

Self-Assembly

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Self-Assembly of Size-Controlled *m*-Pyridine–Urea Oligomers and Their Biomimetic Chloride Ion ChannelsHualong Chen[†], Yajing Liu[†], Xuebo Cheng, Senbiao Fang, Yuli Sun, Zequn Yang, Wei Zheng, Xunming Ji,^{*} and Zehui Wu^{*}

Abstract: The *m*-pyridine urea (mPU) oligomer was constructed by using the intramolecular hydrogen bond formed by the pyridine nitrogen atom and the NH of urea and the intermolecular hydrogen bond of the terminal carbonyl group and the NH of urea. Due to the synergistic effect of hydrogen bonds, mPU oligomer folds and exhibits strong self-assembly behaviour. Affected by folding, mPU oligomer generates a twisted plane, and one of its important features is that the carbonyl group of the urea group orientates outwards from the twisted plane, while the NHs tend to direct inward. This feature is beneficial to NH attraction for electron-rich species. Among them, the trimer self-assembles into helical nanotubes, and can efficiently transport chloride ions. This study provides a novel and efficient strategy for constructing self-assembled biomimetic materials for electron-rich species transmission.

Introduction

Chloride, as the most abundant free anion in the body, is transported across plasma membranes by carriers or ion channels. Chloride channels are widely distributed in the body and involved in numerous physiological processes, including the regulation of cell volume,^[1] the stability of membrane potential,^[2] signal transduction,^[3] and transepithelial transport.^[4] The malfunction of chloride ion transport can lead to a variety of “channel diseases”, such as congenital myoto-

nia,^[5] recessive hereditary systemic myotonia, cystic fibrosis,^[6] and hereditary kidney stone disease.^[7] Therefore, in recent years, the study of artificial chloride ion channels or carriers that can mimic the function of natural ion channels has not only furthered our understanding of ion migration mechanisms but also helped elucidate the potential applications of these materials in ion transport-related diseases.^[8] Based on single molecule or self-assembled architectures, such as cyclodextrins, cyclic peptides, aromatic macrocycles, aromatic urea derivatives and iodobenzo derivatives, various strategies for synthesizing artificial chloride ion channels or carriers have been introduced.^[8a,9] However, the design of ion channels based on the self-assembly of small molecules still faces great challenges because monomer preassembly ability, hydrophilicity and hydrophobicity as well as the stability and geometric configuration of the assembly are difficult to control.^[8d,9c,10]

Compared with macrocyclic channels that are difficult to synthesize and have low yields, oligomers with easy-to-modify structures, various types and high synthesis yields have more advantages in constructing channels through folding and self-assembly.^[11] Aromatic oligourea is one of these attractive chemical moieties for building channels because they can form rigid and stable conformations,^[12] by introducing different numbers of hydrogen bonds along the backbones to limit the conformation degrees of freedom.^[12a,13] In previous reports, the backbones of the most widely used aromatic oligoureas were constrained by intramolecular hydrogen bonds between the urea NH groups and adjacent oxygen atoms of ester carbonyl or alkoxy groups (Figure 1a).^[14] However, such oligoureas cannot form intermolecular hydrogen bonds due to lack of free NH and O, which disfavors self-assembly. We propose a new design strategy that combines intra and intermolecular hydrogen bonding interactions, allowing the oligoureas to self-assemble into supramolecular systems, such as hollow nanotubes, nanowires, and nanomicrotubes.

Other consideration is that urea groups are widely used in the design of chloride ion carriers or channels because they can form N–H...Cl hydrogen bonds with chloride ions.^[8b,9f,j] An *m*-pyridine urea (mPU) monomer unit is used to construct aromatic urea oligomers (Figure 1b); this strategy offers the following advantages: (1) A stable hexagonal form is likely to be formed by intramolecular hydrogen bonds, involving the nitrogen atom of pyridine and the adjacent urea NH bond. This intramolecular hydrogen bonding induces the orientation of the carbonyl group and NH of the mPU oligomer to be completely different from the orientation of previous aro-

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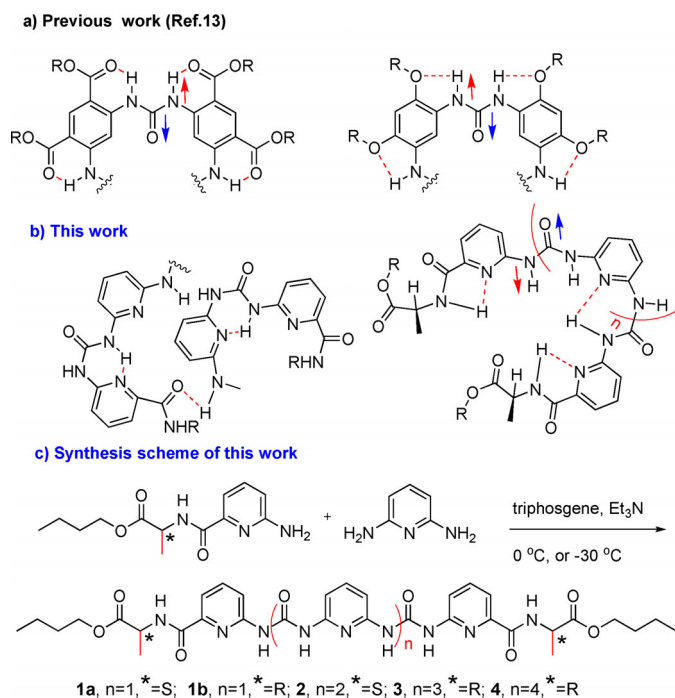


