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## ARTICLE

# Assembly of encapsulated water in hybrid bisamides: Helical and zigzag water chains†

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The diverse assembly of encapsulated water molecules in hybrid bisamide hosts has been investigated. The hybrid bisamides containing aromatic terminal groups and flexible aliphatic spacers restrict the intermolecular amide-amide hydrogen bonding and  $\pi$ -stacking interactions. But the addition of water promotes the self-assembly processes by bridging between the bisamide molecules and stabilized helical or zigzag one dimensional water chains. The bisamide **1** containing ethylenediamine adopted extended shape and stabilized one-dimensional hydrogen bonded helical water chain inside the supramolecular frameworks. In contrast, bisamide **2** containing trimethylenediamine adopted U-shape structure and entrapped an isolated water molecule. The X-ray crystallography reveals that the bisamide **4** containing cadaverine adopted an extended structure and stabilized one-dimensional hydrogen bonded zigzag water chain in higher order packing. Moreover, by U-tube experiments using pH gradient as the driving force across a liquid chloroform phase, bisamide **4** was found to be much active proton transporter than bisamide **1**.

## Introduction

Encapsulated water and single-column water chain inside nanopores are highly important due to their occurrence in several biological processes.<sup>1</sup> One dimensional water chains are existed in membrane aquapores that are important for the function of nicotinic receptor M2858 and influenza A M2 virus.<sup>2</sup> Mainly, the supramolecular arrangements, the hydrogen-bonding interactions and their fluctuations determine the properties of the bulk water as well as the water in molecular confinements.<sup>3</sup> Several attempts are being made to develop water clusters in restricted environments such as organic and inorganic host lattices with precise structural data of water clusters ((H<sub>2</sub>O)<sub>n</sub>, where n = 2–10) in diverse environments.<sup>4</sup> Recently, metalloorganic complexes<sup>5</sup> and polar hosts such as tetraaza and phenolic cavitands,<sup>6</sup> carboxylic acids,<sup>7</sup> N-oxides,<sup>8</sup> and amino acids<sup>9</sup> have been employed to stabilize water clusters, layers, and channels. Natarajan et al. have reported the water chain inside a supramolecular analogue of carbon nanotubes.<sup>10</sup>

Buchanan et al. reported the solid-state dynamics of 1D water chains inside hydrates of imidazole.<sup>11</sup> Balaram and co-workers reported the stabilization of water wire by a hydrophobic pentapeptide channel.<sup>12</sup> Banerjee et al. have reported the one-dimensional helical alignment of water molecules within a supramolecular pseudopeptide helix.<sup>13</sup> There are many reports on confined water-assisted conduction in metal-organic frameworks (MOFs),<sup>14</sup> but most of them contain not only water but also high boiling solvents like DMSO, DMF, DEF and DMA.<sup>15</sup> Barboiu and co-workers have reported the imidazole-quartet water channels<sup>16</sup> and fabricated an artificial mimic of Gramicidin-A channel.<sup>17</sup>

Intrigued by the previous report, we wanted to investigate the diverse assembly of encapsulated water molecules with hybrid bisamide hosts. Herein we present supramolecular frameworks stabilized by one-dimensional hydrogen bonded water chains. The series of bisamides **1-4** contain pyridine 2,6-dicarboxylic acid monomethyl ester and ethylenediamine, trimethylenediamine, putrescine and cadaverine respectively. Interestingly the bisamides exhibit spherical morphology in dry methanol. But the addition of water promotes the self-assembly processes and frameworks formation. The interaction between bisamides **1-4** and water was studied by FTIR and NMR spectroscopy. Single crystal X-ray diffraction studies exhibit that the bisamide **1** stabilized one-dimensional hydrogen bonded helical water chain inside the supramolecular frameworks. The bisamide **2** containing trimethylenediamine adopted U-shape conformation and crystallized with an isolated

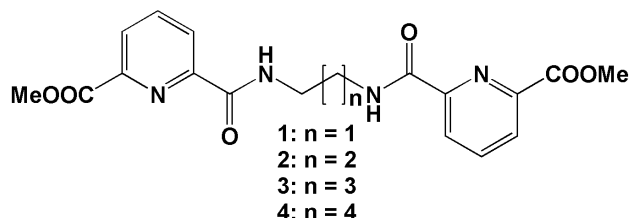
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† Electronic Supplementary Information (ESI) available: Synthesis and characterization of bisamides, <sup>1</sup>H NMR, <sup>13</sup>C NMR, Figures ESI S1-S10, Figure S11-S26. CCDC 1000665, 918262, 918259 and 918261 or other electronic format see DOI: 10.1039/b000000x/

water molecule. However, the bisamide **3** adopted extended conformation and crystallized with an isolated water molecule in the open cavity. But, the bisamide **4** containing cadaverine stabilized one-dimensional hydrogen bonded zigzag water chain inside the supramolecular frameworks.

