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Identification of Absolute Helical Structures of Aromatic Multilayered Oligo(*m*-phenylurea)s in Solution

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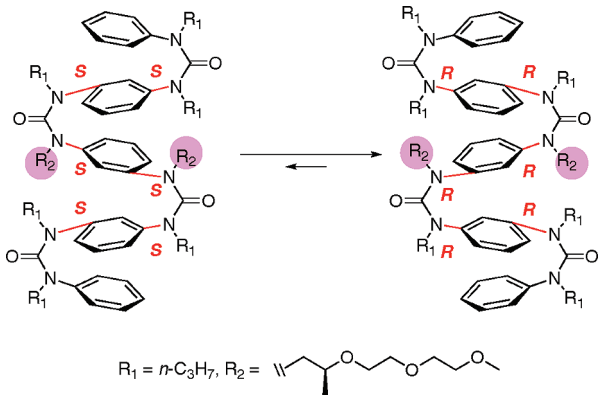

The oligomeric aromatic ureas bearing *N*,*N*′-dimethylated urea bonds such as **3** have aromatic multilayered structure, based on the (*cis*,*cis*)-urea structure, and also have dynamic helical structure (all-*R* or all-*S* axis chirality) when the benzene rings are connected at the *meta* positions. The absolute helical structure of oligo(*m*-phenylurea)s were identified by the empirical and theoretical studies on the CD and vibrational CD (VCD) spectra. Thus, each enantiomer of the oligo(*m*-phenylurea)s **4** bearing a chiral *N*-2-(methoxyethoxyethoxy)propyl group were synthesized. Intense dispersion-type CD spectra of **4** were observed, which indicated the induction of handedness in the helical structure. In the VCD spectra of **4** in the film state, the signals due to the carbonyl and aromatic ring vibrations were seen with negative and positive values for compounds **4a** and **4b**, respectively. The calculations of both CD and VCD spectra of oligo(*m*-phenylurea)s **3** without any chiral *N*-substituent gave the same assignment about the axis chirality of **4**. Thus, the absolute configurations of **4a** and **4b** are all-*R* and all-*S* structures, respectively.

Introduction

The helix is a unique structural motif; for example, the double helix of DNA and α-helical structure of proteins play key roles in living systems.[1] Therefore, many functional polymers utilizing such structures have been synthesized, not only to mimic biological compounds but also to develop so-called intelligent materials.[2] In addition to stable helical

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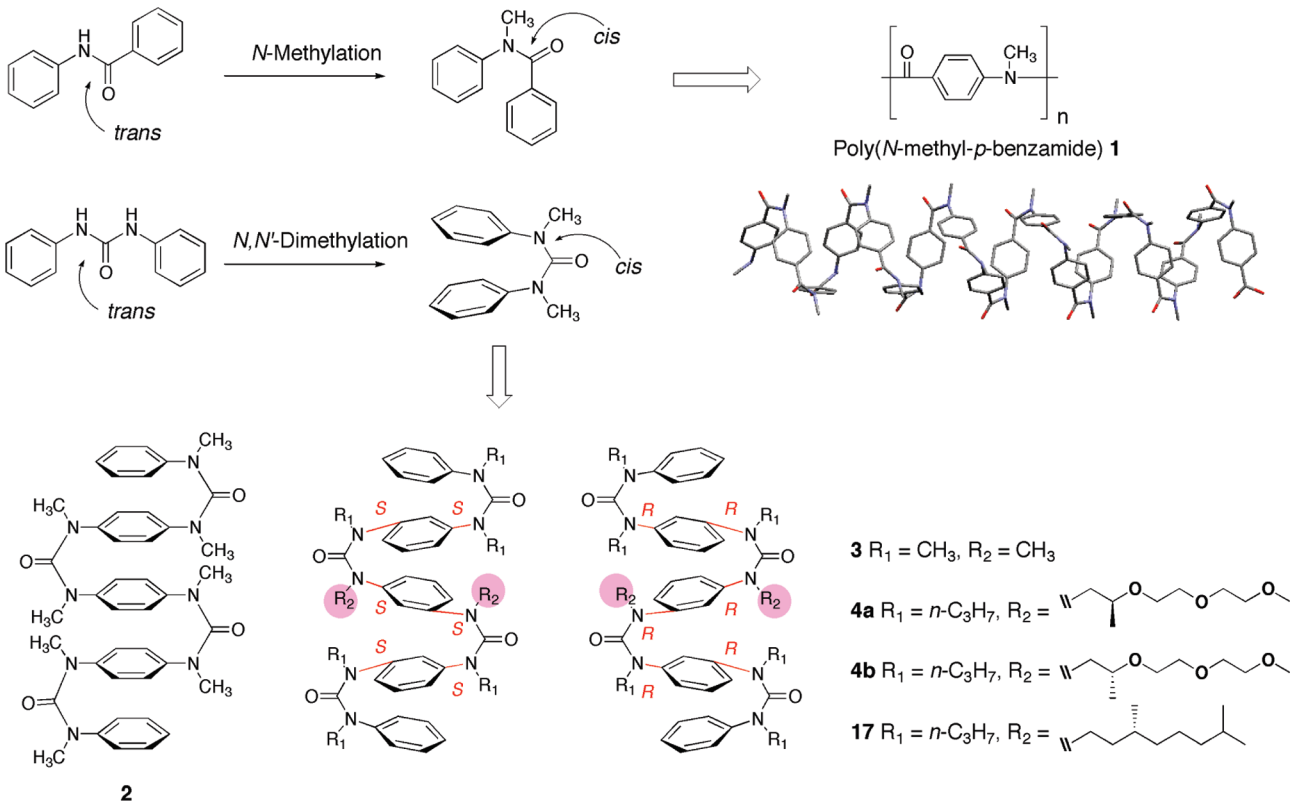