Figure 1. Design of aromatic oligourea backbones bound by hydrogen bonds and a synthetic scheme accessing the R/S alanine–pyridine oligourea derivatives. The blue arrow represents the direction of the carbonyl, the red arrow represents the direction of the NH group.

matic oligoureas (Figure 1b).^[14] (2) Intramolecular hydrogen bonds can be introduced between the NH and the terminal C=O group of oligomers. (3) An intermolecular hydrogen bond may be formed between a terminal carbonyl group in one oligomer and NH of a urea or a terminal amide in another oligomer. All three types of hydrogen bonds in the mPU oligomer promote the formation of a self-assembled supramolecular structure. Because the nitrogen atom of the pyridine of the mPU oligomer is electron-withdrawing, it can interact with the NH of adjacent urea, which is likely to form hydrogen bonds (N–H...Cl) with chloride ions consequently. Therefore, the supramolecular structures formed by self-assembly of mPU oligomers are inclined to transport chloride ions in the form of channels. The results show that small linear organic molecules can be folded into pseudomacrocycles or foldamers and used as biomimetic organic nanotubes for the transport of chloride ions or electron-rich species. To the best of our knowledge, although there are many different kinds of amide or urea oligomers used in cation channel research,^[11a–g] this is the simplest oligourea derivative to construct chloride ion or other electron-rich species channels.

Results

The folded conformation of the mPU oligomer in the solid was confirmed by single-crystal analysis

To achieve the goal of multiple hydrogen bonding synergies, a series of mPU oligomers were designed and

synthesized (Figure 1c). Oligomers **1–4** were obtained by altering the reaction temperature and the ratio of pyridinodi-amine derivatives to triphosgene. After obtaining the target compound, we first tried to investigate the conformation of the oligomer under solid conditions by single crystal analysis. Under various crystallization conditions, single crystals of **1a**, **1b** and **2** were obtained (Table S1). The crystal structure of **1a** (Figures 2a, S1a, S4 and Tables S2–7) reveals strong intramolecular hydrogen bonding between the NH group of the terminal amide group and the C=O group of *n*-butyl ester (Figure 2a). In addition, three other strong intramolecular hydrogen bonds are formed in **1a** between the pyridine N atom and the NH of amide or urea in the molecule. These intramolecular hydrogen bonds distort the original linear backbone of the molecule into planarity and form a pseudo-macrocyclic (Figures 2a, S1a and S4). Similar conformations are observed in the crystal structure of **1b** (Tables S1 and S8–13 and Figures 2b, S2a and S5).

With increased number of mPU repeating units, oligomer **2** is also able to form a similar asymmetric pseudomacrocyclic (Figures 2c, S3a, S6 and Table S1). In the folded conformation of **2**, three strong intramolecular hydrogen bonds exist between the pyridine N atom and the NH of amide or urea

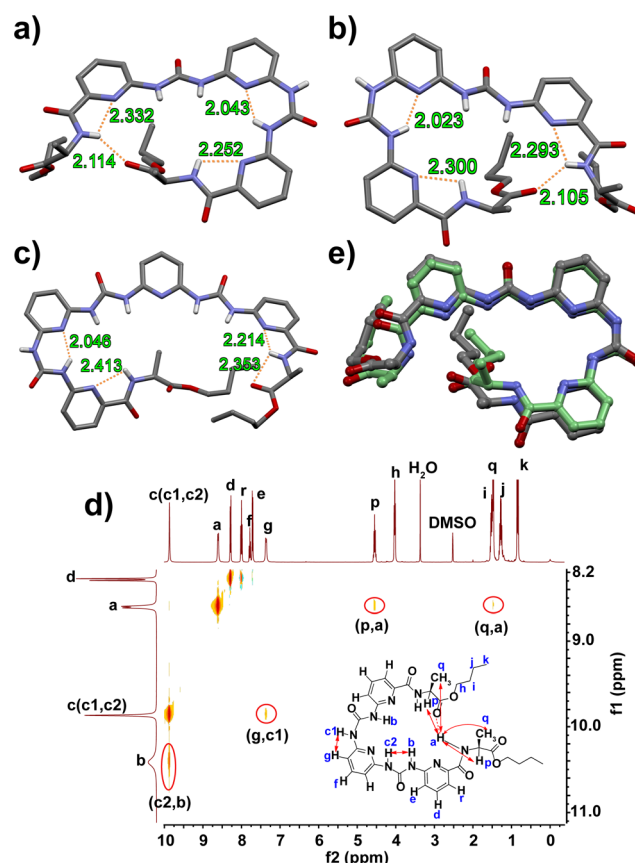


Figure 2. The asymmetric pseudomacrocyclic structures of a) **1a**, b) **1b** and c) **2**. d) Partial NOESY spectra containing major NOEs revealed the pseudomacrocyclic configuration of **1a** in $[\text{D}_6]\text{DMSO}$ (8 mM, 25 °C, 400 MHz, mixing time: 300 ms); red arrows represent interactions. e) The stacked profile between the DFT-optimized geometry (light green) and the single-crystal X-ray structure of **1a** (dark grey).

