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Synthesis, crystal structure, and different local conformations of pyridine–imide oligomers

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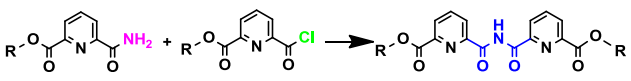
ABSTRACT

In this article, we report a new approach toward synthesis of pyridine–imide oligomers (PIOs). Using this approach, both dimer and trimer were one-pot synthesized from acylation of monomeric monoamide with monomeric dichloride. The yield of trimer was dependent on the alkoxyl terminals: it was 30% for methoyl group, whereas it was 95% for 3-chloro-1-propoxyl terminal. Acylation of dimeric monoamide with monomeric dichloride produced trimer, tetramer, and pentamer in a yield of 34%, 33%, and 28%, respectively. The synthesis was proposed to be mediated through an exchange between pyridine-2-carboxamide and pyridine-2-carbonyl chloride, both forming intramolecular or intermolecular hydrogen-bonds between pyridine–nitrogen and pyridine-2-amide hydrogen atoms. Crystal structure from three trimers with different terminal groups was reported. Analysis on the crystal structures revealed that these three trimers had different local conformations. The different local conformations were originated from the structural tunability of the imide unit in either the coplanarity or bond parameters.

1. Introduction

A biomacromolecule, such as nucleic acid and peptide is able to fold into secondary structures through noncovalent forces, for examples, hydrogen-bonding, hydrophilic, and hydrophobic interactions. Inspired by this, a number of synthetic foldamers have been developed in the past decades.[1] These foldamers have opened a way to mimic the secondary and higher structures and even functions of natural biomacromolecules.[2] They are constituted chemically by diverse building blocks varying from aliphatics to aromatics, for instances, aliphatic analogues of the α-peptides,[3,4] α-helix face mimetics by projecting the side chains of oligo-aromatics into an analogous fashion to the natural peptides,[5] aromatic oligoamides (AOAs),[1b–d] and others.[6–9] Among which AOAs are constructed from aromatics, such as pyridine-,[10] benzene-,[11–13] quinoline-,[14] and phenanthroline-derivatives[15,16] and hydrogen-bonding functions, such as amide,[10–16]urea,[17] and hydrazine.[18] The coherent intra-strand or inter-strand hydrogen-bonds formed between the aromatic units and hydrogen-bonding functions direct formation of either canonical helical conformations or linear hydrogen-bonding assembly.[1] One of the outstanding features of AOAs is the strong structural predictability due to the predictable hydrogen-bonding direction and rigidity of the molecular strand, as compared to the aliphatic analogues.

By selecting the imide as a hydrogen-bonding function, we have developed pyridine–imide oligomers (PIOs), a type of AOAs. Crystal structure revealed that the imide–hydrogen atom was able to form highly stable intra-strand hydrogen-bonds with the pyridine nitrogen atom, which compressed the molecular strand into a highly compact helix with every three pyridine and two imide units constituting a helical turn.[19] A way to synthesize the pyridine–imide function is through acylation of pyridine-2-carboxamide with pyridine-2-carbonyl chloride (Scheme 1). However, synthesis of PIOs is relatively difficult because the yield is relatively low, for example, the yield to trimer and tetramer is only about 15% and 10%, respectively.[19a] Thus, it is difficult for us to get longer oligomers than tetramer through such step-by-step synthesis. Herein, we present an approach toward synthesis of trimeric, tetrameric, and pentameric PIOs. This approach is based on a hydrogen-bonding enhanced exchange between pyridine-2-carboxamide and pyridine-2-carbonyl chloride.



Scheme 1. Formation of a typical pyridine–imide function.

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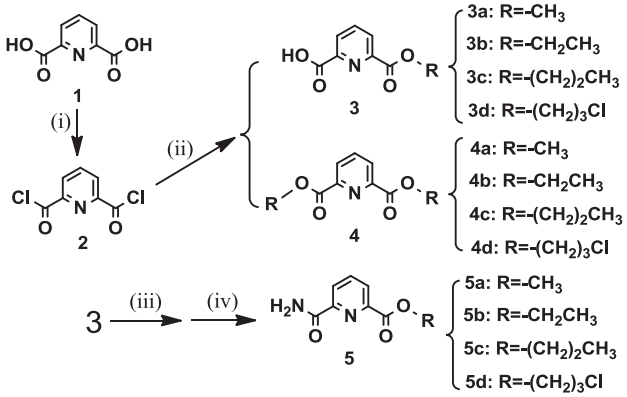
2. Results and discussion

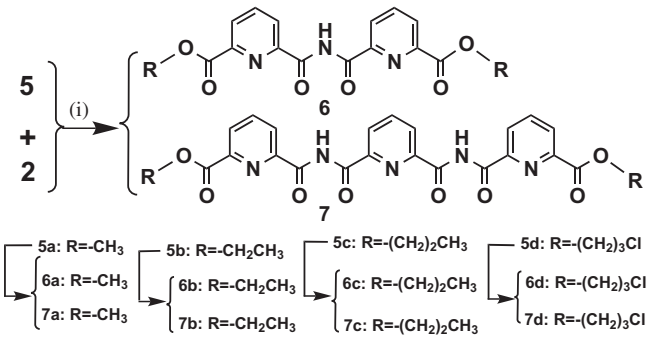
2.1. One-pot synthesis of dimeric and trimeric PIOs

Scheme 2 shows the synthetic procedure of the monomeric monoamide. Pyridine-2,6-dicarboxylic acid (**1**) was first converted into pyridine-2,6-dicarbonyl chloride (**2**), which was then reacted with 1.2 equivalence of alcohol to yield monomeric monoacid (**3**) and monomer (**4**). Reaction of **3** and $SOCl_2$ produced monomeric monochloride that was then converted into monomeric monoamide (**5**) by bubbling ammonia gas into the dichloromethane solution of the monochloride.



Scheme 2. Synthesis of monomeric monoamide (**5**). Reactants and conditions: (i) $SOCl_2$/reflux; (ii) alcohol (1.2 equiv), DIEA (1.2 equiv), THF/reflux, and then H_2O, yield: 50–70% for **3** and 30–40% for **4**; (iii) $SOCl_2$/reflux, and (iv) NH_3, CH_2Cl_2/rt, yield: 70–90% for **5**.

