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Oligopyridones: preparation and their folding behavior in polar aprotic solvents

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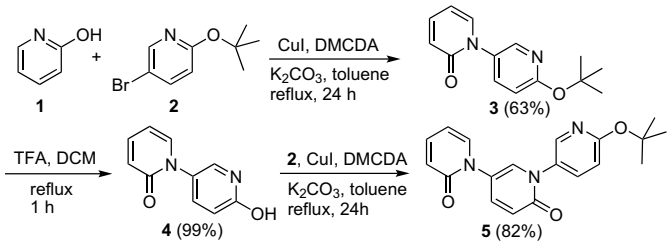
ABSTRACT

The oligomerization of 5-bromo-2-hydroxypyridine through a CuI catalyzed one-pot condensation tactics was developed. A series of oligopyridones, from dipyridione to penta-pyridone, were therefore synthesized via the CuI-promoted C–N coupling reactions. The oligopyridones favor to have folded conformations in polar aprotic solvents. These were confirmed by using ^{1}H NMR, NOESY, and 1D-NOE experiments.

1. Introduction

Folding of organic molecules into three-dimensional tertiary structures is important self-organization phenomena of proteins, nucleic acids, and oligosaccharides. The molecular folding process could be governed by static or dynamic reasons. The design of foldamers provided valuable models for investigation of these phenomena and allowed researchers to identify those major interactions for the folding process.[1] In addition, folding of polymers provided synthetically simple means of architectures that could potentially rival the biopolymers in their complexity and functionality.[2] It is therefore no surprise that researches on foldamers have received increasing attention in biomimetic and synthetic super-molecular systems.[1f,g,3] Many important factors including covalent conformational restrictions,[4] metal complexation,[5] solvophobic[6] and dipolar effects,[7] chirality-induced folding,[6c,8,9] intermolecular interactions,[6b,10] and non-bonding intramolecular interactions[1h,11] were identified.

In our ongoing efforts to develop the copper-iodide-promoted C–N coupling conditions for organic synthesis,[12] we successfully devised an iterative approach for preparation of oligopyridones (Scheme 1).[12a] The iterative synthetic sequence started from 5-bromo-2-*tert*-butoxypyridine. Copper iodide/*trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (DMCDA) promoted the C–N coupling of **2** with 2-hydroxypyridine (**1**) and gave **3**, which could be effectively deprotected to afford **4**. An additional pyridone ring could then be further introduced by repeating the iterative synthetic sequence to give **5**.



Scheme 1.

Unfortunately, when we attempted to apply the synthetic sequence for the higher oligopyridone homologues, the synthetic yields were not ideal. Therefore, new strategies for the higher oligopyridone homologues were desired. Herein we report modified procedures for the sequential and one-pot synthesis of the oligopyridones, and the study of their folding behavior in polar aprotic solvents.

2. Results and discussion

When the original C–N coupling conditions were applied to transform **6** to **7**, the synthetic yield dropped to 5%. Even after changing the solvent from the non-polar toluene to the polar

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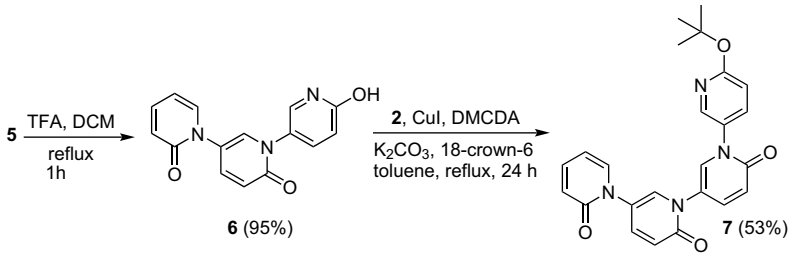
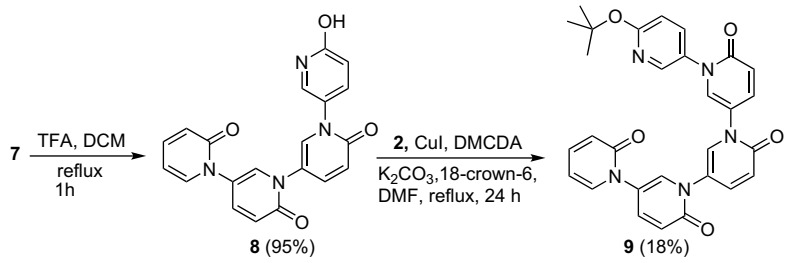


Scheme 2.

aprotic DMF, the synthetic yield slightly increased to 11%. In order to further enhance the solubility and reactivity of K_2CO_3, 18-crown-6 was adopted as the co-catalyst. Under these conditions, the synthetic yield of **7** was improved to 53% (Scheme 2). Desiccation of 18-crown-6 was a crucial requirement for obtaining good yields. If 18-crown-6 was not desiccated appropriately before use, the reaction yield dramatically dropped back to 17%.

might be terminated by hydro-debromination at the early stage, giving the dimeric pyridone **3** as a predominant product.

To improve the oligomerization, more effective C–N coupling conditions were desired to overwhelm the hydro-debromination. Since the CuI/DMCDA ratio could be a crucial factor for the reaction, we adjusted their ratio in order to optimize the yields. Indeed, the use of CuI/DMCDA in a ratio of 0.2 equiv/0.16 equiv did not effec-



Scheme 3.

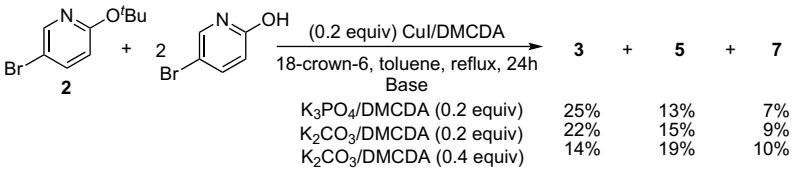
Surprisingly, when the same conditions were applied to convert **8** to **9**, the synthetic yield dropped again to 18% (Scheme 3). Since the iterative synthetic sequence was definitely time-consuming and became less effective while being extended to higher homologues, more simple ways to get **9** were therefore desired.

In the next trial, we attempted to self-condense 2-hydroxy-5-bromopyridine to give the oligomeric product in one pot. In this reaction, limited amounts of 2-*tert*-butoxy-5-bromopyridine were added to construct the *tert*-butyl protected terminal (Scheme 4). Several inorganic bases, including K_2CO_3, K_3PO_4, Cs_2CO_3, and Na_2CO_3, had been tried and only K_2CO_3 and K_3PO_4 would result in reasonable yields.