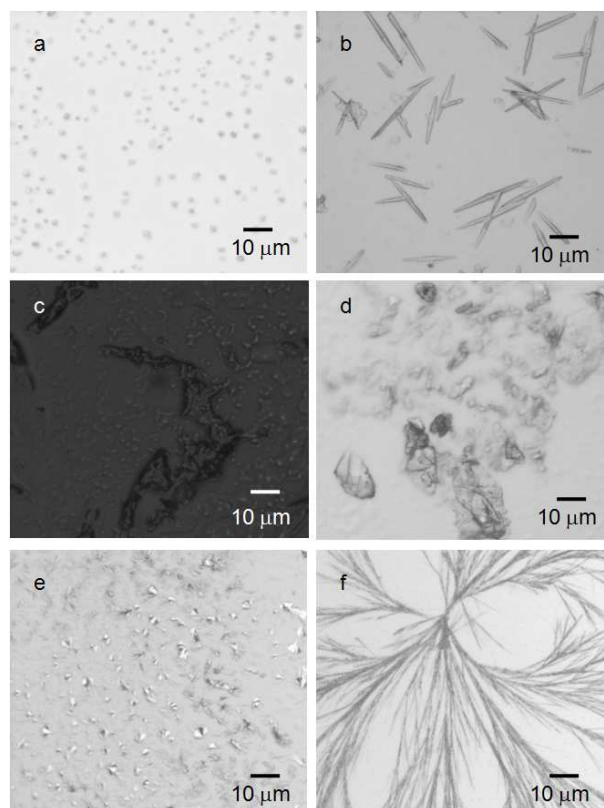
### Results and discussion

The hybrid bisamides were designed with assumption that the rigid pyridine 2,6-dicarboxylic acids should impart a curvature in the compound and the flexible diamine should adjust itself accordingly and the bulky head groups may restrict the intermolecular hydrogen bonding interaction (Scheme 1). The pyridine N may help with additional hydrogen bonding. In this context the variation of spacer length will be interesting.<sup>3d</sup> The hydrophobicity of the spacer diamines are increasing from bisamides **1** to **4** and the spacer may exhibit diverse folding. Target bisamides **1-4** were synthesized by coupling pyridine 2,6-dicarboxylic acid monomethyl ester with diamine like ethylenediamine, trimethylenediamine, putrescine and cadaverine following a high purity, as confirmed by <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, FTIR and mass spectrometry (MS) analysis.



**Scheme 1** The schematic presentation of bisamides **1-4**.

The bisamides **1-4** are solid at room temperature. The bisamides **1-4** exhibit polydisperse microspheres morphology in dry methanol. The polarized optical microscope based on an Olympus platform with a rotatable stage has been used to study the nature of the growth of bisamides **1-4** with addition of water in dry methanol solution. For better contrast and magnification, a ‘dry’ 50× long distance objective was used which allowed high-resolution measurements without contaminating the samples with oil or water. From Fig. 1a, the diameter of the microspheres of bisamide **1** is ca 1.25 μm. But with addition of water, several micrometer long needle shape crystals have appeared (Fig. 1b). The dramatic morphological changes have been observed on heating the needle shape crystals of bisamide **1** at 80°C. The water molecules are coming out, the crystal ruptured and the bisamide adopts spherical morphology again (Fig. 1c). However, for bisamide **2** containing trimethylenediamine, with addition of water to dry methanol solution no particular growth fashion has been observed (Fig. 1d). The bisamide **3** containing putrescine also does not exhibit any regular shape and growth with addition of water to dry methanol solution (Fig. 1e). However, the bisamide **4** containing cadaverine facilitates to form highly branched fiber like growth with addition of water to dry methanol solution (Fig. 1f).



**Fig. 1** (a) Micrograph of the microspheres of bisamide **1** in dry methanol. (b) Micrograph of long needle shaped crystal of bisamide **1** appeared after addition of water in dry methanol solution. (c) Micrograph showing the morphology of bisamide **1** crystals after heating at 80 °C. (d) Micrograph of bisamide **2** after addition of water in dry methanol solution. (e) The optical microscopic image of bisamide **3** after addition of water in dry methanol solution. (f) Micrograph showing the highly branched fiber likes growth of bisamide **4** by addition of water in dry methanol solution.

