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Remarkable Effects of Terminal Groups and Solvents on Helical Folding of *o*-Phenylene Oligomers

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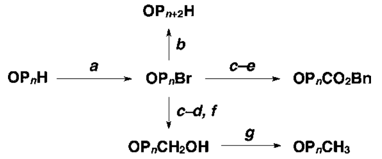
Supporting Information

ABSTRACT: Although *o*-phenylene oligomers (OP_nR) made of dimethoxyphenylene units are thought to be intrinsically dynamic due to π-electronic repulsion, we show that they fold into a regular helical geometry in CH_3CN when they carry terminal groups such as CH_3, CH_2OH, Br, CO_2Bn, and NO_2. We evaluated their helical inversion kinetics via optical resolution of long-chain oligomers (e.g. 16- and 24-mers) by chiral HPLC. $OP_{24}Br$ at 298 K shows a half-life for the optical activity of 5.5 h in CH_3OH/water (7/3 v/v) and requires 34 h for complete racemization. The perfectly folded helical conformers of OP_nR, unlike their imperfectly folded ones, are devoid of extended π-conjugation and show a cyclic voltammogram featuring reversible multistep oxidation waves.

Because of the lack of readily accessible synthetic methods, oligomeric *o*-phenylenes, unlike their *m*- and *p*-connected analogues, have scarcely been investigated until recently.[1] Due to a heavily angled aromatic connection, oligomeric *o*-phenylenes are considered to adopt a helical conformation. Simpkins et al. reported in 1998 that an *o*-phenylene hexamer in the crystalline state folds into a regular 3_1-helical geometry.[1d] This beautiful crystal structure gave us a preconceived notion that 3_1-helical geometry is also preferred in solution. Recent conformational studies by Hartley et al. on *o*-phenylene oligomers in solution indicated that, regardless of the type of solvent, they are considerably dynamic and hardly fold into a regular helical geometry.[2] We recently developed terminally functionalized *o*-phenylene oligomers OP_nR from 1,2-dimethoxybenzene and discovered that an octamer featuring nitro groups at both termini (OP_8NO_2) undergoes chiral symmetry breaking upon crystallization, affording optically pure crystals, each having either a right- or left-handed 3_1-helical conformer.[3] Using its optical activity as a probe, we investigated the stability of this helically folded conformer in solution. Consistent with Hartley's reports,[2] the optical activity disappeared very quickly when the chiral crystal was dissolved in organic solvents. We thought this dynamic nature might stem from π-electronically repulsive character of the closely packed phenylene units in cofacial orientation.[4] One-electron oxidation of the helical conformer of OP_8NO_2 resulted in a remarkable elongation of the optical activity in solution.[3]

Scheme 1. General Synthesis of OP_nR^a



[a] R = H, *n* = 6–24; R = Br, *n* = 4–24; R = CH_3 and CH_2OH, *n* = 10; R = CO_2Bn, *n* = 4–10. Reagents and conditions: (a) NBS, DMF, 0→25°C; (b) 3,4-dimethoxyphenylboronic acid, $Pd(OAc)_2$, SPhos, K_3PO_4, THF, water, 60°C; (c) *t*-BuLi, THF, −78°C; (d) CO_2, −78→25°C; (e) BnBr, Cs_2CO_3, DMSO, 100°C; (f) $LiAlH_4$, THF, 60°C; (g) Et_3SiH, BF_3OEt_2, CH_2Cl_2, 0→25°C. SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl. For OP_nBr (*n* = 4, 8) and OP_nH (*n* = 16, 24), see ref 3.

If the π-electronically repulsive character indeed hampers the perfect folding of OP_nR, this potentially interesting helical motif would not be usable for many applications. We investigated in detail the conformation of OP_nR carrying different terminal groups (R = H, CH_3, CH_2OH, Br, CO_2Bn, and NO_2) in varying solvents and observed that all the oligomers except OP_nH fold into a stable helical conformation only in a limited solvent such as CH_3CN. This finding precluded investigating the helical inversion kinetics of long oligomers but also unveiled that the perfectly folded helical conformers, unlike their imperfectly folded ones,[2a] are devoid of extended π-conjugation and well behaved in electrochemistry.