When K_2CO_3 was used, the hydro-debrominated oligopyridones **3**, **5**, and **7** were isolated, respectively, in 22%, 15%, and 9%. Similar product distribution was obtained when K_3PO_4 was used. These results indicated that the chain growth of the oligomerization

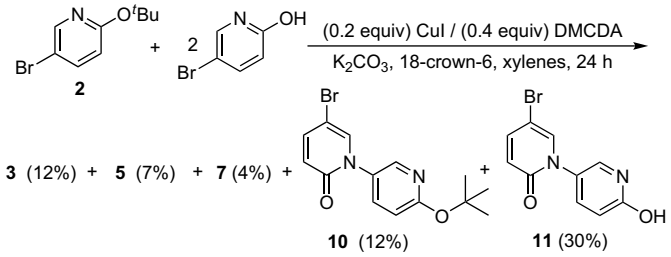
tively result in any oligomerization products. However, as mention in Scheme 4, increasing the ratio to 0.2 equiv/0.2 equiv successfully facilitated the reaction to give **3**, **5**, and **7** in 22%, 15%, and 9%, respectively. Further raising the amounts of DMCDA to 0.4 equiv afforded **3**, **5**, and **7** in 14%, 19%, and 10% yields. The increasing yields of the higher homologues of **5** and **7** implied that the turn over number for the oligomerization increased when the ratio of DMCDA to CuI increased. We attributed these results to the competitive complex formation between CuI and hydroxypyridine that inhibited the formation of the active CuI/DMCDA complex. The activity was therefore diminished. To maintain the catalytic power of the active complex, higher equivalence of DMCDA was necessary to secure the active complex formation.[13]

Another tactic for improving the oligomerization efficiency is to suppress the hydro-debromination. Since the moisture contents in the reaction mixture might accelerate the hydro-debromination,



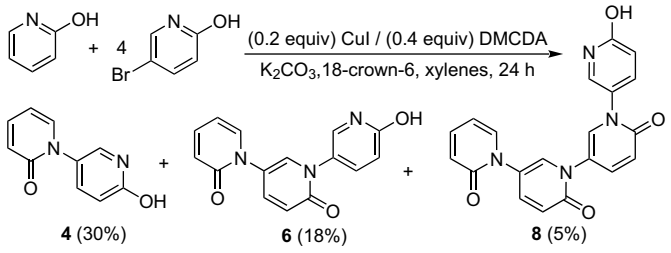
Scheme 4.

we desiccated all reagents and solvents before use. Under the anhydrous conditions, besides **3**, **5**, and **7**, **10** and **11** were isolated, respectively, in 12% and 30% yields (Scheme 5). Formation of **11** was of particularly interesting because this implied the occurrence of the self-coupling of 2-hydroxy-5-bromopyridine under the reaction conditions.



Scheme 5.

We therefore attempted to oligomerize the un-protected 2-hydroxy-5-bromopyridine under similar anhydrous conditions in one pot, using 2-hydroxypyridine as the terminal groups to afford **4**, **6**, and **8** (Scheme 6). Although the higher homologues could not be isolated from the oligomerization process, the synthesis could be still be accelerated by first preparing tetramer **8** in the one-pot condensation, followed by using the CuI catalyzed coupling reaction with 2-*tert*-butoxy-5-bromopyridine to afford **9**.



Scheme 6.

2.1. Conformational analysis by semi-empirical calculations

The conformational analyses were performed using semi-empirical PM5 calculations. In our systems, the pyridone moieties were connected through the nitrogen atom of one ring to C-4 of the other ring. Although the pyridine units might favor to have a planar conformation due to the π-resonance delocalization, presumably as a consequence of the steric repulsions between the C=O′ and the *ortho* H-3 and H-5, the pyridone rings were found to be non-planar. As a result, four atropisomeric conformers could be identified, among which two of them were essential for the folded conformations and the other two would lead to the extended conformations (Fig. 1).

To further understand the relative stability of each conformations, we adopted the corresponding bipyridone as our model to study. In the folded conformations, an estimated distance of 2.84 Å between H(5) and H(5′) was obtained, which was shorter than that of 4.14 Å for H(5′)···H(5) in the extended conformations. Our PM5 calculations also revealed that the folded and extended conformations would have the estimated heat of formations of −33.0 and −34.0 kcal/mol, with the dihedral angles of 64.5° and 124.3° for C(5′)–N′–C(4)–C(5), respectively. The extended conformations were found to be slightly more stable than the folded conformations by 1 kcal/mol. Either the calculated C=O′···H(3) distance of 2.79 Å in the folded conformers or the C=O′···H(5) distance of 2.78 Å in the extended conformers would allow the O′···H–C intramolecular hydrogen bond interactions.

When three pyridone rings were connected, two types of diastereomeric conformations that are important for occurrence of the molecular folding could be identified (Fig. 2): (a) pyridone rings were aligned in a unique direction so that the terpyridone regime would form a helical twist; (b) pyridone rings were aligned in an opposite direction. Similar situations also occurred for the extended conformations.

When we expanded our theoretical treatments to the penta-pyridone, several special conformers, including the fully extended or the fully folded conformers, could be identified. Similar to the previous results, the fully extended conformations were found to be slightly more stable than the fully folded ones.

Three selected representations of the penta-pyridone are shown in Figure 3 for discussion. Figure 3a shows an extended conformer with the pyridone units aligned in a linear way. The calculated heat of formation obtained was −62.0 kcal/mol. Figure 3b shows the conformer of the folded form with the carbonyl groups aligned in an alternating way of up and down. The heat of formation obtained was −57.5 kcal/mol. Figure 3c shows the conformer of the folded form with the carbonyl groups aligned in a helical way. The heat of formation obtained was −58.6 kcal/mol. The linear conformer is relatively stable than the fully curled conformations by around 3–4 kcal/mol according to the results of our calculations.

2.2. ^{1}H NMR and NOE analysis

Since the oligopyridones contain a polar array of carbonyl groups, their conformational equilibriums may be highly solvent dependent. Although the extended conformations were predicted to be more stable by our calculations, the polar interactions between the carbonyl groups and the solvent molecules might drive the C=O groups pointing outwards to lead to a coiling structure with the hydrophobic interior pointing toward the helical axis. Therefore, we wondered if the folding behavior of the oligopyridones could be tuned by using the solvent effects.

To examine the solvent effects on **5**, we first subjected **5** to ^{1}H NMR analysis in various deuterated solvents, including CD_2Cl_2, $CDCl_3$, CD_3CN, acetone-d_6, DMSO-d_6, and CD_3OD at 298 K. In good agreement with our predictions, their ^{1}H NMR spectra really

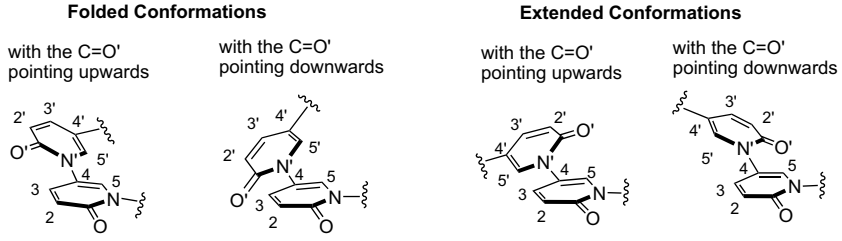


Figure 1. Atropisomeric conformations of bipyridone units. The pyridone ring in front, denoted as C2–C3–C4–C5–N, was kept on the horizontal plane. The pyridone rings behind with the C=O' pointing upward and downward were illustrated.