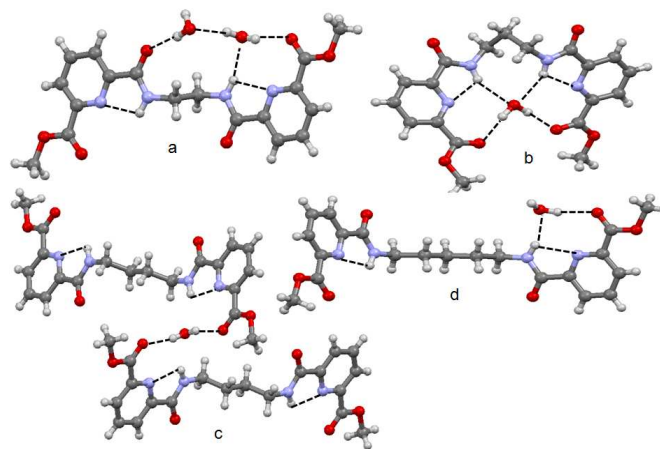
Solid state FT-IR spectroscopy is an excellent method to investigate the self-assembly of the bisamides as well as their interactions with water. The region 3500–3200 cm<sup>-1</sup> is responsible for the N–H stretching vibrations and O–H stretching frequency of hydrogen bonded water molecules. The region 1800–1600 cm<sup>-1</sup> corresponding to C=O stretching vibration of amide and ester groups. The FT-IR spectra of as synthesized dry bisamide **1** (Supporting Information Figure S1a) exhibits N-H stretching frequency at 3417 cm<sup>-1</sup> for non hydrogen bonded N-H and amide peaks at 1728, 1657 and 1538 cm<sup>-1</sup>. But the solid obtained from methanol-water solution exhibits a new peak at 3462 cm<sup>-1</sup> which is the characteristic for O-H stretching frequency of hydrogen bonded water<sup>18</sup> molecule and N-H stretching frequency shifted to 3377 cm<sup>-1</sup> (Supporting Information Figure S1b). The amide peaks and non hydrogen bonded methyl ester appear at 1732, 1657 and 1542 cm<sup>-1</sup>. Hence, water molecules are interacting with bisamide **1**. The solid obtained from methanol-water solution of bisamide **2** exhibits peak at 3560 cm<sup>-1</sup> for O-H stretching frequency of hydrogen bonded water<sup>18</sup> and 3328 cm<sup>-1</sup> for N-H stretching frequency. The amide and methyl ester have appeared at 1723, 1669 and 1530 cm<sup>-1</sup> (Supporting Information Figure S1c).

Similarly bisamide **3** exhibits peaks at 3550, 3328, 1734, 1668, 1535  $\text{cm}^{-1}$  and bisamide **4** exhibits peaks at 3511, 3311, 1734, 1669, 1546  $\text{cm}^{-1}$  (Supporting Information Figure S1d,e). These results indicate that the water molecules are interacting with the bisamides **1-4**.

The interactions between the reported bisamides **1-4** and water were further studied by solvent titration experiments using NMR spectroscopy. The effect of adding  $\text{D}_2\text{O}$  to  $(\text{CD}_3)_2\text{SO}$  solutions of bisamides **1-4** at 298 K are represented in Supporting Information Figure S2. The solvent titration shows that all bisamide NHs are solvent exposed as it is evident from their significant chemical shift upon the addition of  $\text{D}_2\text{O}$  in  $(\text{CD}_3)_2\text{SO}$  solutions. Upon gradual addition of  $\text{D}_2\text{O}$  to  $(\text{CD}_3)_2\text{SO}$  solution of bisamide **1** results a significant down field chemical shifts of the N-H ( $\Delta\delta = 0.407$  ppm) and water protons ( $\Delta\delta = 0.674$  ppm). Bisamides **2, 3** and **4** exhibit similar results (Supporting Information Figure S2). This chemical shifts indicate strong interaction between water and bisamides.

X-ray crystallography sheds some light on molecular structure and self-assembly pattern of the bisamides. Colorless crystals of bisamides **1-4** suitable for X-ray crystallography were obtained from methanol-water solutions by slow evaporation.<sup>19</sup> Bisamide **1** crystallizes with two molecules of water in the asymmetric unit and lies about an inversion centre (Supporting Information Figure S3). The ethylene diamine adopts *anti* conformation. The torsion angles around the pyridine dicarboxylic acid ( $177.85^\circ(3)$ ,  $-1.48^\circ(5)$ ,  $1.48^\circ(5)$  and  $-177.93^\circ(3)$ ) are also important to generate the extended structure. Two five member intramolecular hydrogen bonds between pyridine N and ethylene diamine NH ( $\text{N2-H22}\cdots\text{N1}$ ) result a rigid conformation in the solid state. The extended bisamide **1** formed three intermolecular hydrogen bonds with the water molecules ( $\text{N2-H2}\cdots\text{O2S}$ ,  $\text{O2S-H4S}\cdots\text{O2}$  and  $\text{O1S-H2S}\cdots\text{O3}$ ) (Figure 2a). The water molecules are also hydrogen bonded ( $\text{O2S-H3S}\cdots\text{O1S}$ ). Bisamide **2** crystallizes with half molecule of water and half molecule of **2** in the asymmetric unit and lies about a twofold axis (Supporting Information Figure S4). The trimethylenediamine adopts *gauche-gauche* conformation. The torsion angle around the conformationally flexible trimethylenediamine ( $58.46^\circ(19)$ ) plays a crucial role in dictating the overall U-shape structure. The torsion angles around the pyridine dicarboxylic acid ( $178.19^\circ(19)$ ,  $4.26^\circ(3)$ ,  $4.26^\circ(3)$  and  $178.19^\circ(19)$ ) are also important to stabilize the U-shape structure (Figure 2b). There are two intramolecular five member hydrogen bonds between pyridine N and trimethylenediamine NH ( $\text{N2-H2}\cdots\text{N1}$ ). The U-shape bisamide **2** encapsulated an water molecule by four intermolecular hydrogen bonding interactions ( $\text{N2-H2}\cdots\text{O1SA}$  and  $\text{O1SA-H40A}\cdots\text{O2}$ ) (Figure 2b). The asymmetric unit has one water molecule in a general position and half a molecule of bisamide **3** lying about an inversion centre (Supporting Information Figure S5). The putrescine adopts *anti-anti-anti* conformation. The torsion angle around the conformationally flexible putrescine ( $-177.88^\circ(18)$ ,  $-180^\circ(18)$ ,  $177.88^\circ(16)$ ) are mainly responsible for the overall extended structure. The torsion angles around the pyridine dicarboxylic acid