(Figure 2c). However, it is more distorted than those in **1a,b** and the dihedral angle formed by the four pyridine groups is approximately 30.46° (Figure S3c and Tables S14–19). The additional pyridine might increase the stiffness of the molecule and contribute to the greater deformation, resulting in the weaker terminal interaction in **2**. From the representative single crystal structures of **1a,b** and **2**, it can be seen that the urea carbonyl group of the mPU oligomer directs outward of the twisted plane and most of its NHs direct into the twisted plane.

The folded conformation of the mPU oligomer in solution was inferred by 2D NMR spectroscopy

Whether the pseudomacrocyclic of **1a** and **1b** can exist in solution condition is detected by 2D NMR experiments. ^1H NMR and ^{13}C NMR signals of **1a** in $[\text{D}_6]\text{DMSO}$ were assigned (Figure S7a–d). Subsequently, the conformation of the solution phase of **1a** was examined by the nuclear Overhauser effect (NOE) correlations. It can be seen from Figure 2d that there are obvious NOE cross peaks of urea NH (c1) and pyridine hydrogen (g) (Figure S7e), which indicates that NH (c1) is directed out of the pseudomacrocyclic. Similarly, if urea NH (b) is directed out of the pseudomacrocyclic, NH (b) and H (e) on the pyridine ring will have NOE cross peaks (Figure 2d and S7e). However, the peak was not found, indicating that NH (b) directs inward the pseudomacrocyclic (Figure 2d and S7e). Similar to NH (b), NH (a) of a terminal amide directs into the pseudomacrocyclic (Figure 2d and S7e). The NOE data also suggests that the carbonyl groups of urea and amide are directed to the outside of the pseudomacrocyclic. Except for the urea NH (c1), the other NHs are directed to the inside of the pseudomacrocyclic (Figure 2d and S7e). NH (a) has a strong NOE effect with protons p and q (Figure S7e,f). The above results are in accord with the analytical data of a single crystal of **1a**, which indicates that the pseudomacrocyclic conformation of **1a** exists in DMSO solution. That is, the orientations of the carbonyl group and NH are consistent in solid or liquid phases.

The trend in the folding conformation of the mPU oligomer is predicted by DFT calculations

To further study the conformational change trend of mPU oligomers with the increase of repeating units, quantum chemistry calculations was performed.^[15] Taking **1a** as an example, the most stable configuration calculated by density functional theory (DFT) calculations is closer to single crystal structure than Hartree–Fock and semi-empirical methods (Figure 2e and Table S20). Therefore, the subsequent optimization and frequency analysis of mPU oligomers are performed using the DFT method. The pseudomacrocyclic formed by **1a** has a very high coplanarity (Figure 2e), but the planarity of **2** is more distorted (Figure S9). Through further DFT calculations, **3** tends to fold into S-shape (Figure S10).

Therefore, we speculate that with the increase of repeating units, mPU oligomers tend to be helix folding.

mPU oligomers exhibit strong self-assembly behaviour

We further explored the self-assembly behaviour of mPU oligomers. In the unit cell of **1a**, intermolecular hydrogen bonds are formed between adjacent molecules and the dihedral angle formed by the two molecules is approximately 67.35° (Figures 3a and S1b,c). Induced by the three types of intermolecular hydrogen bonding, molecules of **1a** self-assemble along the *oa* axis to form a spiral two-holed nanotube (Figure 3c,e). Interestingly, in the *oc* axis direction, there is also a set of intermolecular hydrogen bonds between two **1a** molecules (Figure 3b). With these interactions, oligomer **1a** is arranged in sheets (Figure S1e). Notably, a single two-holed nanotube and another anti-parallel nanotube are further aggregated into a porous nanomaterial with the help of the intermolecular hydrogen bonding of $\text{N6} \cdots \text{O3i}$ (Figure S1f). What's more, the nanotubes formed by **1a** in a mixed solvent containing THF and *n*-hexane can also be observed by transmission electron microscope (Figure 3g,h). The aggregation mode of **1b** is similar to that of

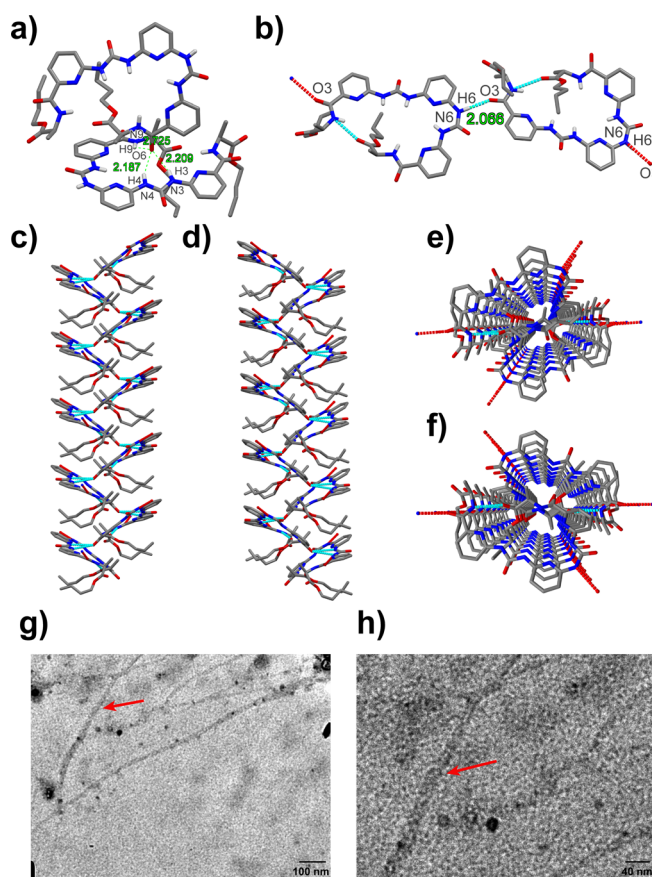


Figure 3. Intermolecular hydrogen bonding of **1a** along the *oa* axis (a) and *oc* axis (b). The side views of **1a** (c) and **1b** (d), top views of **1a** (e) and **1b** (f) of the helical tubules obtained from the crystals. TEM images of **1a** (g,h) at different scales; the nanotube is marked with a red arrow.

