

## Folding Directed N-Oxidation of Oligopyridine–Dicarboxamide Strands and Hybridization of Oxidized Oligomers

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Folding in natural polymers provides specific chemical environments that enhance the reactivity of some organic functions, as in enzyme catalysis, or, on the contrary, that prevent some reactions from occurring. In this report, we present a synthetic system that features both effects simultaneously. The folding of an oligomer leads to the promotion of a reaction at peripheral reactive sites and also to the inhibition of the same reaction at central reactive sites.

We have shown that oligoamides of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid (AOAs) fold into stable single helices<sup>1</sup> and hybridize into double-helical dimers in solution and in the solid.<sup>2</sup> These hybrids represent very rare examples of stable double helices that are not derived from natural motifs and that are held by direct interactions between the strands<sup>3</sup> and not by coordination to metal ions.<sup>4</sup> It has been demonstrated that the hybridization of AOAs is mainly driven by aromatic stacking.<sup>2,5</sup> However, the phenomenon is overall poorly understood and remains specific to this family of oligomers among a large number of related structures.<sup>6,7</sup> For example, even the closely resembling oligoamides of 6-amino-2-pyridinecarboxylic acid do not hybridize.<sup>8</sup> To gain insight into these double helices, we set to investigate the effect of simple chemical modifications.<sup>2</sup> So as to avoid the full synthesis of new oligomers from modified monomers, we explored the direct functionalization of oligomers already available. Our first investigation focused on pyridine *N*-oxidation of heptamer **1a**<sup>2a</sup> and pentamer **2a**<sup>2c</sup> (Figure 1) and led to the results reported hereafter.

*N*-oxidation was chosen because it should not alter much the conformational behavior of 2-acylamino-2-pyridine and 2-pyridinecarboxamide units.<sup>9</sup> In both cases, aryl–amide bonds are expected to adopt an *s*-trans conformation with the amide carbonyl away from the *N*-oxide. We first tested the oxidation of heptamer **1a** (5 mM in CDCl<sub>3</sub>) in the presence of 8 equiv of *m*-CPBA. NMR monitoring shows that the starting material has completely reacted in less than 10 min, and that a single product forms. No other reaction can be detected in the next 4 h. Mass spectrometry indicates that two pyridine rings have been oxidized. The NMR spectrum shows that the oligomer is symmetrical, and that the signal of terminal amide protons is shifted downfield ( $\Delta\delta = 2.3$  ppm), suggesting that the oxidation product is **1b**. Similarly, pentamer **2a** is selectively oxidized twice to lead to a symmetrical structure, shown to be **2b** by crystallographic analysis (see below). Both **1b** and **2b** can be purified by a simple basic aqueous extraction.

That the 2,6-dicarbonylpyridines do not react under these mild conditions arises from their deactivation by electron-withdrawing groups. However, the absence of reaction of diaminopyridine units at the center of **1a** and **2b** is surprising. Most likely, it is caused by steric hindrance within the helically folded oligomers. Upon

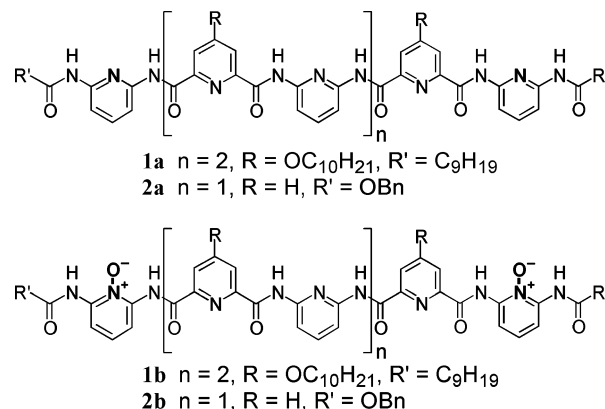


Figure 1. Structure of oligomeric strands **1a**, **2a**, **1b**, and **2b**.