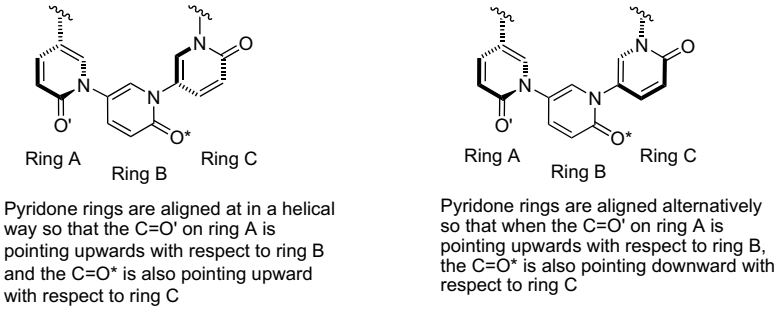


Figure 2. Conformation analysis of the curled terpyridone moieties. The central pyridone ring B was kept on the horizontal plane. The pyridone rings on both sides with the C═O' pointing upward and downward were illustrated.

showed high solvent dependency (Fig. 4). Due to the aromatic anisotropic effect as well as the high electronegativity of the nitrogen atom, the outmost pyridinyl H(a) appeared at the most down-field region of 8.1–8.3 ppm. The δH(a) shifted slightly by about 0.14 ppm, from 8.10 ppm in CD_2Cl_2 to 8.24 ppm in acetone-d_6. Similar situation was observed for δH(j). On the other hand, δH(b) shifted by about 0.52 ppm from 7.46 ppm in CD_2Cl_2 to 7.98 ppm in acetone-d_6. Since the outmost protons were only shifted slightly in various solvents, the large shift of δH(b) could not be simply explained by the solvation effects. This result indicated that the environment of H(b) was highly solvent dependent. It is noteworthy to mention that the ^{1}H NMR patterns of **5** could be classified into two categories: the spectra of **5** in less polar solvents, such as CD_2Cl_2 or $CDCl_3$, are grouped in one category. Their ^{1}H NMR spectra were relatively similar. The chemical shifts of δH(b) appeared in the much up-field region, at around 7.4–7.5 ppm. On the other hand, the spectra of **5** in polar solvents such as d_6-DMSO, d_6-acetone, or CD_3OD are relatively similar, in which the chemical shifts of δH(b) appeared in the much down-field region, at around 7.82–7.98 ppm.

To further understand the conformational preference of **5** in polar environment, we selected DMSO-d_6 as the solvent to study (Fig. 5). The ^{1}H NMR of **5** in DMSO-d_6 show 10 sets of well-separated aromatic and vinyl signals that fall into three groups. The COSY experiments correlated: (1) H(c), H(d), H(e), and H(f) to ring A; (2) H(b), H(g), and H(h) to ring B; and (3) H(a), H(i), and H(j) to ring C. The assignments of protons on ring C were further confirmed by the NOE experiments which correlated H(j) to the *tert*-butyl protons. The correlations among H(a), H(b), and H(c) were also examined by NOE difference spectroscopy. When H(a) was selectively double irradiated (spin-decoupling), NOE enhancement on H(b) occurred (Fig. 5, spectrum I), indicating that H(b) and H(a) are within a close distance to each other. On the other hand, when H(b) was double irradiated, NOE on H(a), H(c), and H(i) were observed (Fig. 5, spectrum II). The NOE on H(a) was higher in comparison to that of H(i), with a ratio of 1:0.79. This result indicated that the average distance between H(a)···H(b) might be shorter than that of H(i)···H(b). Selective irradiation on H(c) without affecting H(i) was almost impossible in our cases due to the pulse-width problem. Therefore we adopted the 2-D NOESY experiment in which strong correlation among H(c), H(d), and H(b) and weaker correlation between H(c) and H(g) were clearly shown.

Similarly, ^{1}H NMR assignments in acetone-d_6 for **7** were achieved using ^{1}H–^{1}H COSY and NOESY techniques (Fig. 6). Although the coupling patterns and the chemical shifts of the protons on ring B and ring C were very similar, they could be distinguished by NOE: (i) when H(a) was irradiated, signal enhancement occurred on H(b) along with decoupling on H(l) and H(m) (Fig. 6l); (ii) when H(b) was irradiated, signal enhancements on H(a), H(c), and H(l), with the

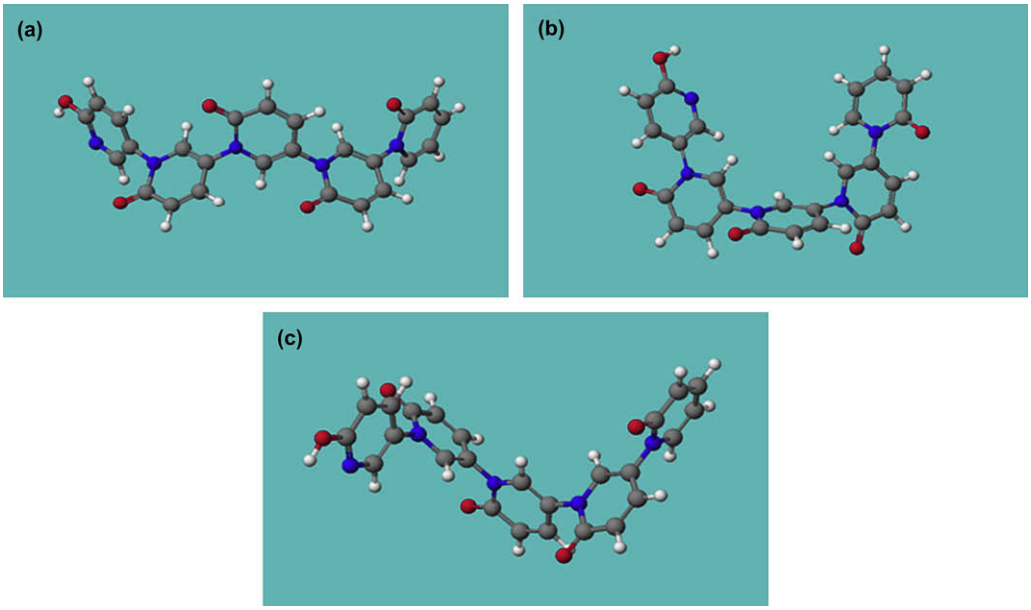


Figure 3. Selected representations of the penta-pyridone: red for oxygen; blue for nitrogen; black for carbon.

