Chiral Oligomers

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Amplification of Chirality in Monodisperse, Enantiopure Alleno-Acetylenic Oligomers**

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There is growing interest in the design of synthetic monodisperse oligomers that acquire well-defined conformations in solution (foldamers),[1] analogous to the folded state of proteins or nucleic acids. Chiral oligomers can fold into single-handed helices as a consequence of chiral induction,[2] and their chiroptical properties can be greatly enhanced by conformational stability. Nevertheless, much remains to be explored on how to achieve conformational uniqueness in solution. Geometries of oligomers can be controlled by a variety of factors, such as backbone conformational preferences,[3a] intra-strand interactions,[3b] solvophobic interactions,[3c] and metal ion coordination.[3d] Furthermore, an increase in the solvent entropy, owing to the minimization of the solvent-excluded volume in the folded state, may play a role in the preferred conformation.[4]

The nature of the monomeric unit determines to a large extent the secondary structure of monodisperse oligomers. We have shown that 1,3-di-*tert*-butyl-1,3-diethynylallenes (DEAs) are stable chiral building blocks.[5–7] Recently, we reported the synthesis of (*P*)-(+)-**1** (Scheme 1) and (*M*)-(−)-**1** with an enantiomer ratio of 96:4 by a palladium-mediated enantioselective *syn*-S_N2'-type cross-coupling reaction of an alkyne with an optically pure bispropargylic ester.[8] The DEA derivatives were obtained in completely enantiopure form by HPLC resolution on a chiral stationary phase and subsequently used to induce chirality into sterically crowded donor-substituted 1,1,4,4-tetracyanobuta-1,3-diene chromophores[9] and to prepare enantiopure, shape-persistent alleno-acetylenic macrocycles.[10]

Chiroptical methods, such as electronic circular dichroism (ECD) and optical rotatory dispersion (ORD), are highly sensitive to conformational features, and they are commonly used for the characterization of chiral secondary structures.[11] For example, helical secondary structures exhibit stronger ECD intensities and higher optical rotation values in comparison to random coil analogues.[12,13]

Herein, we report the synthesis, characterization, and chiroptical properties of the first length-defined, enantiopure alleno-acetylenic oligomers, and we demonstrate high chiral amplification upon changing from monodisperse dimer to hexadecamer.

The enantiopure DEA derivative (*P*)-(+)-**1** was dimerized by palladium-catalyzed oxidative homocoupling to obtain $(P)_2$-(+)-**2** in excellent yield (Scheme 1).[14] Removal of the acetonide protecting groups proceeds in a stepwise fashion,[15] enabling the isolation of monoprotected dimer $(P)_2$-(+)-**2a** in good yield. This homocoupling and partial deprotection procedure was repeated to obtain the tetramers $(P)_4$-(+)-**3**, $(P)_4$-(+)-**3a**, and $(P)_4$-(+)-**3b**, the octamers $(P)_8$-(+)-**4**, $(P)_8$-(+)-**4a**, and $(P)_8$-(+)-**4b**, and the hexadecamer $(P)_{16}$-(+)-**5** (Scheme 1). Similarly, the (*M*)-enantiomers were obtained starting from enantiopure (*M*)-(−)-**1**.

The proposed structures of all compounds were confirmed by full spectroscopic analysis (for details, see the Supporting Information). The readily soluble oligomers show no decomposition, racemization, or isomerization upon heating in solution to 90 °C, as ascertained by both ^{1}H NMR and ECD spectroscopy. They are stable under atmospheric conditions for weeks, and they do not undergo photoisomerization under daylight.

The CD curves for each oligomer (*P*)-(+)-**1** to $(P)_{16}$-(+)-**5** and their corresponding (*M*)-configured enantiomers in *n*-hexane are mirror images (Figure 1). We found essentially no difference in the intensity and CD signature for fully protected $(P)_2$-(+)-**2** to $(P)_{16}$-(+)-**5**, monoprotected $(P)_2$-(+)-**2a** to $(P)_8$-(+)-**4a**, and deprotected derivatives $(P)_2$-(+)-**2b** to $(P)_8$-(+)-**4b**.

