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Double versus single helical structures of oligopyridine-dicarboxamide strands. Part 2: The role of side chains☆

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Abstract—A series of heptameric oligoamides comprising 4-alkoxy-substituted 2,6-diaminopyridine and 2,6-pyridine-dicarbonyl units have been synthesized using convergent methods. The hybridization of these compounds into double helical dimers was studied in solution by ^{1}H NMR spectroscopy in $CDCl_3$ or DMSO-d_6 at various concentrations, and in the solid state using X-ray crystallographic analysis. Both solid state and solution data suggest that these compounds follow identical hybridization schemes. In $CDCl_3$, the oligomers possess dimerization constants considerably (up to 2000-fold) higher than related compounds having no alkoxy substituents on their 2,6-diaminopyridine units. The origin of this effect can be in part interpreted as a result of interactions between the 4-alkoxy side chains when they are present on all pyridine rings. For example, 4-benzyloxy-substituted oligomer **2** has a higher dimerization constant than 4-decyloxy and 4-methoxy-substituted analogues **1** and **3**. The crystal structure of **2** reveals multiple aromatic–aromatic interactions between the benzyl side chains, both face-to-face and edge-to-face at various angles surrounding the duplex. In the solid state, these double helices are stacked on top of each other to form long channels filled with water molecules. The 4-methoxy and 4-decyloxy-substituted analogues **1** and **3** have similar dimerization constants, showing that interactions between side chains are not significant between purely aliphatic residues. Consequently, the high stability of the double helices formed by **1** and **3** compared to related compounds having alkoxy substituents on their 2,6-pyridine-dicarbonyl units only does not find its origin in interactions between side chains but in the direct effect of the alkoxy substituents upon main chain aryl–aryl interactions.

1. Introduction

Nature has found very diverse applications of the hybridization of organic molecular strands into double or triple helical architectures. In nucleic acids, sequence selective hybridization is key to genetic information storage, duplication, and transcription. In the triple helix of collagen or in coiled coils (e.g., keratin) hybridization contributes to the stiffness and mechanical properties of the polymer fibers. In the bacterial peptide gramicidin D, hybridization gives rise to a double stranded β-barrel architecture that can bind metal ions in its hollow.[1] It is thus no surprise that chemists have made extensive efforts to design and synthesize artificial oligomers that can also wind around one another and form multiple helices. Numerous families of synthetic oligomers have been reported to wind into multiple stranded helices upon coordinating to transition metal ions.[2] Helical hybrids held solely by direct non-covalent interactions between organic strands are much less common. They include oligoresorcinols,[3] oligo-*m*-terphenyl derivatives,[4] and oligoamides of 2,6-diaminopyridine and 2,6-pyridine-dicarboxylic acid.[5–12] The latter oligomers adopt single helical conformations in solution at low concentration[13–16] but also possess the remarkable ability to extend like springs and entwine to form double helical dimers (Fig. 1).

The peculiar hybridization of pyridine dicarboxamide oligomers into double helices has been characterized in solution in chlorinated solvents and in the solid state.[5–11]

Additionally, a computational approach has led to the hypothesis that a slippage mechanism involving a series of roller-coaster-like discrete steps operates during hybridization.[12] Intramolecular π–π stacking interactions within the single helical monomers are replaced by intermolecular aromatic stacking when the tail of one of the strands proceeds inside the other single helical strand in an eddy-like process. From these studies, it can be concluded qualitatively that hybridization is driven by intermolecular aromatic stacking, which compensates the energy cost of extending and doubling the helical pitch of the single helical monomers. The competition between these two factors results in an unexpected trend of hybridization strength as a function of oligomers' length as reported in Part 1 of this study.[10] Indeed, the

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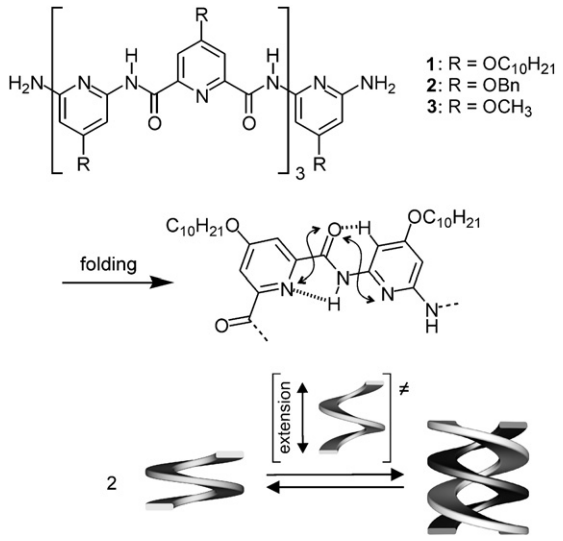


Figure 1. Structure of oligomers **1–3**. Intramolecular hydrogen bonds involved in helical conformations of pyridine oligoamides and schematic representation of single helix/double helix equilibrium implying a spring-like extension/compression of the strands. The double headed arrows indicate electrostatic repulsions.

observed dimerization constant was found to increase with strand length to reach a maximum and then to decrease down to undetectable levels upon increasing strand length further.

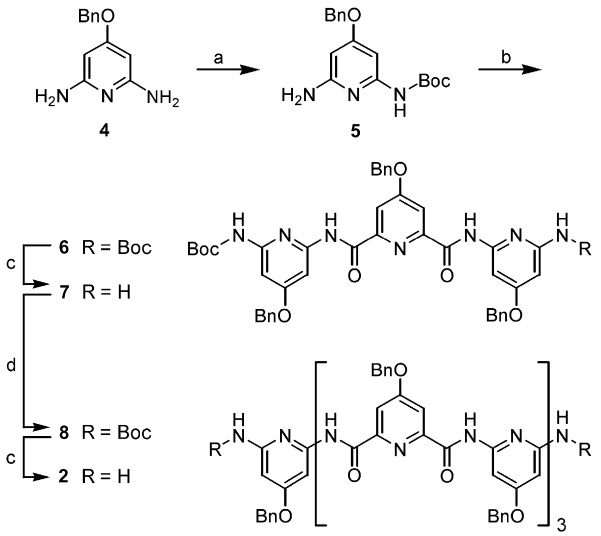
However, numerous aspects of this hybridization phenomenon remain unclear. For example, we have very early-on observed that the presence of 4-decyloxy groups on all pyridine rings lead to a dramatic enhancement of the dimerization constant (K_{dim}). In $CDCl_3$, a heptameric strand comprising three 2,6-pyridine-dicarbonyl units and four 2,6-diaminopyridine units show K_{dim}=30 L mol^{-1} when it has 4-decyloxy chains on the three 2,6-pyridine-dicarbonyl rings only, and a K_{dim}=6.5×10^4 L mol^{-1}—a 2000-fold increase—when it has 4-decyloxy chains on all rings![5,6] To explain this effect, we proposed that multiple long side chains could undergo extensive interstrand van der Waals interactions that would stabilize the duplex.[5,6] In a recent communication, we showed that such side chain–side chain interactions do take place between the aryl groups of 4-benzyloxy-substituted oligomers and result in an enhanced hybridization.[11] However, it remains unclear whether such interactions are also taking place in the decyloxy-substituted oligomers. In particular, the poor crystallinity associated with long alkyl chains has made it impossible to obtain crystals suitable for a solid state analysis.

