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Photomodulated Chiral Induction in Helical Azobenzene Oligomers

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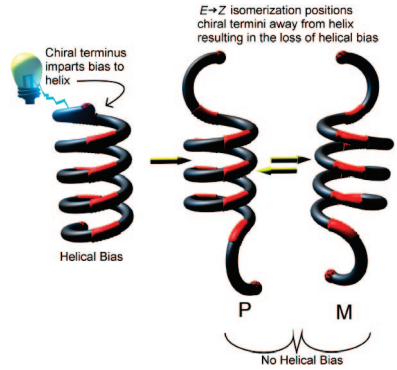
ABSTRACT



Appending L-alanine to the terminal positions of a helical azobenzene oligomer produced a *P* helical bias, which increased with oligomer length. Irradiation gave rise to *E* → *Z* isomerization of the terminal azo linkages, which displaced the stereogenic center of L-Ala from the helix backbone and suppressed chiral induction. Theoretical simulations of the CD spectrum of the *P* helical conformation are in qualitative agreement with the experimental spectra.

The creation of supramolecular structures that recreate the folding and dynamics of biological molecules has emerged as a promising strategy to merge structure with function in abiotic systems.[1] In particular, the prevalence of molecular helices in nature has inspired many diverse strategies to induce helicity in synthetic oligomers.[2] Helical systems offer the potential to amplify weak chiral influences via coupled equilibria that propagate local perturbations along the helical chain resulting in the predominance of a single helical sense.[3] This type of chiral amplification requires a dynamic helical conformation with infrequent, highly mobile helical reversal points that interconvert the helical antipodes. The ability of such dynamic systems to amplify small chiral perturbations appears to be a general phenomenon among fluxional helical oligomers,[4] polymers,[5] and supramolecular assemblies.[6] In

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this Letter, we report that helical oligomers composed of alternating pyridine-2,6-dicarboxamides and *m*-(phenylazo)azobenzenes adopt a preferred helical sense upon attachment of L-alanine at the terminal positions. Exposure to 350 nm light induces a predominant $E \rightarrow Z$ photoisomerization of the terminal azo linkages, which decouples the helix and terminal interactions in a manner that suppresses chiral amplification.

We recently described a series of oligomers composed of repeating azobenzene chromophores exhibiting conformational properties ideally suited to permit the induction of a helical handedness.[7] These oligomers adopt remarkably stable helical conformations lacking an observable unfolded state in both polar and nonpolar media. However, NMR line shape studies indicated a highly dynamic equilibria interconverting the *M* and *P* helical antipodes with energetic barriers ranging from 11.1 to 13.8 kcal/mol for two- and four-turn helices, respectively.

Replica-exchange molecular dynamics (REMD)[8] simulations suggest that helical exchange proceeds via intermediates composed of right- and left-handed segments separated by helical reversal points, which circumvents the need to access any fully unfolded states (Figure 1).[9] The nature of this

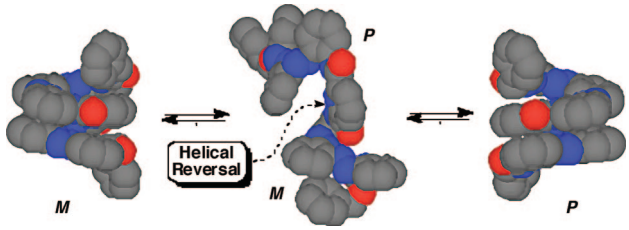

Figure 1. Helical reversal conformation interconverting *M* and *P* helical forms calculated by REMD simulations. *M* and *P* conformations taken from previously reported X-ray data.[7] Details are in the supporting info.

helical exchange resembles the stepwise unfolding process attributed to related oligoamide foldamers[4d,10] and helical polymers.[3] Further details on these calculations are presented in the Supporting Information.