The CD intensity ($\Delta\varepsilon$ in $M^{-1}cm^{-1}$) increases remarkably from the monomer ($\Delta\varepsilon = \pm 9$, $\lambda = 225$ nm) to the octamer ($\Delta\varepsilon = \pm 825$, $\lambda = 265$ nm), and it reaches exceptionally high values of up to $\Delta\varepsilon = \pm 1360$ at $\lambda = 266$ nm for the hexadecamer. For the Cotton effect of the hexadecamer at shorter wavelength ($\lambda = 212$ nm), the intensity even amounts to $\Delta\varepsilon = \pm 1690$. The CD spectra are nearly independent of

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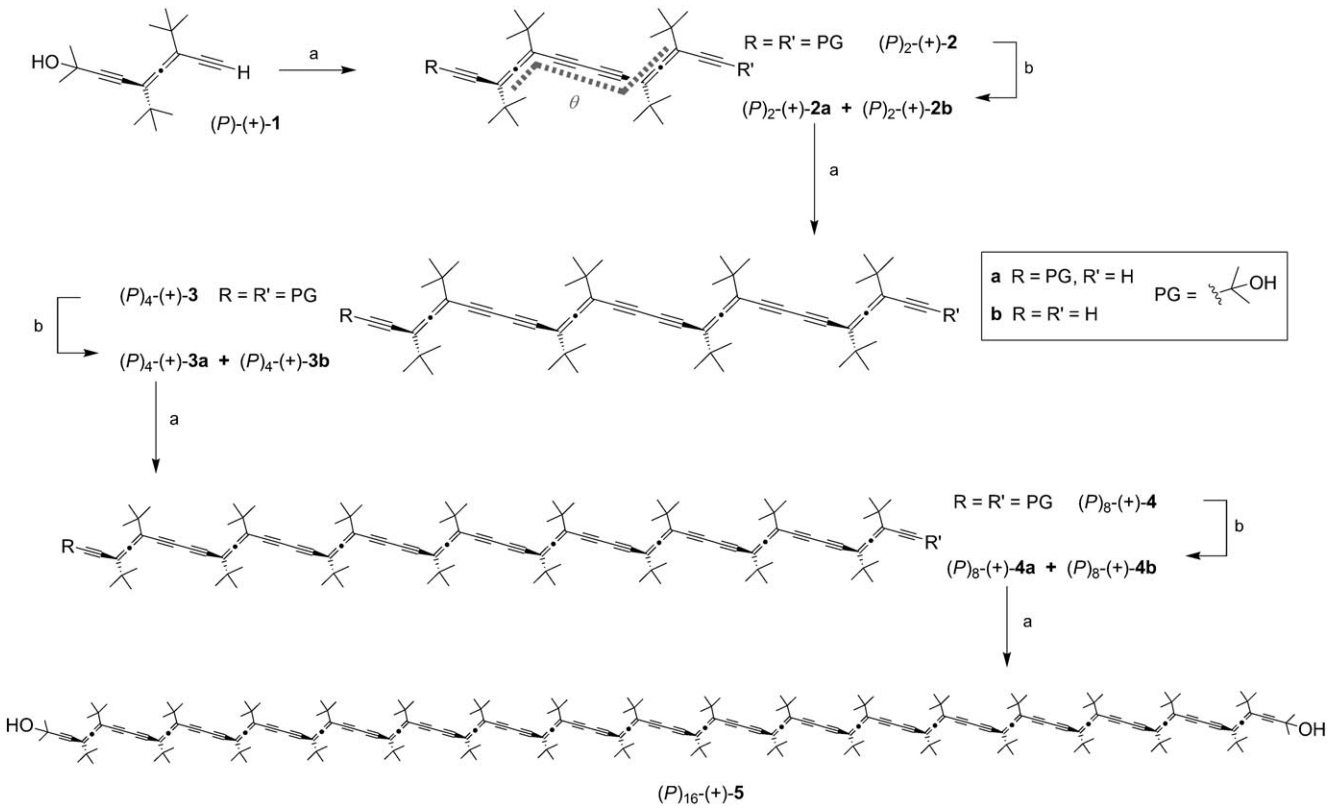