1a in the crystal, except that the spiral aggregation direction is opposite (Figures 3d,f and S2d). Similar nanotubes are not found in the crystal of **2**, which may be due to the poor planarity of the molecule or DMSO disrupting the hydrogen bond between the molecules of **2**.

The aggregation of the oligomers in solution was further investigated by ^1H NMR analysis. In CDCl_3 containing $[\text{D}_6]\text{DMSO}$, as the ratio of $[\text{D}_6]\text{DMSO}$ increases, the ^1H NMR signal of **1a** gradually exhibits well-resolved peaks; that is, the hydrogen bonding gradually weakens, which indicates that the self-assembly of **1a** is affected by the solvent (Figure 4a). As mPU repeating units increasing, even in $[\text{D}_6]\text{DMSO}$, the signals of the amide and aromatic protons of **4** either broaden or become invisible, indicating that the molecular motion of oligomers is further limited and its aggregation is enhanced (Figure S8). Both single crystal analysis and NMR experiments show that mPU oligomers possess strong self-assembly ability, even in the polar solvent DMSO.

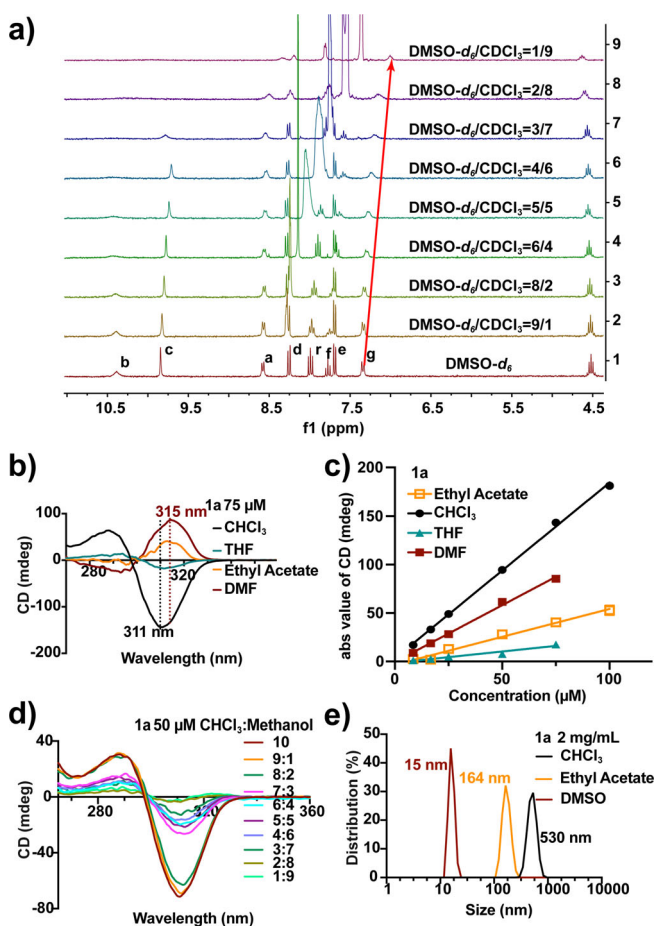


Figure 4. a) The ^1H NMR spectra of **1a** (20 μM) in different $[\text{D}_6]\text{DMSO}/\text{CDCl}_3$ solvent mixtures at room temperature. b) The CD spectra of 75 μM **1a** in different solvents. c) The CD spectra value is positively correlated to the concentration of **1a** in different solvents. $Y = 1.814X + 3.199$ ($R^2 = 0.9984$, $P < 0.0001$, CHCl_3), $Y = 1.171X - 0.4443$ ($R^2 = 0.9954$, $P < 0.0001$, THF), $Y = 0.5758X - 3.298$ ($R^2 = 0.9775$, $P < 0.0001$, ethyl acetate), $Y = 2323X - 1.274$ ($R^2 = 0.9984$, $P < 0.0001$, DMF) d) CD spectra of **1a** in different ratios of chloroform and methanol. e) Particle size of **1a** (2 mg mL^{-1}) in CHCl_3 , ethyl acetate and DMSO, respectively.

