MULTITURN HELICAL SELF-ORGANIZATION OF EXTENDED ALTERNATING PYRIDINE-PYRIMIDINE STRANDS[1]

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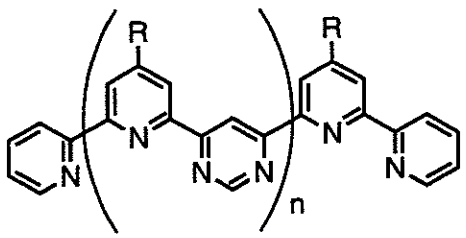
Abstract - The preprogrammed achiral oligomers (**3**) and (**4**), composed of pyridine-pyrimidine sequences containing up to 27 heterocycles, undergo self-organization into extended multiturn helical structures both in solution and in the solid state, with spontaneous chiral resolution of **3** on crystallization.

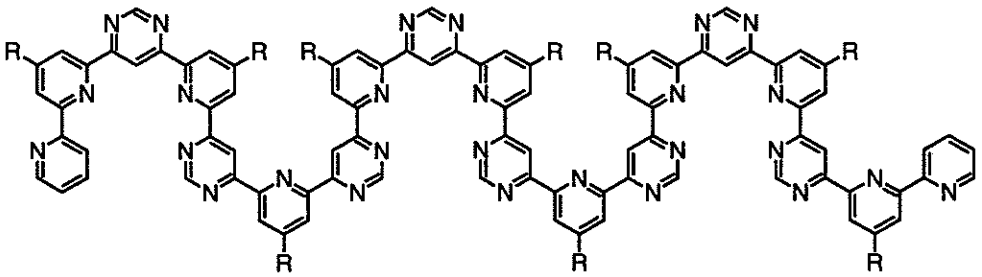
The design of molecules that spontaneously organize into helical architectures is of considerable interest because of their fascinating structural features as well as their potential applications.[3] Such self-organizing systems may provive structural and functional analog of biological helical species, such as double helices of nucleic acids[4] and α-helices of polypeptides,[5] and may generate helical oligomers and polymers with novel physical and material properties.[6] To date, various approaches to helical and multiple helical structures have been exploited primarily based on hydrogen bonding,[7] metal coodination,[8] steric interactions,[9] solvophobic interactions,[10] and donor-acceptor interactions.[11] We have recently designed an alternating pyridine-pyrimidine (py-pym) sequence as a new structural motif for helicity induction and demonstrated that the py-pym strands (**1**)[12] and (**2**)[13] adopt a helical conformation with one-turn and two-turns, respectively, both in solution and in the solid state. Our



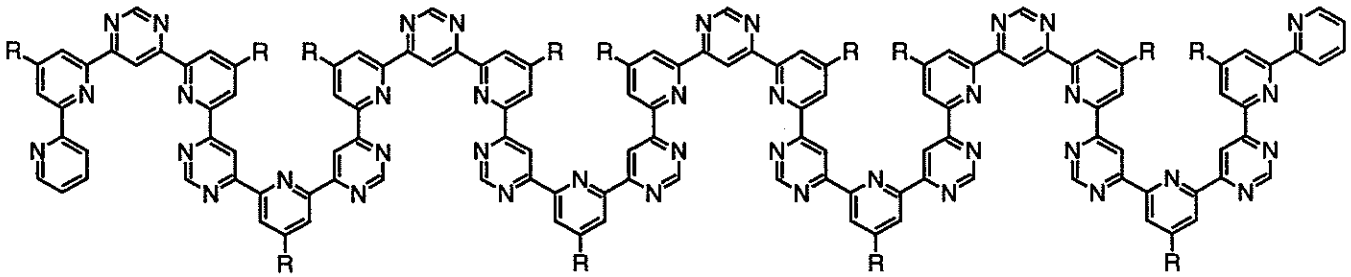
1 n = 2, R = H
2 n = 5, R = SPr

continuous interest in the spontaneous formation of helical entities through appropriate structural instruction, prompted us to synthesize the extended strands (**3**) and (**4**), composed of nineteen and twenty seven heterocycles,respectively, which were indeed, found to generate three- and four-turn helical superstructures, respectively. Here we report the synthesis and helical self-organization of **3** and **4**, including the X-Ray structure determination of **3**. Our approach is based on three key features: (1) an

alternating pyridine-pyrimidine (py-pym) sequence, (2) linkage at specific positions, and (3) the preference for a *transoid* conformation about the single bonds between the alternating units. The preference for the *transoid* conformation may be attributed to electrostatic repulsion between the nitrogen dipoles and steric repulsion between the α, α' hydrogens in the *cisoid* conformation as well as weak CH···N hydrogen bonding in the *transoid* form.