Scheme 1. Synthesis of length-defined oligomers. Reagents and conditions: a) $[PdCl_2(PPh_3)_2]$, CuI, TMEDA, toluene, 50 °C, 24 h; b) NaOH, toluene, 90 °C, 10 h. For details and yields of individual steps, see the Supporting Information. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, PG = protecting group.

solvent polarity, from *n*-hexane to MeOH. Based on a plot of CD intensities per DEA unit ($\Delta\varepsilon/N$) for each *N*-mer (Supporting Information, Figure S1a), a nonlinear dependence is observed. Therefore, the CD response among oligomers cannot be explained just as a summation of the contributions from isolated chromophores as is often the case for chiral macrocyclic,[16a–c] polycyclic,[16d,e] and acyclic[16f–j] compounds with very strong CD intensities. In fact, the $\Delta\varepsilon$ intensity (at 265 nm) of hexadecamer $(P)_{16}$-(+)-**5** is approximately 150 times greater than that of the corresponding monomer (at 225 nm). This amplification of the chiroptical properties can be a consequence of the formation of an ordered, most likely helical conformation, steadily stabilized as the oligomer grows from the monomer to the octamer. Interestingly, some degree of saturation of the nonlinear enhancement of the chiroptical properties is observed from the octamer to the hexadecamer. A similar amplification of chirality can be observed in the *g* factor ($\Delta\varepsilon/\varepsilon$) plot (see the Supporting Information).

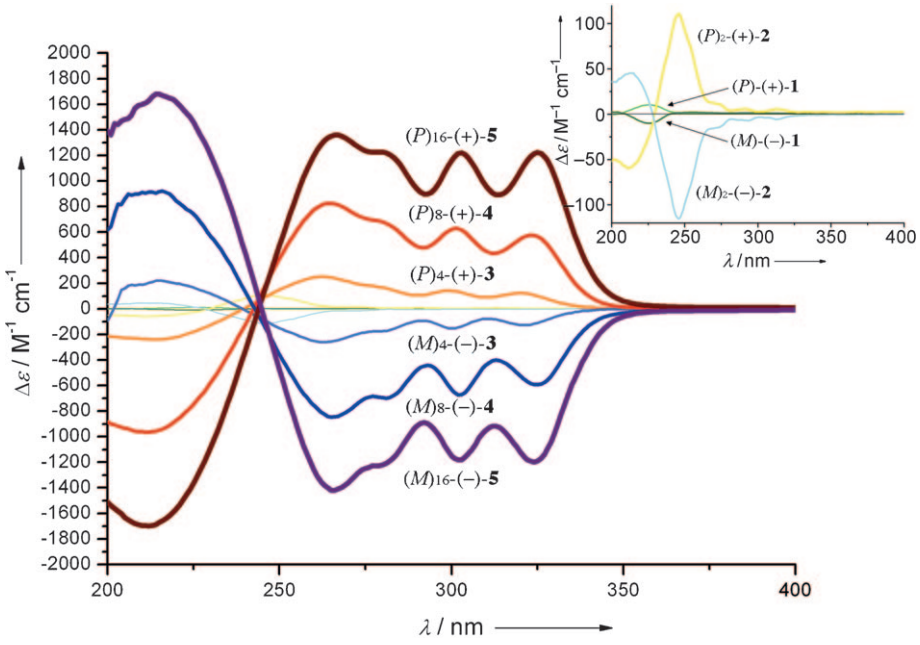

Figure 1. CD spectra of alleno-acetylenic oligomers (*P*)-(+)-**1** to $(P)_{16}$-(+)-**5** and (*M*)-(−)-**1** to $(M)_{16}$-(−)-**5** in *n*-hexane. Inset: enlarged spectra of (*P*)-(+)-**1**, (*M*)-(−)-**1** (dark green line), $(P)_2$-(+)-**2**, and $(M)_2$-(−)-**2**. Further details about the vibronic fine structure can be found in the Supporting Information.