Aggregation of mPU oligomer in solution was investigated with CD spectroscopy

The circular dichroism (CD) spectrum of **1a** showed a strong negative Cotton effect at wavelength of 311 nm in CHCl_3 , indicating the formation of a right-handed helical supramolecular structure (Figures 4b and S11). The CD signal did not shift but its intensity raised linearly as **1a** concentration increased, suggesting that the aggregation form has not changed (Figures 4c and S11). However, for **1b**, which has side chains with an *R*-configuration, the CD signal was the opposite of that of **1a**, which is consistent with the results of single crystal diffraction, implying that the terminal side chain determines the aggregation direction of the oligomer (Figure S12). The solvent effect on **1a** self-assembly has also been investigated. When the polarity of the solvent was increased, the maximum wavelength was red shifted, and the CD signal was even reversed from a strong negative effect to a positive Cotton effect, indicating that the handedness of the helix has switched (Figure 4d). When **1a** was in a carbonyl-containing solvent such as ethyl acetate or DMF, the CD signal was opposite to the signal in a non-carbonyl solvent such as chloroform or THF (Figure 4b). This may be due to the competition between the carbonyl group and the hydrogen bonding sites of **1a**, which causes the aggregation direction to change. Temperature is another important factor affecting self-assembly. In our study, when the temperature was increased, the CD signal of **1a** did not change significantly in certain solvent conditions, indicating that the self-assembly ability of **1a** was not influenced by temperature (Figure S13). The CDs of **1b** and **2-4** were further studied (Figures S12 and S14-16), and their self-assembly behaviours are similar to those of **1a**. Conclusively, the aggregation of mPU oligomers is greatly affected by the chirality of the terminal side chain and solvent constituents, and not sensitive to temperature change.

The aggregation of mPU oligomer in different solvents has been studied using dynamic light scattering (DLS)

To investigate the influence of solvent effect on self-assembly, DLS experiment of **1a** (2 mg mL^{-1}) was carried out. In CHCl_3 , the average particle size of **1a** is approximately 530 nm and the distribution is wide (Figure 4e). The average particle size decreases to approximately 164 nm in ethyl acetate and approximately 15 nm in DMSO (Figure 4e). It can be explained that an intermolecular hydrogen bond is supposed be formed between the high polar solvent and **1a**, which might weaken the intermolecular hydrogen bonding between **1a** molecules. DLS experiments show that in weakly or moderately polar solutions, **1a** forms a supramolecule through self-assembly, and then a strong negative Cotton effect is observed. However, as the solvent polarity increased, the self-assembly behaviour of **1a** changed, the CD signal changed from negative to positive, and the average particle size of the aggregates gradually became smaller (Figure 4b).



The ability of **1a** to transport chloride ions was explored with the transmembrane experiment

Various detection means have revealed that mPU oligomers exhibit strong self-assembly behaviour. Next, it's time to validate whether it is suitable for electron-rich species transport. The nanotubes formed by self-assembly of **1a** have been clearly confirmed, so **1a** was selected as the research object of the channel. The ion transport capacity of **1a** was investigated by monitoring the fluorescence intensity of 8-hydroxypyrene-1,3,6-trisulfonic acid (HPTS) in large unilamellar vesicles (LUVs) with or without **1a**.^[11a,16] As Figure 5a shows, addition of **1a** can lead to fluorescence change by 44 %, which was caused by pH gradient driving ion transport. The corresponding EC_{50} value was determined by Hill analysis to be 10 μ M (mol % of transporter to lipid = 0.5, Figure 5e).^[17] The results suggest that the nanotubes formed in **1a** can be used as ion channels.

The transport mechanism of **1a** was explored

Several mechanisms might be responsible for the observed pH changes in HPTS-LUVs, such as Cl^-/OH^- antiport, Na^+/H^+ antiport, Na^+/OH^- symport and Cl^-/H^+ symport. To find out the most likely mechanism, a range of experiments were carried out. First, to test whether the metal ions are involved in the process of pH change in the vesicles, the types of metal counter ions outside the vesicles were changed (Li^+ , Na^+ , K^+ and Cs^+). The fluorescence intensity did not change significantly when different cations were used (Figure S17). It is an indication that little involvement of metal ions and the H^+/M^+ antiport or M^+/OH^- symport was excluded during the process.

Second, a halide-specific probe 6-methoxy-N-(3-sulfo-propyl) quinolinium (SPQ) was used to monitor the chloride ion concentration variation. As Figure 5b showed, the SPQ fluorescence was rapid quenched upon **1a** presence. The result suggests that Cl^- is one of the transported species. A