Trimeric PIO was synthesized from acylation of 2-alkoxycarbonyl-pyridine-6-carboxamide (**5**) and pyridine-2,6-dicarbonyl chloride (**2**) in a molar ratio of 1:0.7 (**5**:**2**) and this reaction yielded about 10–20% of trimer and more than 80% of **5** was recovered. Occasionally, the molar ratio of **5b** and **2** was adjusted to 1:2.5 and it was surprising that both dimer (**6b**) and trimer (**7b**) were isolated in a yield of 54% and 37%, respectively, whereas no unreacted **5b** was detected (Scheme 3). The total yield of **6b** and **7b** was 91%, meaning that **5b** was almost completely converted into products. A change in the molar ratio of **5b** and **2**, for example, into 1:2.0 and 1:1.5 lowered the yield of dimer (30–45%) and trimer (15–30%), accompanying 20–35% of **5b** unreacted.

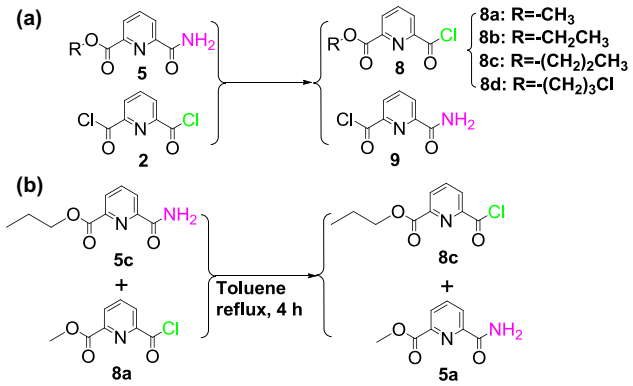


Scheme 3. Synthesis of dimer (**6**) and trimer (**7**) by acylation of monomeric momoamide with pyridine-2,6-dicarbonyl chlorides. Reactants and conditions: (i) toluene/reflux, overnight.

Replacement of ethoxyl group in **5b** with methoxyl or *n*-propoxyl yielded similar results (Scheme 3). When the molar ratio of **5a** and **2** was controlled as 1:0.7, trimer **7a** was isolated in a yield of 15%. However, if the molar ratio was adjusted as 1:2.5, both dimer **6a** and trimer **7a** were got in a yield of 60% and 30%, respectively. Similarly, trimer **7c** was isolated in a yield of 20% when the molar ratio of **5c** and **2** was 1:0.7. Adjustment of the molar ratio into 1:2.5 produced both dimer **6c** and trimer **7c** in a yield of 42% and 50%, respectively.

When 3-chloro-1-propoxyl was introduced, reaction of **5d** and **2** in a molar ratio of 1:0.7 produced trimer **7d** in a yield up to 95%. Dimer **6d** was isolated only in a yield of 5%. No **5d** was detected.

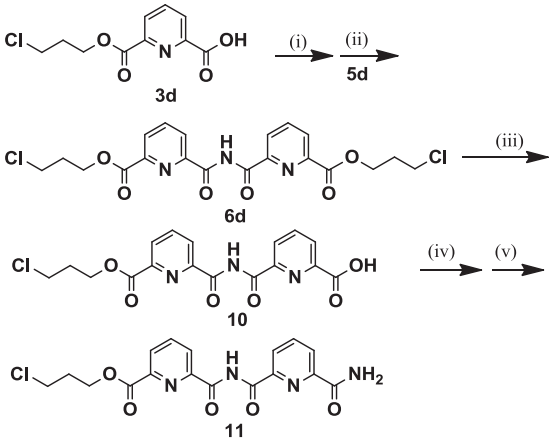
Formation of dimer **6a**, **6b**, **6c**, and **6d** suggests an exchange appears between pyridine-2-carboxamide and pyridine-2-carbonyl chloride (Scheme 4a). To address this, we preformed a reaction between **5c** and **8a** (Scheme 4b). 4 h later, the reaction yielded a dimeric product formed from condensation of **5c** and **8a**. TLC revealed trace of **5a** was detected, in addition to **8a**. ^1H NMR spectra further confirmed formation of **5a**. This strongly supports the amide/chloride exchange. The one-pot yield toward the dimer and trimer likely relates with solubility of the reactants. The solubility of 2-alkoxycarbonyl-pyridine-6-carbonyl chloride in toluene is in the sequence of **5a**<**5b**<**5c**<**5d**.



Scheme 4. The exchange between pyridine-2-carboxamide and pyridine-2-carbonyl chloride.

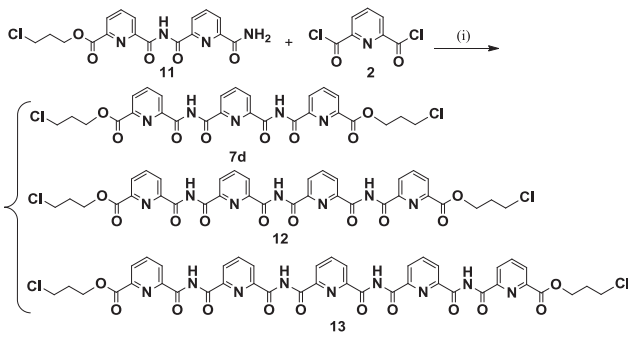
2.2. One-pot synthesis of trimeric, tetrameric, and pentameric PIOs

To further address the amide/chloride exchange, we performed acylation reaction of dimeric monoamide and **2**. Dimeric monoamide was synthesized by following the procedure in Scheme 5. Compound **3d** was converted into chloride and then reacted with **5d** to yielded dimer **6d** in a yield of 68%. Partial hydrolysis of **6d** in a mixture of dioxane and water (10:1 in v/v) by dropwise adding 1 M aqueous solution of NaOH inside produced dimeric monoacid (**10**) in a yield of 55%. Compound **10** was then converted into dimeric monochloride and then dimeric monomamide (**11**) in a yield of 90%.



Scheme 5. Synthesis of dimeric monoamide (**11**). Reactants and conditions: (i) $SOCl_2$/reflux; (ii) toluene/reflux, overnight; (iii), dioxane/H_2O (10:1), NaOH (1 M), yield: 60–70%; (iv) $SOCl_2$/reflux; (v) NH_3/CH_2Cl_2, yield: 80–95%.

