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BINOL-Based Foldamers—Access to Oligomers with Diverse Structural Architectures

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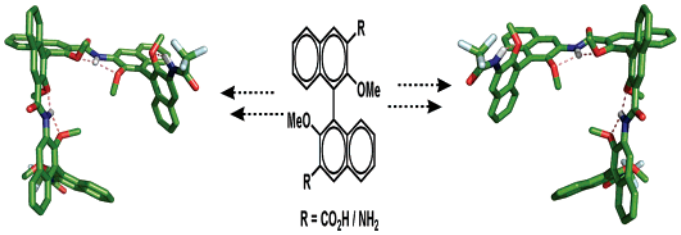

In this article, we report on the synthesis and conformation of a new family of aromatic oligoamide foldamers based on binaphthol (BINOL) monomers. A series of oligomers with differing chirality of the individual BINOL building blocks and mixed sequences of alternate BINOL and pyridyl building blocks has been synthesized and structurally characterized. NMR and quantum chemical calculations on the basis of ab initio MO theory were performed to obtain insight into the conformational features of these oligomers. It is shown that the combination of these inherently chiral aromatic building blocks provides a novel access to a wide variety of conformationally ordered synthetic oligomers with diverse and dazzling structural architectures distinct from those classically observed.

Introduction

Foldamers are synthetic oligomers with discrete folding propensities similar to biopolymers.[1,2] In the past decade, foldamer research has attracted immense attention.[1−3] Numerous examples show that foldamers are well-suited to mimic peptide structures and that they contribute to a deeper understanding of the structure and function of biopolymers.[3−5] The discovery of foldamers with biological activity[6] and special material properties[7] was of particular importance and increased the activities to find novel foldamers with diverse backbone structures not easily achievable by their small molecule counterparts.[8]

Extensive investigations by several groups led to the generation of a myriad of such synthetic oligomers with diverse backbone structures.[3−5,9] To extend the repertoire of foldamer design, oligomers containing different residues of independent conformational preferences were recently suggested. For instance, several groups demonstrated that α,β-hybrid peptides

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composed of alternately changing α- and β-amino acid constituents showed convincing evidence for the formation of special helix types.[10] We ourselves have recently provided theoretical insight into the helix formation propensities in α,β-, α,γ-, and β,γ-hybrid peptides.[11] Furthermore, the potential of using unconventional foldamer building blocks for the design of protein secondary structure mimics has also been described.[12]

In an effort to augment the repertoire of conformational space available for foldamer design, we recently suggested novel hybrid foldamers composed of conformationally constrained α-amino acid/aromatic amino acid building blocks as subunits.[13,14] The investigation of hybrid foldamers consisting of intrinsically constrained amino acid residues of independent conformational preferences resulted in the discovery of a foldamer that stabilizes a polymeric array of water clusters held dexterously by the backbone amide groups of the foldamer with a peculiar architecture.[13] It is noteworthy that the exploration of conformationally ordered synthetic oligomers interacting with water molecules enables a better understanding of the much debated issue of water interaction with anti-freeze proteins (AFPs) and anti-freeze glyco proteins (AFGPs).[15] Our hybrid foldamer strategy involving the use of constrained α-amino acid/aromatic amino acid-conjugated building blocks as subunits also revealed a novel Pro-Amb-derived foldamer with periodic γ-turn motifs, which is extensively stabilized by intramolecular hydrogen bondings.[14]

In this article, we report on the synthesis and conformation of a new family of BINOL-based foldamers. These foldamers are characterized by the occurrence of inherently chiral BINOL building blocks in the backbone. It was anticipated that the introduction of BINOL building blocks of varying chiralities in the foldamer backbones would lead to a great number of oligomers with diverse conformations and intriguing structural architectures.

Results and Discussion

1,1′-Bi(2-naphthols), popularly known as BINOLs, exhibit the phenomenon of atropisomerism, a type of stereoisomerism occurring in systems where the rotation around a single bond is restricted to allow for different stereoisomers.[16] The BINOL building blocks required for the present study were synthesized in an optically pure form by starting from 3-hydroxy-2-naphthoic acid in 12 steps. The oligomers **1a**−**d** were then assembled by a segment doubling strategy as described in Scheme 1. The racemic BINOL ester **4**, obtained by the oxidative coupling of a methyl ester of 3-hydroxy-2-naphthoic acid **3**, was saponified to furnish the BINOL bis-acid **5**, which was subjected to kinetic resolution using a leucine methyl ester as the base to afford both *R* and *S* antipodes of **5**.[17] Both *R* and *S* antipodes of the BINOL acid **6** were subjected to a series of transformations involving Curtius rearrangement as a key step to furnish the BINOL bis-amines (*R*)-**9** and (*S*)-**9**. The oligomers **1** were made accessible by coupling excess BINOL amines (*R*)-**9**/(*S*)-**9** with the acid chlorides (*S*)-**7**/(*R*)-**7** followed by capping the terminal amines as trifluoroacetamides (Scheme 1).

All efforts to investigate the solid-state conformation of the trimers **1a**−**d** by X-ray studies did not succeed since diffraction-quality crystals could not be grown in any of the cases. Therefore, NMR and quantum chemical studies were performed to obtain insight into the conformational features of the oligomers.