( $179.40^\circ(14)$ ,  $3.20^\circ(2)$ ,  $-3.20^\circ(2)$  and  $-179.40^\circ(14)$ ) are also important to stabilize the extended structure (Figure 2c). There are two intramolecular five member hydrogen bonds between pyridine N and putrescine NH ( $\text{N2-H2}\cdots\text{N1}$ ). The water molecule acts as a bridge between two molecules of bisamide **3** by two intermolecular hydrogen bonding interactions ( $\text{O1S-H40}\cdots\text{O2}$ ) (Figure 2c). Bisamide **4** crystallizes with one molecule of water in the asymmetric unit lies about a twofold axis (Supporting Information Figure S6). The cadaverine adopts *anti-anti-anti-anti* conformation. The torsion angles around the pyridine dicarboxylic acid ( $-177.10^\circ(2)$ ,  $-0.88^\circ(2)$ ,  $-0.88^\circ(2)$  and  $-177.10^\circ(3)$ ) are also important to generate the extended structure. Two five member hydrogen bonds between pyridine N and cadaverine NH ( $\text{N2-H2}\cdots\text{N1}$ ) result a rigid conformation in the solid state (Figure 2d). The extended bisamide **4** formed two intermolecular hydrogen bond with the water molecule ( $\text{N2-H2}\cdots\text{O1S}$  and  $\text{O1S-H40}\cdots\text{O3}$ ) (Figure 2d). The hydrogen bonding parameters of bisamides **1** to **4** are listed in Table 1.<sup>20</sup>



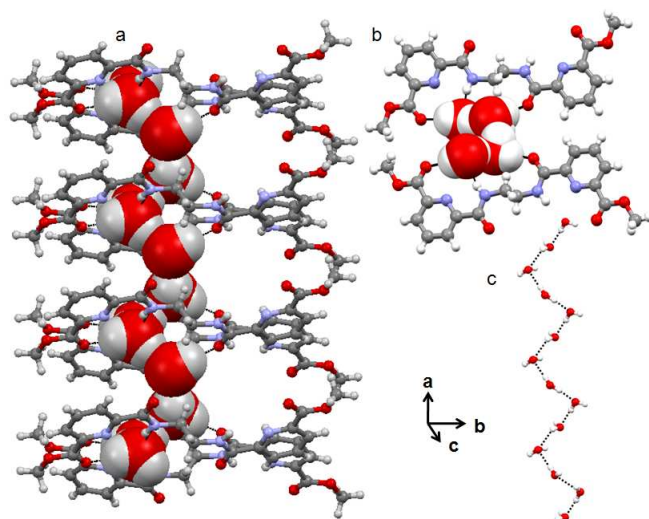
**Figure 2.** The solid state structures of bisamides (a) **1**, (b) **2**, (c) **3** and (d) **4** with water molecules. The intramolecular N-H...N and intermolecular N-H...O and O-H...O hydrogen bonds are shown as dotted lines.

Table 1. Hydrogen bonding parameters of bisamides **1, 2, 3** and **4**<sup>a</sup>

	D-H...A	D...H(Å)	H...A(Å)	D...A(Å)	D-H...A (°)
<b>1</b>	N2-H22...N1	0.87(3)	2.27(4)	2.649(4)	106(3)
	N2-H22...O2S	0.87(3)	2.16(3)	2.995(5)	160(3)
	O2S-H4S...O2	0.82(4)	2.07(4)	2.882(4)	170(3)
	O1S-H1S...O1Sa	0.92(3)	2.363(19)	2.761(5)	105(13)
	O1S-H2S...O3b	0.87(4)	1.97(4)	2.841(4)	173(5)
<b>2</b>	O2S-H3S...O1S	0.86(5)	1.91(5)	2.749(5)	165(5)
	N2-H2...O1SA	0.860	2.250	3.043(4)	153
	N2-H2...N1	0.860	2.250	2.650(3)	108
	O1SA-H40A...O2c	0.94(3)	2.08(3)	3.014(3)	177(3)
	<b>3</b>	N2-H2...O1S	0.860	2.350	3.168(3)
N2-H2...N1		0.860	2.320	2.706(2)	107
O1S-H40...O2		0.85(3)	2.18(3)	3.014(3)	169(3)
<b>4</b>	N2-H2...O1S	0.860	2.220	3.045(4)	160
	N2-H2...N1	0.860	2.340	2.725(4)	108
	O1S-H40...O3	0.87(5)	2.14(5)	2.948(4)	154(6)
	O1S-H41...O1Sd	0.94(6)	1.85(6)	2.771(4)	165(5)