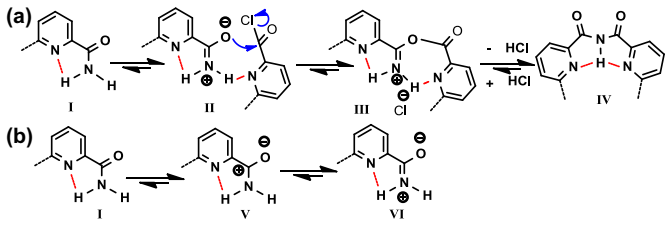
Reaction of dimeric monoamide (**11**) and **2** in an equivalence of 1:0.7 yielded trimer (**7d**), and tetramer (**12**), pentamer (**13**) in a yield of 34%, 33%, and 28%, respectively (Scheme 6), suggesting nearly 100% conversion of the starting material of **11**. Pentamer (**13**) is the expected product. It should be noted that pentameric PIO was first achieved by following this approach. Yield of tetramer (**12**) reveals an amide/chloride exchange between **11** and **2**. Formation of trimer **7b** is likely due to decomposition of **11**.



Scheme 6. One-pot synthesis of trimer (**7d**), tetramer (**12**), and pentamer (**13**) by acylation of dimer monoamide (**11**) and pyridine-2,6-dicarbonyl chloride (**2**). Reactants and conditions: (i), toluene/reflux, overnight.

2.3. Possible models of the amide and chloride exchange

On the basis of H-bonding possibility formed between amide–hydrogen and pyridine–nitrogen atoms,[19] we proposed that the amide/chloride exchange in toluene be mediated by intramolecular and intermolecular H-bonding (Scheme 7a). Pyridine-2-carboxamide may be represented as resonance hybrids of three structures (Scheme 7b).[20] The intramolecular H-bonding stabilizes the zwitterionic resonance VI, whereas the intermolecular H-bonding formed between pyridine-2-carboxamide hydrogen atom and 2-chloro-carbonyl-pyridine nitrogen atom brings two molecules close to each other (II). Thus, the intramolecular and intermolecular H-bonding both favor electrophilic substitution that appears between VI and pyridine-2-carbonyl chloride to form carboxylate III. Rearrangement of carboxylate III yields pyridine–imide function (IV). Obviously, equilibrium between IV and I is reversible and this yields the amide/chloride exchange and decomposition of the dimeric monoamide **11**.



Scheme 7. Possible models of the exchange between pyridine-2-carboxamide and pyridine-2-carbonyl chloride.

Intramolecular and intermolecular H-bonding has been reported to promote some reactions, for examples, leading to a high degree of stereocontrol in the nucleophilic addition to quinolines,[21a] Michael addition of methylene compounds to α,β-unsaturated imides,[21b] and asymmetric addition to α-amino aldehydes,[21c] an efficient macrocyclization of preorganized peptidomimetics[21d] and peptides,[21e] stereoselectivity in synthesis of imidazolidin-4-one,[21f] and structural selectivity in synthesis of 4-*iso*-butoy-10-hydroxy-1,7-phenanthroline-2,8-dicarboxylic acid dimethyl ester.[21g]

2.4. NMR spectra of the PIOs

Fig. 1 shows ^{1}H NMR spectra of PIOs **4d**, **6d**, **7d**, **12**, and **13**. As compared to the monomer (**4d**), the pyridine hydrogens of the dimer (**6d**) is downfield shifted, due to the formation of intramolecular hydrogen-bonding between the imide hydrogen and the pyridine nitrogen atoms. Similar to our previous observations,[19a] formation of helical conformations with the oligomeric length going from dimeric (**6d**) up to trimeric (**7d**) led to a distinct upfield shift of the 3-Cl-1-propyl hydrogens because of overlapping of propyl hydrogens with the pyridine ring. Formation of helical structure is further confirmed by the distinctly upfield shift of the imide hydrogens: the imide hydrogens are downfield shifted firstly from 12.88 ppm for the dimer (**6d**) to 13.02 ppm for the trimer (**7d**) and then upfield shifted dramatically to 12.81 and 12.53 ppm for the tetramer (**12**) and to 12.38 and 12.30 ppm for the pentamer (**13**) because of the shielding effects from the pyridine units upon formation of helical structure.

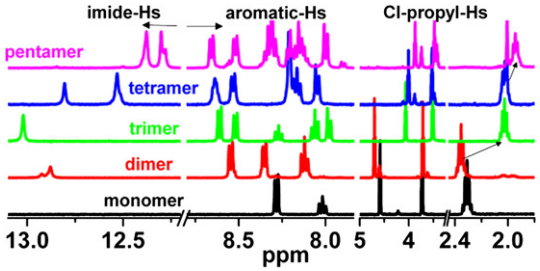


Fig. 1. ^{1}H NMR spectra of the monomer (**4d**), dimer (**6d**), trimer (**7d**), tetramer (**12**), and pentamer (**13**) in $CDCl_3$ with a typical concentration of 5 mg/mL.

2.5. Crystal structure and different local conformations of the trimeric PIOs

Helical structure was further supported by the crystal structure. Fig. 2 shows the crystal structure of trimers **7a**,[22] **7b**,[19b] **7c**,[23] and **7d**.[24] All these four trimers form a similar helical structure with every two imide and three pyridine units forming a helical turn. However, the local conformations are different to each other, which is due to the structural tunability of the imide unit.[19a] Bond parameters and coplanarity of the imide unit are not only different to each other for the two imide units located in the two arms of **7a**, **7b**, **7c**, or **7d** but also different to each other for the imide units in the trimers of **7a**, **7b**, **7c**, and **7d**. As a result, the distance between the two armed imide–hydrogens is 2.777 Å for **7a**, whereas it is 2.788, 2.851, and 2.910 Å, respectively, for **7b**, **7c**, and **7d**. The helical pitch measured between the terminal pyridine rings is 3.660 Å for **7a**, which is larger than that value for the other three trimers (all close to 3.40 Å).