As shown in Scheme 1, a series of OP_nR (Figure 1a) with different chain lengths (*n* = 4–24) and termini were synthesized (see Supporting Information). OP_6H and $OP_{10}H$ were prepared from OP_4Br and OP_8Br,[3] respectively, by $Pd(OAc)_2$/SPhos-catalyzed Suzuki–Miyaura coupling with 3,4-dimethoxyphenylboronic acid in THF. The H-terminated oligomers thus obtained were subjected to bromination with *N*-bromosuccinimide (NBS) in DMF, affording OP_6Br and $OP_{10}Br$. Longer H-terminated oligomers such as $OP_{16}H$ and $OP_{24}H$[3] were successfully converted into $OP_{16}Br$ and $OP_{24}Br$, respectively. OP_nCO_2Bn (*n* = 4–10) with ester termini were synthesized from OP_nBr (*n* = 4–10) by terminal lithiation in THF with *t*-BuLi, followed by carboxylation with CO_2 and

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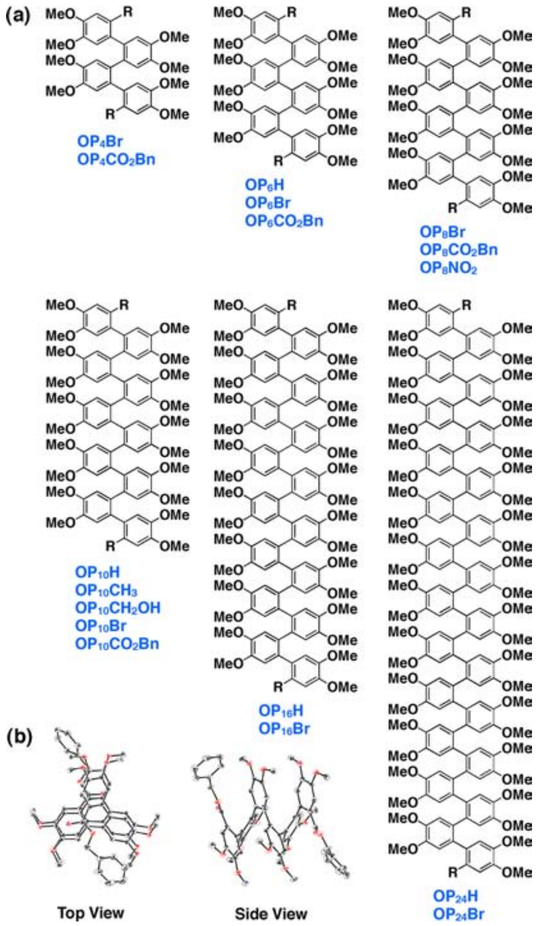

Figure 1. (a) Molecular structures of *o*-phenylene oligomers OP_nR (R = H, CH_3, CH_2OH, Br, CO_2Bn, and NO_2). (b) ORTEP drawings of the crystal structure of OP_6CO_2Bn at 90 K, showing 50% probability thermal ellipsoids. H atoms omitted for clarity.

esterification with benzyl bromide (BnBr) in DMSO containing Cs_2CO_3. $OP_{10}CH_2OH$ was obtained from the corresponding carboxylated compound by reduction with $LiAlH_4$ and converted into $OP_{10}CH_3$ by reduction using Et_3SiH/BF_3OEt_2. All these oligomers were unambiguously characterized by NMR spectroscopy and high-resolution mass spectrometry. Short-chain oligomers OP_4CO_2Bn and OP_6CO_2Bn were crystallographically defined, both adopting perfect 3_1-helical conformation in the crystalline state (Figures 1b and S1).