FIGURE 1. Preference for *cis* conformation of aromatic *N*-methylated amides and ureas and their application to helix construction.

polymers with a rigid backbone, there is great interest in polymers such as polyisocyanates,[3] polysilanes,[4] and polyacetylenes,[5] which show rapid helical reversal and are classified as dynamic helical polymers.[6] Induction of handedness in such helical polymers has attracted widespread interest because of its possible applications in optical devices or for data storage[7] and also because of its relevance to chiral amplification, which may have occurred at the early stages in the evolution of living things.[8] Several methodologies have been developed, including the introduction of optically active side chains or the addition of chiral components that interact with the polymers,[9−11] though it remains still difficult to identify strictly right- or left-handed helical conformation, especially for the artificial polymers. We previously reported that *N*-alkylated poly(*p*-benzamide)s such as **1** (Figure 1) take a helical structure in solution.[12] The proposed helical structure of *N*-alkylated aromatic polyamides is clearly supported by the results of exciton analysis of the electronic absorption and CD spectra of polyamides bearing a chiral side chain on the nitrogen atom. Recently, the assignment of absolute handedness of several helical polymers were achieved.[11,13−15]

Monomeric or oligomeric folded components are necessary to construct helical structure, and the helical oligomers with dynamic behaviors are classified as foldamers.[16] In the case of polyamides **1**, the helical conformation results from the *cis* conformational properties of *N*-alkylated benzanilides (Figure 1). Benzanilide exists in *trans* form both in the crystal and in solution, whereas *N*-methylbenzanilide exists

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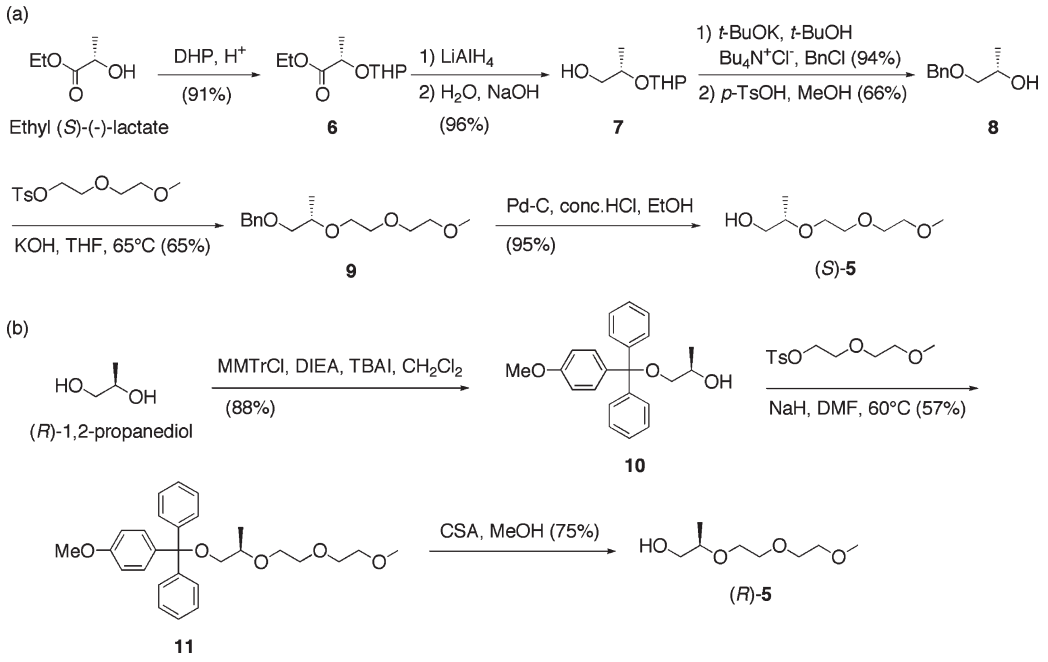
SCHEME 1. Synthesis of Chiral 2-(Methoxyethoxyethoxy)propanols 5



in *cis* form in the crystal and predominantly in *cis* form in solution.[17] Thus, various well-known polyamides, such as poly(*p*-phenylene terephthalamide) and poly(*p*-benzamide), contain secondary amide bonds with *trans* conformation and form hydrogen bonds between polymer chains to generate a sheet structure (rod-like).[18] On the other hand, the helical structure of *N*-alkylated poly(*p*-benzamide)s **1** arises from the inherent structural propensity of *N*-alkylated amide bonds for folded *cis* conformation.[12]

The *cis* conformational character induced by *N*-methylation is also observed in aromatic ureas (Figure 1).[19,20] Thus, *N*,*N*′-dimethyl-*N*,*N*′-diphenylurea exists in (*cis*,*cis*) conformation, in which two phenyl rings lie in a face-to-face position with a dihedral angle (∼30°) smaller than that of *N*-methylbenzanilide (∼60°). As a result of the difference of the two folded conformations in the dihedral angles between aromatic rings, *N*-methylated oligo- and polyamides form helical structures, whereas *N*,*N*′-dimethylated oligoureas **2** and **3** form aromatic multilayered structures. Further, when the phenyl rings are connected by *N*,*N*′-dimethylurea bonds at the meta position, the oligomers **3** shows well-ordered helical structure based on the all-*R* or all-*S* axial chirality of (*cis*,*cis*)-urea bonds in the crystal, in which both enantiomers exist in a 1:1 ratio.[20] In solution, the equilibrium between the enantiomers is rather fast. Recently, Clayden et al. reported that chiral or prochiral probes introduced at the terminal of the oligoureas could detect the chirality of the backbone.[21] The NMR technique using such diastereotopicity is very useful to evaluate the well-defined three-dimensional structures of foldamers. On the other hand, the detailed helical structure of the oligo(*m*-phenylurea)s **3**, especially the distinction of the enantiomeric isomers, remains an issue. Here we report the helical structure of aromatic multilayered oligoureas in solution and the identification of their absolute structure based on empirical and theoretical studies of CD and vibrational CD (VCD) spectra.