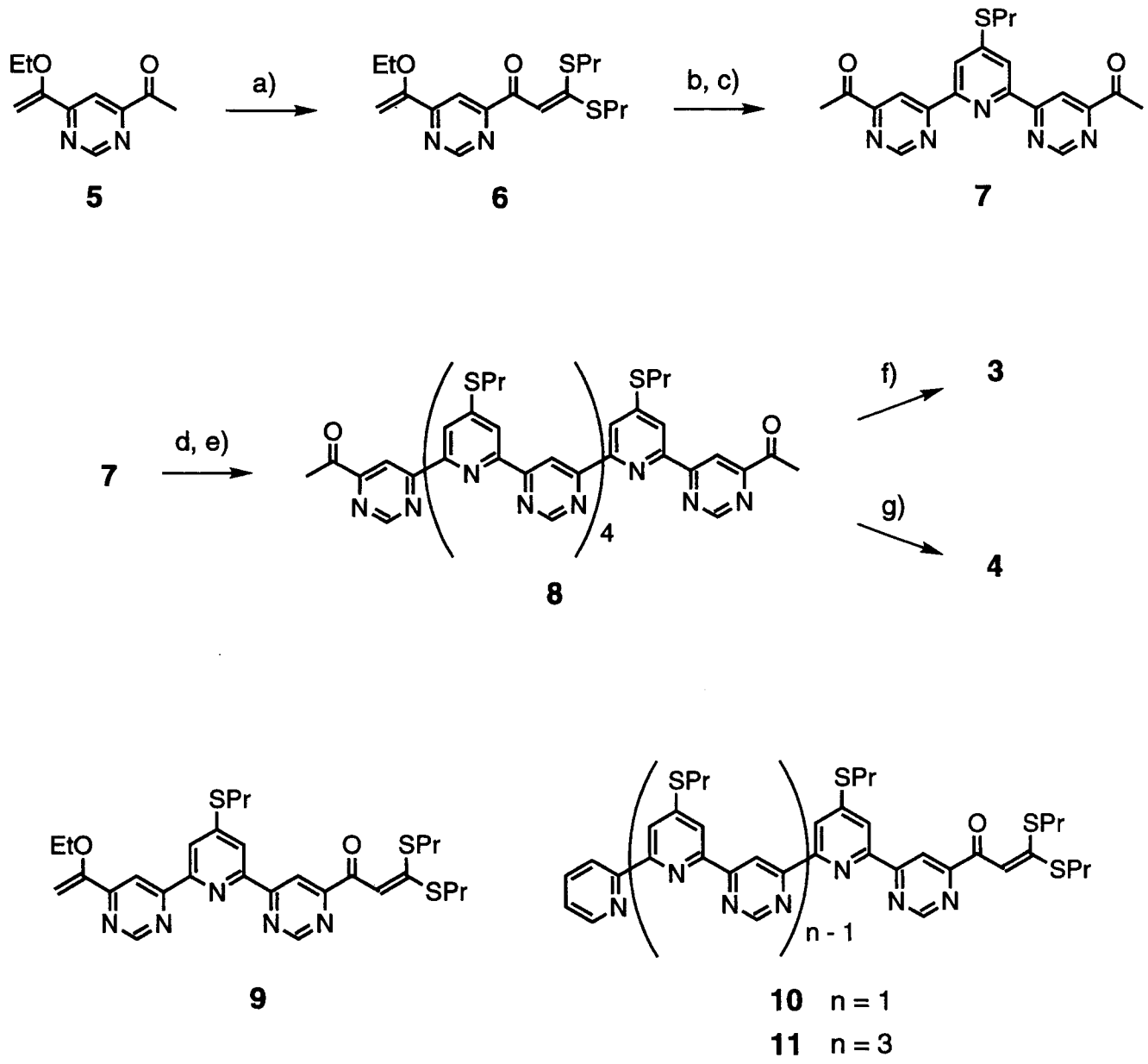


3 R = SPr



4 R = SPr

Initially the synthesis of **3** and **4** was attempted by using the method previously developed for **2**.[12] However, simple extension of this approach, in which the strand was constructed by starting from the terminal pyridine units and combining the two subunits thus prepared in the final stage, was found to be fruitless for the preparation of longer strands so that modification in the synthetic strategy was required. The synthesis of **3** and **4** was finally achieved by an alternative approach based on the homologation of the central unit as outlined in Scheme 1. Thus, successive treatment of **5** with sodium hydride, carbon disulfide and propyl iodide in DMSO afforded the corresponding α-oxoketene dithioacetal (**6**) in 68% yield. Reaction of **6** with **5** gave diketone (**7**) in 36% yield after hydrolysis. Two fold condensation of **7** with the homologating building block (**9**), having a Michael acceptor group and a protected carbonyl moiety, gave diketone (**8**) in 28% yield after hydrolysis. Reaction of **8** with the Michael acceptor (**10**) afforded oligomer (**3**), possessing 19 heterocycles, in 34% yield while reaction of **8** with the extended Michael acceptor (**11**) produced oligomer (**4**), possessing 27 heterocycles, in 5% yield. Oligomers (**3**) and (**4**) were isolated as colorless powders after extensive chromatography on alumina followed by reprecipitation from chloroform/acetone. They are soluble in chloroform, slightly soluble in dichloromethane and THF, but insoluble in ether, methanol, acetone, and acetonitrile.