Previously, we observed that the methylene protons, Ha and Hb, in Cbz-protected oligomers (**A**) exhibited chemical shifts differing by ca. 0.5 ppm at −37 °C (Figure 2).[7] This difference emerged from the disparity in anisotropic shifting caused by the positioning of one methylene proton toward and the other away from the helix backbone. On that basis,

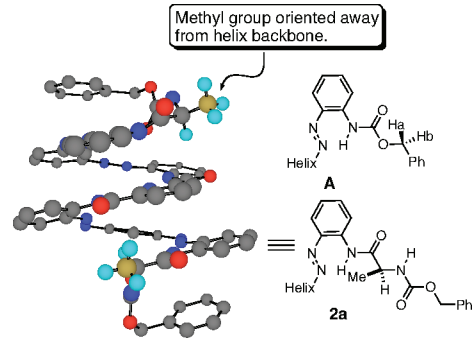

Figure 2. Lowest energy conformation of Cbz-L-ala terminated two-turn helix **2a** determined by a Monte Carlo conformational search using the AMBER* force field (details in Supporting Information).

we reasoned that capping the terminal amines with Cbz-L-alanine would place a stereogenic center at approximately this position. The orientation of the methyl and hydrogen groups relative to the helix backbone on this carbon would then differentiate the stabilities of the *M* and *P* helical forms (Figure 2). This supposition was supported by Monte Carlo conformational searching of two-turn helix **2a**, which indicated an energetic preference for a *P* helical form, thereby positioning the methyl group away from the helical backbone.[11]

The UV−vis spectra of oligomers **1a**−**3b** shown in Figure 3 feature a strong absorption at ca. 385 nm corresponding

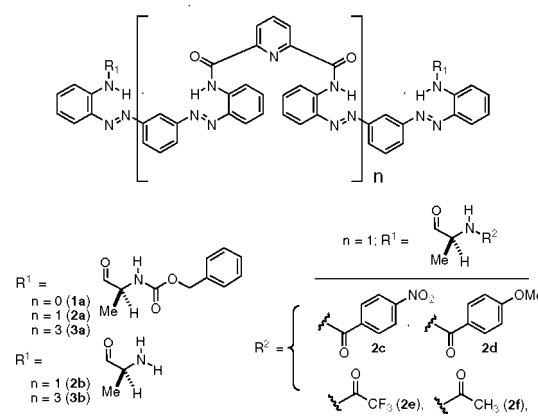

Figure 3. Helical oligomers **1a**−**3b**.

to a $\pi \rightarrow \pi^*$ transition of the azobenzene chromophore. Additionally, a weak $n \rightarrow \pi^*$ transition broadened over the 450−490 nm range, typical of *E*-azobenzene chromophores, is also present in the spectra.[12] Bis-azo oligomer **1a** ((Cbz-L-Ala)$_2$(N=N)$_2$) is too short to adopt a helical conformation and, therefore, did not exhibit any observable circular dichroism (CD) transitions above 200 nm (Figure 4). In

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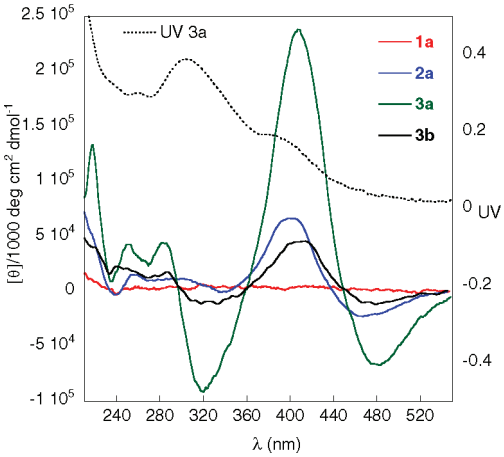

Figure 4. Molar CD spectra of oligomers **1a**−**3b** and UV−vis spectra of **3a** in MeCN at −10 °C.