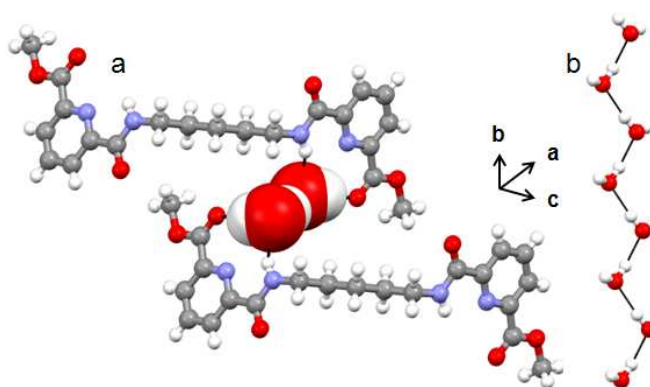
<sup>a</sup>Symmetry equivalent *a*:  $-1-x, y, -1/2-z$ , *b*:  $-x, -y, -z$ , *c*:  $2-x, 2-y, z$ , *d*:  $3/2-x, 1/2+y, -z$

The crystal structure further reveals that the water molecules act as bridge between individual bisamide **1** subunits and generate a supramolecular framework with diameter ca 13 Å and the internal diameter is ca 9 Å (Fig. 3a,b and Supporting Information Figure S7). The water molecule interacts with bisamide **1** host molecules by intermolecular hydrogen bonds (N2-H2...O2S, O2S-H4S...O2 and O1S-H2S...O3). The two water molecules also connected with each other through an intermolecular hydrogen bond (O2S-H3S...O1S) (Fig. 3a, b). This set of molecules containing one host molecule and two water molecules are connected with another set through intermolecular hydrogen bonding interactions between symmetrically identical water molecules (O2s-H4s...O2) to form the helical one dimensional water chain inside the supramolecular frameworks of bisamide **1** along crystallographic *a* axis (Fig. 3c). The unit cell-packing diagram exhibits the presence of four water helices with both left and right-handedness in a 1:1 ratio (Supporting Information Figure S8).



**Figure 3.** (a) Side view and (b) top view packing presentation of the water assisted supramolecular frameworks of bisamide **1**. (c) The hydrogen bonded helical water chain along crystallographic *a* direction.

For bisamide **4**, the molecules are assembled via bridging water molecules to form the supramolecular framework structure with an internal diameter ca 5 Å along the axis parallel to the crystallographic *b* axis (Supporting Information Figure S9). The water molecule interacts with bisamide **4** molecules by two intermolecular hydrogen bonds (Figure 4a). This set of molecules containing one host molecule and one water molecule are connected with another set through intermolecular hydrogen bond between symmetrically identical water molecules (O1S-H41...O1S) to form the zigzag one dimensional water chain inside the supramolecular frameworks of bisamide **4** along *b* axis (Figure 4b).



**Figure 4.** (a) Top view packing presentation of the water assisted supramolecular frameworks of bisamide **4**. (b) The hydrogen bonded zigzag water chain along crystallographic *b* direction.

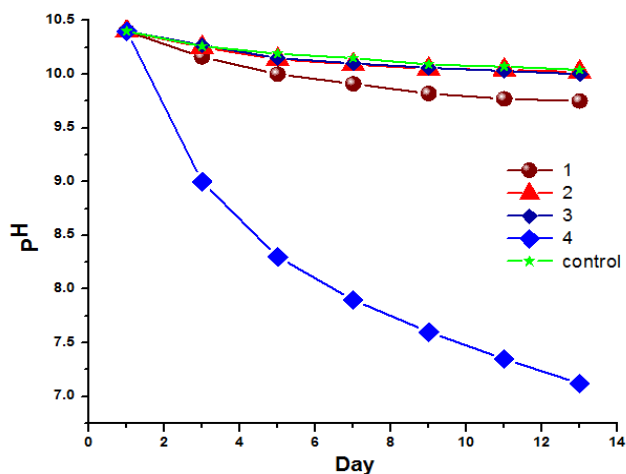
The proton transport ability of the bisamides were measured by U-tube experiment using pH gradient as the driving force (Supporting Information Figure S10).<sup>20</sup> At the source phase, 6.0 mL of hydrochloric acid solution at pH 5.2 was used and the receiving phase consisted of 6.0 mL of sodium hydroxide solution at pH 10.4. 25mL chloroform containing  $6.0 \times 10^{-3}$  mmol bisamides (**1**, **2** or **4**) were used as transport layer. For the control experiment, the exact same setup and procedure was used without bisamide. The proton transport activities of the bisamides were determined by measuring the steady decrease of pH in the receiving phase. This decrease in pH is attributed to a decrease in concentration of OH<sup>-</sup> ion in receiving phase due to neutralisation by transported H<sup>+</sup> ion from source phase. The proton transport rates through bisamides were determined by fitting the curves to equationn (1),<sup>21</sup>