Consistent with Hartley's reports,[2] the ^1H NMR spectral profiles of OP_nCO_2Bn (n = 6−10) were very complicated in a variety of solvents, e.g. $CDCl_3$, toluene-d_8, DMSO-d_6, and DMF-d_7 (Figures 2h, S3, and S8). However, in CD_3CN solvent, the NMR spectra were exceptionally simple. $OP_{10}CO_2Bn$ afforded one set of well-defined ^1H NMR signals characteristic of C_2 symmetry (Figures 2g and S2d), indicating $OP_{10}CO_2Bn$ adopts a regular 3_1-helical geometry. Taking full advantage of 2D NMR techniques (HSQC, HMBC, and NOESY spectra; Figures S31−S33), all the signals in Figures 2g and S2d were unambiguously assigned. Ten singlet signals at 3.3−3.7 ppm are due to methoxy protons. Certain aromatic protons at 5.1−5.7 ppm originate from the internal phenylene units that are upfield-shifted considerably due to a ring-current effect. Strong NOEs were observed for four sets of proximal aromatic protons in folded $OP_{10}CO_2Bn$ with 3_1-helical geometry (Figure S13); the methylene protons in the benzyl ester termini split diastereotopically into two sets of doublets at 4.48 and 4.79 ppm. In CD_3CN, $OP_{10}CO_2Bn$ and shorter-chain OP_nCO_2Bn (n = 4, 6, and 8) showed well-defined NMR features (Figures S2 and S21−S30) characteristic of a perfect 3_1-helical conformation. The same holds true for the conformational behaviors of OP_nR carrying bromo (R = Br; n = 8, 10, 16, and 24), nitro (R = NO_2; n = 8), and hydroxymethyl groups (R = CH_2OH; n = 10) in CD_3CN (Figures 2e,f, S4−S7, S9, S10, and S34−S37). In sharp contrast, as also Hartley reported,[2a−d] H-terminated OP_nH (n = 6, 10, 16, and 24) had very complicated ^1H NMR features even in CD_3CN (Figures 2a,b and S11). We thought that OP_nR might require polar terminal groups for perfect helical folding, but $OP_{10}CH_3$ showed in CD_3CN a simple ^1H NMR spectrum (Figures 2c,d and S12a) analogous to those of $OP_{10}R$ with polar terminal groups. Thus we conclude that a steric factor at the termini is critical in the perfect folding of OP_nR. It is interesting to note that no steric effect of the terminal functionalities emerges in other solvents (e.g. $CDCl_3$ and DMF; Figure S12b,c).

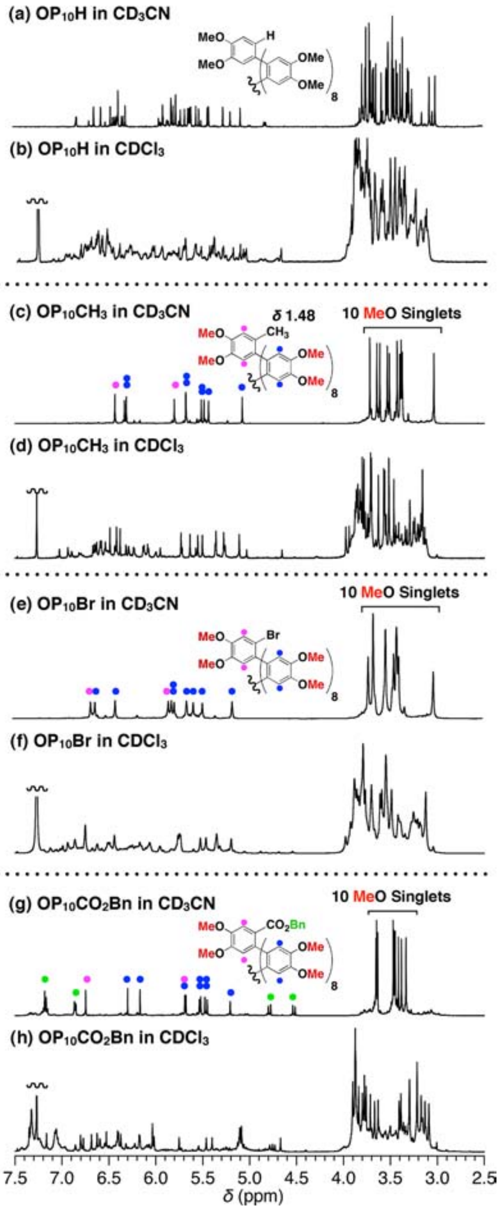

Figure 2. ^1H NMR (500 MHz) spectra at 273 K of OP_nR.