All oligomers are highly soluble in nonpolar organic solvents (≫100 mM in $CDCl_3$) at ambient temperature. Thus, it can be concluded that the polar hydrogen-bonding groups of **1a**−**d** are

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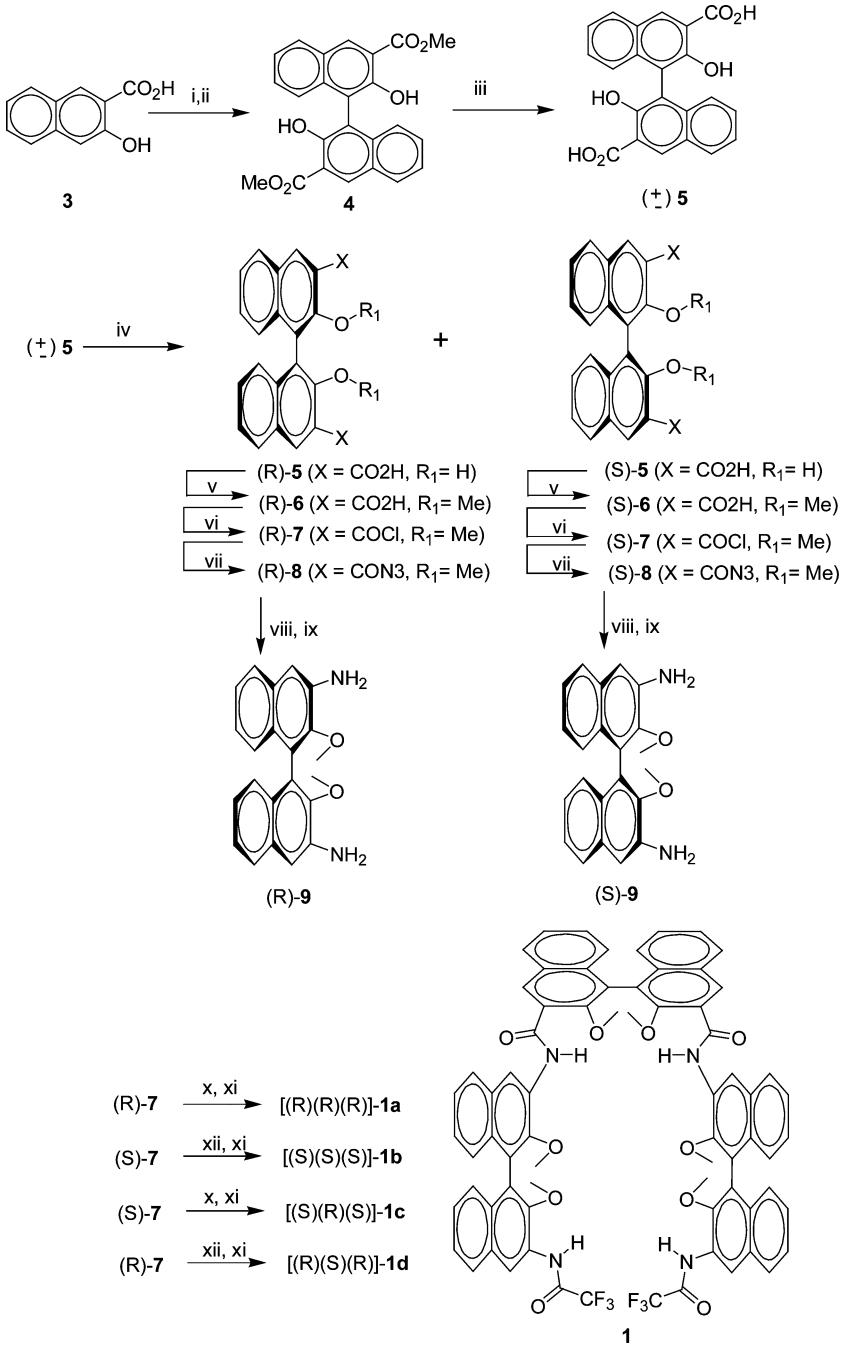
SCHEME 1. Synthesis of BINOL-Based 2-D Foldamers 1a−d[a]



[a] Reagents and conditions: (i) MeOH, H_2SO_4 (cat.), reflux, 24 h; (ii) Cu(OH)Cl·TMEDA (cat.), MeOH, reflux, 48 h; (iii) KOH, MeOH, reflux, 2 h; (iv) leucine methyl ester (resolution); (v) (a) dimethyl sulfate, K_2CO_3, acetone, reflux, 6 h and (b) KOH, MeOH, reflux, 2 h; (vi) oxalyl chloride, DCM, DMF (cat.), rt, 2 h; (vii) NaN_3, acetone, water, 15 min; (viii) benzene, reflux, 1 h; (ix) NaOH, benzene, water, reflux, 1 h; (x) (*R*)-**9** (4 equiv), triethylamine, DCM; (xi) TFA, DCC, DCM; and (xii) (*S*)-**9** (4 equiv), triethylamine, DCM.

strongly involved in intramolecular hydrogen bonding, preventing the formation of polymeric aggregates.[12] The ^{1}H NMR spectra (400 MHz) of all oligomers show well-resolved single sets of signals in $CDCl_3$ at ambient temperature, which confirm that these oligomers exist in a single conformation. The signal assignments were made using a combination of 2-D COSY, HMBC, HSQC (^{1}H−^{13}C), HSQC (^{1}H−^{15}N), and NOESY NMR experiments (for details, see the Supporting Information). It should be mentioned that the pairs of enantiomers of the oligomers (*R*)(*R*)(*R*)/(*S*)(*S*)(*S*) and (*R*)(*S*)(*R*)/(*S*)(*R*)(*S*) show identical ^{1}H spectra, suggesting their mirror-image architecture.