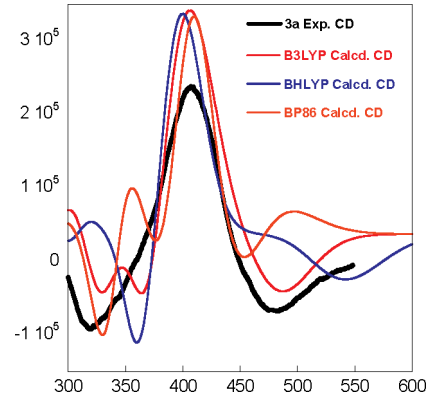

Figure 5. (a). Comparison of the experimental CD spectrum of oligomer **3a** (black) and predicted CD spectra of **3a** (RI-BP86/TZVP in orange, B3LYP/SV(P) in blue, and BHLYP/SV(P) in red), calculated for geometries optimized at the respective levels of theory. A comparison with oligomer **2a** is in the Supporting Information (Figure S1).

contrast, two-turn oligomer **2a** ((Cbz-L-Ala)$_2$(N═N)$_4$) displayed negative CD bands at 320 and 477 nm, and an intense positive band at 407 nm. The presence of the CD transitions in this region of the spectrum indicate the induction of a preferred sense of helicity in the azobenzene oligomer. The four-turn oligomer **3a** ((Cbz-L-Ala)$_2$(N═N)$_8$) also exhibited these CD bands with intensities greater than 2-fold that of **2a**, as might be expected based on the difference in the number of azobenzene chromophores. This nonlinear enhancement of the CD intensity for **3a**, compared with **2a**, indicates a more efficient amplification of the terminal chiral influences.

The UV−vis and CD spectra of the optimized geometry of oligomer **2a** were calculated using time-dependent density-functional theory (TD-DFT) at the RI-BP86/TZVP, B3LYP/SV(P), and BH&HLYP/SV(P)[13] levels of theory (Figure 5).[14] The resulting spectra were uniformly blue-shifted by 0.5, 0.1, and −0.55 eV, respectively, and a 0.3 eV Gaussian line-broadening was applied to each excitation.

The prediction of CD spectra has only recently been applied to the analysis of conformations of large molecules, and our protocol mirrors that utilized successfully elsewhere.[15] Oligomers **2a** and **3a** are ideal candidates for CD calculations because, as suggested by the REMD studies, the *M* and *P* helical forms interconvert without going through a fully unfolded state. Hence, the calculated CD spectra of a static *M* or *P* helix would qualitatively reproduce the features of an experimental spectrum. The agreement between the simulated spectra and experiment was fairly good, with the B3LYP spectrum most closely matching experiment. The qualitative properties of the spectrum and, in particular, the trough at ∼475 nm and the peak at ∼400 nm were reproduced; however, the trough at 340 nm shows significantly more negative polarization in the calculated spectra. The BH&HLYP and RI-BP86 spectra show larger deviations than the B3LYP spectrum, suggesting that the latter has the proper amount of inclusion of Fock-exchange.[15] It should be noted that the geometries optimized using hybrid DFT most closely resemble the crystal structure,[7] with RI-BP86 overestimating the spacing between the helical turns. Interestingly, the molecular mechanics geometry was also similar to experiment (see Supporting Information).

The calculated spectra most closely resemble the experimental spectrum of the 4-turn oligomer **3a**, particularly in the region around 320−370 nm, compared with the 2-turn oligomer **2a**. The B3LYP spectrum, in particular, matches exceptionally well. As the CD spectra were calculated using static, helical structures, it is reasonable that they might resemble the experimental spectrum of the very strongly biased oligomer **3a** more closely than that of 2**a**. Although oligomers **2a** and **3a** differ in length, the chromophores are identical and the excited-state properties are likely quite similar. With the multiple levels of theory employed, including the generally more accurate hybrid DFT methods, and a clear similarity with the spectrum of oligomer **3a**, the calculated CD spectra strongly support the conclusion that the *P* helical sense is present in the experimental oligomers.

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Further, it suggests that the difference in experimental CD spectra is the result of changes in the helical bias.