Scheme 1 *Reagents and conditions*: a) NaH, CS_2, PrI, DMSO, rt (68%); b) *t*-BuOK, **5**, THF, rt, then NH_4OAc, AcOH, reflux (40%); c) aq. HCl, acetone (90%); d) *t*-BuOK, **9**, THF, then NH_4OAc, AcOH, reflux (28%); e) aq. HCl, acetone (90%); f) *t*-BuOK, 18-crown-6, **10**, refluxing THF, then NH_4OAc, AcOH, reflux (34%); g) *t*-BuOK, 18-crown-6, **11**, refluxing THF, then NH_4OAc, AcOH, reflux (5%).

The fast atom bombardment (FAB) MS spectra of **3** and **4** clearly display their molecular ion peaks with consistent isotope patterns. The ^1H NMR spectrum of **3** is rather simple, in agreement with its symmetric nature, and shows twenty one resonance signals in the aromatic region (Figure 1a): eight doublets (J = 1.8 Hz) for the trisubstituted pyridine protons, eight doublets (J = 1.2 Hz) for the pyrimidine protons, one singlet for the central trisubstituted pyridine protons, and four multiplets assignable to the terminal pyridine protons. Similarly, **4** presents the expected resonance signals in the aromatic region (Figure 1b). Oligomers (**3**) and (**4**) exhibited characteristic features of helix formation in

their ^{1}H NMR spectra. Thus, marked high-field shifts were observed for the terminal pyridine protons of H-C(4) owing to the shielding effect of the aromatic ring lying directly below the proton in the helix: δ = 7.64 ppm for pyridine, 6.03 ppm for **3**, and 5.90 ppm for **4** in $CDCl_3$. Moreover, distinct NOE effects were observed between the protons oriented toward the interior of the helix, e.g. the pyrimidine protons of H-C(5) and the terminal pyridine protons of H-C(3). These observations closely resemble those made for the previously established helices of the lower homologues (**1**) and (**2**) indicating that the extended py-pym strands (**3**) and (**4**) also adopt a helical conformation in solution.