Conformational investigations in solution by 2-D NOESY studies (400 MHz, $CDCl_3$) clearly support the existence of bifurcated hydrogen-bond arrangements in **1a**−**d**. One of the most characteristic NOE interactions that can be anticipated for such a bifurcated hydrogen-bonded network with (*S*)-**5**- and (*S*)-**6**-type arrangements[18] would be the dipolar coupling between the aryl NH and the adjacent aryloxy methyls. The analysis of the 2-D NOESY data (Figure 1) indeed revealed the existence of such dipolar couplings. Furthermore, the characteristic NOE

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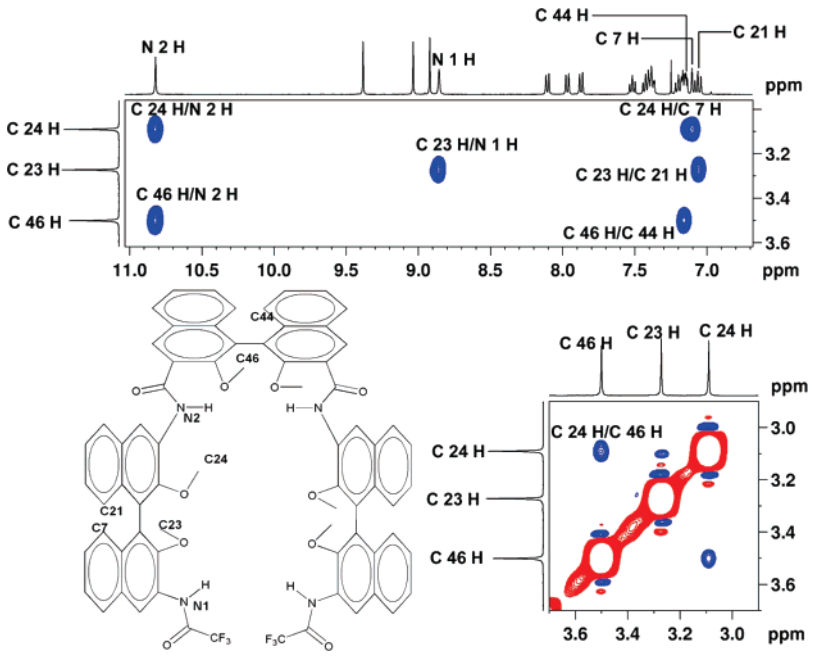

FIGURE 1. Partial 2-D NOESY spectra of **1b** (400 MHz, $CDCl_3$) showing characteristic NOE interactions. The chemical structure with selected labeled atoms is also shown to facilitate the signal assignments.

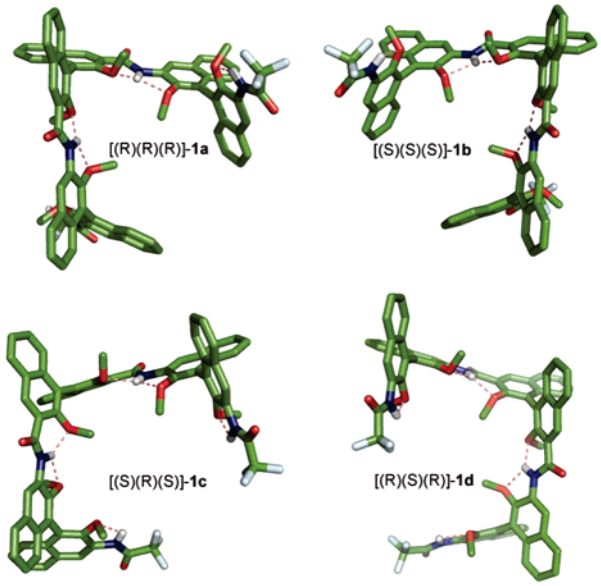

FIGURE 2. Structural architecture of the oligomers **1a**−**d** obtained at the HF/6-31G* level of ab initio MO theory. The positioning of the BINOL enantiomers (*R* and *S*) is given along with the compound number.

interactions between aryl-NH and the adjacent *O*-aryloxymethyls strongly suggest their syn orientation, thereby making space for the (*S*)-**5**-type hydrogen-bonded arrangement. This is a common feature in *O*-alkoxy arylamines and a prerequisite for the bifurcated hydrogen bonding[19] in (*S*)-**5**- and (*S*)-**6**-type arrangements.[18] A strong support of the perpendicular disposition of the napthyl rings in BINOLs, as seen in their crystal structure,[20] is the characteristic nOes observed between the methoxy and the peripheral aryl protons of the adjacent napthyl rings.

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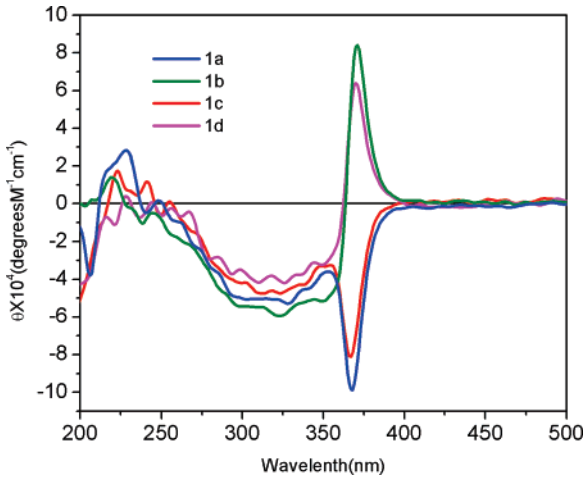