Results

1. Synthesis of Oligo(*m*-phenylurea)s with Chiral *N*-Substituents. To distinguish right- and left-handed helical structures of aromatic multilayered oligoureas, chiral side chains were introduced into the urea bonds of **3**. Since *N*-methylated oligo(*m*-phenylurea)s have rather poor solubility, we designed tetraureas **4a** and **4b** with two chiral *N*-2-(methoxyethoxyethoxy)propyl groups on the two nitrogen atoms attached to the central benzene ring and *N*-*n*-propyl groups on the other nitrogen atoms of the urea bonds. The enantiomers of 2-(methoxyethoxyethoxy)propanol **5** were prepared via different synthetic routes (Scheme 1). (*S*)-**5** was synthesized from ethyl (*S*)-lactate as the starting material by modification of the reported synthetic procedures.[22] After protection of the hydroxyl group, reduction of the ester group of **6** afforded alcohol **7**. Compound **7** was benzylated, followed by deprotection of the THP group, and then reacted with methoxyethoxyethyl tosylate to give **9**, which in turn was hydrogenated over Pd−C to afford (*S*)-**5.** (*R*)-**5** was prepared by a more convenient procedure from (*R*)-1,2-propanediol. Protection of the primary hydroxyl

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SCHEME 2. Synthesis of Tetraureas 4 Bearing Chiral Substituents

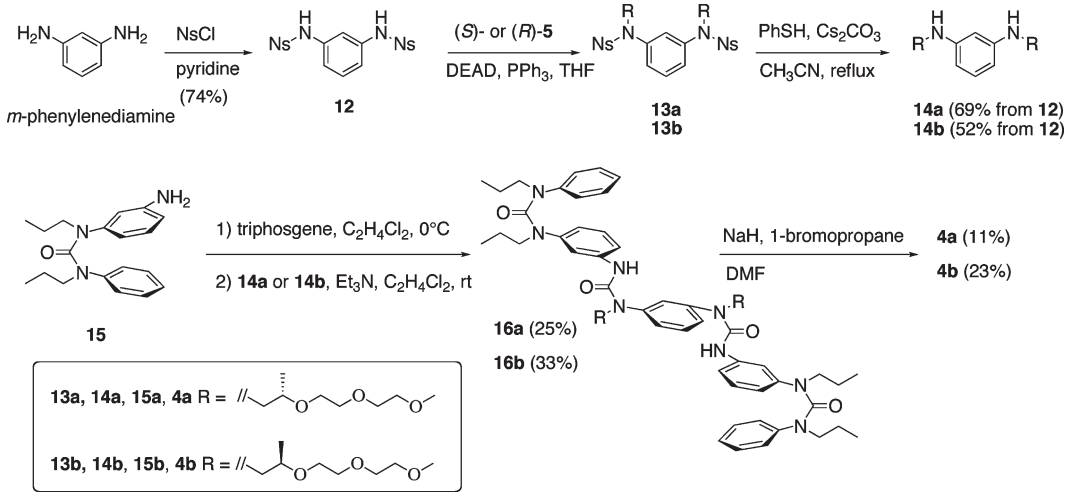
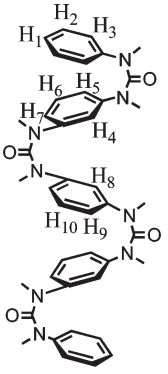


TABLE 1. ^{1}H NMR Chemical Shifts of Aromatic Protons of the Oligoureas in $CDCl_3$



	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9	H_{10}
3 at rt	6.89	6.99	6.70	6.04	6.42[b]	6.72	6.33[b]	6.04	6.33	6.72
3 at 223 K	6.89	6.98	6.66	5.88	6.43[b]	6.72	6.33[b]	5.86	6.33	6.72
3 (calcd)[a]	6.94	6.94	6.48	5.66	6.76	6.94	6.68	5.67	6.65	6.88
		7.15	7.09							
4 at rt	6.85	6.94	6.60	5.92	6.40[b]	6.63	6.29[b]	6.27	6.29	6.52
4 at 243 K	6.83	6.92	6.55	5.73	6.36[b]	6.61	6.29[b]	6.21 br	6.21 br	6.44
17 at rt	6.85	6.95 t	6.62	5.99	6.33[b]	6.60 t	6.20[b]	6.08	6.15	6.52
17 at 243 K	6.83	6.91	6.57	5.82	6.32[b]	6.59	6.19[b]	5.93	6.10	6.45

[a]Values were calculated by the B3LYP/6-31G** method. [b]Proton signals for H_5 and H_7 could not be distinguished from each other and are tentatively assigned.

group of (*R*)-1,2-propanediol with monomethoxytrityl chloride (MMTrCl) in the presence of tetrabutylammonium iodide (TBAI) and *N*,*N*-diisopropylethylamine (DIEA) gave monoalcohol **10**. Compound **10** was reacted with methoxyethoxyethyl tosylate, followed by deprotection to give (*R*)-**5.** The optical purity of each enantiomer was confirmed by the values of the angle of rotation.