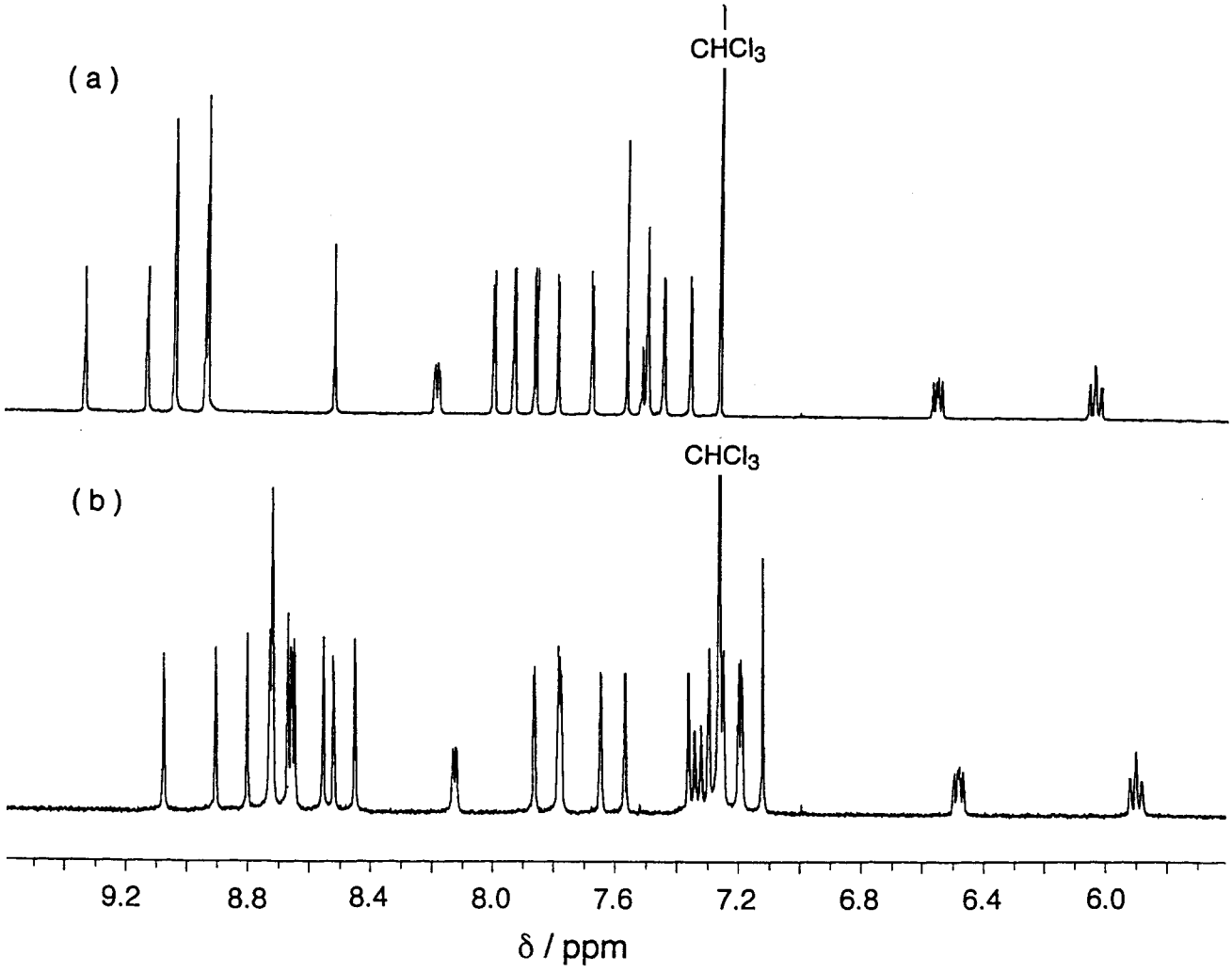


Figure 1. 400 MHz ^{1}H NMR spectra (aromatic region) of (a) **3** and (b) **4** in $CDCl_3$.

The electronic absorption spectra of **3** and **4** in dichloromethane show very strong maximum at 289 nm with absorption coefficients of 203000 and 251000, respectively. Compounds (**3**) and (**4**) exhibit broad structureless fluorescence bands at 532 and 519 nm, respectively, in dilute dichloromethane solution ($c \approx 1 \times 10^{-5}$ M), attributable to pyridine excimer emission resulting from the stacking of the pyridine residues in the helical structures.

Crystals of **3** suitable for X-Ray structure determination were obtained by slow diffusion of acetonitrile into a chloroform solution at room temperature. The molecular structure and crystal packing of **3** are presented in Figure 2, which revealed a helical structure composed of six aromatic rings for each turn of the helix.[14] The crystal is chiral and the unit cell contains two molecules of only one enantiomer of the helix of **3**, together with two chloroform molecules. The helical molecules are stacked on each other and the long axis of the unit cell coincides with that of the helical molecule itself (Figure 2b). Accordingly, the achiral linear strand (**3**) generates unique chiral channel structures in the solid state through the self-organization process. Thus, chirality induction with spontaneous chiral resolution on crystallization is taking place. Such a process, where the two enantiomeric forms are in dynamic equilibrium in solution, may in principle lead to spontaneous optical activity generation in the solid state by full transformation into a single enantiomer on crystallization.