Optical rotation, which has been used successfully to characterize both rigidly locked and conformationally flexible σ-helicenes,[17]

also indicates nonlinearity (Supporting Information, Figure S1b). In the absence of a secondary structural preference, the plot of the normalized specific rotation $[\alpha]_D/N$ as a function of the number of residues in the *N*-mer should be linear.[18] Therefore, both ECD and ORD provide experimental support for a conformational preference (a summary of intensities of Cotton effects and optical rotations can be found in the Supporting Information).

Rotational barriers about buta-1,3-diynediyl moieties are typically very low. As a consequence of these low-energy internal rotations, a potential energy surface (PES) could not be defined (for details, see the Supporting Information). Instead of relying on a PES for characterizing the secondary structure, we simulated both ORD and ECD profiles[19] on a pool of conformers evenly distributed around the torsion angle θ across the buta-1,3-diynediyl moieties (0°, +45°, +90°, +135°, 180°, −45°, −90°, and −135°; see the Supporting Information, Figures S2 and S3). Semi-empirical ZINDO, time-dependent Hartree–Fock (TDHF), and time-dependent density functional theory (TDDFT) calculations were used. Resulting theoretical profiles that best resembled the experimental signature were proposed to belong to the prevailing conformers.[17e]

Generally, the comparison between experimental and theoretical ORD profiles is qualitative, which means that the sign and the curvature of the trend line are the relevant criteria for finding the optimal agreement. Experimental optical rotation values of $(P)_2$-(+)-**2b** were measured at five wavelengths (589, 578, 546, 436, and 365 nm), and theoretical values were calculated at the HF/6-31G(d) level of theory for the selected conformers.[20] In comparing the experimental and theoretical ORD curves (Supporting Information, Figure S3), we concluded that any of the conformers within the range $0° \le \theta \le +135°$ could be prevalent in solution. The same type of analysis was performed for the longer oligomer $(P)_4$-(+)-**3b**, and in this case ORD comparison provides a narrower pool of prevalent conformers ($0° \le \theta \le +45°$; Supporting Information, Figure S4).

ECD provides a cross-validation method that, in the case of the dimer, narrows the pool of conformers. Calculations of the ECD response were carried out at the ZINDO, HF/6-31G(d), and B3LYP/6-31G(d) levels of theory. All methods provided a similar profile for a given conformer (comparison between experimental and HF/6-31G(d)-predicted ECD traces for $(P)_2$-(+)-**2b** can be seen in the Supporting Information, Figure S2). The signals in the region between 340 nm and 270 nm are a consequence of vibronic coupling (further details can be found in the Supporting Information). Careful consideration of the sign of the Cotton effects at ca. 245 nm and the vibronically resolved band at ca. 330 nm shows that the best agreement with the experimental ECD is displayed by conformers in the $0° \le \theta \le +45°$ range.

Analogously, ECD calculations at the ZINDO level of theory were performed for tetramer $(P)_4$-(+)-**3b** on conformers with the uniformly set θ. Upon comparing the experimental and theoretical signatures, we identified that, in analogy with the dimer, the conformers in the $0° \le \theta \le +45°$ range provide the best agreement (Supporting Information, Figure S5). Further calculations for the $\theta = +45°$ conformer at the HF/6-31G(d) level of theory are also in good agreement with the experimental data (Figure 2).

Considering the similarity of ECD profiles between the tetramer, the octamer, and the hexadecamer along with the proposed conformational preference, it is reasonable to assume that longer oligomers exhibit secondary structures with the same torsion angles ($0° \le \theta \le +45°$) propagated along the backbone. A depiction of an ensemble of right-handed helical conformers of octamer $(P)_8$-(+)-**4b** with $0° \le \theta \le +45°$ is shown in Figure 3.