Construction of aromatic tetraureas is shown in Scheme 2. Introduction of each chiral substituent was performed by means of Fukuyama's nosyl methodology.[23] Thus, *m*-phenylenediamine was converted to sulfonamide **12** by treatment with *o*-nitrobenzenesulfonyl chloride (NsCl). Alkylation of **12** was carried out under Mitsunobu conditions with each chiral **5**. Removal of the *o*-nitrobenzenesulfonyl group of **13** was performed by treatment with PhSH and Cs_2CO_3 to give **14**. *N*-(Aminophenyl)-*N*′-phenyl-*N*,*N*′-di(*n*-propyl)urea **15**, prepared from *m*-nitroaniline in three steps, was converted to the isocyanate by treatment with triphosgene, followed by addition of **14** to give tetraurea **16**. The alkylation of two secondary nitrogen atoms by using sodium hydride as a base afforded compounds **4**.

The conformations of **4** in solution were examined by means of ^{1}H NMR spectroscopy (Table 1). Both **3** and **4** showed the signals of the aromatic protons at higher fields

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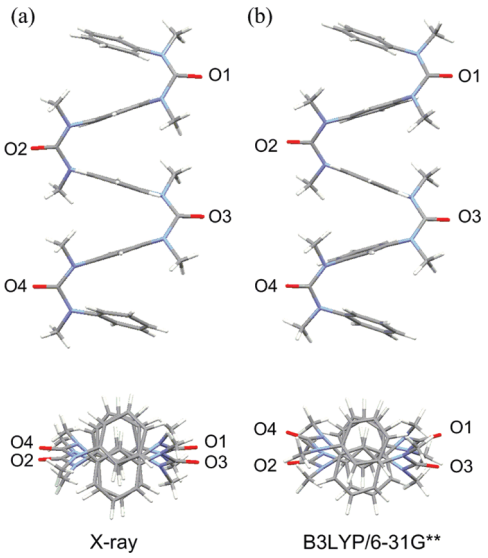

FIGURE 2. (a) X-ray and (b) optimized structures of *N*-methylated oligo(phenylurea) **3** with all-*R* axis chirality.

(6.0−7.0 ppm) compared with the unfolded ureas (bearing *N*-H atoms), as well as *N*,*N*′-dimethyl-*N*,*N*′-diphenylurea. Comparison of the chemical shifts between these ureas indicated that compounds **4** also exist predominantly in aromatic multilayered structure with all-*cis* forms of the four urea bonds, as observed in the crystal structure of **3**.[20,21] The existence of minor conformers could not be observed at lower temperature, possibly due to the lower rotational barrier of the C−N bond, compared with aromatic amides (Figure S2, Supporting Information).

2. Geometry Optimizations. To rationalize the relationship between the spectral features and helical structure of the oligo(phenylurea)s in solution, we performed geometry optimization calculation on *N*-methylated oligo(*m*-phenylurea) (**3**) at the B3LYP/6-31G** level. The optimized conformation of the oligourea exhibits a helical structure with multilayered aromatic rings, as observed in the X-ray structure of **3**.[20] As shown in Figure 2, we found a close similarity between the optimized and X-ray structures, but these structures, especially their terminal geometries, do not strictly match. This may arise from crystal packing forces, which sometimes have considerable influence on the conformations of flexible molecules. When ^{1}H NMR chemical shifts were calculated for the optimized structure of **3** using the B3LYP method, there was good agreement between calculated and experimental shifts (Table 1). Therefore, it can be concluded that the present oligoureas predominantly adopt a helically stacked structure in solution.

3. UV and CD Spectra of Chiral Oligo(*m*-phenylurea)s. The oligoureas **4** showed broad electronic absorption in the 190−310 nm region, which consisted apparently of a strong absorption at 190−220 nm and absorption at 230−310 nm in acetonitrile (Figure 3b). In the CD spectra of **4a**, a plus−minus pattern was detected in the region of 200−290 nm, viewing from longer wavelength. A very weak positive signal was detected at 270−290 nm, with a strong negative signal at 200−270 nm, and an intense positive signal at 190−200 nm (Figure 3a). Monomeric chromophore **13a** showed much weaker integral type CD signals, so that the

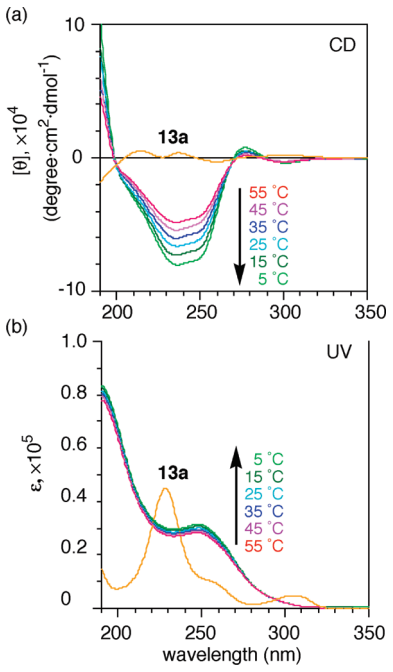

FIGURE 3. (a) CD and (b) UV spectra of **4a** in CH_3CN.