$$\text{Rate} = Ae^{-k_1t} + Be^{-k_2t} + C \dots\dots\dots(1)$$

where  $k_1$  and  $k_2$  correspond to the bisamide and chloroform transport rate respectively. The  $k_2$  value in equation (1) was determined by the control experiment and kept fixed while fitting the data. Bisamides **1** and **4** were found to be active proton transporters (Figure 5). Whereas the transport ability of bisamide **2** and **3** is very close to that of control experiment (Figure 5). Beside this, bisamide **4** was found to be much active proton transporter ( $k_{\text{bisamid}} = 26.06 \times 10^{-1} \text{ day}^{-1}$ ) than bisamide **1** ( $k_{\text{bisamide}} = 6.410 \times 10^{-1} \text{ day}^{-1}$ ). The solubility of bisamide.HCl salt in aqueous HCl part is very close for bisamides **1-4** and not significant with respect to the solubility of bisamides in chloroform part (Supporting Information Figure S11).

## Conclusions

In conclusion, the solution and solid state analysis reveal the diverse assembly of encapsulated water in hybrid bisamides host. The bisamides containing bulky terminal groups and flexible spacers restrict the intermolecular hydrogen bond formation, but the addition of water promotes the self-assembly in well-defined pattern that has been directed by intermolecular N-H...O and O-H...O hydrogen bonds. In addition, from X-ray crystallography, the bisamide **1** stabilized the one



**Figure 5.** Comparison of proton transport ability of the bisamides **1**, **2**, **3** and **4** hydrates measured in U-tube experiment using pH gradient as the driving force.

dimensional hydrogen bonded helical water chain inside the supramolecular frameworks. In contrast, bisamide **2** adopted U-shape structure and entrapped an isolated water molecule. However, the bisamide **4** adopted an extended structure and stabilized one-dimensional hydrogen bonded zigzag water chains. From U-tube experiments using pH gradient as the driving force across a liquid chloroform phase, bisamide **4** was found to be much active proton transporter than bisamide **1**. These findings indicate that the modulation of spacers can be used as a crucial tool to control the assembly and function of bisamides.

## Experimental

### General

All chemicals were purchased from Sigma chemicals.

### Bisamides synthesis

The bisamides were synthesized by solution-phase methodology. All the bisamides were fully characterized by 500 MHz and 400 MHz  $^1\text{H}$  NMR spectroscopy,  $^{13}\text{C}$  NMR spectroscopy, FTIR spectroscopy and mass spectrometry. The bisamides 1-4 were characterized by X-ray crystallography.

**(a) Dimethyl pyridine 2,6 dicarboxylate (6):** 1.67g (10 mmol) pyridine 2,6 dicarboxylic acid was dissolved in 30 mL, cooled in ice-bath, 2 mL of  $\text{SOCl}_2$  was added drop wise and stirred for 8h. After completion of reaction the total liquid has evaporated under reduced pressure, the product was then dissolved in ethyl acetate and washed with fresh water repeatedly. The ethyl acetate layer was dried in anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure to obtained di-ester as white crystalline solid.

Yield: 1.687g (8.65 mmol, 86.5%)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz,  $\delta$ ppm): 8.274-8.258 (d, 2H,  $J=7$  Hz, aromatic protons), 8.005-7.974 (t, 1H,  $J_1=7.5$  Hz,  $J_2=8.0$  Hz, aromatic proton), 4.012 (s, 6H, 2 x COOMe).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz,  $\delta$ ppm): 164.91, 148.07, 138.29, 127.92, 53.068. FT-IR (cm $^{-1}$ ): 3452, 3063, 2969, 1742, 1572, 1438,

1290, 1246. Anal. calcd for  $\text{C}_9\text{H}_9\text{NO}_4$  (195.05): C, 55.39; H, 4.65; N, 7.18. Found: C, 55.42; H, 4.67; N, 7.07.

**(b) 6-(Methoxycarbonyl) picolinic acid (7):** 1.66 g (8.51 mmol) compound **6** was dissolved in 50 mL of methanol water mixture (9:1), cooled and 340 mg of NaOH was added and stirred for 6h. Then methanol was evaporated under reduced pressure, about 20 mL water was added and washed with diethylether. The water portion was acidified with dilute HCl solution, the compound was extracted with ethyl acetate. The organic layer was then dried over anhydrous  $\text{Na}_2\text{SO}_4$  and dried under reduced pressure. The crude was purified with column chromatography using DCM: Methanol as eluent.