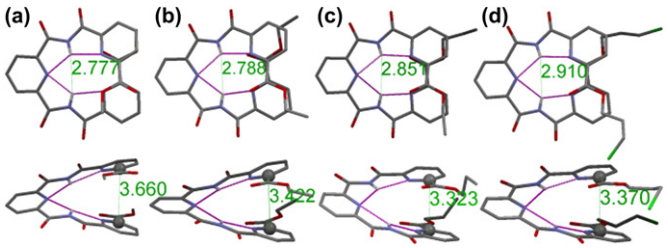


Fig. 2. Solid state structures of trimers **7a**, **7b**, **7c**, and **7d**. The green numbers represent distances between the imide hydrogen atoms (top) and helical pitch between two terminal pyridine rings (bottom). All values are in Å. The pink lines represent intramolecular H-bonding between the imide hydrogen and pyridine nitrogen atoms.

Different local conformations were even observed from the P- and M-helices for the trimer **7c**, in which the two armed imide units are separated by 2.851 and 2.919 Å, respectively, whereas the helical pitch is 3.323 and 3.358 Å, respectively (Fig. 3).

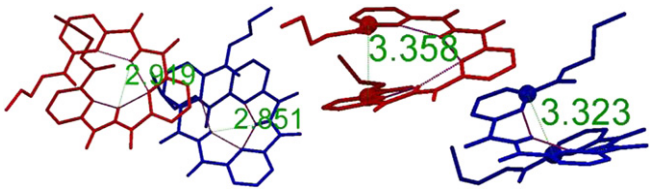


Fig. 3. Different local conformations between the P- (colored in red) and M-helices (colored in blue) of trimer **7c**. The green numbers represent distances between the imide hydrogen atoms (left) and helical pitch between two terminal pyridine rings (right). All values are in Å. The pink lines represent intramolecular H-bonding between the imide hydrogen and pyridine nitrogen atoms.

3. Conclusions

We have developed an approach to one-pot synthesize PIOs on the basis of an exchange between pyridine-2-carboxamide and pyridine-2-carbonyl chloride. The trimeric PIO is in a yield of 30–90% while dimeric PIO in a yield of 5–60%, depending on the length of alkoyl tail. Acylation reaction of dimeric monoamide and pyridine-2,6-dicarbonyl chloride yielded trimeric, tetrameric, and pentameric PIOs in a yield of 34%, 33%, and 28%, respectively. One of the features is that the amide reactant is nearly converted into products, the PIOs, in 100%. Crystal structure of the trimers with different terminal groups reveals variability of the local conformations of the trimers, due to the structural tunability of the imide units.

4. Experimental part

4.1. Apparatus and materials

Starting materials are all commercially available reagents and solvents used as received except for statements. Tetrahydrofuran (THF) was distilled on sodium. All solvents were purified using standard procedures. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates (Yantai Shi Huagxue Gongye Yanjiusuo) and visualized using UV irradiation (254 nm). Flash chromatography was performed on silica gel H60 (Giandao Haiyang Huagongchang).

Crystals suitable for the X-ray crystal diffraction studies were obtained by a 'vapor-diffusion' method: ethyl ether, a poor solvent, was allowed to diffuse into a solution of the *N*,*N*-dimethyl formamide (DMF) solution of PIOs with a typical concentration of 40–50 mM.

^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AVANCE 400 or AVANCE 600 spectrometer and referenced to solvent signals. Chemical shifts were referenced to adamantane signals. ESI mass spectrometric were obtained on LC–MS 2010 and BRUKER Apex IV FTMS and MALDI-TOF mass spectrometric measurements were performed on Bruker Biflex III MALDI-TOF spectrometer. Crystal data were collected using Rigaku Saturn diffractometer with graphite monochromated Mo Kα radiation (λ=0.71073 Å). All calculations were performed using the CrystalStructure crystallographic software package except for refinement, which was performed using SHELXL-97.

4.2. Synthesis of 2-alkoycarbonyl-pyridine-6-carboxylic acid (3) and alkoyl pyridine-2,6-dicarbolic ester (4)

A general synthetic procedure is as follows. Pyridine-2,6-dicarboxylic acid (**1**, 1.5 g, 8.98 mmol) was mixed with 24 mL of $SOCl_2$. The resulted mixture was refluxed for 3 h. The excess of $SOCl_2$ was then removed under vacuum. To the white solid of **2**, 50 mL of THF was added. After the solid dissolved, alkyl alcohol (10.5 mmol) and DIEA (10.5 mmol) were added using a syringe. The resulted solution was allowed to reflux for 4 h. After removal of the solvent the residue was applied to chromatography to afford the desired products **3** and **4**.

*4.2.1. 2-Methoxycarbonyl-pyridine-6-carboxylic acid (**3a**) and dimethyl pyridine-2,6-dicarboxylate (**4a**).* After removal of the solvent, the residue was applied to chromatography with CH_2Cl_2/acetonitrile (20:1) and CH_2Cl_2/ethyl acetate (20:1) as eluents for **3a** and **4a**, respectively. Compound **3a** was isolated as a white powder (1.06 g, 5.84 mmol, yield=65%) and **4a** as a white solid (0.53 g, 2.69 mmol, yield=30%). For **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.43 (d, *J*=7.60 Hz, 1H), 8.37 (d, *J*=7.60 Hz, 1H), 8.13 (t, *J*=7.60, 7.60 Hz, 1H), 4.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 164.4, 147.9, 146.9, 139.8, 139.6, 128.7, 127.3, 51.5. TOF MS: *m*/*z*=182.1 $[M+H]^+$, 204.1 $[M+Na]^+$. For **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.30 (d, *J*=7.60 Hz, 2H), 8.03 (t, *J*=8.00, 8.00 Hz, 1H), 4.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.5, 148.7, 138.2, 127.8, 51.6. TOF MS: *m*/*z*=196.1 $[M+H]^+$.