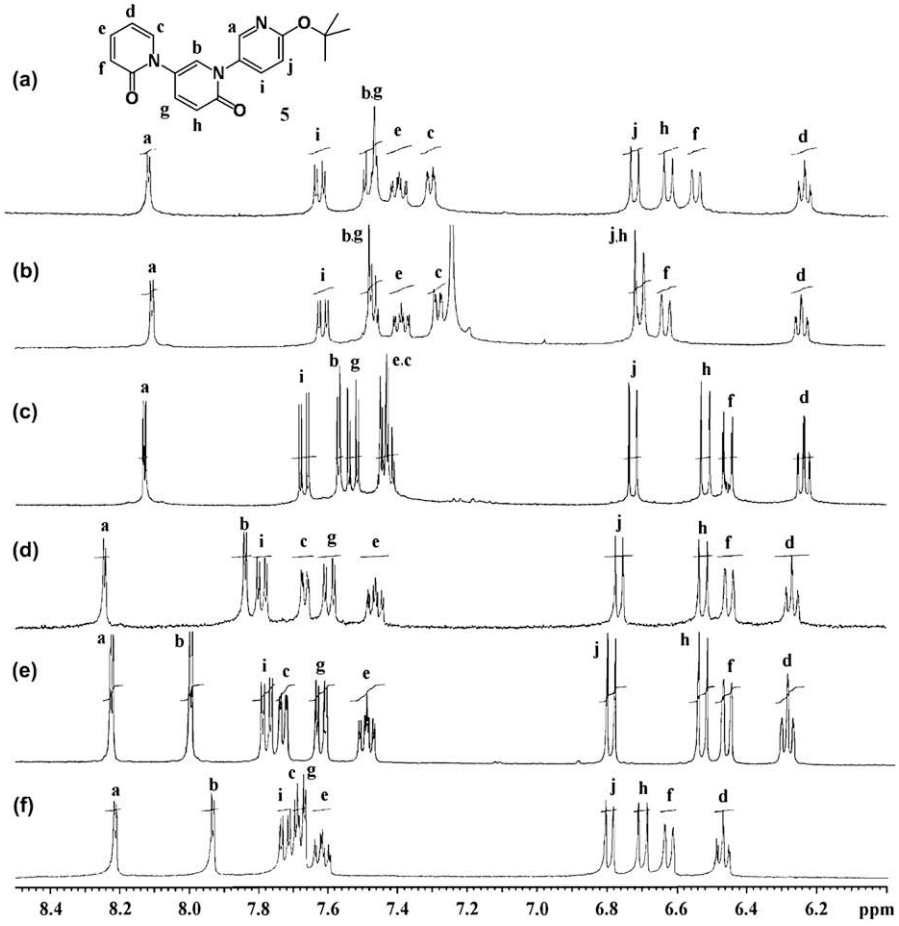


Figure 4. ^{1}H NMR of **5** in various deuterated solvents, including (a) CD_2Cl_2, (b) $CDCl_3$, (c) CD_3CN, (d) acetone-d_6, (e) DMSO-d_6, and (f) CD_3OD at 298 K.

relative ratio of 1.00:0.16:0.51, were observed, along with decoupling on H(j) and H(k) (Fig. 6II). The observation of the relatively strong NOE on H(a) over H(l) (1:0.51) in Figure 6II suggested that the average distance between H(b)···H(a) is shorter than that of H(b)···H(l); (iii) when H(c) was irradiated, signal enhancements on H(b), H(j), and H(d), with the relative ratio of 1.00:0.46:1.48, were observed along with decoupling on H(h) and H(i) (Fig. 6III). Similarly, stronger NOE on H(b) over H(j) (1:0.46) again indicated that

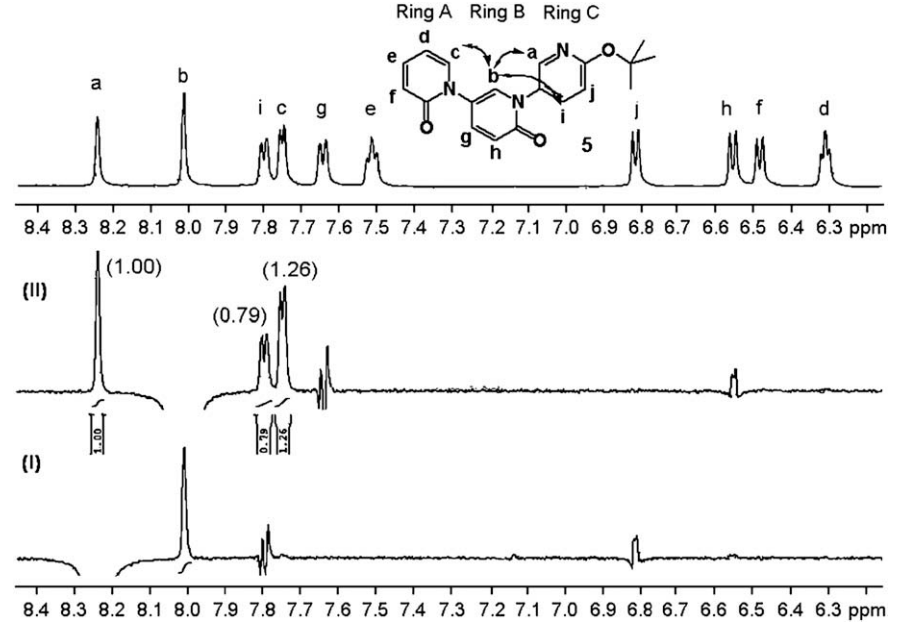


Figure 5. ^{1}H NMR assignments and NOE experiments for **5**: (I) selectively irradiated at H(a); (II) selectively irradiated at H(b) at 298 K.

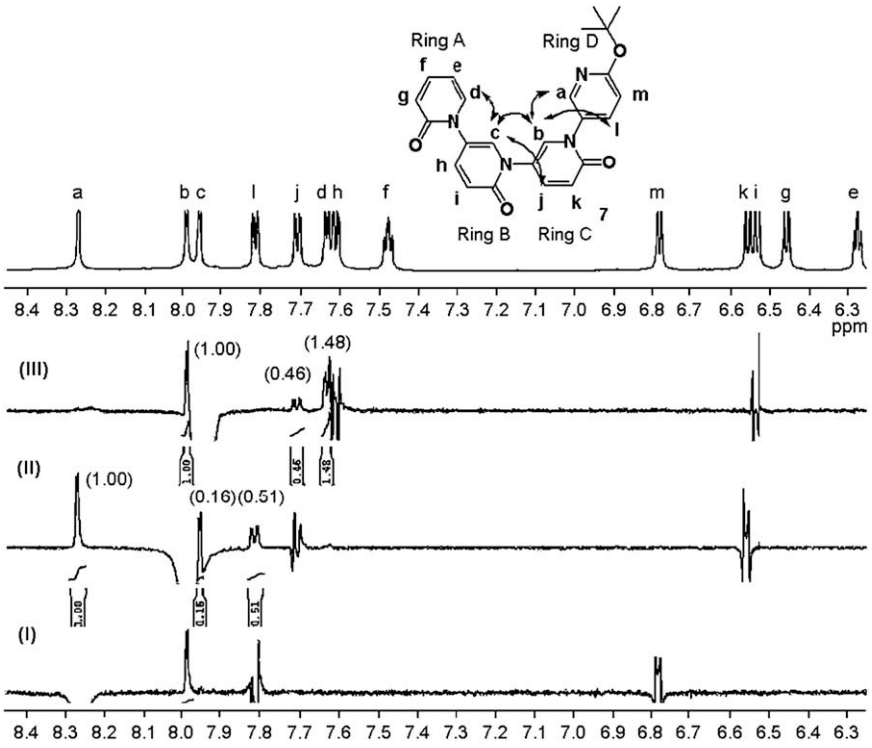


Figure 6. ^{1}H NMR assignments and NOE experiments for **7**: (I) selectively irradiated at H(a); (II) selectively irradiated at H(b); (III) selectively irradiated at H(c) at 298 K.

H(c) stayed closer to H(b) rather than to H(j). All of these observations supported the assumption of having folded conformations for **7** in the polar aprotic solvents. However, due to the small chemical shift's differences between H(d) and H(h), selectively double irradiation on H(d) without affecting H(h) became difficult to achieve.