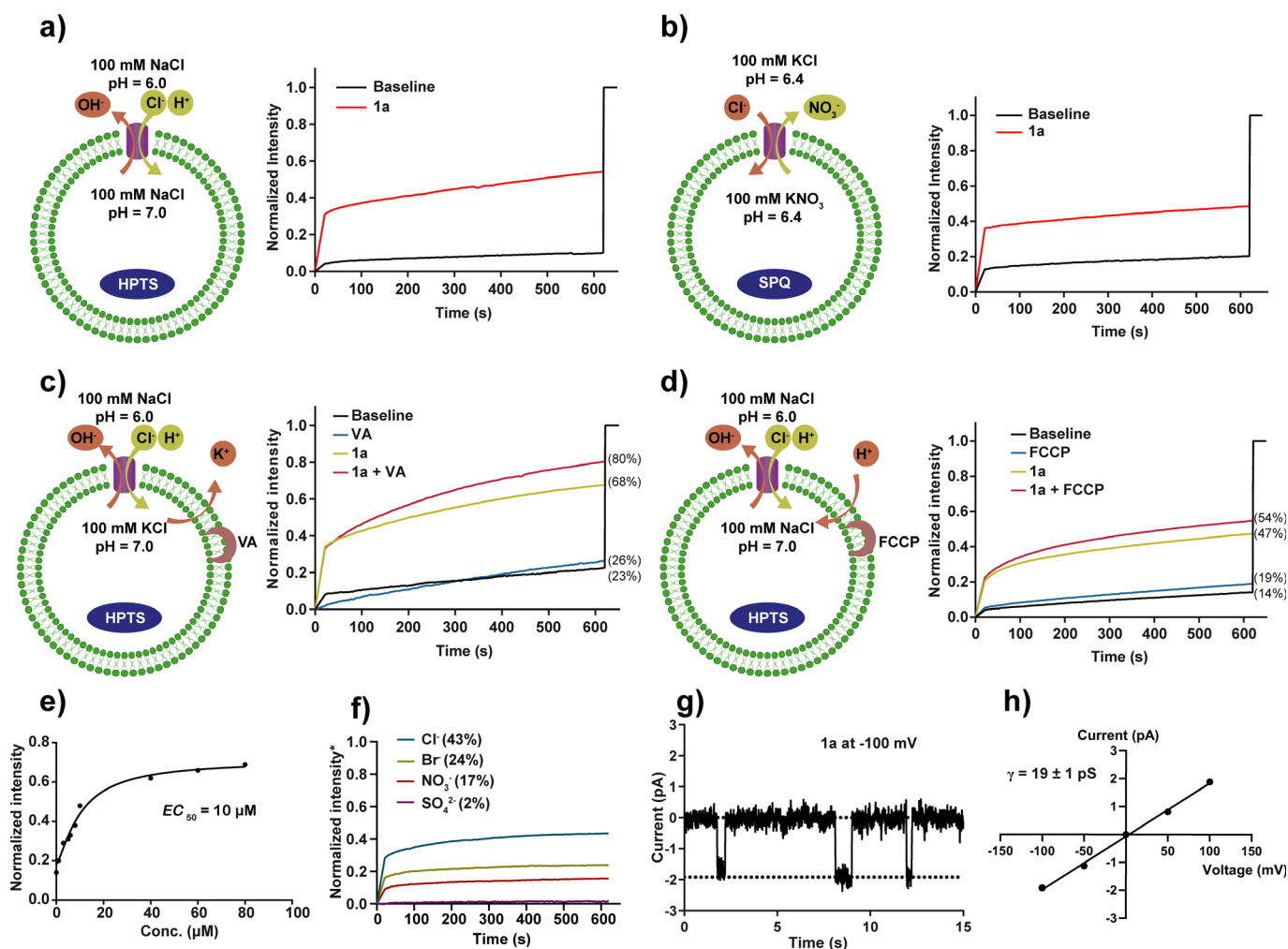


Figure 5. a) Transport selectivity of chloride ions by **1a** (10 μ M, mol % of transporter to lipid = 0.5) obtained from the HPTS assays. b) Changes in the fluorescence intensity of the chloride-sensitive SPQ dye after the addition of **1a** (10 μ M). c) Ion transport activities of **1a** (10 μ M) determined in the absence or presence of a potassium carrier, valinomycin (VA, 25 μ M). d) Ion transport activities of **1a** (10 μ M) determined in the absence or presence of a proton transporter, FCCP (1 mM). e) Determination of the EC_{50} value for the **1a**-mediated transport of chloride anions. f) Anion selectivity assayed for **1a** (* baseline corrected). g) Single current trace of **1a** recorded at -100 mV with symmetric baths (cis chamber = trans chamber = 1 M KCl). h) I-V curve for obtaining the Cl^- conductance (γ_{Cl^-}) of **1a**.

confocal imaging experiment was performed for reconfirmation. SPQ-encapsulated LUV was aggregated in 4-morpholineethanesulfonic acid buffer for live imaging. When **1a** was added, the fluorescence was rapidly quenched (see video, confocal_1a.mp4), whereas without **1a**, the fluorescence did not change significantly (see video, confocal_DMF.mp4). Furthermore, the selectivity of **1a** for the transmembrane transport of anions was also investigated. Changes in the fluorescence of HPTS-labeled vesicles in the presence of different anionic sodium salts (NaX , $\text{X}^- = \text{Cl}^-$, Br^- , NO_3^- or Na_2SO_4) were determined (Figure S18). Figure 5 f shows that **1a** has anion selectivity for the transport of chloride ions.

OH^-/Cl^- antitransport or H^+/Cl^- symtransport is the predominant mechanism in **1a** mediated ion transport. VA(valinomycin)-LUV^[18] and FCCP (carbonyl cyanide 4-(trifluoromethoxy)phenyl hydrazone)-LUV^[19] experiments were carried out and we try to deconstruct the two possible mechanisms. Under VA mediation, K^+ flows out of the LUV, which can be expected to induce OH^- or Cl^- efflux through the ion channel to maintain the overall charge balance. If the influx velocity of Cl^- through **1a** is higher than that of OH^- , the fluorescence intensity will not markedly change. However, after adding VA, the fluorescence intensity increased from 68% to 80% vs. (26–23%) without **1a** (Figure 5c), suggesting that the flow rate of OH^- was greater than that of Cl^- . In FCCP-LUV assay, due to the low pH outside the membrane, H^+ ions were able to flow into the membrane via FCCP. If the rate of Cl^- entering the membrane through **1a** is greater than the H^+ inflow rate, upon increasing the FCCP content, more H^+ will enter the membrane, which can be expected to mitigate the decrease in fluorescence intensity. However, in the presence of FCCP, the transport efficiency of **1a** did not improve significantly (e.g., (54–47%)—(19–14%), Figure 5d), indicating that the transport rate of H^+ was faster than that of Cl^- . The above results suggest that the transport mechanism of the ion channel formed by **1a** is OH^-/Cl^- reverse transport and H^+/Cl^- symport mechanism.