To further investigate the role of the side chains in the hybridization of pyridine carboxamide oligomers into double helices, we set to prepare and study oligomers **1–3** (Fig. 1). These oligomers all possess an identical amine-terminated backbone bearing 4-alkoxy substituents on all pyridine rings: 4-decyloxy, 4-benzyloxy, and 4-methoxy for **1**, **2**, and **3**, respectively. Solid state and solution studies of their hybridization behavior show that side chain–side chain interactions are significant only the case of the benzyloxy-substituted oligomer. Consequently, the high stability of the double helices formed by **1** and **3** compared to related compounds having alkoxy substituents on their 2,6-pyridine-dicarbonyl units only does not find its origin in interactions between side chains but in the direct effect of the alkoxy substituents upon main chain aryl–aryl interactions.

2. Results and discussion

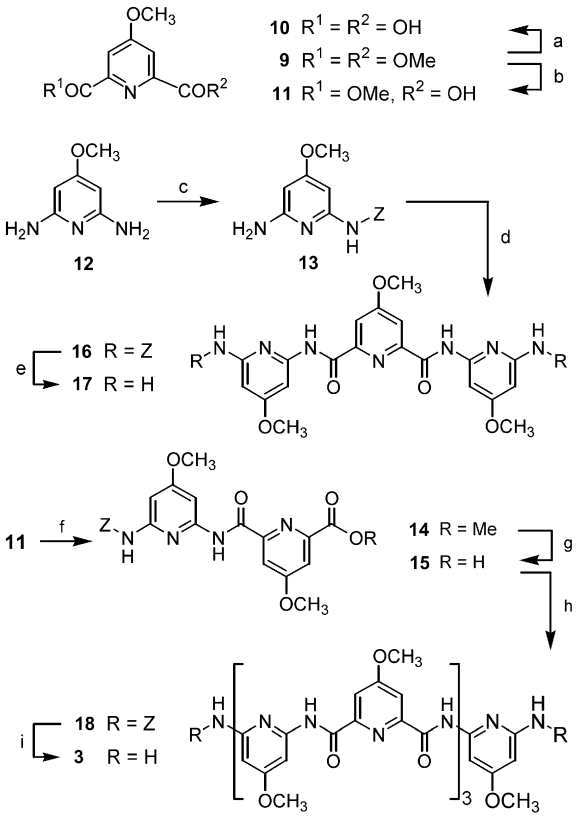
2.1. Synthesis

Heptamer **1** having two terminal amine residues was prepared by hydrogenolysis of the corresponding previously described bis-benzylcarbamate precursor.[10] The benzyloxy-substituted heptamer **2** was synthesized from 4-benzyloxy-2,6-diaminopyridine[17] and 4-benzyloxy-2,6-pyridine-dicarboxylic acid[17] following a convergent strategy developed for heptamers having no substituents in position 4 of the pyridine rings (Scheme 1).[13] This approach involves two desymmetrization steps: one at the monomer level to convert diamine monomer **4** into monoamine **5**; and the other at the trimer level to convert bis-Boc protected trimer **6** into monoamine **7**.



Scheme 1. Reagents and conditions: (a) THF, LiHMDS, $(BOC)_2O$ (1 equiv), rt, 3 h, 65% yield; (b) CH_2Cl_2, 4-benzyloxypyridine-2,6-dicarbonylchloride (0.45 equiv), Et_3N, 0 °C, 85% yield; (c) CH_2Cl_2, TMSI (1 equiv), 30 min, then MeOH, reflux, 45 min, 62% yield; (d) CH_2Cl_2, 4-benzyloxypyridine-2,6-dicarbonylchloride (0.45 equiv), Et_3N, 0 °C, 71% yield; (e) CH_2Cl_2, TFA, 2 h, 99% yield.

Methoxy-substituted heptamer **3** was synthesized using a strategy (Scheme 2) similar to that employed in the 4-decyloxy series using benzylcarbamate as amine protective group.[10] Monomers 4-methoxy-2,6-pyridine-dicarboxylic acid dimethyl ester **9**, 4-methoxy-2,6-pyridine-dicarboxylic acid monomethyl ester **11**, 4-methoxy-2,6-pyridine-dicarboxylic acid **10**, 4-methoxy-2,6-diaminopyridine **12**, and 2-amino-6-benzyloxycarbonylamino-4-methoxy-pyridine **13** were all obtained from chelidamic acid using standard procedures.[10,17–20] Monoprotected amine **13** was coupled to the acid chloride of **10** to yield trimer **16**, which was hydrogenated to diamine **17**. Monoamine **13** was also coupled to the acid chloride of **11** to yield dimer **14**. After saponification of ester **14** and activation on $SOCl_2$, the acid chloride of dimer **15** was coupled to diamine **17** to produce diprotected heptamer **18**. Hydrogenolysis of the benzylcarbamates of **18** gave the desired heptamer **3**.



Scheme 2. Reagents and conditions: (a) MeOH–dioxane, rt, NaOH (5 equiv), 4 h, 99% yield; (b) MeOH–dioxane, 0 °C, NaOH (1 equiv), 2 h, 85% yield; (c) THF, −78 °C, *n*-BuLi (1 equiv), $ClCO_2Bn$ (1 equiv), 51% yield; (d) toluene, 4-methoxypyridine-2,6-dicarbonylchloride (0.45 equiv), *i*-Pr_2EtN, 0 °C, 78% yield; (e) DMF, MeOH, rt, H_2/Pd–C, quant. yield; (f) $SOCl_2$, reflux, then **13**, toluene, *i*-Pr_2EtN, 0 °C, 75% yield; (g) H_2O–dioxane, rt, NaOH (5 equiv), 2 h, 99% yield; (h) $SOCl_2$, reflux, then **17** (0.45 equiv), toluene, *i*-Pr_2EtN, 0 °C, 29% yield; (i) DMF, EtOAc, AcOH, 60 °C, H_2/Pd–C, 74% yield.