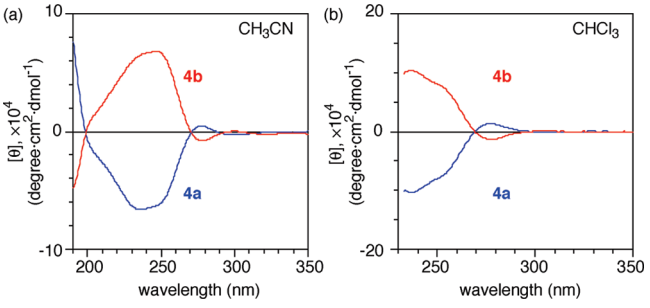

FIGURE 4. Mirror-image CD spectra of **4a** and **4b** in (a) CH_3CN and (b) $CHCl_3$ at 25 °C.

intense dispersion-type CD spectra are not due to the intrinsic chirality of the side chain of **4a** but to an excess of a single-handed helical structure of **4a**.[24]

Compound **4b** showed mirror-image CD spectrum (Figure 4a). Similar mirror-image CD spectra were obtained for **4a** and **4b** in $CHCl_3$ (Figure 4b). To examine the effect of a chiral *N*-substituent, the tetraurea with *N*-(*R*)-3,7-dimethyloctyl groups **17** (Figure 1) was synthesized. Compound **17** exhibited only very weak CD signals in acetonitrile (see Figure S3, Supporting Information). Thus, the distance between the chiral center of the *N*-substituent and the aromatic multilayered structure is significant for the observation of CD signals.[25] Further, the CD signals of oligoureas **4a** and **4b** were highly temperature-dependent,[26] decreasing with increasing temperature. This observation suggested that

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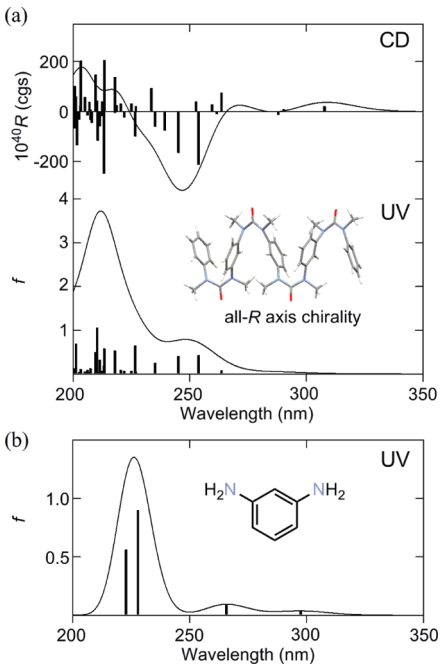

FIGURE 5. Calculated spectra for the optimized structure of *N*-methylated oligo(phenylurea) (**3**) with all-*R* axis chirality (a) and 1,3-diaminobenzene (b) obtained using the ZINDO/S method. Gaussian bands with a half-bandwidth of 3000 cm^{-1} were used.

the predominant dynamic helicity of oligoureas **4** was induced by the chiral side chains. The CD magnitude of **4** showed almost linear correlation with temperature in the examined range of temperature. The conversion between two helices would exist at the temperature. Further study at lower temperature will be needed to clarify the dynamic behaviors of **4** in solution.

4. Calculated UV and CD Spectra. We employed the semiempirical ZINDO/S method to calculate the UV and CD spectra of the oligo(phenylurea)s. The ZINDO method was chosen to obtain results in a reasonable computational time.[27] Lewis et al. have applied this method to interpret the electronic excited states of tertiary naphthyl oligoarylureas.[28] Figure 5a shows the simulated spectra of the optimized structure of **3** with all-*R* axial chirality. The UV spectrum of 1,3-diaminobenzene was also calculated for comparison (Figure 5b). As can be seen from the figures, the appearance of the calculated UV spectra of both the monomeric unit and the oligo(phenylurea) is in close agreement with the spectral features observed for **13a** and **4**. As for the simulated CD spectrum, **3** with all-*R* axial chirality was calculated to have intensely negative CD signals corresponding to a less intense absorption band in the 230−260 nm region, reproducing well the observed spectral features of **4a**. Negative CD signals were also predicted on the basis of the X-ray structure of **3** with all-*R* axial chirality (Figure S4, Supporting Information). Because the chiral side chains in the present system are not chromophoric, the effect of the chiral chains on the spectroscopic properties in the 200−350 nm range should be negligible. From these results, induction of the handedness of **4a** and **4b** resulted from the preferable all-*R* and all-*S* conformations, respectively.

5. Vibrational CD Analysis. Comparison of empirically and theoretically obtained CD spectra is a powerful tool to identify the absolute structures of well-defined molecules. Recently, infrared and vibrational CD (VCD) spectra have proven to be useful for such purposes. There are many reports on the VCD analysis of molecular chirality, though most of them are studies on natural polymers such as peptides and nucleic acid derivatives or small organic molecules or inorganic compounds.[29−31] Recently, the usefulness of VCD analysis for some synthetic helical polymers was reported.[11,15b] We then applied VCD analysis to our oligourea system. The region (1500−1800 cm^{-1}) corresponding to the carbonyl C−O (ca. 1650 cm^{-1}) and aromatic ring (ca. 1600 cm^{-1}) vibrations was examined, since the other signals, especially in the fingerprint region, would overlap with those derived from the chiral substituent. First, the VCD spectra of compounds **4** in $CDCl_3$ were examined. However, the VCD intensity was very small, even after 10,000 accumulations, while the signals corresponding to the aromatic ring vibrations reproducibly showed negative and positive values for compounds **4a** and **4b**, respectively (Figure S5, Supporting Information). Then, we examined the VCD spectra of compounds **4** in the film state. To eliminate minor absorption artifacts and increase the signal-to-noise ratio, the sample was examined 10,000 times, and the average VCD spectrum of the enantiomers was used as the baseline (Figure 6a). In this case, clear signals due to the carbonyl and aromatic ring vibrations were seen with negative and positive values for compounds **4a** and **4b**, respectively. The intensity of the VCD signal was different between **4a** and **4b**. One possible reason was that the thickness of the films was not uniform over the incident area, since they were prepared by the cast method. The sign of each signal was the same as that observed for the weak signal in $CDCl_3$ solution.