Yield: 838 mg (4.63 mmol, 54.4%)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz,  $\delta$ ppm): 8.237-8.200 (m, 2H, aromatic protons), 8.167-8.143 (m, 1H, aromatic proton), 3.917 (s, 3H, COOMe).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz,  $\delta$ ppm): 165.80, 164.91, 138.97, 127.69, 127.08, 52.64. FT-IR (cm $^{-1}$ ): 3422, 2925, 2854, 1726, 1700, 1581, 1458, 1431, 1325, 1304, 1261. Anal. calcd for  $\text{C}_8\text{H}_7\text{NO}_4$  (181.04): C, 55.04; H, 3.89; N, 7.73. Found: C, 55.11; H, 3.94; N, 7.68.

**(c) Bisamide 1:** Acid chloride derivative of compound **7** was prepared by refluxing 815 mg compound **6** in 10 mL thionyl chloride. 895 mg (4.5 mmol) of acid chloride derivative was dissolved in dry DCM, cooled in ice-bath. Then 625  $\mu\text{L}$  (4.5 mmol) of dry triethylamine was added drop wise with stirring followed by the addition of 232  $\mu\text{L}$  (2.25 mmol) ethylenediamine. After 12h the solution was taken in separating funnel, washed with water, the organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate:hexane (1:1) as eluent.

Yield: 627 mg (1.63 mmol, 72.4 %)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz,  $\delta$ ppm): 8.904 (b, 2H, 2 x NH), 8.423-8.406 (d,  $J=8.5$  Hz, 2H, aromatic protons), 8.239-8.222 (d,  $J=8.5$  Hz, 2H, aromatic protons), 8.030-7.997 (t,  $J_1=8.0$  Hz,  $J_2=8.5$  Hz, 2H, aromatic protons), 4.045 (s, 6H, 2 x COOMe), 3.802-3.790 (m, 2H, aliphatic protons).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz,  $\delta$ ppm): 165.15, 163.98, 150.34, 146.29, 138.55, 127.25, 125.78, 52.98, 29.68. FT-IR (cm $^{-1}$ ): 3407, 2925, 2854, 1723, 1657, 1546, 1436, 1319, 1137. Anal. calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_6$  (386.12): C, 55.96; H, 4.70; N, 14.50. Found: C, 55.93; H, 4.73; N, 14.45.

**(d) Bisamide 2:** Same procedure like bisamide **1** but with trimethylenediamine.

Yield: 636 mg (1.59 mmol, 70.7 %)

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz,  $\delta$ ppm): 8.749 (b, 2H, 2 x NH), 8.220-8.185 (m, 6H, aromatic protons), 3.927 (s, 6H, 2 x COOMe), 3.407-3.341 (m, 4H, aliphatic protons), 1.833-1.806 (m, 2H, aliphatic protons).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz,  $\delta$ ppm): 165.46, 164.22, 150.73, 146.70, 138.80, 127.52, 125.80, 53.32, 36.97, 29.48. FT-IR (cm $^{-1}$ ): 3560, 3328, 2957, 1723, 1669, 1530, 1441, 1297, 1248, 1159.

**(e) Bisamide 3:** Same procedure like bisamide **1** but with putrescine.

Yield: 662.6 mg (1.60 mmol, 71.1 %).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz, δppm): 8.618 (b, 2H, 2 x NH), 8.220-8.184 (m, 6H, aromatic protons), 3.916 (s, 6H, 2 x COOMe), 3.374-3.348 (m, 4H, aliphatic protons), 1.582-1.589(m, 4H, aliphatic protons). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz, δppm): 165.43, 164.12, 150.54, 146.81, 138.49, 127.15, 125.46, 59.91, 39.24, 27.08. FT-IR (cm<sup>-1</sup>): 3550, 3328, 2929, 1734, 1668, 1535, 1441, 1297, 1253, 1143.

**(f) Bisamide 4:** Same procedure like bisamide **1** but with cadaverine.

Yield: 663 mg (1.55 mmol, 68.9 %)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz, δppm): 8.38 (b, 2H, 2 x NH), 8.216-8.179 (m, 4H, aromatic proton), 8.011-7.992 (d, *J* = 8 Hz, 2H, aromatic protons), 4.006 (s, 6H, 2 x COOMe), 3.511-3.477 (m, 4H, aliphatic protons), 1.742-1.723 (m, 4H, aliphatic protons), 1.527-1.492(m, 2H, aliphatic protons). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz, δppm): 165.37, 163.80, 150.65, 146.72, 138.85, 127.44, 125.74, 53.21, 39.71, 29.62, 24.66. FT-IR (cm<sup>-1</sup>): 3511, 3311, 2940, 1734, 1669, 1546, 1436, 1292, 1236, 1137.