2.2. Solid state studies

Single crystal X-ray diffraction provided details about the double helical structures of heptamers **2** and **3** (Table 1 and Fig. 2). Colorless orthorhombic crystals of heptamer **2** suitable for crystallographic analysis were obtained upon diffusion of MeOH into a DMSO–$CHCl_3$ solution. The asymmetric unit contains two molecules of **2**, each belonging to a distinct double helix possessing a C_2-symmetry axis. The two double helices closely resemble but are not related by symmetry elements; one of them is shown in Figure 2a.

The double helical structure of **2**, belongs to one of the two main types of duplexes previously observed in oligoamides of diaminopyridine and pyridine-dicarboxylic acid. These two types of duplexes share a similar helical pitch (about 7 Å) and number of units per turn (around 4), but differ by the relative position of the two stands with respect to one another.[7] In the case of **2**, the first pyridine ring of a strand stacks over the second pyridine ring of the other strand. The screw offset between the two strands is thus approximately a quarter of a turn. Consequently, the helices consist of stacks of pyridine rings that are alternatively diaminopyridine and pyridine-dicarboxylic acid units. The duplex possesses a C_2-symmetry axis perpendicular to the helical axis. In contrast, an analogue of **2** having an additional two units but the same side chains and terminal residues was shown to belong to the second type of duplex in the solid state,[11] with the two strands helically offset by two aromatic groups (half a turn), stacks of identical pyridine rings (either diaminopyridine or pyridine-dicarboxylic acid units) and a (*pseudo*) C_2-symmetry axis parallel to the helical axis.

An original feature of the structure of **2** resides in the way the duplexes are arranged in the crystal lattice. Double helices having the same handedness form columnar stacks, which

Table 1. Crystallographic data for **2** and **3**

	Compound	
	2	**3**
Formula	$C_{90}H_{73}N_{15}O_{13}$–$(CH_3OH)_{1.88}$–$(H_2O)_{3.56}$	$C_{48}H_{45}N_{15}O_{13}$–$(C_2H_5SO)_{2.25}$–$(H_2O)_{1.38}$
FW (g mol^{-1})	1681.65	1237.90
Cryst. dimensions (mm)	0.15×0.10×0.10	0.15×0.10×0.10
Solvent/precipitant	DMSO–$CHCl_3$/MeOH	DMSO/CH_3CN
Crystal color	Colorless	Colorless
Crystal system	Orthorhombic	Monoclinic
Space group	Pnna	*C*2/*c*
Z	16	8
a (Å)	19.564(7)	15.311(5)
b (Å)	49.684(19)	30.149(6)
c (Å)	35.633(15)	26.602(7)
β (°)	90	100.3652(11)
ν (Å^3)	34,636(2)	12,079.8(6)
ρ (g cm^{-3})	1.290	1.361
T	−153 °C	−153 °C
λ (Å)	1.54178 (Cu Kα)	1.54178 (Cu Kα)
θ measured (°)	6.5–50.4	6.4–39.9
Refl. measured/unique	17,860/2321	24,842/3522
No. of param.	2106	815
R_1 ($I>2\sigma(I)$)	0.2232	0.1758
WR_2 (all data)	0.6277	0.5084
GOF	1.014	1.06
CCDC #	6,31,915	6,31,916

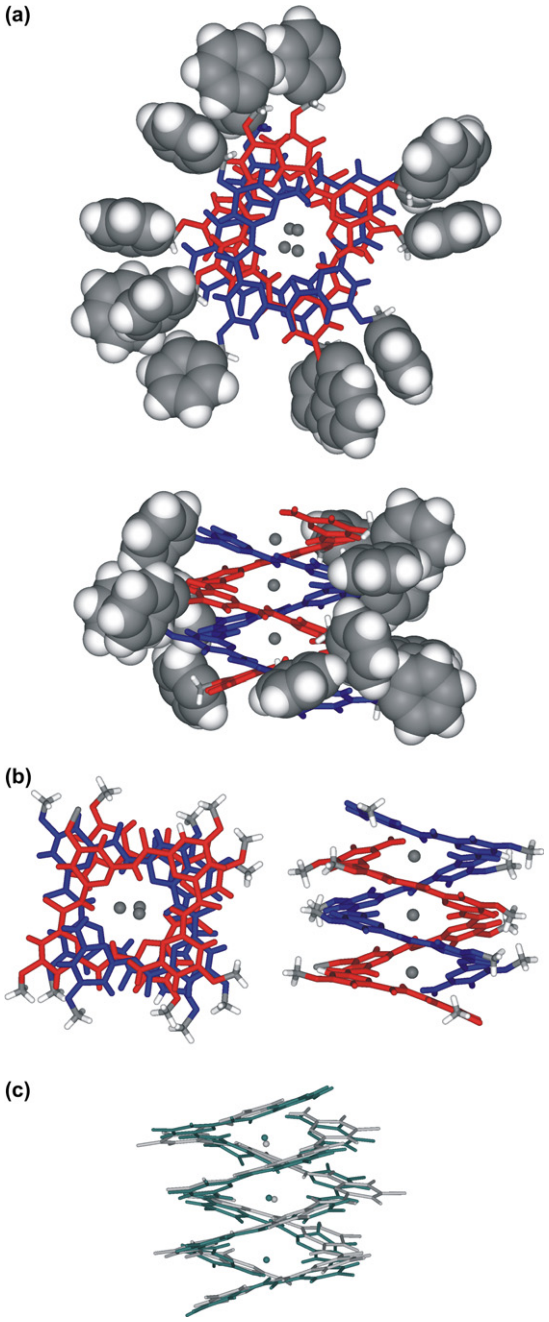


Figure 2. Crystal structures of the double helical dimers of **2** (a) and **3** (b). In both cases, the main chains of the two strands of a duplex are color coded in blue and red while the side chains are shown in gray and white. Water molecules included in the helix hollow are shown as gray spheres. Other included solvent molecules are omitted for clarity. The superposition of the main chains of duplexes of **2** and **3** is shown in (c).

define long channels along the *B*-axis—the hollows of the helices—that are filled with water molecules (Fig. 3). The water molecules reside at well-defined sites and form hydrogen bonds with the amide protons of the strands within the helices. It is not clear whether the water molecules could hop from site to site and whether the columnar stacks could actually work as water channels.