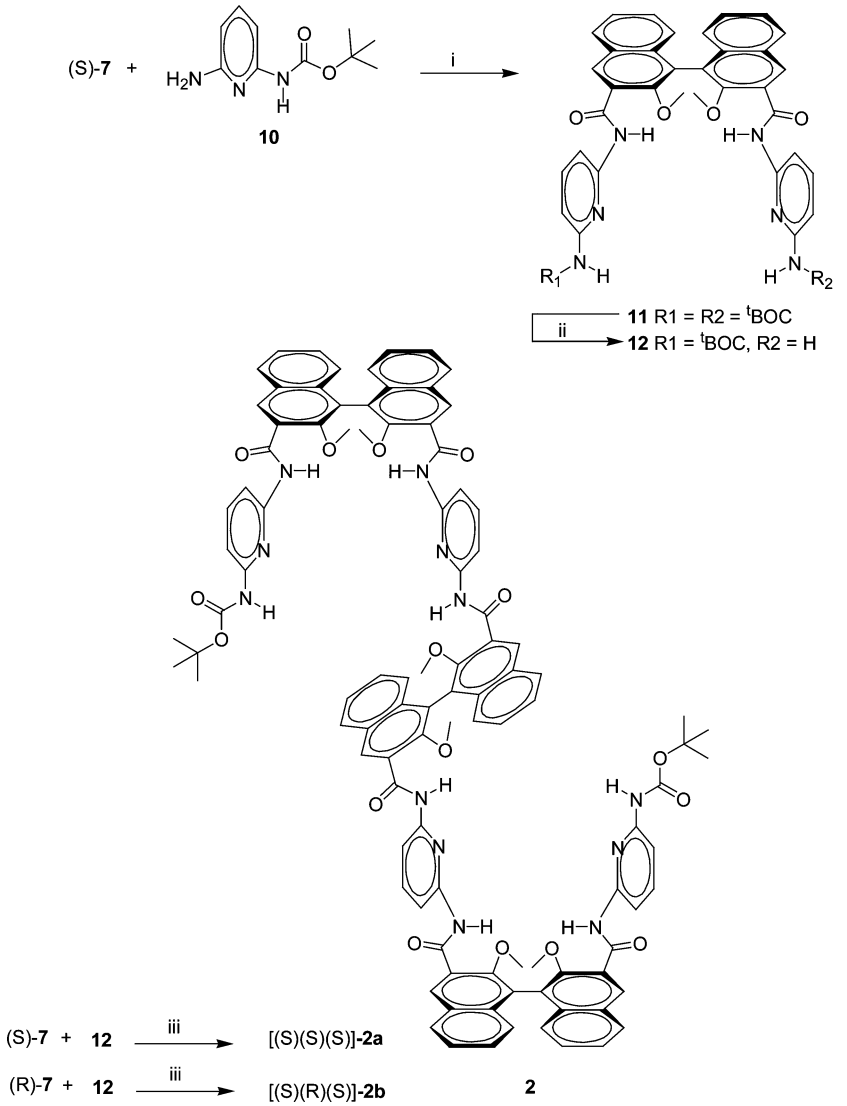
FIGURE 3. CD spectra of the oligomers **1a**−**d** (8.019×10^{-4} M, acetonitrile).

Additional support for the prevalence of intramolecular hydrogen bonds came from DMSO-d_6 titration studies of **1a** and **1d** as representative examples (for details, see the Supporting Information). All the NH signals appear downfield, suggesting their involvement in extensive hydrogen-bonding interactions. They show little shifting when the solutions of **1a** and **1d** were gradually titrated with DMSO-d_6 ($\Delta\delta < 0.09$ ppm), which confirms their involvement in strong intramolecular hydrogen bonding.

To obtain insight into the backbone structures of **1a**−**d**, quantum chemical calculations at the HF/6-31G* level of ab initio MO theory and the B3LYP/6-31G* level of density functional theory (DFT) were performed. It is noteworthy that both approximation levels are reliable enough to describe the conformational characteristics of peptides and peptide foldamers.[21,22]

Both formalisms, the HF/6-31G* level of ab initio MO theory and the B3LYP/6-31G* level of DFT, provide the conformers visualized in Figure 2, in perfect agreement. Their detailed

SCHEME 2. Synthesis of BINOL Pyridine-Based Hybrid Foldamers 2a,b[a]



[a] Reagents and conditions: (i) triethylamine, THF, rt; (ii) NaI, TMSCl, acetonitrile, 2 h and then MeOH reflux, 1 h; and (iii) triethylamine, THF, 50 °C, 4 h.

structural data are given in the Supporting Information. The calculations validate two sets of intramolecular bifurcated hydrogen bonds with (*S*)-**5**- and (*S*)-**6**-type arrangements,[18] as evidenced from NMR studies (vide supra). It should be noted that conformational alternatives of the methoxy groups do not influence the backbone conformation as long as the intramolecular hydrogen bonds are allowed to be maintained. Obviously, the bifurcated hydrogen-bonded networks with (*S*)-**5**- and (*S*)-**6**-type arrangements[18] and the conformationally locked naphthyl rings restrict the conformational space considerably and fix the backbone structure of the oligomers, alleviating alternate conformers. A closer inspection further reveals that the four oligomer sets are composed of two oligomer subsets with their non-superimposable mirror-images ((*R*)(*R*)(*R*) vs (*S*)(*S*)(*S*) and (*R*)(*S*)(*R*) vs (*S*)(*R*)(*S*)); a fact that is clearly vindicated by their mirror-image circular dichroism (CD) profiles (vide infra).