To assign the configuration, the VCD for compound **3** with all-*R* axis chirality was calculated at the B3LYP/6-31G** level (Figure 6c). Comparison of the bands corresponding to the carbonyl or aromatic region in the empirical and calculated results showed that the calculated VCD spectrum of **3** with all-*R* chirality has negative bands similar to those of compound **4a** with the (*S*)-substituent. To

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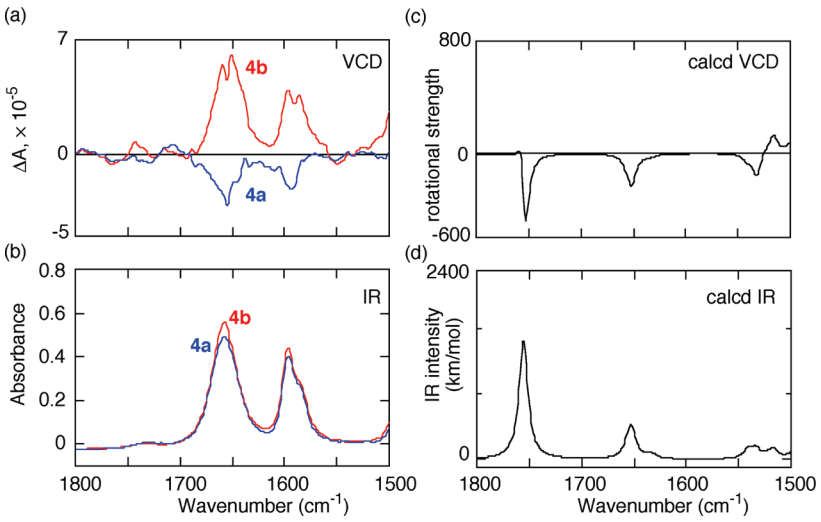

FIGURE 6. VCD (a) and IR (b) spectra of **4a** (blue line) and **4b** (red line). Calculated VCD (c) and IR (d) spectra of **3** with all-*R* axis chirality. No correction of introducing a scale factor was made in the calculated spectra.

examine the effect of a chiral *N*-substituent on the vibration of the carbonyl groups or aromatic rings, we calculated the IR and VCD spectra of compound **18**, an analogue of **3** bearing two *N*-(*S*)-2-methoxy-1-propyl substituents (Figure S6, Supporting Information) and obtained similar results. Thus, the assignment of the absolute structure by VCD analysis was identical to that by CD analysis.

Discussion

The *cis* conformational preference of aromatic *N*-methylated amide, urea, and related compounds affords folded aromatic structures that are useful as monomer units to construct helical foldamers.[16] In contrast to the polyamides **1**, in which the phenyl ring is oriented parallel to the helical axis with three monomer units per turn,[12] *N*-alkylated oligo(*m*-phenylurea)s such as **3** are expected to adopt a helical conformation in which the phenyl ring is arranged vertical to the helical axis. As observed in the crystal of **3**, configurations of the axis chirality were consistent (all-*R* or all-*S*), probably due to steric hindrance. In solution, the origoureas such as **3** exist mainly in the folded structures as observed in the crystal, which was deduced from ^{1}H NMR chemical shifts (Table 1) and NOE study (data not shown), as discussed by us[20] and Clayden et al.[21] ^{1}H NMR spectra of **3**, **4**, and **17** even at 223 K did not show any signals corresponding to the possible minor conformers. Further, the addition of some chiral reagents could not distinguish the two folded conformers (all-*R* and all-*S*) of **3** at 223 K in ^{1}H NMR.[20] Therefore, the conversion between the enantiomeric helices of **3** seems to be quite fast in solution, although it would require the inversion of all axis chirality.

In the present study, chiral substituents were introduced at the two nitrogen atoms of the central benzene rings of the *N*-alkylated oligo(*m*-phenylurea) structure. The presence of aromatic layered structures of **4** was indicated by ^{1}H NMR analysis, and the induction of handedness could be observed clearly in the CD spectra and also in the VCD spectra. The calculations about both CD and VCD spectra on *N*-alkylated oligo(*m*-phenylurea)s gave the same results for the absolute configuration of **4**, that is, the preferable structure of **4a** and **4b** are all-*R* and all-*S* conformations, respectively. The results indicate that VCD analysis is useful to analyze the conformation and configuration of macromolecules of this type.[11,15]

The CD spectra of **4** were strongly temperature-dependent, as is the case for polyamides **1**. Introduction of only two chiral *N*-substituents is enough for the induction of handedness, while the distance of the chiral center of the substituent from the oligo(*m*-phenylurea) backbone seemed important, deduced from the comparison of CD spectra of **4** and **17**. Clayden et al. reported that a diastereotopic probe at the terminal benzene ring of *N*-methylated oligo(*m*-phenylurea)s could distinguish the prochirality even when separated by 24 bond lengths (corresponding to the tetraureas), though longer distances diminished the effect.[21] Overall, the results indicate that *N*-alkylated oligo(*m*-phenylurea)s have dynamic helical properties in solution.

In conclusion, the *N*-alkylated oligo(*m*-phenylurea)s have helical conformations in solution, and handedness could be induced by the introduction of chiral *N*-substituents. The absolute structures of the helices in **4** were determined from the CD and VCD spectra. Since *N*-alkylated oligo(*m*-phenylurea)s have both dynamic helical and aromatic multilayered properties, these systems should be applicable to construct aromatic functional molecules with unique physicochemical properties.