*4.2.2. 2-Ethoxycarbonyl-pyridine-6-carboxylic acid (**3b**) and diethyl pyridine-2,6-dicarboxylate (**4b**).* After removal of the solvent, the residue was applied to chromatography with CH_2Cl_2/acetonitrile (20:1) and CH_2Cl_2/ethyl acetate (20:1) as eluents for **3b** and **4b**, respectively. Compound **3b** was isolated as a white powder (1.26 g, 6.46 mmol, yield=72%) and **4b** as a white solid (0.47 g, 2.06 mmol, yield=23%). For **3b**: ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.41 (d, *J*=7.74 Hz, 1H), 8.37 (d, *J*=7.80 Hz, 1H), 8.13 (t, *J*=7.77, 7.77 Hz, 1H), 4.60 (q, *J*=7.13, 7.13, 7.13 Hz, 2H), 1.46 (t, *J*=7.13, 7.13 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 164.5, 147.7, 146.8, 139.9, 139.7, 128.8, 127.2, 62.4, 14.5. TOF MS: *m*/*z*=196.1 $[M+H]^+$, 218.1 $[M+Na]^+$. For **4b**: ^{1}H NMR (400 MHz, $CDCl_3$) ppm 8.29 (d, *J*=7.76 Hz, 2H), 8.02 (t, *J*=8.00, 8.00 Hz, 1H), 4.59 (t, *J*=6.12, 6.12 Hz, 2H), 1.46 (t, *J*=7.13, 7.13 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.6, 148.6, 138.2, 127.8, 62.3, 14.2. TOF MS: *m*/*z*=224.1 $[M+H]^+$.

*4.2.3. 2-(n-Propoxycarbonyl)-pyridine-6-carboxylic acid (**3c**) and 2-(n-propyl)-pyridine-2,6-dicarboxylate (**4c**).* After removal of the solvent, the residue was applied to chromatography with CH_2Cl_2/acetonitrile (20:1) and CH_2Cl_2/ethyl acetate (20:1) as eluents for **3c** and **4c**, respectively. Compound **3c** was isolated as a white powder (1.26 g, 6.02 mmol, yield=67%) and **4c** as a white solid (0.72 g, 2.87 mmol, yield=32%). For **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.41 (d, *J*=7.74 Hz, 1H), 8.37 (d, *J*=7.80 Hz, 1H), 8.13 (t, *J*=7.77, 7.77 Hz, 1H), 4.47 (t, *J*=6.40, 6.40 Hz, 2H), 1.86 (q, *J*=6.80, 6.80, 6.80 Hz, 2H), 1.05 (t, *J*=7.20, 7.20 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 163.8, 146.7, 146.8, 139.8, 139.7, 128.9, 127.2, 68.9, 21.9, 10.5. TOF MS: *m*/*z*=210.1 $[M+H]^+$, 232.1 $[M+Na]^+$. For **4c**: ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.31 (d, *J*=7.76 Hz, 2H), 8.02 (t, *J*=8.00, 8.00 Hz, 1H), 4.47 (t, *J*=6.40, 6.40 Hz, 4H), 1.86 (q, *J*=6.80, 6.80, 6.80 Hz, 4H), 1.05 (t, *J*=7.20, 7.20 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.6, 148.5, 138.3, 127.7, 68.8, 21.9, 10.4. TOF MS: *m*/*z*=252.1 $[M+H]^+$.

*4.2.4. 2-(3-Chloro-1-propoxycarbonyl)-pyridine-6-carboxylic acid (**3d**) and 2-(3-chloro-1-propyl)-pyridine-2,6-dicarboxylate (**4d**).* Application to chromatography using CH_2Cl_2/ethyl acetate/acitic acid (100:100:1 and 10:1) as the eluents afforded the product **3d** (1.66 g, 6.82 mmol, yield: 76%) as a yellow solid and **4d** as a white solid (0.72 g, 2.25 mmol, yield=25%). For **3d**: ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.44 (d, *J*=7.60 Hz, 1H), 8.37 (d, *J*=7.60 Hz, 1H), 8.137 (t, *J*=7.76 and 7.76 Hz, 1H), 4.61 (t, *J*=6.16 and 6.16 Hz, 2H), 3.72 (t, *J*=6.28 and 6.28 Hz, 2H), 2.31 (quintet, *J*=6.20, 6.24, 6.24, 6.20 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 163.7, 146.8, 146.7, 139.8, 139.8,

128.9, 127.1, 63.3, 41.3, 31.6. TOF MS: m/z=242.1 $[M-H]^-$. For **4d**: ^1H NMR (400 MHz, $CDCl_3$) ppm: 8.29 (d, J=7.76 Hz, 2H), 8.02 (t, J=8.00, 8.00 Hz, 1H), 4.59 (t, J=6.12, 6.12 Hz, 2H), 3.73 (t, J=6.28 and 6.28 Hz, 2H), 2.31 (quintet, J=6.20, 6.24, 6.24, 6.20 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 164.5, 148.3, 138.8, 128.0, 62.9, 41.2, 31.5. TOF MS: m/z=320.1 $[M+H]^+$.

4.3. Synthesis of 2-alkoxycarbonyl-pyridine-6-carboxamide (5)

A general synthetic procedure is as follows. Compound **3** (2.16 mmol) was mixed with 20 mL of $SOCl_2$. The resulted mixture was refluxed for 3 h. The excess of $SOCl_2$ was then removed under vacuum. The resulted white solid was then dissolved in 50 mL of CH_2Cl_2. To which ammon gas was bubbled inside for 2 h. Then the solution was washed with 1 M hydrochloric acid aqueous solution, dilute Na_2CO_3 aqueous solution, and water each for twice. Removal of the solvent afforded **5**.

*4.3.1. 2-Methoxycarbonyl-pyridine-6-carboxamide (**5a**).* This product was obtained as a yellow solid in a yield of 80%. ^1H NMR (400 MHz, $CDCl_3$) ppm: 8.40 (d, J=7.60 Hz, 1H), 8.26 (d, J=7.60 Hz, 1H), 8.02 (t, J=7.60, 7.60 Hz, 1H), 7.94 (s, 1H), 5.76 (s, 1H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 165.9, 164.5, 149.9, 147.2, 138.5, 127.4, 125.4, 51.8. TOF MS: m/z=181.0 $[M+H]^+$.