By applying similar NOE difference spectroscopy and ^{1}H–^{1}H COSY techniques, the ^{1}H NMR assignments for **9** could

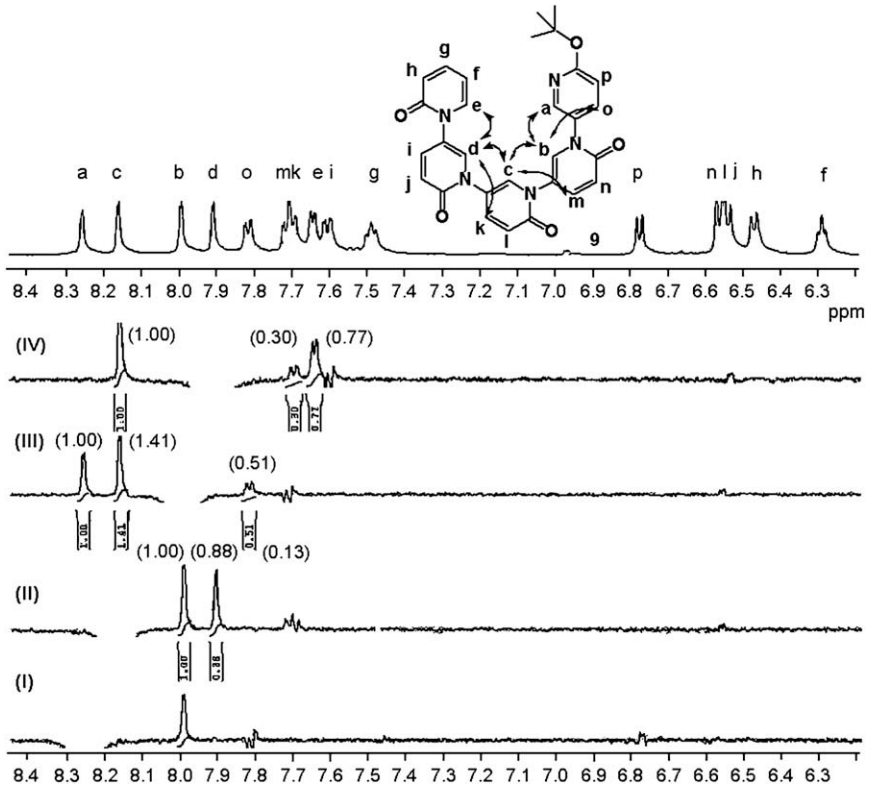


Figure 7. ^{1}H NMR assignments and NOE experiments of **9**: (I) selectively irradiated at H(a); (II) selectively irradiated at H(c); (III) selectively irradiated at H(b); (IV) selectively irradiated at H(d) at 298 K.

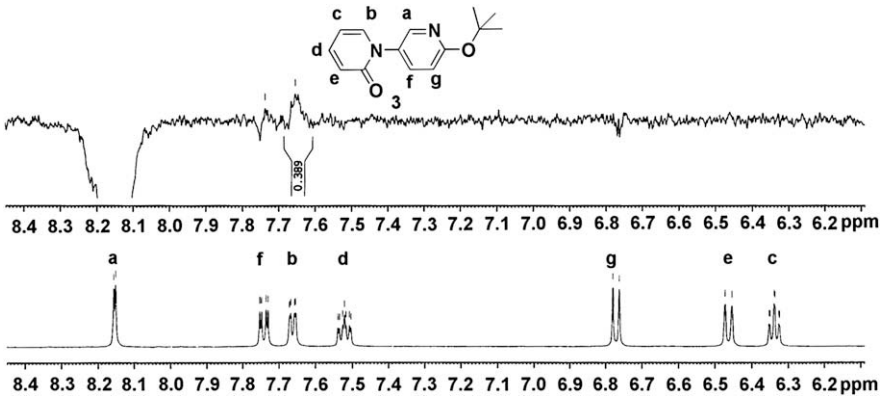


Figure 8. NOE spectrum of **3** in acetone-d_6 at 223 K. Signal enhancement on H(b) was observed when H(a) was irradiated.

unambiguously achieved as depicted in Figure 7. Again, observations of the preferential NOE enhancements on H(a) over H(o) (1:0.51), H(b) over H(m) (1: 0.13), and H(c) over H(k) (1:0.30) suggested that **9** prefers to have the folded conformation over the extended form. However, due to the small chemical shift's difference between H(e) and H(i), selective irradiation on H(e) without affecting H(i) became difficult to achieve.

On the contrary, when the dimeric pyridone **3** was subjected to NOE measurement at 298 K in acetone-d_6, no NOE signals could be observed. This is probably due to the fast rotation of the rings about the C–N σ-bond. To further obtain more evidences to support this argument, the NOE measurement was carried out at 223 K (−50 °C). Under this circumstance, weak NOE signal on H(b) was observed when H(a) of **3** was irradiated (Fig. 8). Similar NOE correlation was also observed in the 2D-NOESY spectrum at 223 K. This result suggested that our previous assumption about the fast C–N σ-bond rotation is correct. Since the NOE on the higher oligopyridone homologues could clearly be observed, this indicated that the fast σ-bond rotation along the C–N bond was slowed down in folded oligopyridones.

The conformational preference of the oligopyridones in non-polar solvents is also important to know. However, due to the small chemical shift differences between the vinyl protons in non-polar solvents such as CD_2Cl_2 and $CDCl_3$, it is very difficult to selectively double irradiate one proton without touching the adjacent ones. This limited our chance to fully evaluate their conformational preferences in non-polar solvents. Nevertheless, we have attempted using **5** as our target to study. Different from the observations in polar solvents, we discovered that NOE enhancements on H(b) and H(g) were simultaneously observed when H(a) was double irradiated in $CDCl_3$ (Fig. 9). This could be rationalized if we assumed that H(a) favored to turn outwards in $CDCl_3$, leading to similar average distances between H(a)–H(b) and H(a)–H(g). This observation is consistent with our PM3 calculations, which suggested that the distance between H(a)–H(b) should be 4.45 Å and the distance between H(a)–H(g) should be 4.56 Å. In addition, signal enhancement on H(h) was also observed even though it might be complicated by the decoupling of H(j).

In summary, our NMR evidence suggested that the conformational equilibriums of oligopyridones **5**, **7**, and **9** are solvent dependent. The oligopyridones favored to stay in the folded conformations over the extended ones in highly polar solvents such as DMSO-d_6 or acetone-d_6. However, factors that governed the solvent effects on the conformational preference are still unclear. To rationalize this phenomenon, we employed semi-empirical PM5 method to calculate the charge density on the oligopyridones. In our calculations, instead of using the *tert*-butyl substituted **5**, an *O*-methyl substituted tripyridone had been adopted in order to simplify the calculations (Fig. 10). Our results revealed that more negative charge was distributed onto the α-carbon atom C(2) rather than onto the nitrogen atom. The result is in good agreement with the resonance theory, in which charge delocalization from the nitrogen lone pair to the carbonyl group is predicted. The charge distributions either on the extended form or on the folded form were found to be similar. In non-polar environment where weak intermolecular solvent-molecule interactions are expected, the conformation of the oligopyridones will be adjusted so as to minimize the intramolecular electrostatic repulsion. As illustrated in Figure 10, the inter-distance between O′···C(2) in the extended conformation is longer in comparison to that in the folded

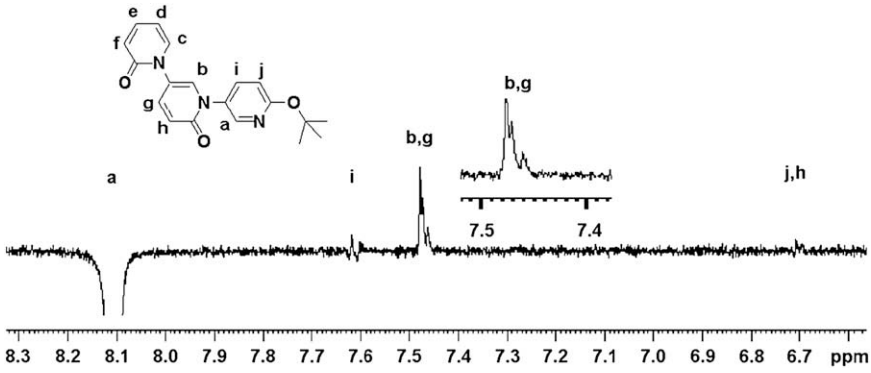


Figure 9. NOE spectrum of **5** in $CDCl_3$ at 298 K. Signal enhancement on H(b) and H(g) was observed when H(a) was irradiated. In addition, signal enhancement on H(h) was also observed.