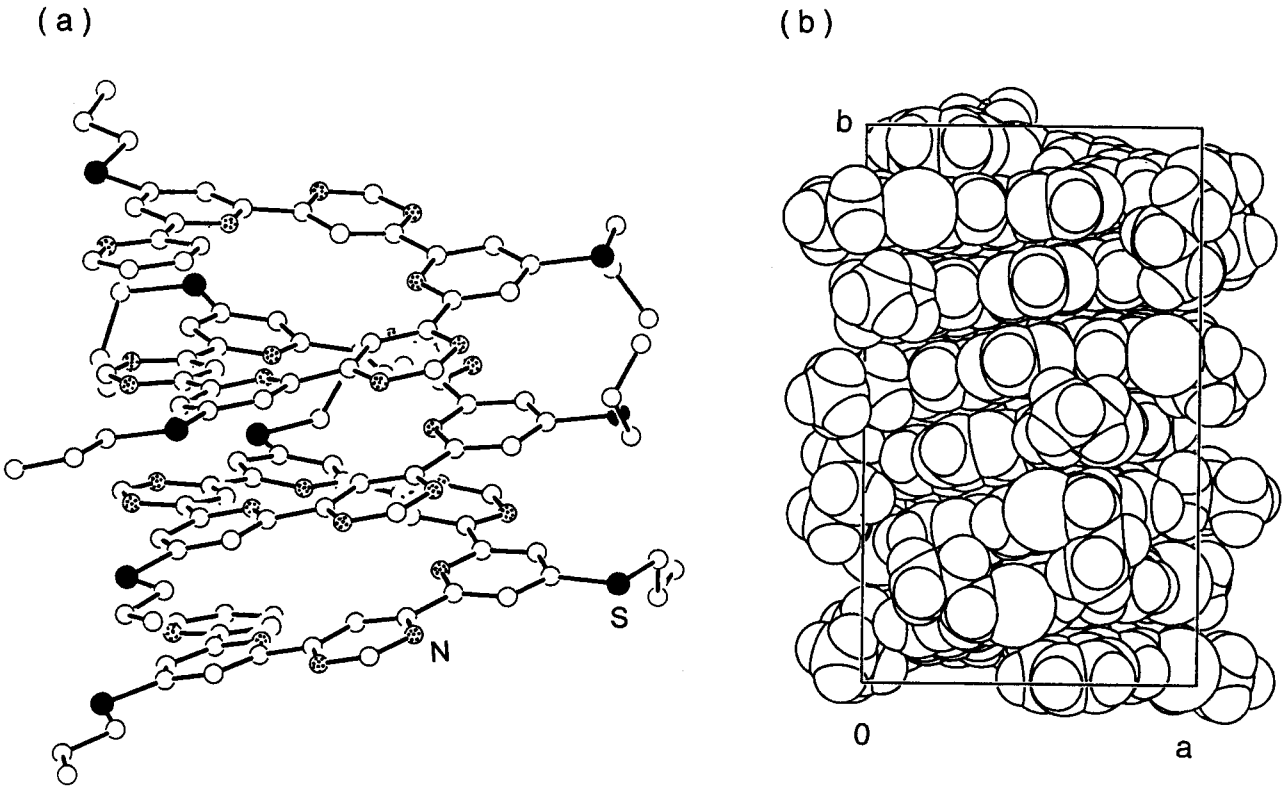


Figure 2. (a) Ball and stick representation of the crystal structure of **3**; hydrogen atoms are omitted for clarity. (b) Space filling representation of the packing arrangement of **3**.

In conclusion, we have successfully synthesized and characterized alternating py-pym oligomers that spontaneously generate multiturn helical superstructures both in solution and in the solid state. The present results demonstrate the generality of our helicity induction approach based on the py-pym unit as *helicity codon* and allow to envisage other heterocyclic sequences as structurally instructed units.[13b] They also provide prospects for the formation of helical polymers. Such spring-type polymers can be expected to have interesting physical and mechanical properties.

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14. Crystal data for **3**: $C_{114}H_{105}N_{27}S_9 \cdot CHCl_3$, 0.20 x 0.20 x 0.10 mm, M_r = 2261.16, monoclinic, $P2(1)$, a = 15.565(3), b = 24.386(5), c = 15.634(8) Å, β = 109.24(5)°, V = 5603(3) Å^3, Z = 2, ρ_{calcd} = 1.340 Mgm^{-3}, $2\Theta_{max}$ = 52°, $\lambda(Mo_{K\alpha})$ = 0.71073 Å, μ = 0.312 mm^{-1}, $F(000)$ = 2360, $-19 \le h \le 14$, $-26 \le k \le 27$, $-19 \le l \le 19$, 19611 reflections were independent (R_{int} = 0.0488), R =

0.0643 with 1394 parameters [$I > 2\sigma(I)$], 0.521/-0.376 eÅ^{-3}. The measurements were carried out on a STOE-IPDS diffractometer ($Mo_{K\alpha}$ radiation with graphite monochromator) at $T = 200$ K. All calculations were performed with SHELX-97 package. The structures were solved by direct methods and were refined by full-matrix least-square techniques based on F^2. All hydrogen atoms, the disordered SPr groups, and solvent molecules were refined isotropically. The hydrogen atoms were placed in calculated positions with $U(H) = 1.5U_{eq}(C)$ for methyl groups and $U(H) = 1.2U_{eq}(C)$ for others. Molecular graphics were performed with SCHAKAL97.

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