Experimental Section

Synthesis of 6. Pyridinium toluene-*p*-sulfonate (0.245 g, 0.98 mmol) was added to a solution of ethyl (*S*)-(−)-lactate (30.21 g, 256 mmol) and 3,4-dihydro-2*H*-pyran (27.72 g, 330 mmol) in dry CH_2Cl_2 (340 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was washed with saturated $NaHCO_3$ and dried over sodium sulfate. After evaporation, the residue was distilled (64 °C at 1 Torr) to yield **6** (47.07 g, 91%) as a mixture of two diastereomers (ratio is 1:1): ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.72 (t, 1 H, J = 3.6 Hz), 4.70 (t, 1 H, J = 3.6 Hz), 4.42 (q, 1 H, J = 7.0 Hz), 4.16−4.23 (m, 5 H), 3.91−3.95 (m, 1 H), 3.83−3.87 (m, 1 H), 3.50−3.54 (m, 1 H), 3.44−3.48 (m, 1 H), 1.84−1.89 (m, 2 H), 1.67−1.79 (m, 4 H), 1.52−1.61 (m, 6 H), 1.46 (d, 3 H, J = 6.9 Hz), 1.40 (d, 3 H, J = 6.9 Hz), 1.28 (t, 3 H, J = 7.3 Hz), 1.27 (t, 3 H, J = 7.3 Hz).

Synthesis of 7. A solution of **6** (30.44 g, 151 mmol) in ether (150 mL) was added dropwise to an ice cooled solution of $LiAlH_4$ (12.65 g, 333 mmol) in dry ether (300 mL) under Ar atmosphere over 1 h. The reaction mixture was stirred for 1.5 h, and saturated aqueous ammonium chloride (80 mL) was added. Precipitated salts were filtered off and washed well with ether. The combined organic layers were dried over magnesium sulfate and filtered. Evaporation afforded crude **7** (23.28 g, 96%) as a mixture of two diastereomers (ratio is 1:0.6): ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.74 (dd, 0.6 H, J = 5.2, 2.7 Hz), 4.55 (m, 1 H), 3.98−4.01 (m, 1 H), 3.93−3.96 (m, 0.6 H), 3.86−3.91 (m, 0.6 H), 3.80−3.85 (m, 1 H), 3.67 (dd, 1 H, J = 9.4, 2.9 Hz), 3.59 (m, 0.6 H), 3.45−3.57 (m, 3.2 H), 2.22 (dd, 0.6 H, J = 7.6, 5.2 Hz), 1.72−1.87 (m, 3.6 H), 1.52−1.62 (m, 7 H), 1.22 (d, 1.8 H, J = 6.5 Hz), 1.14 (d, 3 H, J = 6.5 Hz).

Synthesis of 8. A solution of *t*-BuOK (49.24 g, 439 mmol) in *t*-BuOH (450 mL) was added dropwise to **7** (23.28 g, 146 mmol). The solution was stirred for 2 h, concentrated in vacuo, and subsequently diluted with dioxane (150 mL). A catalytic amount of tetrabutylammonium chloride (1.28 g, 4.61 mmol) was added after which benzyl chloride (55 mL, 434 mmol) was added dropwise at room temperature. The mixture was heated at 80 °C for 1 h. Upon reaction completion, water was added, and the mixture was extracted with ether twice. The organic layers were combined, washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo leaving a yellow oil. Distillation (104−114 °C at 1 Torr) afforded (*S*)-1-benzyloxy-2-propane tetrahydropyran-2-yl ether (34.34 g, 94%).

p-TsOH·H_2O (1.18 g, 137 mmol) was added to an ice cooled solution of (*S*)-1-benzyloxy-2-propane tetrahydropyran-2-yl ether (34.34 g, 137 mmol) in methanol (150 mL). The solution was subsequently stirred at room temperature overnight. After addition of $NaHCO_3$, dihydropyran were evaporated. The residue was extracted with ether, dried over magnesium sulfate, and filtered. After evaporation, the crude yellow product was distilled (77−81 °C at 1 Torr) to give **8** (15.01 g, 66%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.38 (m, 5 H), 4.56 (t, 2 H, J = 12 Hz), 3.97−4.04 (m, 1 H), 3.48 (dd, 1 H, J = 9.3, 3.0 Hz), 3.29 (dd, 1 H, J = 9.3, 8.2 Hz), 2.40 (d, 1 H, J = 3.2 Hz), 1.15 (d, 3 H, J = 6.3 Hz).

Synthesis of 9. A mixture of **8** (16.45 g, 0.099 mol), 2-(methoxyethoxy)ethyl tosylate (38.20 g, 0.139 mol), and potassium hydroxide (18.43 g, 0.328 mol) in THF (200 mL) was heated under reflux for 24 h under Ar atmosphere. Subsequently water (40 mL) was added to hydrolyze excess tosylate. The reaction mixture was extracted with dichloromethane, dried over magnesium sulfate, and filtered. Evaporation of the solvent gave the crude yellow product, which was distilled (117−132 °C at 1 Torr) to give **9** as a colorless oil (13.35 g). The distillation residue was chromatographed on silica gel (ethyl acetate/hexane 1:2) to afford 8.17 g of **9** (totally 65%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, 4 H, J = 4.5 Hz), 7.26−7.30 (m, 1 H), 4.57 (d, 1 H, J = 12 Hz), 4.54 (d, 1 H, J = 12 Hz), 3.67−3.71 (m, 3 H), 3.63−3.66 (m, 4 H), 3.53−3.54 (m, 2 H), 3.51 (dd, 1 H, J = 10, 5.8 Hz), 3.42 (dd, 1 H, J = 10, 4.6 Hz), 3.37 (s, 3 H), 1.18 (d, 3 H, J = 6.2 Hz).