At its periphery, the duplex is surrounded by 14 benzyloxy chains. These are engaged in multiple intraduplex

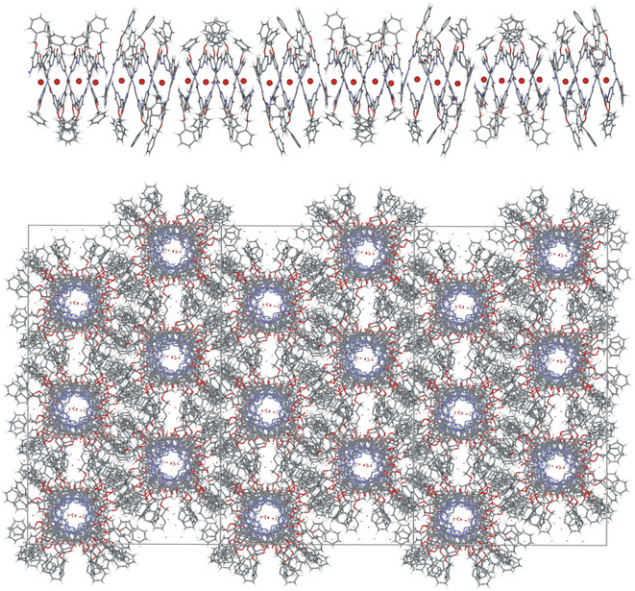


Figure 3. Views down the *C*-axis (top) and down the *B*-axis (bottom) of the crystal structure of **2**. The view down the *C*-axis shows a columnar stack of double helices having the same handedness, which define a channel containing water molecules (red balls). The view down the *B*-axis illustrates the hexagonal packing of the channels and the interdigitation of the benzyl groups belonging to different channels.

interstrand face-to-face and edge-to-face interactions at various angles (Fig. 2a). No well-defined motif emerges in the arrangement of these chains and not every benzyl group lies in contact with a benzyl group of the same duplex. In fact, the side chains are also interdigitated (and involved in interduplex interactions) with neighboring molecules, as illustrated in Figure 3. The structure of **2** may thus be considered as a snapshot of one of the many possible conformations of the side chains. This structure is consistent with that of a longer oligomer[11] and demonstrates that multiple benzyloxy residues at the periphery of a duplex do interact. As detailed in Section 2.3, this results in an enhanced dimerization constant in solution.

The structure of the double helix of methoxy-substituted heptamer **3** could be solved from small single crystals obtained upon diffusing CH_3CN in a DMSO solution (Fig. 2b). As expected, the methoxy groups are too small to bring about significant interstrand side chain–side chain interactions. Nevertheless, the structure of **3** is strikingly similar to that of **2** (Fig. 2c). Even the sites where water molecules are bound in the hollows of the helices are almost identical. This shows that the interactions between the two main chains within a duplex define the relative positioning of the two strands and overrule interactions between side chains and interduplex interactions within the crystal lattice. Importantly, these crystal structures do not fundamentally differ from those of oligomers that do not possess any alkoxy subsituent in position 4 of the diaminopyridine units and which thus have considerably lower dimerization constants: whatever is responsible for a strongly enhanced hybridization when 4-alkoxy residues are found on all rings, it does not lead to an observable change in the solid state structures.

2.3. Solution studies

As has been extensively discussed previously,[5–11] the characterization of the double helices in solution and the calculation of the dimerization constants K_{dim} are easily performed using ^{1}H NMR. For heptameric strands like **1**–**3** or longer, the single helical monomer and the double helical dimer are in slow exchange on the NMR time scale and give rise to distinct signals, which can conveniently be integrated. The proportions between monomer and dimer deduced from integral values give the dimerization constants as previously described.[5–11] A qualitative indication of the formation of the hybrids is also provided by electrospray ionization mass spectrometry (ESIMS). The double helical dimers often appear as low intensity peaks corresponding to a singly charged double helix $[2M+H]^+$ (not shown) and much more intense peaks of the doubly charged double helix $[2M+2H]^{2+}$, which can be recognized by the fact that the peaks corresponding to the various isotopes are separated by half a mass unit (Fig. 4). Every other peak of the isotopic mass distribution of the doubly charged double helix $[2M+2H]^{2+}$ overlaps with a peak belonging to the isotopic mass distribution of the singly charged single helix $[M+H]^+$, which are separated by a full mass unit. Thus the overall aspect of the isotopic distribution provides a qualitative measure of the proportions between the single helix $[M+H]^+$ and double helix $[2M+2H]^{2+}$. For example, upon changing solvent or concentration, we observe that the proportions between the single helix and double helix signals on the mass spectra correlate to those observed by NMR. However, no quantitative analysis could be derived from the mass spectra.

The dimerization constants of **1**–**3** measured in $CDCl_3$ and DMSO-d_6 are shown in Table 2. All of them are characteristic of oligomers bearing alkoxy residues in position 4 of all pyridine rings. They are considerably higher than those of comparable oligomers having no 4-alkoxy substituents on the diaminopyridine rings, which are typically found in the range of 100 L mol^{-1} in chlorinated solvents and below detection levels in DMSO. The dimerization constant of the benzyloxy substituted heptamer **2** in $CDCl_3$ is almost 10-fold higher than those of **1** and **3**, suggesting that interactions between benzyl groups do stabilize the double helix. This is in agreement both with the solid state structure of **2** (Fig. 2) and with previous results obtained for a longer analogue of **2** for which the effect is even more pronounced.[11] Duplex stabilization due to interstrand interactions between benzylic side chains apparently does not operate in more polar solvents like DMSO, in which methoxy-substituted oligomer **3** is actually found to hybridize slightly more strongly than **2**.

Table 2. Dimerization constants of **1**–**3** at 25 °C calculated from 400 MHz ^{1}H NMR measurements

	Compound		
	1	**2**	**3**
K_{dim} ($CDCl_3$)	6.9×10^4	52.8×10^4	8.2×10^4
K_{dim} (DMSO-d_6)	—[a]	120	320

[a] Insoluble.