### NMR experiments

All NMR studies were carried out on a Bruker ADVANCE 500 MHz spectrometer at 278 K. Compound concentrations were in the range 1–10 mM in CDCl<sub>3</sub> and (CD<sub>3</sub>)<sub>2</sub>SO.

### FTIR spectroscopy

All reported solid-state FTIR spectra were obtained with a Perkin Elmer Spectrum RX1 spectrophotometer with the KBr disk technique.

### Mass spectrometry

Mass spectra were recorded on a Q-ToF Micro YA263 high-resolution (Waters Corporation) mass spectrometer by positive-mode electrospray ionization.

### Single crystal X-ray diffraction study

Single crystal X-ray analysis of bisamides 1-4 was recorded on a Bruker high resolution X-ray diffractometer instruments with MoK $\alpha$  radiation. Data were processed using the Bruker SAINT package and the structure solution and refinement procedures were performed using SHELX97.<sup>23</sup> CCDC 1000665, 918262, 918259 and 918261 contain the supplementary crystallographic data for bisamides 1-4 respectively.

### Proton Transport

The proton transport ability of the bisamides was measured by U-tube experiment using pH gradient as the driving force. For source phase, 6.0 mL of hydrochloric acid solution at pH 5.2 was used. For receiving phase, 6.0 mL of sodium hydroxide solution at pH 10.4 was used. 25mL chloroform containing 6.0x10<sup>-3</sup> mmol bisamides (1, 2 or 4) were used as transport layer. For the control experiment, the exact same setup and procedure was used without bisamide. The proton transport activities of the bisamides were determined by measuring the steady decrease of pH in the receiving phase.

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(19) Crystal data: Bisamide **1**:  $C_{18}H_{18}N_4O_6 \cdot 4(H_2O)$ ,  $M_w = 458.43$ , monoclinic,  $C2/c$ ,  $a = 6.886(7) \text{ \AA}$ ,  $b = 19.68(2) \text{ \AA}$ ,  $c = 16.336(19) \text{ \AA}$ ,  $\alpha = 90^\circ$   $\beta = 100.08(2)^\circ$ ,  $\gamma = 90^\circ$ ,  $V = 2180(4) \text{ \AA}^3$ ,  $Z = 4$ ,  $d_m = 1.397 \text{ Mg m}^{-3}$ ,  $T = 296$ ,  $R1 = 0.0647$  and  $wR2 = 0.2005$  for 2051 data with  $I > 2\sigma(I)$ . Bisamide **2**:  $C_{19}H_{20}N_4O_6(H_2O)$ ,  $M_w = 418.41$ , orthorhombic,  $P2_12_12$ ,  $a = 21.196(11) \text{ \AA}$ ,  $b = 4.605(3) \text{ \AA}$ ,  $c = 10.551(6) \text{ \AA}$ ,  $V = 1029.9(10) \text{ \AA}^3$ ,  $Z = 2$ ,  $d_m = 1.349 \text{ Mg m}^{-3}$ ,  $T = 296$ ,  $R1 = 0.0379$  and  $wR2 = 0.1193$  for 1406 data with  $I > 2\sigma(I)$ . Bisamide **3**:  $C_{20}H_{22}N_4O_6(H_2O)$ ,  $M_w = 432.43$ , monoclinic,  $C2/c$   $a = 27.963(13) \text{ \AA}$ ,  $b = 5.091(2) \text{ \AA}$ ,  $c = 16.890(8) \text{ \AA}$ ,  $\alpha = 90^\circ$   $\beta = 118.873(7)^\circ$ ,  $\gamma = 90^\circ$ ,  $V = 2105.6(16) \text{ \AA}^3$ ,  $Z = 4$ ,  $d_m = 1.364 \text{ Mg m}^{-3}$ ,  $T = 296$ ,  $R1 = 0.0508$  and  $wR2 = 0.1631$  for 2275 data with  $I > 2\sigma(I)$ . Bisamide **4**:  $C_{21}H_{24}N_4O_6 \cdot 2(H_2O)$ ,  $M_w = 464.47$ , monoclinic,  $C2$ ,  $a = 18.863(16) \text{ \AA}$ ,  $b = 4.534(4) \text{ \AA}$ ,  $c = 14.980(12) \text{ \AA}$ ,  $\alpha = 90^\circ$   $\beta = 113.37(2)^\circ$ ,  $\gamma = 90^\circ$ ,  $V = 1176.1(17) \text{ \AA}^3$ ,  $Z = 2$ ,  $d_m = 1.312 \text{ Mg m}^{-3}$ ,  $T = 296$ ,  $R1 = 0.0338$  and  $wR2 = 0.1054$  for 1608 data with  $I > 2\sigma(I)$ . CCDC 1000665, 918262, 918259 and 918261 contain the crystallographic data for bisamides **1-4** respectively.

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## TOC Graphic

**Assembly of encapsulated water in hybrid bisamides: Helical and zigzag water chains**

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The addition of water promotes the self-assembly of hybrid bisamides by bridging between the molecules and stabilized the helical or zigzag one dimensional water chains.