The amplification of the chiroptical response with the increase of number of monomeric units is remarkable, even though these oligomers are not conformationally locked. This behavior suggests that further amplification of Cotton effects and optical rotations can be expected for alleno-acetylenic oligomers with further stabilized helical structures (that is, by functionalization of the side chains to introduce noncovalent

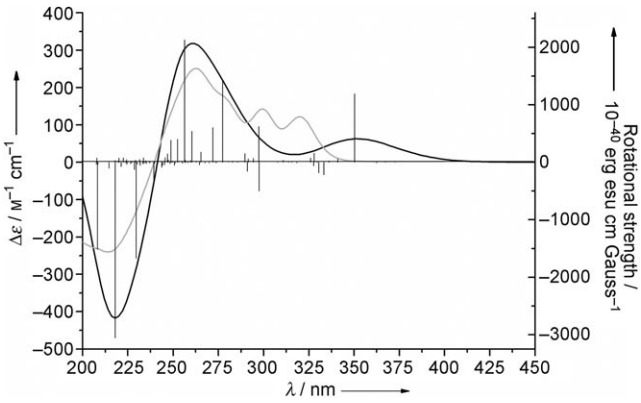

Figure 2. Experimental CD spectrum of $(P)_4$-(+)-**3b** (gray line, in *n*-hexane), calculated rotational strengths for the conformer with $\theta = +45°$ (black bars, HF/6-31G(d)), and simulated spectrum (black line). For further details, and an explanation of how the calculated Cotton effect at ca. 350 nm should be split into three maxima and blue-shifted from this position owing to vibronic coupling, see the Supporting Information.

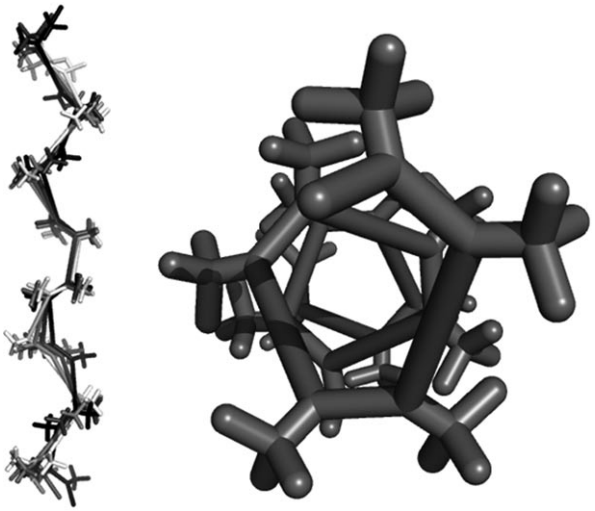

Figure 3. Ensemble of four helical conformers of P_8-(+)-**4b** in the $0° \le \theta \le +45°$ range (left), and view along the helix axis of the conformer at $\theta = 0°$ (right).

intramolecular interactions, or by "stapling" the helix by ring-closing metathesis[21]).

In summary, these novel enantiopure alleno-acetylenic oligomers exhibit chiroptical properties that are among the most intense ever reported. The nonlinear enhancement of these chiroptical responses suggests the existence of a conformational preference preserved along the backbone of all oligomers. On the basis of quantum mechanical calculations, we suggest that the oligomers bearing (*P*)-DEAs exist predominantly as an ensemble of right-handed helical conformers, with the torsion angle across the butadiyne axes ranging from 0° to +45°. The synthesis of oligomers, starting from enantiomerically pure DEAs with different side chains to further stabilize the helical conformation, is now underway. Such stabilization is expected to further enhance the chiroptical properties.

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[20] It has been shown that some DFT functionals, such as B3LYP, are often inadequate for the calculation of polarizabilities and excited state energies of extended π systems. Therefore, HF-calculated ORD and ECD curves are shown, even though semi-empirical and DFT methods gave qualitatively the same results. For a discussion, see: a) Z.-L. Cai, K. Sendt, J. R. Reimers, *J. Chem. Phys.* **2002**, *117*, 5543–5549; b) S. Grimme, M. Parac, *ChemPhysChem* **2003**, *4*, 292–295.

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