The most striking result is the similar hybridization of decyloxy-substituted oligomer **1** and methoxy-substituted oligomer **3**. This shows that interactions between numerous long aliphatic chains at the periphery of a double helix have no effect on its stability and thus do not account, as was initially hypothesized,[5,6] for the high K_{dim} values of those oligomers, which bear 4-alkoxy residues on all pyridine rings with respect to those which do not. The very large effect of the alkoxy residues thus finds its origin in other factors. Given that the crystal structures of **2** and **3** (Fig. 2) do not show any remarkable difference from the solid state structures of less stable double helices,[5–9] the effect appears to belong to the strength of π–π interactions between the two strands within the duplex with respect to those of the single helical monomers. This is surprising in a way because electron donor groups such as alkoxy residues are a priori expected to enhance electron density of the pyridine π-clouds and thus to weaken π–π interactions.

We also envisioned that 4-alkoxy substituents could enhance the hydrogen bonding acceptor strength of the corresponding endocyclic pyridine nitrogen.[21] Some bifurcated interstrand hydrogen bonds which have occasionally been

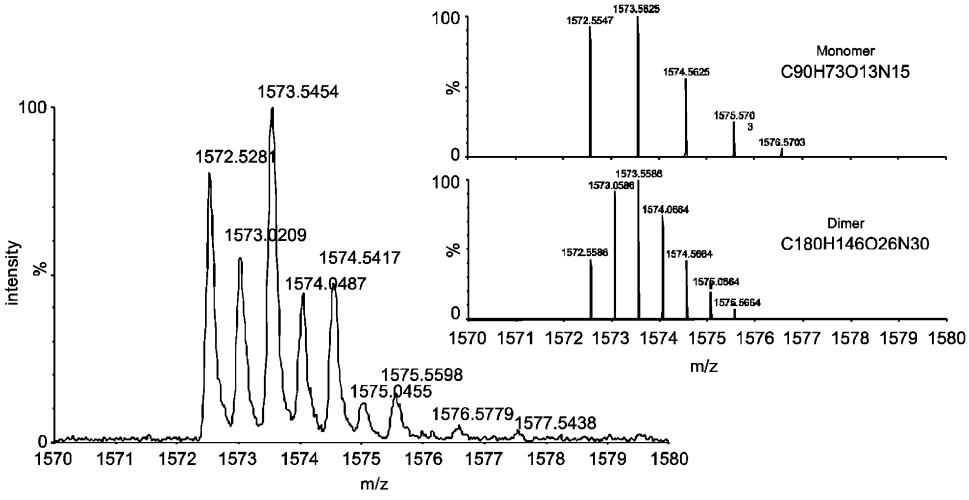


Figure 4. Experimental high-resolution ESI mass spectrum of **2** showing the isotopic mass distribution of the single helical monomer $[M+H]^+$, which adds to that of the diprotonated double helical dimer $[2M+2H]^{2+}$. The inset shows the theoretical isotopic distributions of $[M+H]^+$ (top) and $[2M+2H]^{2+}$ (bottom).

observed in the double helices of aromatic amide oligomers[4] (though not in **2** and **3**) could then be reinforced. However, this hypothesis was ruled out after measuring that 2,6-diacetylamino-pyridine has the same hydrogen-bonding directed dimerization constant whether it bears a 4-alkoxy substituent or not (not shown). Finally, the most plausible, though unsubstantiated hypothesis that we could formulate concerned dipolar effects. Considering that all the components that constitute the oligomeric backbone—amide groups and pyridine rings—possess relatively large dipole moments, it is possible that some unfavorable dipolar interactions are reduced in those oligomers bearing 4-alkoxy residues on the diaminopyridine rings, which are expected to possess a much smaller dipole moment than pyridine itself.

3. Conclusion

In summary, this study has confirmed our preliminary report[11] that interstrand interactions between side chains may stabilize the double helices of aromatic oligoamides of 2,6-diaminopyridine and 2,6-pyridine-dicarboxylic acid when the side chains consist of benzyl residues. Larger aromatic side chains or side chains endowed with specific recognition properties may thus be envisaged to amplify this phenomenon. However, no significant side chain–side chain interactions occur between exclusively aliphatic side chains. Thus, the large dimerization constants of oligomers such as **1** and **3** result from the direct effect of the alkoxy substituents on interactions at the level of the aromatic backbone. It is fair to say that this effect, despite its large amplitude, remains largely unexplained. Detailed investigations involving the replacement of the alkoxy groups by substituents having various electron donor and acceptor strengths may provide better insights into these complex phenomena and are now underway.

4. Experimental section

4.1. General

Solvents (THF, toluene, CH_2Cl_2) were dried by filtration over activated alumina on a commercially available setup. FTIR spectra were recorded on a Brucker IFS 55 FTIR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker 400 Ultrashield spectrometer. The chemical shifts are expressed in parts per million (ppm) using the residual solvent peak as an internal standard. The following notations are used for the ^{1}H NMR spectral splitting patterns: singlet (s), doublet (d), triplet (t), multiplet (m), broad (br). Melting points are uncorrected.

4.1.1. Heptamer 1. A mixture of the bis-benzylcarbamate protected precursor of **1** (7.5 mg, 0.0034 mmol)[10] dissolved in DMF/EtOAc 1:1 vol/vol (6 mL), 10% Pd/C (75 mg), and acetic acid (1 mL) was stirred in an autoclave under 4 bar of hydrogen at 55 °C for 3 days. After cooling, the mixture was filtered through Celite. The solvents were removed under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/EtOAc 96:4 vol/vol to afford compound **1** in 76% yield (5 mg, 0.0026 mmol) as a light yellow waxy solid. ^{1}H NMR ($CDCl_3$, 1 mM, 25 °C, dimer, 400 MHz): δ 0.90 (br, 30H), 1.33 (m, 140H), 2.39 (s, 68H), 3.64 (m, 36H), 4.19 (m, 28H), 4.90 (s, 4H), 5.33 (s, 2H), 5.48 (br, 10H), 6.71 (s, 4H), 6.87 (s, 1H), 6.99 (s, 2H), 7.52 (s, 2H), 7.59 (br, 8H), 7.66 (s, 4H), 7.77 (s, 2H), 7.83 (s, 2H), 7.98 (s, 2H), 8.21 (s, 1H), 8.24 (s, 1H), 10.9 (br, 12H), 10.32 (s, 2H), 10.60 (s, 2H), 10.73 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 14.1, 22.7, 25.9, 26.0, 29.1, 29.4, 29.6, 31.9, 66.5, 67.6, 68.1, 69.1, 69.3, 89.4, 91.7, 96.2, 110.4, 110.6, 110.7, 110.8, 111.1, 111.3, 149.1, 149.4, 149.6, 149.7, 149.9, 150.1, 150.2, 150.3, 150.5, 151.7, 157.4, 160.5, 160.8, 161.0, 161.1, 161.4, 161.5, 161.7, 161.8, 166.9, 167.0, 167.1, 167.2, 167.4, 167.5, 167.6, 167.7. IR (liquid layer) ν_{max}: l3319, 2924, 2854, 1701, 1610, 1578, 1528, 1439, 1343, 1174, 1047. HRMS calcd for $C_{111}H_{172}N_{15}O_{13}$: 1923.3259; found (ESI), 1923.3250 $[M+H]^+$.