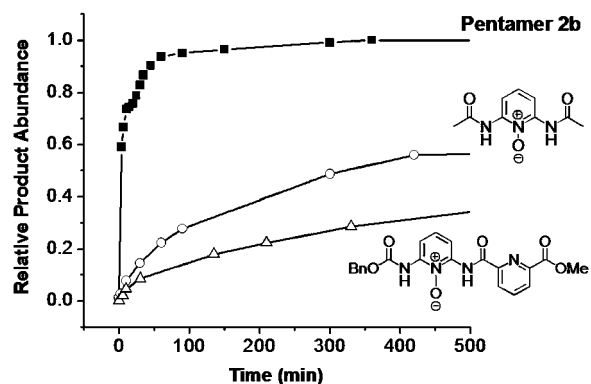


Figure 2. NMR monitoring in CDCl<sub>3</sub> at 25 °C of oxidations of **2a** (2.5 mM, ■, sum of the product and mono-oxidized intermediate), reference monomer (5 mM, ○), and reference dimer (5 mM, △) using 7.5 mM *m*-CPBA. The kink in the oxidation curve of **2a** may originate from different rates of the first and second oxidations. The lines are for guiding the eye only.

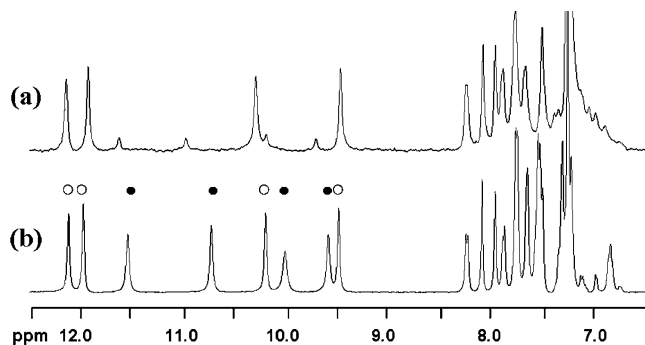
prolonged exposure to excess *m*-CPBA at higher temperature, other rings are oxidized, but the reactions remain incomplete even after several days.

To assess whether oxidation of the peripheral pyridine rings of **1a** and **2a** is also slowed to some extent by the bulky helical environment, we measured the rates of oxidation of smaller structures such as 2,6-diacetylaminopyridine and a dimeric ester derived from the two terminal units of **2a** (Figure 2). Unexpectedly, we found that the reactivity of the terminal units of **1a** and **2a** is not decreased but is, in fact, greatly enhanced compared to the nonhelical reference compounds. For example, the initial reaction rate of **2a** is at least 400 times faster than the oxidation of the dimer derived from its two terminal units.

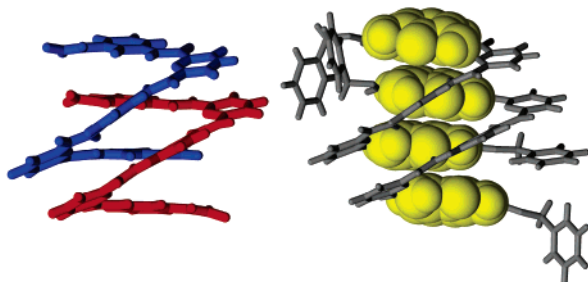
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**Figure 3.** Part of the 400 MHz  $^1\text{H}$  NMR spectra of **1b** in  $\text{CDCl}_3$  at 25  $^\circ\text{C}$  showing the amide and aromatic resonances of the single helix (○) and double helix (●) of these oligomers at 1 mM (top) and at 6.8 mM (bottom).



**Figure 4.** Crystal structure of pentamer (**2b**)<sub>2</sub>. Included solvent and water are not shown for clarity. Benzyl groups are shown on the right only. The stack of four pyridine *N*-oxide rings is represented in CPK.