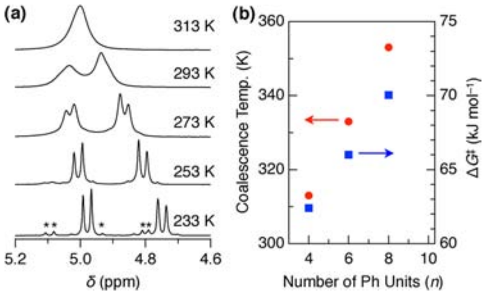

Figure 3. (a) ^{1}H NMR (500 MHz) spectra (4.6−5.2 ppm) of OP_4CO_2Bn in CD_3CN at 233−313 K. Minor signals due to imperfect helical conformation are asterisked. (b) Coalescence temperatures (red circles) and free-energy changes of activation (blue squares) for helical inversion of OP_nCO_2Bn (n = 4−8) in CD_3CN.

Using the diastereotopically split signals in the terminal benzyl ester groups as a probe, we investigated kinetic and thermodynamic aspects of the helical inversion of OP_nCO_2Bn (n = 4−8). For example, tetramer OP_4CO_2Bn at 293 K displayed the corresponding signals at 4.94 and 5.03 ppm in CD_3CN (Figures 3a and S14). Upon cooling to 233 K, each of these signals split into two major doublets and four minor signals with an integral ratio of 1:0.22 (Figure 3a). Using 2D NMR techniques (Figures S21−S23), all the signals observed at 233 K were unambiguously assigned. There are major and minor conformers in the system: the major one (C_2-symmetric) adopts a perfectly folded helical conformation, while the minor one (C_1-symmetric) adopts an imperfect helical conformation with one terminal phenylene unit flipping out. These conformers are thermally interconvertible. In fact, upon heating, the corresponding signals coalesced at 273 K, and the resultant major doublets coalesced at 313 K (Figure 3a) as a consequence of the helical inversion. Using the Gutowsky equation,[5] the rate constant for the helical inversion at the coalescence temperature (313 K) was $k_c = 244$ s^{-1}. Using the Eyring equations, the free-energy change of activation for the helical inversion was $\Delta G^{\ddagger} = 62.5$ kJ mol^{-1}. For the hexamer and octamer (OP_nCO_2Bn, n = 6 and 8; Figures S15−S17) in CD_3CN, we also obtained coalescence temperatures (T_c) and $\Delta G^{\ddagger}$ values for the helical inversion (Figure 3b and Table S1). Both increased monotonically as the number of the repeating phenylene units in OP_nCO_2Bn increased (Figure 3b). This trend is reasonable, provided the helical inversion occurs in a stepwise manner from the terminal phenylene units.