4.1.2. 2-Amino-4-benzyloxy-6-tertiobutoxycarbonylamino-pyridine 5. A LiHMDS solution (21 mL, 1 M, 21 mmol, 2 equiv) was added to a solution of compound **4** (2.25 g, 10.46 mmol)[17] in 40 mL THF at room temperature over 15 min. After an additional 10 min, a solution of di-*tert*-butyl dicarbonate (2.28 g, 1 equiv, 10.46 mmol) in 20 mL THF was added dropwise for 20 min. And the reaction was allowed to proceed at room temperature for 3 h. The solvent was evaporated and the residue was purified by silica gel chromatography using CH_2Cl_2/EtOAc 80:20 vol/vol to afford compound **5** in 65% yield (2.14 g, 6.8 mmol) as a white solid. Mp 105–107 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50 (s, 5H), 1.54 (s, 4H), 4.31 (s, 2H), 5.07 (s, 2H), 5.77 (s, 1H), 6.88 (s, 1H), 7.06 (s, 1H), 7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): 28.2, 69.6, 80.7, 89.2, 89.7, 127.5, 128.0, 128.5, 136.2, 152.1, 152.5, 158.4, 168.2. MS calcd ($C_{17}H_{21}N_3O_3$), 315.16; found (TOFMS ES+), 315.9 $[M+H]^+$.

4.1.3. Trimer 6 and general procedure for coupling reactions. 4-Benzyloxy pyridine-dicarboxylic acid[17] (0.79 g, 2.88 mmol, 1 equiv) and $SOCl_2$ (15 mL) were heated to reflux. Excess $SOCl_2$ was removed by distillation after 1.5 h. Anhydrous toluene (10 mL) was added to the residue, and then evaporated to azeotrope remaining $SOCl_2$ to give the corresponding diacid chloride. To a solution of compound **5** (2 g, 6.35 mmol, 2.2 equiv) and triethylamine (2.3 mL, 15.84 mmol, 5.5 equiv) in CH_2Cl_2, a solution of the abovementioned diacid chloride in anhydrous CH_2Cl_2 (10 mL) was added over a period of 10 min at 0 °C. The reaction mixture was then stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using CH_2Cl_2/EtOAc 98:2 vol/vol to afford compound **6** in 85% yield (2.12 g, 2.45 mmol) as a white solid. Mp 129–131 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.52 (s, 10H), 1.60 (s, 8H), 5.18 (s, 4H), 5.29 (s, 2H), 7.18 (s, 2H), 7.42 (m, 18H), 7.83 (s, 2H), 8.04 (s, 2H), 10.05 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 28.2, 70.1, 70.8, 81.1, 95.1, 96.3, 112.3, 127.6, 128.2, 128.5, 134.7, 135.8, 150.2, 150.6, 151.6, 152.1, 161.5, 167.8, 168.5. IR (liquid layer): ν_{max}: 3301, 2979, 2932, 1731, 1693, 1612, 1582, 1509, 1474, 1392, 1367, 1350, 1289, 1230, 1169, 1082, 1047, 1028. HRMS calcd for $C_{48}H_{49}N_7NaO_9$: 890.3489; found (ESI), 890.3508 $[M+Na]^+$.

4.1.4. Trimer 7. TMSI (0.5 g, 0.38 mL, 2.5 mmol, 1.1 equiv) was added through a dry syringe to a solution of **6** (2 g, 2.3 mmol, 1 equiv) dissolved in dichloromethane

(50 mL). The mixture was stirred at room temperature for 30 min. The solvent was then evaporated; the residue was dissolved in methanol (30 mL) and heated to reflux for 45 min. Excess triethylamine was added. After evaporation of the solvent, the solid residue was purified by silica gel chromatography using CH_2Cl_2/EtOAc 98:2 vol/vol to afford compound **7** in 62% yield (1.1 g, 1.43 mmol) as a white solid. Mp 107–109 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.53 (s, 9H), 4.49 (br, 2H), 5.14 (s, 2H), 5.18 (s, 2H), 5.28 (s, 2H), 5.91 (s, 1H), 7.42 (m, 22H), 7.63 (s, 1H), 7.83 (s, 1H), 8.03 (s, 2H), 10.22 (s, 1H), 10.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 28.2, 69.9, 70.7, 81.1, 90.5, 92.1, 95.1, 196.2, 112.1, 128.2, 127.6, 128.6, 134.7, 135.9, 150.3, 151.6, 152.2, 158.2, 161.5, 167.7, 168.4. IR (liquid layer): ν_{max} 3366, 3315, 3034, 2979, 2932, 1729, 1694, 1613, 1582, 1532, 1447, 1392, 1368, 1348, 1335, 1291, 1233, 1170, 1058, 1047, 1028. MS calcd ($C_{43}H_{41}N_7O_7$), 767.31; found (TOFMS ES+), 768.1 $[M+H]^+$ 790.1 $[M+Na]^+$.