To obtain insight into the CD signature of these novel oligomers, we recorded their CD spectra (Figure 3). CD

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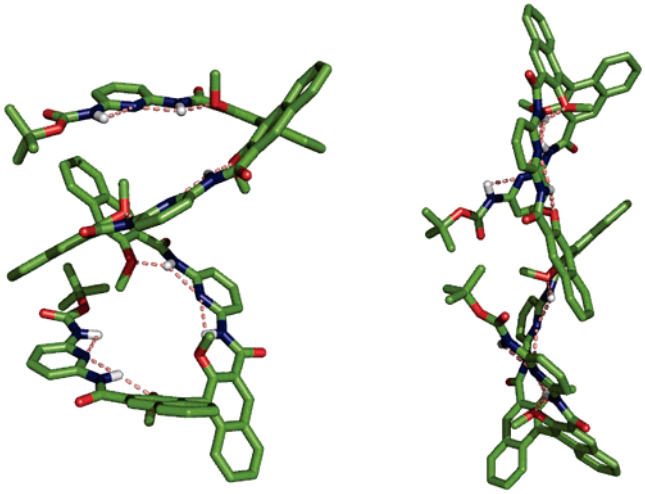

FIGURE 4. Structural architecture of the hybrid oligomers **2a** (left) and **2b** (right) obtained at the HF/6-31G* level of ab initio MO theory. The two oligomers consisting of three BINOL building blocks differ only in the positioning of the BINOL enantiomers (*R* and *S*). **2a**: [(*S*)-(*S*)(*S*)] and **2b**: [(*S*)(*R*)(*S*)].

spectroscopy is a useful tool to investigate the secondary structure of peptides and synthetic oligomers.[23] The CD spectra of the BINOL foldamers **1a**−**d** were recorded in acetonitrile at 8.019×10^{-4} M. As expected, mirror-image CD profiles are clearly evident for the oligomers with opposite chirality. It should be mentioned that the pairs of enantiomers (*R*)(*R*)(*R*)/(*S*)(*S*)(*S*) and (*R*)(*S*)(*R*)/(*S*)(*R*)(*S*), respectively, show identical ^{1}H NMR spectra, which further confirms their mirror-image architecture at the oligomer level.

For a further demonstration of the overwhelming ability of BINOL foldamer building blocks to breed dazzling structural architectures, we designed and synthesized the BINOL pyridine-based hybrid foldamer structures **2a** and **2b**, which differ only in their chirality (Scheme 2).

Again, the synthesis was based on the segment doubling strategy. Reaction of excess mono-boc-2,6-diaminopyridine **10**[24] with the (*S*)-BINOL acid chloride (*S*)-**7** gave the bis-boc-protected diamine **11**, which after mono-boc-deprotection with trimethyl silyl iodide followed by coupling with the BINOL acid chloride (*S*)-**7** provided the hybrid foldamer **2a**, wherein all three BINOLs are in the *S* configuration. The hybrid foldamer **2b** was made accessible by reacting the mono-boc-protected amine **12** with BINOL acid chloride (*R*)-**7**. Herein, the three BINOL building blocks have an (*S*)(*R*)(*S*) configuration. Also, for the oligomers **2a** and **2b**, single crystals suitable for X-ray studies could not be obtained. Thus, their conformation was investigated again on the basis of NMR and quantum chemical studies.

The arguments for the existence of an extensive intramolecular hydrogen-bonding network coming from experimental studies on the oligomers **1a**−**d** can be repeated for the hybrid foldamers **2a** and **2b**. Both are highly soluble in nonpolar organic solvents (≫100 mM in $CDCl_3$) at ambient temperature, suggesting the involvement of the pre-organized hydrogen-bonding groups in intramolecular hydrogen-bonded interactions. Thus, the formation of polymeric aggregates can again be excluded.[12]

The characteristic nOes supporting the bifurcated hydrogen-bonding arrangement and the perpendicular orientation of the napthyl rings in BINOLs are clearly visible (for details, see the Supporting Information). Besides, the strong involvement of all amide NHs in intramolecular hydrogen bonding is supported by DMSO-d_6 titration studies (for details, see the Supporting Information).

The structures obtained at the HF/6-31G* and B3LYP/6-31G* levels are in good agreement. Figure 4 shows that the hybrid oligomers **2a** and **2b** have strongly different shapes, although they only differ in the chirality of the same building block. In both foldamers, extensive hydrogen-bonding interactions of the three-centered (*S*)-**4**-type are visible, which is a common feature found in bis-acylated 2,6-aminopyridines.[24] In addition to the (*S*)-**4**-type interactions, bifurcated hydrogen-bonding interactions can also be seen involving the amino pyridine NHs.

Conclusion

It is shown that aromatic oligoamide foldamers based on BINOL building blocks are able to form conformationally ordered structures even in short oligomers. By different combinations of the enantiomers of the same building block, it becomes possible to induce controlled changes of the direction of the oligomeric strands obtaining access to a great number of diverse structural architectures distinct from those classically observed. In principle, such an immense conformational diversity could be achieved by all rigid aromatic building blocks, whose backbones are inherently chiral. Apart from the vast family of conformationally restricted biaryls,[25] spirobiindanols[26] and conformationally restricted aryl amides[27] might also be suited for the design of such novel foldamer structures. Currently, we are working in this direction.

Experimental Section

***N*^{3},*N*$^{3'}$-Bis-(*R*,*R*)-(2,2′-dimethoxy-3′-(2,2,2-trifluoroacetamido)-1,1′-binaphthyl-3-yl)-(*R*)-2,2′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxamide 1a.** To a solution of 2,2′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxylic acid (*R*)-**6**[17,28] (0.52 g, 1.3 mmol, 1 equiv) in dry DCM (5 mL), oxalyl chloride (0.45 mL, 5.2 mmol, 4 equiv) and a catalytic amount of DMF were added. The reaction mixture was stirred for 2 h at room temperature. The solvent was stripped off under reduced pressure and dried under high vacuum. The resulting acid chloride was dissolved in dry DCM (3 mL) and slowly added to a solution of 2,2′-dimethoxy-1,1′-binaphthyl-3,3′-diamine (*R*)-**9**[29] (1.78 g, 5.2 mmol, 4 equiv) in dry DCM (10 mL) containing triethylamine (0.9 mL, 6.5 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 12 h. The solvent was stripped off under reduced pressure, and a solution of dry DCM (10 mL) containing trifluoroacetic acid (1.15 mL, 15.5 mmol, 12 equiv) and dicyclohexylcarbodiimide, DCC (3.20 g, 15.5 mmol, 12 equiv) was