*4.3.2. 2-Ethoxycarbonyl-pyridine-6-carboxamide (**5b**).* This product was obtained as a yellow solid in a yield of 95%. ^1H NMR (400 MHz, $CDCl_3$) ppm 8.39 (d, J=7.79 Hz, 1H), 8.25 (d, J=7.78 Hz, 1H), 8.02 (t, J=7.79, 7.79 Hz, 1H), 7.98 (s, 1H), 6.02 (s, 1H), 4.48 (q, J=7.14, 7.14, 7.13 Hz, 2H), 1.45 (t, J=7.14, 7.14 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 165.9, 164.4, 149.8, 147.1, 138.4, 127.5, 125.4, 62.0, 14.3. TOF MS: m/z=195.0 $[M+H]^+$.

*4.3.3. 2-(n-Propoxycarbonyl)-pyridine-6-carboxamide (**5c**).* This product was obtained as a yellow solid in a yield of 86%. ^1H NMR (400 MHz, $CDCl_3$) ppm: 8.39 (d, J=7.60 Hz, 1H), 8.25 (d, J=7.60 Hz, 1H), 8.02 (t, J=7.60, 7.60 Hz, 1H), 7.96 (br s, 1H), 5.71 (br s, 1H), 4.37 (t, J=6.40, 6.40 Hz, 2H), 1.84 (q, 6.80, 6.80, 6.80 Hz, 2H), 1.05 (t, J=7.20, 7.20 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 166.2, 164.3, 150.1, 148.5, 138.5, 127.6, 125.8, 68.8, 21.9, 10.4. TOF MS: m/z=209.0 $[M+H]^+$.

*4.3.4. 2-(3-Chloro-1-propoxycarbonyl)-pyridine-6-carboxamide (**5d**).* This product was obtained as a yellow solid in a yield of 90%. ^1H NMR (400 MHz, $CDCl_3$) ppm: 8.41 (d, J=7.76 Hz, 1H), 8.25 (d, J=7.76 Hz, 1H), 8.03 (t, J=7.80 and 7.80 Hz, 1H), 7.92 (br s, 1H), 5.68 (br s, 1H), 4.58 (t, J=6.04 and 6.04 Hz, 2H), 3.72 (t, J=6.28 and 6.28 Hz, 2H), 2.29 (quintet, J=6.20, 6.24, 6.24, 6.20 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 166.1, 164.4, 150.0, 148.4, 138.4, 127.6, 125.7, 62.2, 41.3, 31.6. TOF MS: m/z=243.0 $[M+H]^+$.

4.4. Synthesis of dimer and trimer

A typical procedure is described as follows. Dichloride (**2**) was obtained by refluxing **1** (2.5 mmol) in 30 mL of $SOCl_2$ for 3 h. To the resulted white solid of **2**, 50 ml of toluene and 1 mmol of **6** were added and the reaction was allowed to reflux overnight. Then, the solvent was removed and the resulted residue was applied to chromatography to afford product **6a**–**d** and **7a**–**d**.

*4.4.1. Dimer **6a** and trimer **7a**.* Dimer **6a** was isolated using CH_2Cl_2/ethyl acetate=40:1 as the eluents in a yield of 60%. ^1H NMR (400 MHz, $CDCl_3$) ppm: 12.98 (s, 1H), 8.56 (d, J=7.77 Hz, 2H), 8.39 (d, J=7.73 Hz, 2H), 8.11 (t, J=7.79, 7.79 Hz, 2H), 4.10 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 164.0, 162.1, 149.2, 147.7, 138.9, 128.5, 126.3, 52.2. MALDI-TOF MS: m/z=344.2 $[M+H]^+$ and 366.2 $[M+Na]^+$.

Trimer **7a** was obtained in a yield of 30% with CH_2Cl_2/ethyl acetate=5:1 as the eluents. ^1H NMR (300 MHz, $CDCl_3$) ppm: 13.02 (s, 2H), 8.62 (d, J=7.75 Hz, 2H), 8.52 (d, J=6.80 Hz, 2H), 8.28 (t, J=7.20, 7.20 Hz, 1H), 8.05 (dd, J=7.00, 7.16 Hz, 4H), 3.55 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 163.2, 161.7, 161.3, 149.2, 148.4, 146.0, 140.3, 139.1, 128.4, 127.2, 125.8, 52.7. ESI MS: m/z=492.1 $[M+H]^+$ and 514.1 $[M+Na]^+$.

*4.4.2. Dimer **6b** and trimer **7b**.* Dimer **6b** was isolated using CH_2Cl_2/ethyl acetate=40:1 as the eluents in a yield of 54%. ^1H NMR (400 MHz, $CDCl_3$) ppm: 12.96 (s, 1H), 8.53 (d, J=7.77 Hz, 2H), 8.35 (d, J=7.73 Hz, 2H), 8.10 (t, J=7.79, 7.79 Hz, 2H), 4.61 (q, J=7.10, 7.10, 7.09 Hz, 4H), 1.49 (t, J=7.11, 7.11 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 164.0, 162.1, 149.2, 147.7, 138.9, 128.5, 126.3, 61.0, 14.3. MALDI-TOF MS: m/z=372.2 $[M+H]^+$, 394.2 $[M+Na]^+$, and 410.2 $[M+K]^+$.

Trimer **7b** was obtained in a yield of 37% with CH_2Cl_2/ethyl acetate=5:1 as the eluents. ^1H NMR (300 MHz, $CDCl_3$) ppm: 13.04 (s, 2H), 8.61 (d, J=7.75 Hz, 2H), 8.49 (dd, J=7.00, 1.09 Hz, 2H), 8.27 (t, J=7.75, 7.75 Hz, 1H), 8.02 (q, J=7.99, 7.86, 7.86 Hz, 4H), 3.96 (q, J=7.09, 7.09, 7.09 Hz, 4H), 1.19 (t, J=7.10, 7.10 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 162.6, 161.7, 161.3, 149.3, 148.4, 146.4, 140.2, 138.9, 128.3, 127.2, 125.7, 60.9, 14.0. ESI MS: m/z=520.2 $[M+H]^+$, 542.3 $[M+Na]^+$, and 558.4 $[M+K]^+$.