To confirm that **1a** uses a “channel” mechanism to achieve the transmembrane transport of chloride ions, a planar lipid bilayer patch clamp experiment was performed.^[90] Patch clamp experiments were performed at different voltages, and they showed a linear current–voltage relationship from +100 mV to –100 mV (Figure 5g). The calculated conductance of the ion channel formed by **1a** is $\gamma = 19 \pm 1$ pS (Figure 5h). Whether **1a** can transmit Br^- and NO_3^- , are also verified by patch clamp. No current signal was observed, indicating that **1a** is selective for chloride ion transport.

The interaction between **1a** and chloride was determined by ^1H NMR and MS experiments

In ^1H NMR titration experiments, with increasing chloride ion (TBACl) concentration, the protons of the urea-based NH and the terminal amide NH of **1a** were shifted to a low field (Figure S19), indicating that **1a** interacts with chloride ions through hydrogen bonding ($\text{N}-\text{H}\cdots\text{Cl}$). However, the gradient shift was slight, especially before **1a**/TBACl reached 1:1. This phenomenon may be attributed to the

strong hydrogen bond synergy of **1a** itself, and more chloride ions than expected are required to compete and break the original balance. Therefore, titration was not continued to determine the clear ratio after an obvious shift occurred at **1a**/TBACl = 1:5. The other straightforward evidence for the interaction of **1a** with chloride ions was obtained from Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR-MS) studies. The mass spectrum data provided a peak at $m/z = 726.277076$ (Figure S20), which corresponds to the [**1a** + Cl^-] complex in the solution. Both ^1H NMR titration and FT-ICR-MS results suggest that chloride ions can bind to **1a** molecules through $\text{N}-\text{H}\cdots\text{Cl}$ hydrogen bonding.

Molecular dynamics simulation of chloride ion transmembrane

To further simulate the process of chloride ion transmembrane, molecular dynamics calculations were carried out according to the methods reported in the literature (Figure S21–S23).^[20] It can be seen from Figure 6a that when the chloride ion is close to **1a**, the original intramolecular hydrogen bond interaction of **1a** is competed by the hydrogen bonds between the protons in the pseudomacrocycle of **1a** and the chloride ion (Figure 6b). When the chloride ion is located in the center of **1a**, the direction and distance of the hydrogen bond donor and acceptor in the original molecule will be interfered by the action of $\text{N}-\text{H}\cdots\text{Cl}$ (Figure 6c). This causes the diameter of the corresponding cavity increased (Figure 6c). Under the driving of the directional force, the chloride ion passes through the ring. During this process, the $\text{N}-\text{H}\cdots\text{Cl}$ hydrogen bond just formed gradually disappears (Figure 6d–f). Subsequently, the original intramolecular hy-

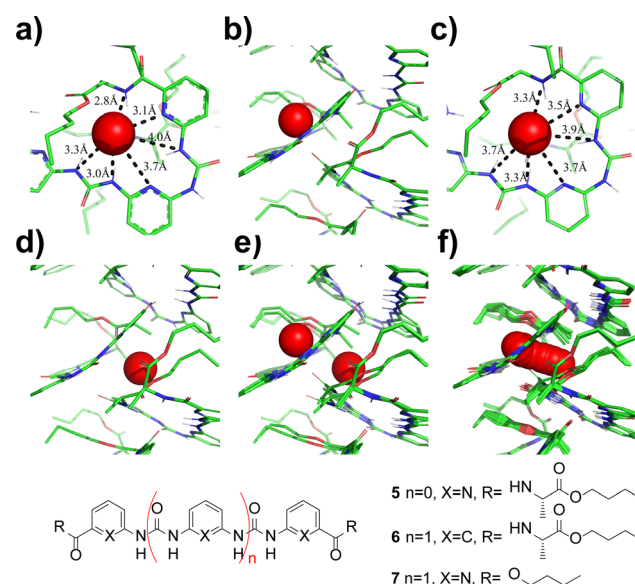


Figure 6. Molecular dynamics simulation of Cl^- crossing the pseudo-macrocycle at different stages. a) Front and b) side views of Cl^- approaching the center of the ring, c) front view of Cl^- located at the ring center, d) side view after Cl^- crosses the pseudo-macrocycle, e) stacked diagram before and after crossing, f) overlay profile of the whole process. Structures of compounds 5–7.



drogen bonds are recovered, and the pseudo-macrocylic skeleton of **1a** is restored to its original state (Figure 6e,f). Based on molecular dynamics simulation and Gaussian calculations, the animation process of **1a** transmission of chloride ions was made using Houdini (18.5.351) and After Effects (2020) animation software (see video, animation.mp4). It can be seen from the dynamic simulation results that **1a** can transport chloride ions thanks to the adjustable pseudo-macrocylic cavity and the N–H···Cl hydrogen bond interaction.

Discussion

It can be deduced from the results that mPU plays an important role for aggregation and the number of repeating units affects the self-assembly ability. To validate the hypothesis further, the other two molecules without the mPU units were synthesized for the control. Compound **5** is lack of pyridyl group and all pyridines of compound **6** are substituted by benzene (Figure 6). ¹H NMR and CD results showed that **5** was unable to self-assemble in weakly polar solvent (Figure S24, S25). There were no intramolecular hydrogen bonds of **6** in ¹H NMR (Figure S24). Though self-assembly can be formed, the Cotton effect and thermal stability of **6** are weaker than those of **1a** (Figure S25–S27). And the influence of hexagonal form hydrogen bond and terminal group hydrogen bond on the formation of pseudo-macrocycle was further compared by DFT calculation. Although mPU oligomers **7** whose terminal groups cannot form hydrogen bonds can form hexagonal form hydrogen bonds, they cannot form pseudo-macrocylic structures (Table S21). Similarly, compound **6** cannot form a pseudo-macrocycle because there is no synergy of hexagonal form hydrogen bonds (Table S21). These results suggest that mPU is essential for the intramolecular and intermolecular hydrogen bonds formation.

