	1.345(9)	C16—C21	1.380(10)
N6—C11	1.372(8)	C17—C24	1.396(8)
N6—C12	1.410(8)	C18—C20	1.375(8)
O7—C14	1.241(8)	C18—C20	1.375(8)
C9—C19	1.371(8)	C22—C25	1.374(10)
C9—C12	1.407(8)		
C24—N2—C19	117.1(5)	N3—C15—C25	118.6(5)
C14—N3—C15	127.0(5)	C10—C15—C25	117.0(6)
C21—N4—C20	116.2(6)	C21—C16—C13	117.6(6)
C22—N5—C23	115.7(5)	C21—C16—C14	118.8(6)
C11—N6—C12	126.1(5)	C13—C16—C14	123.5(6)
C19—C9—C12	119.5(5)	C24—C17—C12	116.8(5)
C23—C10—C15	118.3(6)	C20—C18—C13	119.4(5)
N6—C11—C18	116.1(5)	C20—C18—C11	117.0(5)
C17—C12—C9	118.4(5)	C13—C18—C11	123.6(5)
C17—C12—N6	123.7(5)	N2—C19—C9	123.0(6)

C9—C12—N6	117.9(5)	N4—C20—C18	123.5(6)
C18—C13—C16	117.8(6)	N4—C21—C16	125.4(6)
O7—C14—N3	123.2(6)	N5—C22—C25	124.0(6)
O7—C14—C16	119.8(6)	N5—C23—C10	125.3(5)
N3—C14—C16	116.9(5)	N2—C24—C17	125.2(5)
N3—C15—C10	124.3(6)	C22—C25—C15	119.6(6)

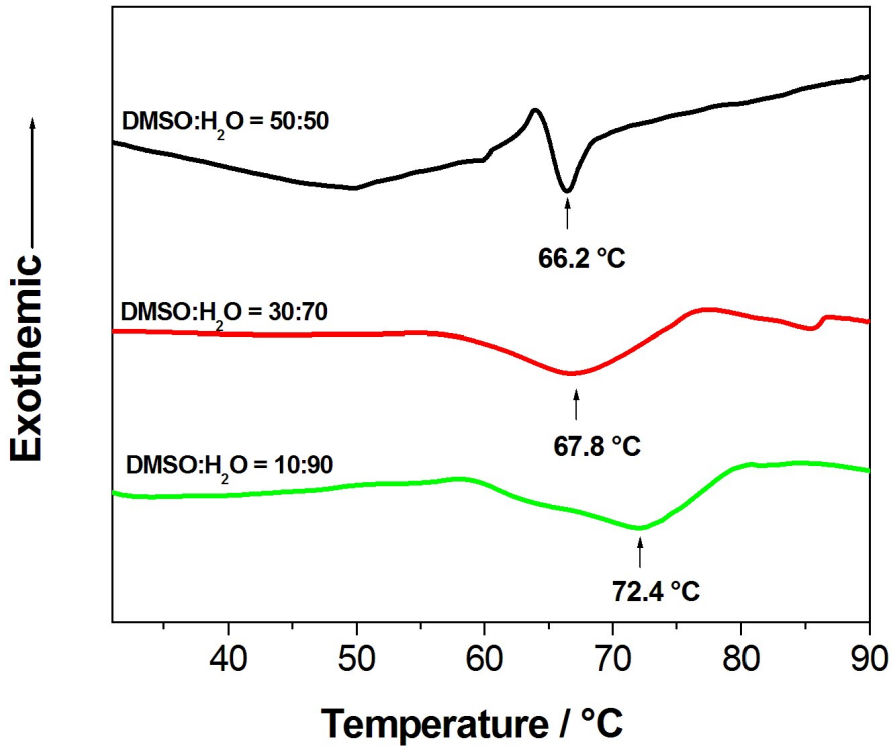


Figure S3. DSC curves for the PDA-N4 gels at different solvent ratios ($c_{PDA\text{-}N4}$ = 15 mg·mL^{-1}).

When 50% water (volume fraction) was added, a gel obtained and the gel-to-sol transition temperature (T_{gel}) was 66.2 °C. The higher T_{gel} (66.2 °C), T_{gel} (72.4 °C) were found when the water content reached 70% and 90%, respectively. It can be clearly seem that the T_{gel} increased as the H_2O content was increased, showing that the solvent ratio plays a significant role to the thermal stability of the supramolecular gel.

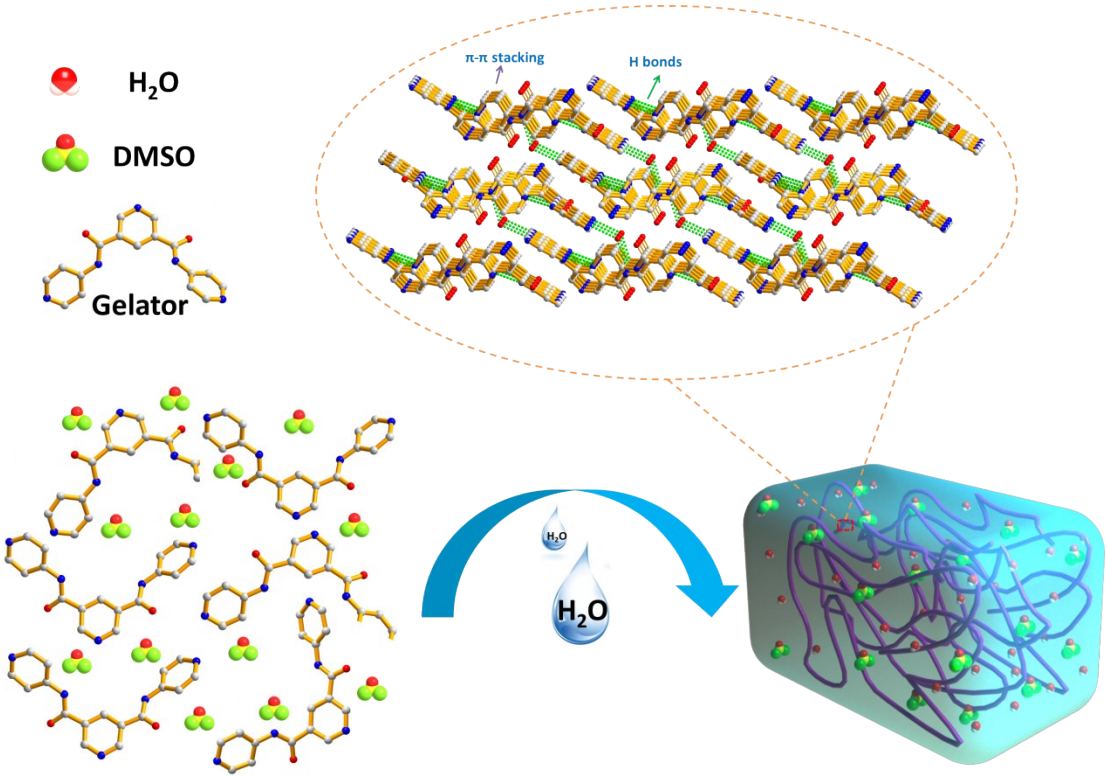


Figure S4. Schematic of the self-assembly mechanism for PDA-N4 in gels

2. References

1 X. Luo, X. Jia, J. Deng, J. Zhong, H. Liu, K. Wang and D. Zhong, *J. Am. Chem. Soc.*, 2013, **135**, 11684-11687.

2 Y. Zhao, M. Lv, J. Fan, L. Luo, Z. Su, W. Sun, *Inorg. Chim. Acta*, 2011, **377**, 138–143.