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added to the residue at 0 °C. After stirring the reaction mixture for 12 h at room temperature, DCU was filtered off, and the solvent was evaporated under vacuum to afford a crude product, which was further purified by column chromatography. Yield: 2.13 g (68.7%); mp 229−231 °C; $[\alpha]_D = -124.6$ ($c = 1.01$, THF); IR ($CHCl_3$) ν (cm^{-1}): 3396.4, 3305.8, 3018.4, 2935.5, 2856.4, 1726.2, 1699.2, 1664.5, 1529.5, 1350.1, 1309.6, 1215.1, 1002.9; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.85 (s, 2H), 9.41 (s, 2H), 9.06 (s, 2H), 8.95 (s, 2H), 8.88 (s, 2H), 8.13 (m, 2H), 7.99 (m, 2H), 7.90 (m, 2H), 7.54 (m, 2H), 7.42 (m, 6H), 7.20 (m, 6H), 7.10 (m, 4H), 3.53 (s, 6H), 3.30 (s, 6H), 3.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 155.2, 154.9, 154.5, 154.1, 153.3, 147.2, 146.4, 135.7, 134.6, 131.3, 131.0, 130.3, 130.2, 129.7, 128.9, 128.4, 127.7, 126.6, 126.1, 126.0, 125.9, 125.7, 125.5, 125.4, 125.1, 123.1, 122.6, 119.9, 118.9, 118.8, 117.0, 114.2, 111.3, 62.1, 61.0, 60.7; MALDI-TOF MS: 1270.3 (M + Na), 1286.4 (M + K); Anal. Calcd for $C_{72}H_{52}F_6N_4O_{10}$: C = 69.34, H = 4.20, N = 4.49; Found: C = 69.09, H = 4.01, N = 4.62.

***N*^{3},*N*$^{3'}$-Bis-(*S*,*S*)-(2,2′-dimethoxy-3′-(2,2,2-trifluoroacetamido)-1,1′-binaphthyl-3-yl)-(*S*)-2,2′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxamide 1b.** Compound **1b** was synthesized according to the procedure described for **1a** (Scheme 1). Yield: 2.3 g (74%); mp 223−226 °C; $[\alpha]_D = +124.0$ ($c = 0.91$, THF); IR ($CHCl_3$) ν (cm^{-1}): 3396.4, 3315.4, 3064.7, 3014.5, 2941.2, 2873.7, 1726.2, 1666.4, 1581.5, 1537.2, 1492.6, 1458.1, 1411.8, 1350.1, 1244.00, 1211.2, 1151.4, 1002.9; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.84 (s, 2H), 9.40 (s, 2H), 9.05 (s, 2H), 8.94 (s, 2H), 8.87 (s, 2H), 8.12 (m, 2H), 7.99 (m, 2H), 7.89 (m, 2H), 7.54 (m, 2H), 7.42 (m, 6H), 7.2 (m, 6H), 7.09 (m, 4H), 3.52 (s, 6H), 3.29 (s, 6H), 3.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 155.2, 154.8, 154.5, 154.1, 153.3, 147.2, 146.4, 135.7, 134.6, 131.3, 131.2, 131.0, 130.3, 130.2, 129.7, 128.9, 128.4, 127.7, 126.6, 126.1, 126.0, 125.9, 125.7, 125.5, 125.4, 125.3, 125.1, 123.1, 122.6, 119.9, 118.9, 118.8, 117.0, 114.2, 111.3, 62.1, 61.0, 60.7; MALDI-TOF MS: 1270.3 (M + Na), 1286.2 (M + K); Anal. Calcd for $C_{72}H_{52}F_6N_4O_{10}$: C = 69.34, H = 4.20, N = 4.49; Found: C = 69.13, H = 4.31, N = 4.59.

***N*^{3},*N*$^{3'}$-Bis-(*S*,*S*)-(2,2′-dimethoxy-3′-(2,2,2-trifluoroacetamido)-1,1′-binaphthyl-3-yl)-(*R*)-2,2′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxamide 1c.** Compound **1c** was synthesized according to the procedure described for **1a** (Scheme 1). Yield: 2.1 g (67.7%); mp 239−241 °C; $[\alpha]_D = -43.5$ ($c = 1.1$, THF); IR ($CHCl_3$) ν (cm^{-1}): 3396.4, 3317.3, 3062.8, 3018.4, 2943.2, 2871.8, 2837.1, 1728.0, 1666.4, 1581.5, 1537.2, 1492.8, 1454.2, 1411.8, 1350.1, 1309.6, 1217.0, 1151.4, 1001.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 2H), 9.40 (s, 2H), 9.03 (s, 2H), 8.97 (s, 2H), 8.90 (s, 2H), 8.10 (m, 2H), 8.00 (m, 2H), 7.92 (m, 2H), 7.47 (m, 6H), 7.36 (m, 2H), 7.24 (m, 4H), 7.18 (m, 4H), 7.10 (m, 2H), 3.55 (s, 6H), 3.32 (s, 6H), 3.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 155.1, 154.8, 154.4, 154.0, 153.1, 147.4, 146.4, 135.5, 134.5, 131.3, 131.0, 130.9, 130.3, 129.6, 128.7, 128.3, 127.7, 126.6, 126.2, 126.0, 125.9, 125.8, 125.7, 125.4, 125.2, 125.1, 123.2, 122.4, 119.9, 119.1, 118.9, 117.0, 114.1, 111.3, 62.1, 61.0, 60.9; MALDI-TOF MS: 1270.5 (M + Na), 1286.6 (M + K); Anal. Calcd for $C_{72}H_{52}F_6N_4O_{10}$: C = 69.34, H = 4.20, N = 4.49; Found: C = 69.57, H = 4.29, N = 4.71.