Meanwhile, most of the macrocycles formed in previous studies mainly transport cations.^[20c,d,21] It is speculated that the orientation of carbonyl in the macro or folding ring might be responsible for the non-transmission. Carbonyl group in amide, urea and other rigid macrocycles orient towards the ring center.^[20c] Carbonyl groups in flexible macrocycles direct vertically out of the ring surface.^[22] Both types of orientations contribute to the repulsion of chloride ions and failure transmission. However, the mPU oligomers designed in this paper are locked by multiple groups of strong hydrogen bonds and have a certain extent of rigidity, and their carbonyl positions are fixed and directed horizontally out of the ring. Therefore, the carbonyl groups of these oligomers will not interfere with the chloride ions. More importantly, the NH of urea of **1a** is directed to the center of the ring, which can form a quadruple N–H···Cl hydrogen bond, thereby promoting the transport of chloride ions. The ion transport efficiency of compounds **2**, **5** and **6** and the known chloride ion carrier perfluorohexyl iodide (**8**) are further compared. **1a** has the highest chloride ion transport efficiency (Figure S28). Although the highly lipophilic **1a** can be quickly inserted into the accessible phospholipid bilayer, a large amount of **1a** cannot be distributed into the bilayer and precipitates due to

the high lipophilicity, which leads to the low transmission efficiency of chloride ions. Therefore, it still needs further optimization.

Some features of the self-assembly or folding of mPU oligomers were summarized below. (1) hexagonal form intramolecular hydrogen bonding is the key factor for mPU to fold or self-assemble. (2) With the increase of mPU repeating units, the self-folding or self-assembly ability of these compounds is gradually enhanced. (3) As the polarity of the solvent increases, the self-assembly ability of the mPU derivative decreases, but the self-folding ability is still strong. (4) In certain solvent, the self-assembly or folding ability of mPU oligomer is not affected by temperature. The most essential feature of the chloride channel function of mPU oligomer is that the carbonyl group of urea is directed out of the twisted plane, and the NHs tend to be directed inward of the twisted plane. Combined with the regulation of the lipid solubility of the terminal group side chain, the number of pyridines in the ring, and the connection with different functional polymers, it is expected to develop specific self-assembly or single molecular channels for electron-rich species transport.

Conclusion

In summary, this paper uses a simple structure mPU as a repeating unit to construct a modifiable and foldable mPU oligomer. Under the action of intramolecular hydrogen bonds and intermolecular hydrogen bonds, these oligoureas exhibit strong folding and self-assembly behaviour, and their carbonyl groups tend to direct out of the twisted plane, and NH tend to direct into the twisted plane. These properties make mPU oligomers tend to transport electron-rich species. Among the prepared oligomers, oligoureas **1a** and **1b** form two-holed chiral helical nanotubes through hydrogen bonding, and the aggregation modes of **2**, **3** and **4** remain to be further studied. Under the action of the N–H···Cl hydrogen bond, **1a** with a dynamically reversible pore size selectively transports chloride ions. Altogether, the current work has established a class of compounds with excellent self-assembly capabilities that are expected to transport electron-rich species, which provides a molecular and supramolecular structural basis for the design of new, efficient and selective biomimetic channels.

Supporting information for this article is on website and includes experimental details, compound characterizations, X-ray single crystal diffraction data for compounds **1a**, **1b**, and **2** and X-ray data for the crystal structures (Deposition Numbers 1902154 (for **1b**), 1902155 (for **1a**), 1902158 (for **2**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures). The pdb file of the **1a**-popc-channel complex contains the original three-dimensional coordinates data. The video for confocal imaging and dynamic simulation.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chloride ion channels · hydrogen bonds · *m*-pyridine–urea oligomers · pseudomacrocycles · self-assembly

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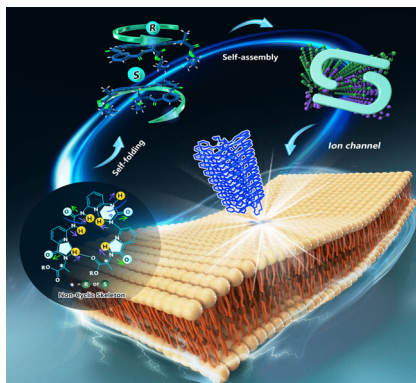
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Research Articles

Self-Assembly

H. Chen, Y. Liu, X. Cheng, S. Fang, Y. Sun,
Z. Yang, W. Zheng, X. Ji,*
Z. Wu* ————— ■■■—■■■

Self-Assembly of Size-Controlled *m*-
Pyridine–Urea Oligomers and Their
Biomimetic Chloride Ion Channels



Oligomers with distinct self-folding and self-assembly behaviour are constructed by using *m*-pyridine–urea repeating units, an important feature of which is that the urea carbonyl tends to point outward and the NH unit tends to direct inward. Among these oligomers, the trimer forms nanotubes, which can efficiently transport Cl[−] ions.