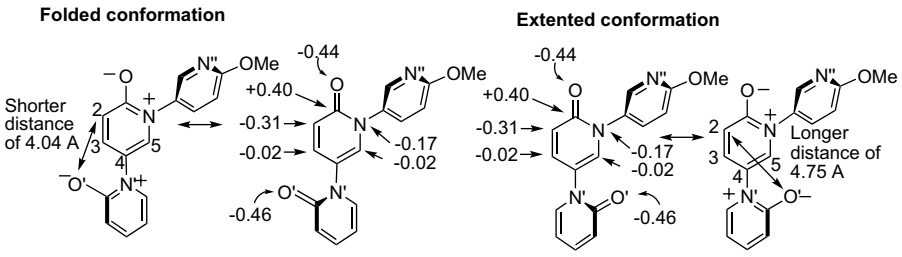


Figure 10. PM5 calculation of the partial charge distribution on the *O*-methyl substituted tripyridone.

conformation. Therefore the extended conformations will become more favorable in less-polar environment. On the other hand, perhaps due to solvent–dipole interactions that may be able to compensate the repulsion in more polar environment, the oligopyridone tends to curl into the folded conformations.

3. Experimental section

3.1. Methods

^{1}H and ^{13}C NMR were recorded in $CDCl_3$ and chemical shifts were reported in parts per million in relative scale to $CHCl_3$ (δ 7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C). Without being noted, the NMR measurements for the oligopyridones were performed at 298 K in various solvents, including CD_2Cl_2, $CDCl_3$, CD_3CN, acetone-d_6, DMSO-d_6, and CD_3OD. Before use, $CDCl_3$ was treated with K_2CO_3 to remove any acidic impurity and dried over CaH_2, followed by molecular sieves 4A, and distilled. CD_3CN, acetone-d_6, and DMSO-d_6 were dried over 4 Å molecular sieves. CD_3OD sealed in an ampoule was purchased and directly used after being opened. The concentration of the sample was about 10^{-3} M. The NOE, NOESY, and COSY experiments were performed on a Bruker 500 MHz or 600 MHz NMR.

*3.1.1. 1-(1-(6-Hydroxypyridin-3-yl)-1,6-dihydro-6-oxopyridin-3-yl)-1H-pyridin-2-one (**6**)*

To an oven-dried flask (25 mL) were charged compound **5** (0.5 g 1.5 mmol), CH_2Cl_2 (8 mL), and trifluoroacetic acid (TFA) (5%). The reaction mixture was stirred and heated at reflux temperature for 1 h. The resulting solution was concentrated and washed with hexane to give white solid. Note that this compound is hygroscopic and soluble in water. Normal extraction workup procedure is inappropriate in this case. The white solid was dried under vacuum at 110 °C for overnight to afford **6** (0.41 g, 95%): mp 290–291 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J=2.4 Hz), 7.71 (dd, J=7.6, 1.8 Hz, 1H), 7.68 (d, J=2.8 Hz, 1H), 7.59 (dd, J=9.6, 2.8 Hz, 1H), 7.54 (dd, J=9.4, 3.0 Hz, 1H), 7.49 (td, J=8.0, 2.2 Hz, 1H), 6.50 (d, 10 Hz, 1H), 6.46 (dd, J=10, 1.6 Hz, 1H), 6.38 (d, J=10 Hz, 1H), 6.38 (d, J=10 Hz, 1H), 6.29 (td, J=6.4, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6, 161.4, 160.5, 141.0, 140.6, 140.3, 139.5, 136.8, 134.0, 121.8, 121.0, 120.1, 118.9, 105.6 (only 14 separated peaks were found); IR (KBr) 3384, 3040, 1680 (C=O), 1654, 1607, 1553, 1531, 1459 cm^{-1}; FAB (NBA) 282.1 (M^++H); HRMS calcd for $C_{15}H_{12}N_3O_3$ 282.0879, found 282.0869 (M^++H). Anal. Calcd for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 63.68; H, 4.33; N, 15.21.

*3.1.2. 6‴-tert-Butoxy-[1,3′:1′,3″:1″,3‴]quaterpyridine-2,6′,6″-trione (**7**)*

To an oven-dried (10 mL) double-necked flask, denoted as flask A, containing a stir-bar were charged **6** (0.5 g, 1.77 mmol), CuI (20 mol %), and K_2CO_3 (2 equiv). The reagents were heated at 75 °C under vacuum for 1 h. To another oven-dried (10 mL) double-necked flask was charged with 18-crown-6 (0.094 g, 0.35 mmol). The 18-crown-6 was dried under vacuum at 100 °C for 1 h. Toluene (1 mL) was then injected to dissolve the dried crown ether. The crown ether solution was then injected into the flask A, followed by a solution of 2-*tert*-butoxy-5-bromopyridine (0.49 g, 2.1 mmol) and DMCDA (20 mol %) in toluene (1 mL) under nitrogen. The reaction mixture was stirred and heated at reflux temperature for 24 h. The resulting mixture was cooled, diluted with CH_2Cl_2, and filtered. The filtrate was washed with water. The organic phase was collected, dried over $MgSO_4$ (anhydrous), and concentrated. The crude product was purified by flash chromatography on silica gel (ethyl acetate/MeOH) to give white solid (0.405 g, 53%). Mp 240–241 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.240 (d, J=2.8 Hz, 1H), 8.07 (dd, J=4.8, 1.2 Hz, 2H), 7.79 (dd, J=8.8, 2.4 Hz, 1H), 7.68–7.73 (m, 2H), 7.62 (dd, J=9.6, 2.8 Hz, 1H), 7.50 (td, J=8.0, 2.0 Hz, 1H), 6.79 (d, J=8.8 Hz, 1H), 6.54 (t, J=9 Hz, 2H), 6.47 (d, J=9.2 Hz, 1H), 6.30 (td, J=6.8, 1.4 Hz, 1H), 1.564 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 160.4, 159.4, 143.1, 140.2, 139.9, 139.6, 138.7, 136.9, 136.0, 135.8, 129.7, 121.2, 120.9, 119.5, 118.3, 112.0, 105.0, 79.5, 28.3 (only 18 aromatic signals were found); IR (KBr) 3032, 2974, 1681 (C=O), 1660 (C=O), 1593, 1531, 1485 cm^{-1}; FAB (NBA) 431.2 (M^++H); HRMS calcd for $C_{24}H_{23}N_4O_4$ 431.1719, found 431.1733. Anal. Calcd for $C_{24}H_{22}N_4O_4$: C, 66.97; H, 5.15; N, 13.0. Found: C, 66.90; H, 5.07; N, 12.93.