4.1.5. Heptamer 8. Compound **8** was prepared from 4-benzyloxy pyridine-dicarboxilic acid[17] (76 mg, 0.28 mmol, 1 equiv) and trimer **7** (0.47 g, 0.62 mmol, 2.2 equiv) using the general procedure for coupling described above. The product was purified by silica gel chromatography using CH_2Cl_2/EtOAc 98:2 vol/vol to afford compound **8** in 71% yield (354 mg, 0.2 mmol) as a white solid. Mp 141–143 °C. ^{1}H NMR (DMSO-d_6, 1 mM, single helix, 75 °C, 400 MHz): δ 1.32 (s, 18H), 5.12 (s, 4H), 5.21 (s, 4H), 5.38 (s, 4H), 5.50 (s, 2H), 7.10 (s 2H), 7.42 (br, 37H), 7.85 (s, 2H), 7.89 (s, 2H), 8.05 (s, 2H), 8.81 (s, 2H), 10.13 (s, 2H), 10.34 (s, 2H), 10.74 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 30.1, 67.9, 70.4, 81.3, 94.2, 97.0, 114.1, 128.9, 129.8, 133.5, 135.1, 141.0, 152.1, 152.6, 161.9, 172.3. IR (liquid layer) ν_{max}: 3312, 3033, 2923, 2852, 1733, 1699, 1609, 1580, 1511, 1435, 1377, 1220, 1169, 1123, 1058, 1046. MS calcd ($C_{100}H_{89}N_{15}O_{17}$), 1771.65; found (TOFMS ES+), 1772.17 $[M+H]^+$.

4.1.6. Heptamer 2. Diprotected heptamer **8** (250 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (5 mL) and TFA (2 mL) was added. After 2 h, the reaction mixture was washed with saturated $NaHCO_3$ solution and extracted with chloroform (2×50 mL). The solvent was evaporated to afford compound **2** in 99% yield (204 mg, 0.13 mmol) as a white solid. Mp 278–280 °C. ^{1}H NMR (DMSO-d_6, 2 mM, 65 °C, single helix, 400 MHz): δ 5.01 (s, 4H), 5.24 (s, 4H), 5.32 (s, 8H), 5.44 (s, 4H), 5.77 (s, 2H), 6.96 (s, 2H), 7.41 (br, 35H), 7.69 (s, 2H), 7.72 (s, 2H), 7.76 (s, 2H), 7.79 (s, 2H), 7.92 (s, 2H), 10.13 (s, 2H), 10.55 (s, 2H), 11.02 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 69.4, 70.4, 89.7, 91.7, 97.1, 111.2, 127.3, 127.5, 128.4, 128.5, 134.7, 135.5, 150.1, 150.4, 157.6, 161.4, 167.3. HRMS calcd for $C_{90}H_{74}N_{15}O_{13}$: 1572.5591; found (ESI), 1572.5575 $[M+H]^+$.

4.1.7. 4-Methoxy-2,6-pyridine-dicarboxylic acid monomethyl ester 11. Dimethyl 4-methoxypyridine 2,6-dicarboxylate **9** (2 g, 8.89 mmol)[20] was dissolved in 1,4-dioxane (32 mL) and methanol (8 mL) and the solution was cooled to 0 °C. Sodium hydroxide (355 mg, 8.89 mmol, 1 equiv) was added and the mixture was stirred at 0 °C for 2 h and another 2 h at ambient temperature. The solution was neutralized with acetic acid and poured into water (50 mL). The product was extracted with CH_2Cl_2 (2×50 mL). The organic phase was evaporated and dried under vacuum. The product contaminated with some starting diester **9** was used without further purification. Mp 159–161 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.00 (s, 3H), 4.01 (s, 3H), 7.83 (s, 1H), 7.87 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 53.1, 56.3, 115.6, 148.2, 164.2, 168.6. MS calcd ($C_9H_9NO_5$), 211.05; found (TOFMS ES+), 212.1 $[M+H]^+$.

4.1.8. 2-Amino-6-benzyloxycarbonylamino-4-methoxypyridine 13. To a solution of 4-methoxy-2,6-diaminopyridine **12** (1.5 g, 10.8 mmol)[20] in anhydrous THF (60 mL) at −78 °C, a 2 M solution of *n*-butyllithium in hexane (2.7 mL, 1 equiv) was added slowly. After 15 min, benzyl chloroformate (0.88 mL, 1 equiv) was added at once. The mixture was stirred at −78 °C for 5 h, then at room temperature for 12 h. The reaction was quenched with a small amount of water. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2. This solution was washed with water, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel chromatography using CH_2Cl_2/EtOAc 96:4 vol/vol to afford compound **13** in 51% yield (1.5 g, 5.5 mmol) as an off-white solid. Mp 91–93 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.57 (s, 3H), 3.79 (s, 3H), 4.21 (s, 2H), 5.19 (s, 2H), 5.71 (s, 1H), 6.99 (s, 1H), 7.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 55.2, 66.9, 88.8, 89.3, 128.2, 128.5, 135.8, 151.6, 153.0, 158.5, 169.1. MS calcd ($C_{14}H_{15}N_3O_3$), 273.11; found (TOFMS ES+), 274.1 $[M+H]^+$.

4.1.9. Dimer ester 14. A solution of acid **11** (1 g, 4.74 mmol) in thionyl chloride (5 mL) was heated to reflux for 30 min. Excess thionyl chloride was distilled under reduced pressure, and azeotroped with dry toluene. The residue was dissolved in dry toluene (10 mL). To this solution at 0 °C, a solution of amine **13** (1.16 g, 4.27 mmol, 0.9 equiv) in dry toluene (10 mL) was added, followed by distilled *N*,*N*-diisopropylethylamine (4 mL, 23.7 mmol, 5 equiv). The mixture was allowed to warm to ambient temperature and stirred overnight. The solvent was removed and the residue was purified by silica gel chromatography using CH_2Cl_2/EtOAc 96:4 vol/vol to afford dimer **14** in 75% yield (1.65 g, 3.55 mmol) as a white solid. Mp 171–173 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.55 (s, 3H), 3.91 (s, 3H), 3.99 (s, 3H), 4.02 (s, 3H), 5.22 (s, 2H), 7.40 (m, 5H), 7.71 (s, 1H), 7.77 (s, 1H), 7.93 (s, 1H), 10.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 53.0, 55.6, 56.1, 67.1, 94.4, 95.5, 110.6, 114.5, 128.1, 128. 6, 135.7, 150.2, 151.1, 152.8, 161.6, 168.1, 169.5. HRMS calcd for $C_{23}H_{23}N_4O_7$: 467.1567; found (ESI), 467.1548 $[M+H]^+$.