A large decrease in the amplitude of the CD spectrum was observed for four-turn oligomer **3b** ($(H_2N\text{-L-Ala})_2(N{=}N)_8$), which lacked the terminal Cbz groups (Figure 6). To explore

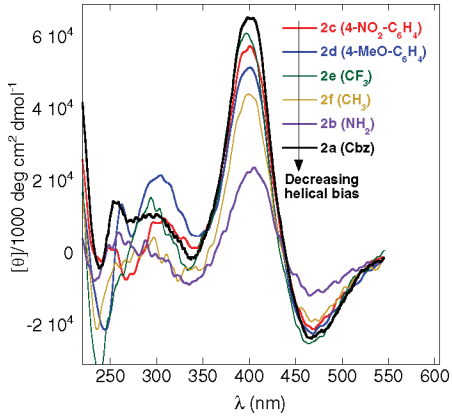

Figure 6. Effect of terminal group: CD spectra of **2a**−**2e** (MeCN, −10 °C).

the impact of the terminal acyl groups on the extent of helical bias, we varied the nature of the acyl groups in analogs of the two-turn oligomer **2a**. The intensity of the CD band at 407 nm was highest for **2a**, lowest for amino-terminated **2b** and generally increased as the acyl group became more electron-withdrawing (Figure 6). The source of this effect is likely due to a stabilizing hydrogen bond between the NH-CO and another donor group that is enhanced by electron-withdrawing groups or a favorable π-stacking effect between electron-rich and electron-poor aromatic rings as seen in

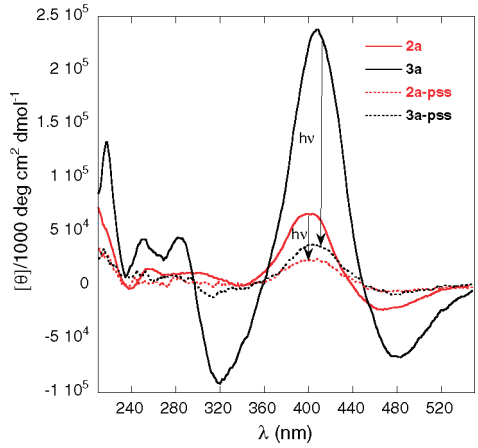

Figure 7. CD spectra in CH_3CN at −10 °C before (solid lines) and after (dashed lines) irradiation with 350 nm light.

Figure 2. However, the exact nature of this interaction remains to be determined.

Previously, we observed that $E \rightarrow Z$ photoisomerization of the azo bonds within the helix was progressively suppressed with increasing oligomer length.[7] Conversely, the azo bonds at the termini of the helices experienced *ca.* 40% isomerization to the *Z* form in both the two-turn and four-turn oligomers. Accordingly, irradiation of the oligomers induces $E \rightarrow Z$ isomerization mainly at the terminal positions without disruption of the helical structure (Figure 8). Irradiating the

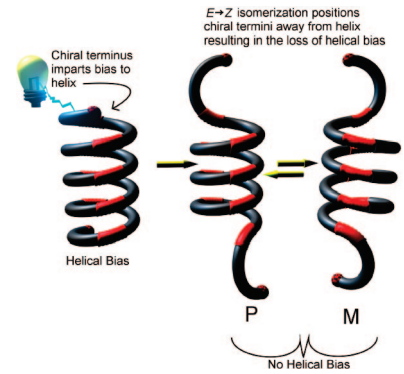

Figure 8. Predominant isomerization of terminal azo linkages decreases chiral induction.

two- and four-turn oligomers, **2a** and **3a**, with 350 nm light afforded a photostationary state within 10 min exhibiting significantly diminished CD spectra (Figure 7). The decrease in helical bias induced by exposure to light emerges from isomerization of the terminal azo linkages which displaces the controlling stereogenic center of the Cbz-L-ala group from the helix backbone (Figure 8).

In conclusion, appending Cbz-L-alanine to the terminal position of azobenzene oligomers biases the twist-sense of their helical structures. Comparison of the experimental and computationally predicted CD spectra indicate the presence of a *P* helical bias. Molecular modeling studies suggest that that the energetic benefit of projecting the methyl group of L-alanine away from the helix backbone produces the *P* helical bias. Exposure to 350 nm light suppresses chiral induction within the helical structure by inducing isomerization of the terminal azo linkages, which orients the chiral terminal groups away from the helix.

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Supporting Information Available: Experimental procedures and compound characterization for **1**−**3**, details of UV and CD calculations for **2a**.

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