*4.4.3. Dimer **6c** and trimer **7c**.* Dimer **6c** was isolated using CH_2Cl_2/ethyl acetate=40:1 as the eluents in a yield of 42%. ^1H NMR (400 MHz, $CDCl_3$) ppm: 12.98 (s, 1H), 8.54 (d, J=7.77 Hz, 2H), 8.37 (d, J=7.73 Hz, 2H), 8.10 (t, J=7.79, 7.79 Hz, 2H), 4.50 (t, J=6.00, 6.00 Hz, 4H), 1.78 (q, 7.20, 7.20, 7.20 Hz, 4H), 0.98 (t, J=7.20, 7.20 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 164.0, 162.1, 149.2, 147.7, 138.9, 128.5, 126.3, 68.8, 21.9, 10.4. MALDI-TOF MS: m/z=400.2 $[M+H]^+$, 422.2 $[M+Na]^+$, and 438.2 $[M+K]^+$.

Trimer **7c** was obtained in a yield of 50% with CH_2Cl_2/ethyl acetate=5:1 as the eluents. ^1H NMR (300 MHz, $CDCl_3$) ppm: 13.04 (s, 2H), 8.62 (d, J=7.75 Hz, 2H), 8.50 (dd, J=7.00, 1.09 Hz, 2H), 8.27 (t, J=7.75, 7.75 Hz, 1H), 8.05 (m, J=6.80, 8.00, 7.20 Hz, 4H), 3.85 (t, J=6.00, 6.00 Hz, 4H), 1.58 (q, J=7.20, 7.20, 7.20 Hz, 4H), 0.88 (t, J=7.20, 7.20 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 162.5, 161.8, 161.3, 149.3, 148.4, 146.3, 140.3, 138.8, 128.2, 127.1, 125.6, 67.3, 21.7, 10.2. ESI MS: m/z=548.2 $[M+H]^+$, 570.2 $[M+Na]^+$, and 586.2 $[M+K]^+$.

*4.4.4. Dimer **6d** and trimer **7d**.* Dimer **6d** was isolated using CH_2Cl_2/ethyl acetate=20:1 as the eluents in a yield of 2%. ^1H NMR (400 MHz, $CDCl_3$) ppm: 12.88 (s, 1H), 8.55 (d, J=8.00 Hz, 2H), 8.36 (d, J=8.00 Hz, 2H), 8.12 (t, J=8.00 and 8.00 Hz, 1H), 4.70 (t, J=6.40 and 6.40 Hz, 4H), 3.71 (t, J=6.40 and 6.40 Hz, 4H), 2.35 (quintet, J=6.40, 6.40, 6.40, 6.40 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 163.8, 162.1, 149.3, 147.2, 139.1, 128.7, 126.6, 63.2, 41.4, 31.6. TOF MS: m/z=467.1 [M] and 490.2 [100%] $[M+Na]^+$.

Trimer **7d** was isolated as a white solid by using CH_2Cl_2/ethyl acetate=20:1 as the eluents in a yield of 95% (278.7 mg, 0.474 mmol). ^1H NMR (400 MHz, $CDCl_3$) ppm: 13.02 (s, 2H), 8.62 (d, J=8.00 Hz, 2H), 8.53 (d, J=7.6 Hz, 2H), 8.27 (t, J=8.00 and 7.60 Hz, 1H), 8.06 (t, J=8.00 and 7.60 Hz, 2H), 7.99 (d, J=8.0 Hz, 2H), 4.06 (t, J=6.20 and 6.16 Hz, 4H), 3.51 (t, J=6.24 and 6.24 Hz, 4H), 2.03 (quintet, J=6.00, 6.28, 6.28, 6.00 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 162.4, 161.8, 161.5, 149.6, 148.5, 146.0, 140.4, 139.2, 128.4, 127.4, 126.0, 62.8, 40.9, 31.3. TOF MS: m/z=615.1 [M], 638.2 [100%] $[M+Na]^+$, and 654.2 $[M+K]^+$.

4.5. Synthesis of dimeric monoamide

*4.5.1. Dimer **6d**.* Compound **3d** (233.1 mg, 1.02 mmol) was mixed with 10 mL of $SOCl_2$. The resulted mixture was refluxed for 3 h. The

excess of $SOCl_2$ was then removed under vacuum to afford a white solid, which was mixed with **5d** (205.4 mg, 0.85 mmol) and dissolved in 40 mL of toluene. The resulted solution was refluxed overnight. After removal of the solvent, the residue was applied to chromatography using CH_2Cl_2/ethyl acetate=20:1 as the eluents to afford product **6d** (256.3 mg, 0.58 mmol, yield: 68%).

*4.5.2. Dimer monoacid **10**.* Compound **6d** (304 mg, 0.80 mmol) was dissolved in a mixed solvents of dioxane (50 ml) and water (5 ml), to which, 1 mol/L of NaOH aqueous solution (0.80 ml) was dropwise added. After stirred for 3 h, the reaction solution was washed with saturated NaCl solution and water each for twice. The organic layer was then dried over Na_2SO_3. After removal of organic solvent, the residue was applied to chromatography using CH_2Cl_2/ethyl acetate/acetic acid=10:10:1 as the eluents to afford product **10** (164.5 mg, 0.435 mmol, yield: 55%). ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 13.01 (s, 1H), 8.68 (d, *J*=7.60 Hz, 1H), 8.59 (d, *J*=8.00 Hz, 1H), 8.39 (d, *J*=8.00 Hz, 1H), 8.26 (t, *J*=7.60 and 7.60 Hz, 1H), 8.17 (t, *J*=8.00 and 8.00 Hz, 1H), 4.72 (t, *J*=6.24 and 6.24 Hz, 2H), 3.70 (t, *J*=6.40 and 6.40 Hz, 2H), 2.33 (quintet, *J*=6.24, 6.24, 6.24, 6.24 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.5, 164.3, 163.7, 163.5, 148.5, 148.4, 148.2, 148.1, 139.4, 139.3, 138.9, 138.8, 128.3, 128.0, 63.0, 41.4, 31.4. TOF MS: *m*/*z*=390.1 $[M-H]^-$.