*3.1.3. 6‴-Hydroxy-[1,3′:1′,3″:1″,3‴]quaterpyridine-2,6′,6″-trione (**8**)*

To an oven-dried flask (25 mL) were charged **7** (0.2 g, 0.46 mmol), CH_2Cl_2 (2 mL), and TFA (5%). The reaction mixture was stirred and heated at reflux temperature for 1 h. The resulting solution was concentrated and washed with hexane to give white solid. Note that this compound is hygroscopic and soluble in water. Normal extraction workup procedure is inappropriate in this case. The white solid was dried under vacuum at 110 °C overnight to afford **8** (0.16 g, 95%). Mp 296–297 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J=2.4 Hz, 1H), 8.03 (d, J=3.2 Hz, 1H), 7.71–7.73 (m, 2H), 7.66 (dd, J=10, 2.8 Hz, 1H), 7.62 (dd, J=10, 2.8 Hz, 1H), 7.55 (dd, J=9.8, 3.2 Hz, 1H), 7.50 (td, J=8.0, 2.0 Hz, 1H), 6.53 (d, J=5.2 Hz, 1H), 6.50 (d, J=4.4 Hz, 1H), 6.47 (d, J=9.2 Hz, 1H), 6.39 (d, J=9.6 Hz, 1H), 6.31 (td, J=7.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6, 161.4, 160.5, 160.4, 141.1, 140.8, 140.4, 139.5, 137.0, 136.8, 121.9, 121.3, 120.2, 119.0, 118.7, 105.7 (only 16 signals were found); IR (KBr) 3438, 1677 (C=O), 1659, 1612, 1574, 1537 cm^{-1}. Although the hygroscopic properties of **8** prevented us to obtain good results in elemental analysis, the high resolution mass spectrum clearly proved the molecular mass of the molecule. FAB (NBA) 375.1 (M^++H); HRMS calcd for $C_{20}H_{15}N_4O_4$: 375.1093, found: 375.1091 (M^++H).

*3.1.4. 6⁗-tert-Butoxy-[1,3′:1′,3″:1″,3‴:1‴,3⁗]quinquepyridine-2,6′,6″,6‴-tetraone (**9**)*

To an oven-dried double-necked flask (A) (10 mL) containing a stir-bar were charged **8** (0.2 g, 0.5 mmol), CuI (20 mol%), and

K_2CO_3 (2 equiv). The flask was heated to 75 °C under vacuum for 1 h. To another oven-dried double-necked flask (B) (10 mL) was charged 18-crown-6 (0.094 g, 0.1 mmol). The crown ether was dried under vacuum at 100 °C for 1 h and dissolved in toluene (1 mL). The crown ether solution, the solution of 2-*tert*-butoxy-5-bromopyridine (0.13 g, 0.5 mmol) in DMF (2 mL), and DMCDA (40 mol %) were then injected into flask A. The reaction mixture was stirred and heated at reflux for 24 h. Note that **9** is highly hygroscopic and soluble in water. The resulting mixture was cooled to room temperature, diluted with dichloromethane, and filtered with Celite. The collected filtrate was dried and concentrated. The crude product was purified by flash chromatography on silica gel (ethyl acetate/MeOH) to give **9** as white solid (0.05 g, 18%). Mp 260–261 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J=3.2 Hz, 1H), 7.61 (d, J=2.8 Hz, 1H), 7.59 (dd, J=8.8, 2.8 Hz, 1H), 7.53 (s, 2H), 7.50 (t, J=2.6 Hz, 1H), 7.47 (t, J=2.6 Hz, 1H), 7.40–7.45 (m, 2H), 7.26 (dd, J=6.8, 2.0 Hz, 1H), 6.69 (d, J=9.2 Hz, 4H), 6.62 (d, J=9.2 Hz, 1H), 6.26 (t, J=4.6 Hz, 1H), 1.571(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 161.6, 160.5, 160.3, 142.9, 140.2, 139.3, 138.8, 138.4, 136.6, 136.0, 135.5, 135.3, 135.0, 129.5, 121.8, 121.5, 121.44, 121.41, 121.0, 113.1, 106.7, 80.6, 28.9 (only 22 signals were found). IR (KBr) 3046, 2946, 1681 (C=O), 1668 (C=O), 1613, 1556, 1538 cm^{-1}. Although the hygroscopic properties of **9** prevented us to obtain good results in elemental analysis, the high resolution mass spectrum clearly proved the molecular mass of the molecule. FAB (NBA) 524.0 (M^++H). HRMS calcd for $C_{29}H_{26}N_5O_5$ 524.1934, found 524.1929 (M^++H).

3.1.5. Oligomerization with 2-tert-butoxy-5-bromopyridine as the terminal group

To an oven-dried double-necked flask (A) (10 mL) containing a stir-bar were charged 2-hydroxy-5-bromopyridine (0.305 g, 1.7 mmol), CuI (20 mol %), and K_2CO_3 (2 equiv) under nitrogen. Another oven-dried double-necked flask (B) (10 mL) containing 18-crown-6 (0.094 g, 0.35 mmol) was pre-dried under vacuum at 100 °C for 1 h, followed by injection of xylenes (1 mL). The crown ether solution, a solution of 2-*tert*-butoxy-5-bromopyridine (0.20 g, 0.85 mmol) in xylenes (1 mL), and DMCDA (40 mol %) were then injected into the mixture prepared in flask A. The reaction mixture was stirred and heated at reflux for 24 h. The resulting mixture was cooled to room temperature and MeOH (5 mL) was added to dissolve the precipitates. The solution was filtered with Celite and concentrated. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate/MeOH) to afford compound **10** (0.034 g, 12%), compound **3** (0.024 g, 12%), compound **5** (0.019 g, 7%), compound **11** (0.067 g, 30%), and compound **7** (0.015 g, 4%). Analytical data for **10**: mp 130–131 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ 8.04 (d, J=2 Hz, 1H), 7.54 (dd, J=8.8, 2.8 Hz), 7.38–7.44 (m, 2H), 6.69 (d, J=8.8 Hz, 1H), 6.55 (d, J=10.4 Hz), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 160.3, 142.8, 142.6, 137.2, 136.0, 129.6, 122.5, 113.1, 98.1, 80.6, 28.8; FAB (NBA) 323.1 (M^++H); HRMS calcd for $C_{14}H_{16}BrN_2O_2$ 323.0395, found 323.0389 (M^++H). Anal. Calcd for $C_{14}H_{15}BrN_2O_2$: C, 52.03; H, 4.68; N, 8.67. Found: C, 52.07; H, 4.65; N, 8.63. Analytical data for **11**: mp 275–276 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (d, J=2.8 Hz, 1H), 7.61–7.68 (m, 3H), 6.54–6.60 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.7, 159.2, 142.5, 139.7, 138.6, 133.5, 120.9, 120.3, 118.2, 96.4. FAB (NBA) 268.0 (M^++H); HRMS calcd for $C_{10}H_8BrN_2O_2$ 266.9769, found 266.9766. Anal. Calcd for $C_{10}H_7BrN_2O_2$: C, 44.97; H, 2.64; N, 10.49. Found: C, 44.63; H, 2.98; N, 10.78.

3.1.6. Oligomerization with 2-hydroxypyridine as the terminal group

To an oven-dried double-necked flask (A) (25 mL) containing a stir-bar were charged 2-hydroxy-5-bromopyridine (0.305 g, 1.7 mmol), 2-hydroxypyridine (0.042 g, 0.42 mmol), CuI (20 mol %), and K_2CO_3 (2 equiv). The reagents were heated to 85 °C for 1.5 h to desiccate. To another oven-dried double-necked flask (B) (10 mL) was charged 18-crown-6 (0.094 g, 0.35 mmol). The 18-crown-6 was then dried under vacuum at 100 °C for 1 h. To flask B was injected xylenes (8 mL) to dissolve the dried crown. The mixture was then injected under nitrogen to the flask A, followed by DMCDA (40 mol %). The reaction mixture was stirred and heated at reflux temperature for 24 h. The resulting mixture was cooled to room temperature. MeOH (10 mL) was added to dissolve the precipitates. The reaction mixture was filtered with Celite. The filtrate was concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/MeOH) to afford **4** (0.125 g, 48%), **6** (0.11 g, 18%), and **8** (0.04 g, 5%).