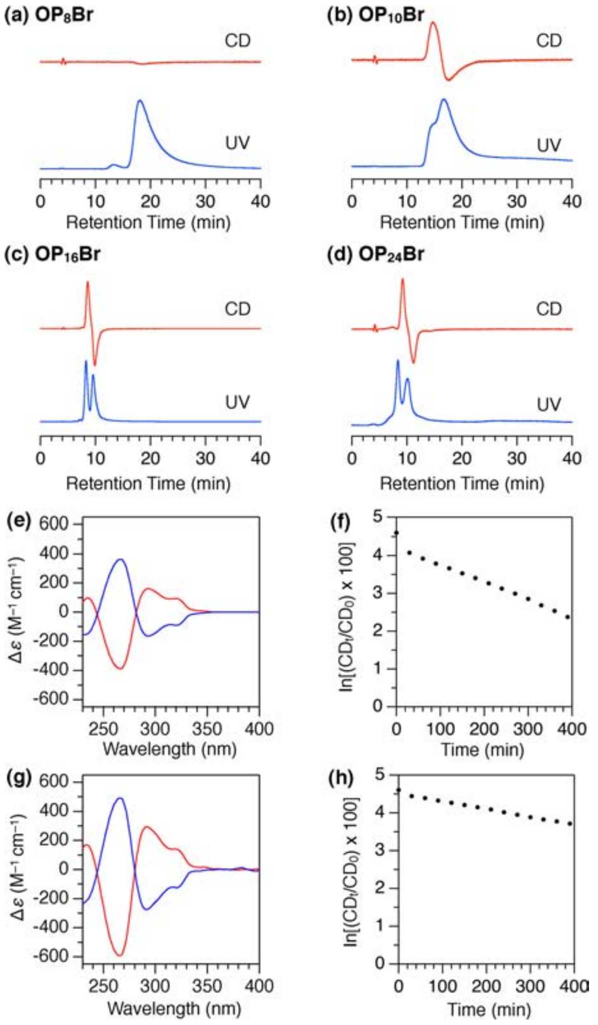

Figure 4. (a−d) Chiral HPLC profiles at 298 K of OP_nBr. Samples, saturated CH_3CN solutions (5 μL); column, CHIRALPAK IA 25 × 0.46 (i.d.) cm; eluent, CH_3OH/water (7/3 v/v);[7] flow rate, 0.8 mL min^{-1}. CD spectra of (e) $OP_{16}Br$ and (g) $OP_{24}Br$ measured at the first (red) and second (blue) peak tops of their chromatograms and (f,h) their spectral decay profiles at 265 nm.

These observations prompted us to investigate whether longer-chain oligomers fold into a regular helical geometry in CH_3CN. We attempted direct chiral HPLC separation[6] of the right- and left-handed helical conformers of $OP_{16}Br$ and $OP_{24}Br$ along with shorter-chain OP_8Br and $OP_{10}Br$. By optimizing the HPLC conditions, we successfully separated their enantiomers. When $OP_{16}Br$ in CH_3CN was charged into a chiral column and eluted using a mixture of CH_3OH and water (7/3 v/v), a poor solvent for $OP_{16}Br$, two well-separated elution peaks developed with positive and negative signs at 290 nm in a circular dichroism (CD) detector (Figure 4c). The fractions corresponding to these two peaks displayed mirror-image CD spectra with intensity maxima at 265, 290, and 320 nm (Figure 4e). Longer-chain $OP_{24}Br$ showed analogous HPLC (Figure 4d) and CD features (Figure 4g). Consistent with the difference in number of the repeating phenylene units, the molar CD ($\Delta\varepsilon$) of $OP_{24}Br$ was 1.5 times larger than that of $OP_{16}Br$. In both cases, the observed CD spectra gradually became less intense with time, indicating helical inversion. Based on time-dependent CD intensity changes (Figure 4f,h), we evaluated their helical inversion kinetics in terms of the half-life ($t_{1/2}$) of the CD intensity at 265 nm and decay rate constants (k_{inv}). As expected from the chain length-dependent dynamic natures of OP_nCO_2Bn (n = 4−8; Figure 3b), $OP_{24}Br$ showed longer $t_{1/2}$ (5.5 h) and smaller k_{inv} (1.75×10^{-5} s^{-1}) than $OP_{16}Br$ (2.5 h and 3.92×10^{-5} s^{-1}) in CH_3OH/water (7/3 v/v) at 298 K (see Supporting Information). Notably, $OP_{24}Br$ required 34 h for complete loss of optical activity. In contrast, shorter-chain $OP_{10}Br$ was only partially optically resolved in chiral HPLC (Figure 4b), and OP_8Br did not show any optical resolution (Figure 4a), indicating their helical inversion events are too fast.