*4.5.3. Dimer monoamide **11**.* Compound **10** (287.8 mg, 0.77 mmol) was dissolved in $SOCl_2$ (5 ml). The resulted mixture was refluxed for 3 h. The excess of $SOCl_2$ was then removed under vacuum. The resulted white solid was then dissolved in 50 mL of CH_2Cl_2. To which ammon gas was bubbled inside for 2 h. Then the solution was washed with 1 M hydrochloric acid aqueous solution, dilute Na_2CO_3 aqueous solution, and water each for twice. Removal of the solvent afforded product **10** (258.3 mg, 0.6857 mmol, yield: 90%). ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 13.01 (s, 1H), 8.68 (d, *J*=7.60 Hz, 1H), 8.59 (d, *J*=8.00 Hz, 1H), 8.39 (d, *J*=8.00 Hz, 1H), 8.26 (t, *J*=7.60 and 7.60 Hz, 1H), 8.17 (t, *J*=8.00 and 8.00 Hz, 1H), 7.92 (br s, 1H), 5.68 (br s, 1H), 4.72 (t, *J*=6.24 and 6.24 Hz, 2H), 3.70 (t, *J*=6.40 and 6.40 Hz, 2H), 2.33 (quintet, *J*=6.24, 6.24, 6.24, 6.24 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 165.2, 163.3, 161.3, 161.0, 149.2, 149.1, 147.5, 146.8, 139.4, 139.3, 128.4, 126.8, 126.3, 125.9, 63.1, 41.6, 31.5. TOF MS: *m*/*z*=390.0 [M].

4.6. One-pot synthesis of trimer (7d), tetramer (12), and pentamer (13)

Pyridine-2,6-dicarboxylic acid (**1**, 77.81 mg, 0.47 mmol) was dissolved in 5 mL of $SOCl_2$. The resulted mixture was refluxed for 3 h. The excess of $SOCl_2$ was then removed under vacuum. The resulted white solid of **2** was dissolved in 60 mL of toluene, to which compound **11** (303.4 mg, 0.78 mmol) was added. The resulted solution was allowed to reflux overnight. After removal of the solvent the residue was applied to chromatography using CH_2Cl_2/acetonitrile=20:1 as the eluents to afford **7d** (105 mg, 0.171 mmol, yield: 34%), using CH_2Cl_2/acetonitrile=10:1 as the eluents to afford **12** (125.6 mg, 0.164 mmol, yield: 33%), using CH_2Cl_2 /acetonitrile=4:1 as the eluents to afford **13** (129 mg, 0.141 mmol, yield: 28%).

*4.6.1. Tetramer **12**.* ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 12.81 (s, 1H), 12.53 (s, 2H), 8.65 (m, *J*=4.72 Hz, 2H), 8.54 (d, *J*=8.0 Hz, 2H), 8.21 (m, *J*=2.80 Hz, 4H), 8.16 (t, *J*=8.00 and 7.60 Hz, 2H), 8.06 (d, *J*=7.60 Hz, 2H), 4.01 (t, *J*=5.44 and 6.00 Hz, 4H×80%), 3.89 (t, *J*=5.60 Hz, 4H×20%), 3.53 (t, *J*=6.00 and 6.00 Hz, 4H×80%), 3.48 (t, *J*=5.60 and 5.60 Hz, 4H×20%), 2.02 (quintet, *J*=6.40, 5.76Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 161.9, 161.4, 160.6, 160.2, 148.9, 148.5, 147.8, 145.3, 140.1, 139.9, 128.9, 127.1, 126.9, 126.7, 62.5, 40.8, 31.1. TOF MS: *m*/*z*=764.1 [M], 786.1 [100%] $[M+Na]^+$, and 802.1 $[M+K]^+$.

*4.6.2. Pentamer **13**.* ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 12.38 (s, 2H), 12.31 and (s, 2H), 8.67 (d, *J*=6.92 Hz, 2H), 8.53 (d, *J*=7.72 Hz, 2H), 8.31 (m, *J*=7.60, 6.00, 1.20, 7.60 Hz, 4H), 8.17 (t, *J*=8.00 and 7.60 Hz, 2H), 8.13 (6.40, 5.6 Hz, 3 Hz), 8.01 (d, *J*=8.00 Hz, 2H), 3.88 (t, *J*=6.00 and 6.00 Hz, 4H×65%), 3.74 (t, *J*=5.44 Hz, 4H×35%), 3.48 (t, *J*=6.00 and 6.00 Hz, 4H×65%), 3.43 (t, *J*=5.60, 6.24 Hz, 4H×35%), 1.94 (quintet, *J*=6.00, 5.76Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 162.1, 161.8, 160.5, 160.2, 160.0, 148.6, 147.7, 147.4, 145.2, 141.3, 140.3, 139.6, 129.0, 128.4, 127.8, 127.2, 126.3, 65.1, 62.4, 44.3, 40.9, 31.1, 29.8. TOF MS: *m*/*z*=934.1 $[M+Na]^+$, and 950.2 $[M+K]^+$.

The splitting of the imide hydrogen and 3-Cl-1-propyl hydrogens for the tetrameric and pentameric PIOs may be due to the different local conformations of 3-Cl-1-propyl terminal after formation of helical structure.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.09.006. These data include MOL files and InChiKeys of the most important compounds described in this article.

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22. Crystal data for **7a**: crystallization solvent/precipitant: DMF/ethyl ether, triclinic, space group $P\bar{1}$, colorless, (a) 7.9371 (1), (b) 9.1064 (18), (c) 15.505 (3) Å, α=76.25 (3)°, γ=87.23 (3)°, β=83.28 (3)°, T=173 (2) K, Z=2, GOF=1.090. The final R indices were $R1$ ($I>2\sigma$ (I))=0.0398, $wR2$ (all data)=0.1187.
23. Crystal data for **7c**: crystallization solvent/precipitant: DMF/ethyl ether, monoclinic, space group $P2_1/c$, colorless, (a) 12.728 (3), b) 19.183 (4), (c) 21.427 (4) Å, α=90°, γ=90.77 (3)°, β=90°, T=173 (2) K, Z=8, GOF=1.197. The final R indices were $R1$ ($I>2\sigma$ (I))=0.0958, $wR2$ (all data)=0.1682.
24. Crystal data for **7d**: crystallization solvent/precipitant: DMF/ethyl ether, monoclinic, space group $P2_1/c$, colorless, (a) 11.6507 (14), (b) 17.887 (2), (c) 13. 6683 (17) Å, $\alpha=\gamma$=90°, β=104.953 (8)°, T=173 (2) K, Z=4, GOF=1.106. The final R indices were $R1$ ($I>2\sigma$ (I))=0.0534, $wR2$ (all data)=0.1445.