4.1.10. Dimer acid 15. Compound **15** was prepared from ester **14** (1.5 g, 3.2 mmol) and NaOH (5 equiv) using a procedure comparable to that of the preparation of **11**. The product was used without further purification (1.4 g, 3.1 mmol, 99%). Mp 245–247 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.86 (s, 3H), 4.01 (s, 3H), 5.18 (s, 2H), 7.30 (s, 1H), 7.41 (m, 5H), 7.59 (s, 1H), 7.77 (s, 1H), 7.86 (s, 1H), 10.37 (s, 1H), 10.44 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 55.4, 56.3, 65.7, 66.9, 94.2, 94.8, 110.7, 113.5, 127.7, 127.3, 150.0, 152.2, 153.3, 165.0, 168.0, 168.4. MS calcd ($C_{22}H_{20}N_4O_7$), 452.13; found (TOFMS ES+), 453.1 $[M+H]^+$, 475.1 $[M+Na]^+$.

4.1.11. Trimer 16. Compound **16** was prepared from amine **13** (0.4 g, 1.46 mmol, 1 equiv) and 4-methoxypyridine-2,6-

dicarboxylic acid **10** (132 mg, 0.67 mmol, 0.45 equiv)[19] (see Section 4.1.3). The residue was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH 99:1 vol/vol to afford compound **16** in 78% yield (0.25 g, 0.35 mmol) as a white solid. Mp 139–141 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.70 (m, 10H), 3.90 (s, 6H), 3.99 (s, 3H), 5.09 (s, 4H), 7.27 (m, 2H), 7.71 (s, 2H), 7.74 (s, 2H), 7.88 (s, 2H), 10.31 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 46.3, 50.8, 55.6, 67.2, 94.4, 95.3, 95.7, 108.7, 111.5, 120.7, 127.8, 128.5, 133.2, 137.7, 138.5, 143.8, 151.7, 156.5, 157.2, 161.5, 162.1, 166.2, 168.9, 169.4. HRMS calcd for $C_{36}H_{34}N_7O_9$: 708.2404; found (ESI), 708.2424 $[M+H]^+$.

4.1.12. Trimer diamine 17. A mixture of trimer **16** (100 mg, 0.14 mmol) dissolved in DMF (5 mL) and methyl alcohol (5 mL), and of 10% Pd/C (10 wt %) was stirred overnight under hydrogen at atmospheric pressure. The mixture was filtered through Celite. The solvents were removed under reduced pressure to give the product, which was used without further purification. Mp 114–116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.86 (6H, s), 4.01 (s, 3H), 4.80 (s, 4H), 5.64 (s, 6H), 5.83 (s, 2H), 7.52 (s, 2H), 7.95 (s, 2H), 10.59 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 46.3, 50.7, 55.7, 67.2, 94.3, 95.3, 95.7, 108.7, 111.6, 151.6, 156.5, 157.5, 161.6, 162.2, 166.2, 168.8, 169.5. MS calcd ($C_{20}H_{21}N_7O_5$), 439.16; found (TOFMS ES+), 440.21 $[M+H]^+$.

4.1.13. Heptamer 18. Compound **18** was prepared from dimer acid **15** (170 mg, 0.37 mmol, 1 equiv) and trimer diamine **17** (75 mg, 0.17 mmol, 0.45 equiv). The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH 99:1 vol/vol to afford compound **18** in 29% yield (70 mg, 0.05 mmol) as a white solid. Mp 159–161 °C. ^{1}H NMR (DMSO-d_6, 75 °C single helix, 400 MHz): δ 1.26 (m, 6H), 3.88 (s, 7H), 3.93 (s, 7H), 4.08 (s, 7H), 5.00 (s, 4H), 6.96 (s, 2H), 7.26 (s, 2H), 7.41 (s, 2H), 7.44 (s, 2H), 7.71 (s, 2H), 7.77 (s, 2H), 9.42 (s, 2H), 10.06 (s, 2H), 10.24 (s, 2H), 10.61 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 44.9, 45.1, 50.7, 51.8, 56.0, 62.4, 66.5, 67.5, 84.7, 90.2, 94.8, 97.5, 99.8, 100.7, 103.7, 112.7, 110.7, 119.4, 120.6, 121.1, 127.9, 128.3, 136.9, 139.7, 141.1, 142.6, 151.6, 154.3, 156.2, 159.9, 161.9, 165.9, 167.6, 169.9, 172.6, 184.6. MS calcd ($C_{64}H_{57}N_{15}O_{17}$), 1307; found (TOFMS ES+), 1308.32 $[M+H]^+$.

4.1.14. Heptamer 3. A mixture of heptamer **18** (30 mg, 0.023 mmol) and 10% Pd/C (10 wt %) in DMF/EtOAc/AcOH (10:10:1, vol/vol/vol, 10.5 mL) was placed in autoclave under 4 bar of hydrogen and was heated at 60 °C for 36 h. The solvents were evaporated and the residue was purified by silica gel chromatography using CH_2Cl_2/MeOH 99:1 vol/vol to afford compound **3** in 74% yield (18 mg, 0.017 mmol) as a white solid. Mp 164–166 °C. ^{1}H NMR ($CDCl_3$, dimer, 1 mM, 400 MHz): δ 3.96 (s, 12H), 4.06 (s, 9H), 5.45 (s, 4H), 4.94 (s, 4H), 6.75 (s, 7H), 6.99 (s, 7H), 7.58 (s, 9H), 7.65 (s, 10H), 7.73 (s, 7H), 10.08 (s, 2H), 10.16 (s, 1H), 10.25 (s, 1H), 10.59 (s, 1H), 10.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 44.8, 45.1, 50.7, 51.8, 55.9, 62.7, 66.4, 67.5, 84.7, 90.2, 94.8, 97.5, 99.8, 100.7, 103.1, 112.7, 110.7, 151.6, 154.3, 156.2, 159.9, 161.8, 165.9, 167.6, 169.8, 172.6, 184.7. HRMS calcd for $C_{48}H_{46}N_{15}O_{13}$: 1040,3400; found (ESI), 1040.3388 $[M+H]^+$.

4.2. X-ray crystallography

Single crystals of heptamers **2** and **3** were mounted on a Rigaku R-Axis Rapid diffractometer equipped with a MM007 micro focus rotating anode generator with monochromatized Cu Kα radiation (1.54178 Å). The data collection, unit cell refinement, and data reduction were performed using the CrystalClear software package. The positions of non-H atoms were determined by the program SHELXS 87, and the position of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. H atoms were included for structure factor calculations but not refined.

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