Perfect helical folding of OP_nR was found to be accompanied by a change in the balance between "through-bond" and "through-space" electronic interactions of the repeating phenylene units. The absorption maximum of OP_nBr in CH_2Cl_2 (Figure 5, blue) shifted toward a longer wavelength region as n increased from 10 to 24; such chain-length dependence was not observed when OP_nBr was allowed to fold into a perfect helical

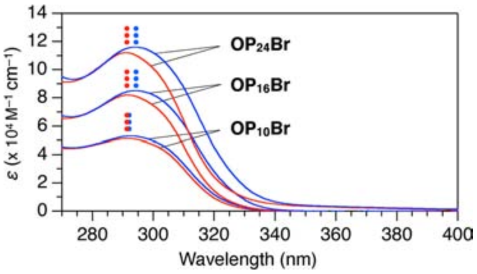

Figure 5. Electronic absorption spectra at 298 K of OP_nBr in CH_3CN (red) and CH_2Cl_2 (blue).

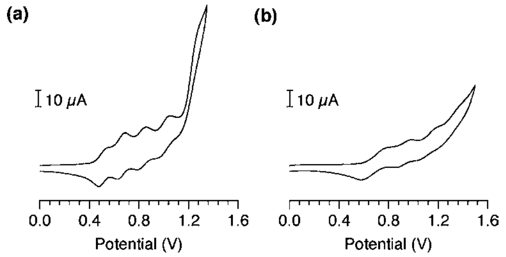

Figure 6. Cyclic voltammograms at 298 K of $OP_{10}CO_2Bn$ in (a) CH_3CN and (b) CH_2Cl_2 containing n-Bu_4NClO_4 (0.1 M) as a supporting electrolyte. Scan rate, 100 mV s^{-1}.

conformation in CH_3CN (red). Thus, the regularly folded *o*-phenylene oligomers are devoid of extended π-conjugation. Also noteworthy, as exemplified by $OP_{10}CO_2Bn$ in Figure 6, OP_nCO_2Bn and OP_nBr with n = 8 and 10 in CH_3CN clearly showed reversible multistep oxidation waves in their cyclic voltammetry (CV) profiles (Figures 6a and S18); in CH_2Cl_2 their CV profiles showed a lower electrochemical reversibility (Figures 6b and S19).[8] For reference, short-chain OP_4CO_2Bn and H-terminated $OP_{10}H$, which are incapable of folding into a perfect helical conformation, showed poor electrochemical reversibility even in CH_3CN (Figure S20). These results indicate the contrasting redox behaviors of terminally functionalized OP_nR (R = CO_2Bn and Br; n = 8 and 10) in CH_3CN and CH_2Cl_2 originate from the difference in conformational characteristics of the oligomers. The perfect helical conformation likely stabilizes an oxidized state by extensive delocalization of a hole through an array of cofacially oriented phenylene units.[3] Foldamers that can change their fundamental electrochemical properties by folding are unprecedented.

In conclusion, we show that *o*-dimethoxyphenylene oligomers (OP_nR, Figure 1a) appended with terminal groups such as CH_3, CH_2OH, Br, CO_2Bn, and NO_2 adopt a perfect helical conformation in CH_3CN, where a steric rather than polar effect of the termini is responsible. In contrast, even in CH_3CN, terminally unsubstituted OP_nH's do not fold into a regular helical geometry. Taking advantage of optical resolution by chiral HPLC, we reveal that long-chain oligomers such as $OP_{24}Br$ undergo a very slow helical inversion at 298 K, $t_{1/2}$ = 5.5 h. Interestingly, perfect helical folding of OP_nR is accompanied by changes in electrochemical properties. These achievements cast aside any concen that *o*-phenylene oligomers are too dynamic[2,3] and allow them to be categorized as a unique class of well-behaved, fully characterized foldamers[9] with many potential applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthesis and characterization of selected OP_nR. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) Conformational behaviors of OP_nR (n > 4) in CH_3OH/water (7/3 v/v; eluent for chiral HPLC) were unavailable because their very low solubilities in this solvent did not allow for NMR spectroscopy.

(8) Oxidation of $OP_{10}CO_2Bn$ in CH_2Cl_2 with $(p\text{-}BrC_6H_4)_3N^{\bullet+}SbCl_6^-$ (see ref 3) and subsequent reduction of the generated radical cation in CH_3CN with Zn powder resulted in quantitative recovery of $OP_{10}CO_2Bn$.

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