***N*^{3},*N*$^{3'}$-Bis-(*R*,*R*)-(2,2′-dimethoxy-3′-(2,2,2-trifluoroacetamido)-1,1′-binaphthyl-3-yl)-(*S*)-2,2′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxamide 1d.** Compound **1d** was synthesized according to the procedure described for **1a** (Scheme 1). Yield: 1.9 g (61.3%); mp 242−244 °C; $[\alpha]_D = +40.9$ ($c = 1.05$, THF); IR ($CHCl_3$) ν (cm^{-1}): 3398.3, 3307.7, 3064.7, 3020.3, 2943.2, 1726.2, 1664.5, 1581.5, 1541.0, 1492.8, 1458.1, 1411.8, 1350.1, 1309.6, 1215.1, 1001.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 2H), 9.39 (s, 2H), 9.02 (s, 2H), 8.95 (s, 2H), 8.89 (s, 2H), 8.08 (m, 2H), 7.98 (m, 2H), 7.90 (m, 2H), 7.44 (m, 6H), 7.34 (m, 2H), 7.20 (m, 8H), 7.09 (m, 2H), 3.54 (s, 6H), 3.31 (s, 6H), 3.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 155.2, 154.9, 154.5, 154.1, 153.1, 147.4, 146.4, 135.6, 134.6, 131.4, 131.1, 130.9, 130.4, 130.3, 129.7, 128.7, 128.4, 127.8, 126.7, 126.2, 126.1, 126.0, 125.9, 125.7, 125.5, 125.2, 125.1, 123.2, 122.5, 119.9, 119.2, 118.9, 117.0, 114.2, 111.3, 62.1, 61.1, 60.9; MALDI-TOF MS: 1270.2 (M + Na); Anal. Calcd for $C_{72}H_{52}F_6N_4O_{10}$: C = 69.34, H = 4.20, N = 4.49; Found: C = 69.29, H = 4.35, N = 4.67.

***tert*-Butyl 6-(3′-(6-(*tert*-Butyloxycarbonylamino)pyridin-2-ylcarbamoyl)-(*S*)-2,2′-dimethoxy-1,1′-binaphthyl-3-carboxamido)-pyridin-2-ylcarbamate 11.** To a solution of 2,2′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxylic acid (*S*)-**6**[17,29] (2.5 g, 6.2 mmol, 1 equiv) in dry DCM (15 mL), oxalyl chloride (2.17 mL, 24.9 mmol, 4 equiv) and a catalytic amount of DMF were added. The reaction mixture was stirred for 2 h at room temperature. The solvent was stripped off under reduced pressure, and the residue was dried under high vacuum. The resulting diacid chloride (*S*)-**7** was dissolved in dry THF (10 mL) and added slowly to a solution of mono-boc-2,6-diaminopyridine **10**[24] (2.6 g, 12.4 mmol, 2 equiv) in dry THF (15 mL) containing triethylamine (2.6 mL, 18.6 mmol, 3 equiv). After stirring the reaction mixture for 4 h at room temperature, it was filtered and directly purified by column chromatography. Yield: 3.49 g (71.6%); mp 285 °C; $[\alpha]_D = +186.2$ ($c = 0.992$, THF); IR ($CHCl_3$) ν (cm^{-1}): 3423.4, 3330.8, 3018.4, 2979.8, 2937.4, 1730.0, 1672.2, 1585.4, 1504.4, 1454.2, 1303.8, 1215.1, 1155.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.31 (s, 2H), 8.96 (s, 2H), 8.11 (m, 4H), 7.75 (m, 2H), 7.69 (m, 2H), 7.52 (m, 2H), 7.39 (m, 2H), 7.14 (m, 2H), 3.41 (s, 5H), 1.49 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 153.2, 152.2, 150.5, 149.8, 140.5, 135.5, 134.5, 130.2, 129.7, 128.9, 126.0, 125.6, 125.3, 125.2, 108.8, 108.0, 80.9, 62.0, 28.1; ESI mass: 785.2 (M + 1), 807.2 (M + Na); Anal. Calcd for $C_{44}H_{44}N_6O_8$: C = 67.33, H = 5.65, N = 10.71; Found: C = 67.14, H = 5.82, N = 10.69.

***tert*-Butyl 6-(3′-(6-Aminopyridin-2-ylcarbamoyl)-(*S*)-2,2′-dimethoxy-1,1′-binaphthyl-3-carboxamido)pyridine-2-ylcarbamate 12.** To a solution of **11** (1.5 g, 1.9 mmol, 1 equiv) and sodium iodide (0.86 g, 5.7 mmol, 3 equiv) in dry acetonitrile (20 mL), dry TMSCl (0.37 mL, 2.9 mmol, 1.5 equiv) was slowly added, and the mixture was stirred for 2 h. The reaction mixture was stripped off the solvent, and the residue was dissolved in methanol (40 mL) and heated to reflux for 1 h to decompose the unstable silylated amine. The solvent was then evaporated under reduced pressure, and the crude product **12** obtained was dried and used for the next step without further purification. ESI mass: 685.1 (M + 1).