The exact origin of this rate acceleration is not obvious. Stabilizing cation- $\pi$  interactions have been observed in aromatic helices<sup>10</sup> and may be involved here, even though their role was dismissed in the enhanced pyridine quaternization within helical oligo-phenylene-ethynyls.<sup>11</sup> Dipolar interactions within the helix may play a role. Amide and pyridine moieties all possess strong dipole moments, and *N*-oxidation possibly relieves dipolar repulsions between overlapping pyridine rings. Preassociation of *m*-CPBA in the polar cavity of **1a** and **2a** may also be envisaged.

NMR studies show that an *N*-oxidized strand can still dimerize into a double helix (Figure 3). For **1b**, a value of  $K_{\text{dim}} = 125 \text{ L}\cdot\text{mol}^{-1}$  is calculated from the proportions of monomer and dimer at various concentrations, which is actually 4-fold larger than the value measured for **1a**<sup>2a</sup> in the same solvent. This slight increase is by itself significant given the extreme sensitivity of the system toward chemical modifications.

Insights into the hybridization mode of the *N*-oxidized oligomers were provided by the structure of a double helix of **2b** in crystals grown from  $\text{CDCl}_3$ /hexane (Figure 4).<sup>12</sup> With its pitch equal to 7 Å, about 4 units/turn, and two water molecules included in the helix hollow, the structure of (**2b**)<sub>2</sub> compares well with the structures of (**2a**)<sub>2</sub> that we previously reported.<sup>2c</sup> An interesting aspect of (**2b**)<sub>2</sub> is the relative position of the two strands. In the duplexes that we have characterized up to now, the two strands are offset by one or two pyridine units. In other words, ring 1 of strand A may stack onto ring 2 or onto ring 3 of strand B. In (**2b**)<sub>2</sub>, the two strands are not offset at all. Ring 1 of strand A stacks onto ring 1 of strand B and so on for the following rings in the sequence. This provides another illustration of the high variability of the relative position of the two strands in these double helices<sup>2c</sup> and of the possibility of screw-type sliding motions within the duplex. A consequence

of this arrangement is that, surprisingly, the four *N*-oxide rings are stacked with their dipoles parallel to each other in (**2b**)<sub>2</sub> (Figure 4).

These data suggest that hybridization of *N*-oxide oligomers proceeds in a similar manner as that for the native strands, thus extending the register of structures capable of forming double-helical dimers and opening the way toward cross-hybridization experiments. This preliminary report also illustrates how folding of a synthetic oligomer gives rise to a sequence-dependent reactivity of identical monomers toward the same reaction. It presents evidence, albeit modest, that foldamers may provide a broader context from which to view not only biopolymer structures but also reactivity. Future developments include the study of oligomers *N*-oxidized at central positions and more detailed kinetic investigations of the oxidation rates of single helices and double helices of various lengths aimed at unraveling the origin(s) of the selectivity and rate enhancements reported here.

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**Supporting Information Available:** Crystallographic data in CIF format, details of the resolution of the structure of **2b**, and NMR monitoring of the kinetic experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (12) Crystal data for **2b**: ( $\text{C}_{90}\text{H}_{70}\text{N}_{22}\text{O}_{20}$ )<sub>2</sub> ( $\text{CHCl}_3$ )<sub>2</sub>( $\text{COCl}_2$ )<sub>2</sub>( $\text{H}_2\text{O}$ )<sub>4</sub>,  $M = 4067.98$ , monoclinic, space group  $P2_1/c$ ,  $a = 27.8066(6)$ ,  $b = 14.6508(3)$ ,  $c = 44.3633(9)$  Å,  $\beta = 91.670(2)^\circ$ ,  $V = 18065.4(7)$  Å<sup>3</sup>,  $T = 193(2)$  K,  $Z = 4$ ,  $\mu(\text{Mo K}\alpha) = 2.228 \text{ mm}^{-1}$ , 62 026 reflections measured, 5067 unique ( $R_{\text{int}} = 0.0265$ ), 4928 with  $I > 2\sigma(I)$ , 1137 parameters in final refinement. The final R indices were  $R_1$  ( $I > 2\sigma(I)$ ) = 0.0986,  $wR_2$  (all data) = 0.2833. The poor quality of this structure is due to weak diffraction intensity and slow crystal decomposition.

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