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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.2008.12.024.

References and notes

1. (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015; (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173; (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893; (d) Cubberley, M. S.; Iverson, B. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 650; (e) Schmuck, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2448; (f) Huc, I. *Eur. J. Org. Chem.* **2004**, 17; (g) Cheng, R. P. *Curr. Opin. Struct. Biol.* **2004**, *14*, 512; (h) Sanford, A.; Yamato, K.; Yang, X. W.; Yuan, L. H.; Han, Y. H.; Gong, B. *Eur. J. Biochem.* **2004**, *271*, 1416; (i) Licini, G.; Prins, L. J.; Scrimin, P. *Eur. J. Org. Chem.* **2005**, 969; (j) Stone, M. T.; Heemstra, J. M.; Moore, J. S. *Acc. Chem. Res.* **2006**, *39*, 11; (k) Li, X.; Yang, D. *Chem. Commun.* **2006**, 3367; (l) Li, Z. T.; Hou, J. L.; Li, C.; Yi, H. P. *Chem. Asian J.* **2006**, *1*, 766.
2. (a) Horne, W. S.; Boersma, M. D.; Windsor, M. A.; Gellman, S. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2853; (b) Norgren, A. S.; Arvidsson, P. I. *J. Org. Chem.* **2008**, *73*, 5272; (c) Holub, J. M.; Jang, H.; Kirshenbaum, K. *Org. Lett.* **2007**, *9*, 3275; (d) Angelo, N. G.; Arora, P. S. *J. Am. Chem. Soc.* **2005**, *127*, 17134.
3. (a) Rowan, A. E.; Nolte, R. J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 63; (b) Cheng, R. P.; Gellman, S. H.; Degrado, W. F. *Chem. Rev.* **2001**, *101*, 3219; (c) Norgren, A. S.; Zhang, S.; Arvisson, P. I. *Org. Lett.* **2006**, *8*, 4533; (d) Shin, S. B. Y.; Yoo, B.; Todaro, L. J.; Kenshenbaum, K. *J. Am. Chem. Soc.* **2007**, *129*, 3218; (e) Barbe, R.; Hasserodt, J. *Tetrahedron* **2007**, *63*, 2199; (f) Chien, C.-H.; Leung, M.-k.; Su, J.-K.; Li, G.-H.; Liu, Y.-H.; Wang, Y. *J. Org. Chem.* **2004**, *69*, 1866; (g) Leung, M.-k.; Mandal, A. B.; Wang, C.-C.; Lee, G.-H.; Peng, S.-M.; Cheng, H.-L.; Her, G.-R.; Chao, I.; Lu, H. F.; Sun, Y.-C.; Shiao, M.-Y.; Chou, P.-T. *J. Am. Chem. Soc.* **2002**, *124*, 4287; (h) Chen, J.-A.; Lai, J.-L.; Lee, G. H.; Wang, Y.; Su, J. K.; Yeh, H.-C.; Lin, W.-Y.; Leung, M.-k. *Org. Lett.* **2001**, *3*, 3999; (i) Liao, C.-F.; Lai, J.-L.; Chen, J.-A.; Chen, H.-T.; Cheng, H.-L.; Her, G.-R.; Su, J. K.; Wang, Y.; Lee, G. H.; Leung, M.-k.; Wang, C.-C. *J. Org. Chem.* **2001**, *66*, 2566.
4. Huck, B. R.; Fisk, J. D.; Guzei, I. A.; Carlson, H. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 9035.
5. (a) Williams, A. *Chem.—Eur. J.* **1997**, *3*, 15; (b) Piguet, C.; Bernardinelli, G.; Hopfgartner, G. *Chem. Rev.* **1997**, *97*, 2005; (c) Dong, Z.; Karpowicz, R. J.; Bai, S.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 14242; (d) Meudtner, R. M.; Ostermeier, M.; Goddard, R.; Limberg, C.; Hecht, S. *Chem.—Eur. J.* **2007**, *13*, 9834; (e) Zhang, F.; Bai, S.; Yap, G. P. A.; Tarwade, V.; Fox, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 10590; (f) Nicoll, A. J.; Miller, D. J.; Fütterer, K.; Ravelli, R.; Allemann, R. K. *J. Am. Chem. Soc.* **2006**, *128*, 9187; (g) Ghosh, S.; Ramakrishnan, S. *Macromolecules* **2005**, *38*, 676.
6. (a) Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793; (b) Prince, R. B.; Okada, T.; Moore, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 233; (c) Gin, M. S.; Yokozawa, T.; Prince, R. B.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 2643; (d) Hou, J.-L.; Jia, M.-X.; Jiang, X. K.; Li, Z.-T.; Chen, G.-J. *J. Org. Chem.* **2004**, *69*, 6228; (e) Cubberley, M. S.; Iverson, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 7560; (f) Zhao, Y. *Curr. Opin. Colloid Interface Sci.* **2007**, *12*, 92.
7. (a) Petitjean, A.; Nierengarten, H.; Van Dorsselaer, A.; Lehn, J.-M. *Angew. Chem., Int. Ed.* **2004**, *43*, 3695; (b) Stadler, A. M.; Kyritsakas, N.; Lehn, J.-M. *Chem. Commun.* **2004**, 2024; (c) Petitjean, A.; Lehn, J.-M. *Inorg. Chim. Acta* **2007**, *360*, 849.

8. (a) Prince, R. B.; Brunsveld, L.; Meijer, E. W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 228; (b) Sinkeldam, R. W.; van Houten, M. H. C. J.; Pieterse, K.; Vekemans, J. A. J. M.; Meijer, E. W. *Chem.—Eur. J.* **2006**, *12*, 6129.
9. (a) Tanatani, A.; Mio, M. J.; Moore, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 1792; (b) Wilson, A. J.; Masuda, M.; Sijbesma, R. P.; Meijer, E. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 2275.
10. (a) Prince, R. B.; Saven, J. G.; Wolynes, P. G.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 3114; (b) Prince, R. B.; Barnes, S. A.; Moore, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 2758; (c) Inouye, M.; Waki, M.; Abe, H. *J. Am. Chem. Soc.* **2004**, *126*, 2022.
11. (a) Yang, X.; Brown, A. L.; Furukawa, M.; Li, S.; Gardinier, W. E.; Bukowski, E. J.; Bright, F. V.; Zheng, C.; Zeng, X. C.; Gong, B. *Chem. Commun.* **2003**, 56; (b) Hu, Z.-Q.; Hu, H.-Y.; Chen, C.-F. *J. Org. Chem.* **2005**, *71*, 1131; (c) Sinkeldam, R. W.; van Houtem, M. H. C. J.; Koechelberghs, G.; Vekemans, J. A. J. M.; Meijer, E. W. *Org. Lett.* **2006**, *8*, 383; (d) Rodriguez, J. M.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 8614.
12. (a) Wang, P.-S.; Liang, C.-K.; Leung, M.-k. *Tetrahedron* **2005**, *61*, 2931; (b) Lee, C.-C.; Wang, P.-S.; Viswanath, M. B.; Leung, M.-k. *Synthesis* **2008**, *9*, 1359.
13. Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120.