***tert*-Butyl 6-(3′-(6-(3′-(6-(3′-(6-(*tert*-Butyloxycarbonylamino)-pyridin-2-ylcarbamoyl)-(*S*)-2,2′-dimethoxy-1,1′-binaphthyl-3-carboxamido)pyridin-2-ylcarbamoyl)-(*S*)-2,2 ′-dimethoxy-1,1′-binaphthyl-3-carboxamido)pyridin-2-ylcarbamoyl)-(*S*)-2,2′-dimethoxy-1,1′-binaphthyl-3-carboxamido)pyridine-2-ylcarbamate 2a.** To a solution of 2,2′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxylic acid (*S*)-**6** (0.2 g, 0.5 mmol, 1 equiv) in dry DCM (5 mL), oxalyl chloride (0.17 mL, 2 mmol, 4 equiv) and a catalytic amount of DMF were added. The reaction mixture was stirred for 2 h at room temperature. The solvent was stripped off under reduced pressure, and the residue was dried under high vacuum. The resulting diacid chloride (*S*)-**7** was dissolved in dry THF (5 mL) and added slowly to a solution of **12** (0.71 g, 1 mmol, 2.1 equiv) in dry THF (10 mL) containing triethylamine (0.2 mL, 1.5 mmol, 3 equiv) at room temperature. The reaction mixture was warmed at 50 °C for 4 h, filtered, and directly adsorbed on silica gel and purified by column chromatography. Yield: 0.59 g (68.4%); mp >300 °C; $[\alpha]_D = -186.1$ ($c = 1.3$, THF); IR ($CHCl_3$) ν (cm^{-1}): 3421.5, 3334.7, 3018.4, 2979.8, 2939.2, 1730.0, 1681.8, 1583.5, 1504.4, 1454.2, 1305.7, 1217.0, 1153.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.22 (s, 2H), 10.14 (s, 2H), 10.10 (s, 2H), 8.97 (s, 2H), 8.90 (s, 2H), 8.85 (s, 2H), 8.26 (m, 4H), 8.04 (m, 8H), 7.89 (m, 2H), 7.73 (m, 2H), 7.64 (m, 2H), 7.50 (m, 2H), 7.37 (m, 8H), 7.24 (m, 2H), 7.05 (m, 8H), 3.39 (s, 3H), 3.36 (s, 6H), 1.44 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 153.1, 152.9, 151.9, 150.1, 150.0, 149.4, 140.6, 135.4, 135.2, 134.5, 134.3, 130.1, 130.0, 129.7, 129.6, 128.9, 128.7, 126.1, 125.3, 125.1, 110.8, 110.5, 108.9, 107.9, 80.9, 61.9, 28.0; MALDI-TOF MS: 1758.4 (M + Na), 1774.5 (M + K); Anal. Calcd for $C_{102}H_{86}N_{12}O_{16}$: C = 70.58, H = 4.99, N = 9.68; Found: C = 70.40, H = 5.13, N = 9.46.

***tert*-Butyl 6-(3′-(6-(3′-(6-(3′-(6-(*tert*-Butyloxycarbonylamino)-pyridin-2-ylcarbamoyl)-(*S*)-2,2′-dimethoxy-1,1′-binaphthyl-3-carboxamido)pyridin-2-ylcarbamoyl)-(*R*)-2,2′-dimethoxy-1,1′-binaphthyl-3-carboxamido)pyridin-2-ylcarbamoyl)-(*S*)-2,2′-dimethoxy-1,1′-binaphthyl-3-carboxamido)pyridine-2-ylcarbamate 2b.** Compound **2b** was synthesized according to the procedure described for **2a** (Scheme 2). Yield: 0.57 g (66%); mp >300 °C; $[\alpha]_D = +62.3$ ($c = 1.02$, THF); IR ($CHCl_3$) ν (cm^{-1}): 3334.7, 3020.32, 2983.7, 2941.2, 1730.0, 1677.9, 1583.5, 1504.4, 1454.2, 1303.8, 1215.1, 1155.3; ^1H NMR (400 MHz, $CDCl_3$): δ 10.06 (s, 2H), 10.00 (s, 2H), 9.95 (s, 2H), 8.99 (s, 2H), 8.90 (s, 2H), 8.45 (s, 2H), 8.30 (m, 2H), 8.24 (m, 2H), 8.11 (m, 2H), 8.03 (m, 2H), 7.89 (m, 6H), 7.64 (m, 2H), 7.53 (m, 4H), 7.45 (m, 4H), 7.39 (m, 2H), 7.31 (m, 6H), 7.03 (m, 6H), 3.36 (s, 6H), 3.32 (s, 6H), 3.27 (s, 6H), 1.36 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 163.4, 153.0, 152.8, 152.7, 152.0, 150.2, 149.9, 140.7, 140.6, 135.7, 135.6, 135.3, 134.6, 133.5, 130.2, 130.1, 130.0, 129.7, 129.5, 128.9, 128.8, 126.6, 126.2, 126.0, 125.5, 125.4, 125.3, 125.2, 110.8, 110.5, 108.9, 108.1, 81.0, 62.1, 62.0, 61.9, 28.0; MALDI-TOF MS: 1758.5 (M + Na), 1774.6 (M + K); Anal. Calcd for $C_{102}H_{86}N_{12}O_{16}$: C = 70.58, H = 4.99, N = 9.68; Found: C = 70.64, H = 5.06, N = 9.51.

Quantum Chemical Calculations. All calculations were performed employing the program package Gaussian 03.[30] Numerical data and structural details are given in the Supporting Information.

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Supporting Information Available: ^1H, ^{13}C, and 2-D NMR data (2-D NOESY, HMBC, and HSQC); ESI/MALDI mass spectra of all oligomers; and B3LYP/6-31G* structural data of **1a**,**c** and **2a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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