Synthesis of (*S*)-5. Compound **9** (2.027 g, 7.6 mmol) was dissolved in ethanol (20 mL) and acidified with concentrated hydrochloride (2 drops). A catalytic amount of 10% Pd−C (0.216 g) was added to the solution, and hydrogenation was carried out at 40 °C. After filtration and evaporation of the solvents, the crude was distilled to give pure (*S*)-**5** as a colorless oil (1.289 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (m, 1 H), 3.60 (m, 9 H), 3.44 (dd, J = 8.0, 11.6 Hz, 1 H), 3.38 (s, 3 H), 2.32 (br s, 1 H), 1.11 (d, J = 6.4 Hz, 3 H). HRMS (ESI+) calcd for $C_8H_{18}NaO_4$ (M^+ + Na) 201.1097, found 201.1093. $[\alpha]_D$ +22.1° ($CHCl_3$).

Synthesis of 10. 4-Methoxytrityl chloride (17.9 g, 57.9 mmol) was added to a solution of (*R*)-1,2-propanediol (3.85 mmol, 52.6 mmol), tetrabutylammonium iodide (1.94 g, 5.26 mmol), and *N*,*N*-diisopropylethylamine (23.5 mL, 137 mmol) in dry dichloromethane (155 mL) at 0 °C, and the mixture was stirred for 2.5 h at room temperature. The reaction mixture was poured into water, and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. After evaporation, residue was purified by silica gel column chromatography (ethyl acetate/hexane 1:3) to give **10** (16.1 g, 46.1 mmol, 88%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 4 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.30 (t, J = 7.2 Hz, 4 H), 7.23 (tt, J = 2.4, 7.2 Hz, 2 H), 6.24 (dt, J = 2.4, 7.2 Hz, 2 H), 3.98 (m, 1 H), 3.80 (s, 3 H), 3.13 (dd, J = 3.6, 9.2 Hz, 1 H), 2.98 (dd, J = 8.0, 9.2 Hz, 1 H), 2.37 (br d, J = 2.4 Hz, 1 H), 1.10 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.7, 144.5, 144.5, 135.7, 130.5, 128.5, 128.0, 127.1, 113.3, 86.5, 69.0, 67.2, 55.4, 19.1. HRMS (ESI+) calcd for $C_{23}H_{24}NaO_3$ (M^+ + Na) 371.1618, found 371.1609.

Synthesis of 11. A solution of **10** (16.1 g, 46.1 mmol) in dry DMF (50 mL) was added to a suspension of sodium hydride (60%, 2.76 g, 6.90 mmol, washed with hexane twice) in dry DMF (50 mL) at 0 °C. After stirring for 1 h at room temperature, a solution of 2-(methoxyethoxy)ethyl tosylate (22.8 g, 83.0 mmol) in dry DMF was added to the mixture at 0 °C, and the mixture was heated at 60 °C for 2 h. The solvent was removed in vacuo, poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. After evaporation, residue was purified by silica gel column chromatography (ethyl acetate/hexane 3:1) to give **11** (11.9 g, 26.5 mmol, 57%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 1.6, 8.0 Hz, 4 H), 7.33 (dt, J = 2.0, 8.8 Hz, 2 H), 7.28 (t, J = 7.2 Hz, 4 H), 7.21 (tt, J = 2.4, 7.2 Hz, 2 H), 6.82 (dt, J = 2.4, 8.8 Hz, 2 H), 3.79 (s, 3 H), 3.70 (m, 2 H), 3.65 (m, 5 H), 3.53 (m, J = 2 H), 3.36 (s, 3 H), 3.19 (dd, J = 6.0, 10.0 Hz), 2.96 (dd, J = 5.2, 9.2 Hz, 1 H), 1.15 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.6, 144.9, 144.8, 136.0, 130.5, 128.6, 127.9, 126.9, 113.1, 86.3, 75.7, 72.1, 71.1, 70.1, 69.0, 67.5, 59.2, 55.3, 17.9. HRMS (ESI+) calcd for $C_{28}H_{34}NaO_5$ (M^+ + Na) 473.2298, found 473.2308.

Synthesis of (*R*)-5. (±)-10-Camphorsulfonic acid (677 mg, 2.91 mmol) was added to a solution of **11** (11.9 g, 26.5 mmol) in dry methanol (60 mL) at 0 °C, and the mixture was stirred for 2.5 h at room temperature. After addition of triethylamine (10 mL) at 0 °C, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane 2:1) to give (*R*)-**5** (3.56 g, 20.0 mmol, 75%) as a colorless oil. (*R*)-**5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (m, 1 H), 3.60 (m, 9 H), 3.44 (dd, J = 8.0, 11.6 Hz, 1 H), 3.38 (s, 3 H), 2.32 (br s, 1 H), 1.11 (d, J = 6.4 Hz, 3 H). $[\alpha]_D$ −25.8° ($CHCl_3$).

Synthesis of 12. 2-Nitrobenzenesulfonyl chloride (12.0 g, 54.0 mmol) was added to a solution of *m*-phenylenediamine (2.53 g, 23.4 mmol) in dry pyridine (15 mL) at 0 °C, and the mixture was stirred for 3 h at room temperature. The raction mixture was poured into 1 M hydrochloric acid and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed in vacuo to afford **12** (8.16 g, 17.1 mmol, 74%) as an orange powder: ^{1}H NMR (400 MHz, DMS0-d_6) δ 10.78 (s, 2 H), 7.98 (d, J = 7.3 Hz, 2 H), 7.85 (d, J = 7.8 Hz, 2 H), 7.84 (t, J = 7.8 Hz, 2 H), 7.75 (t, J = 7.8 Hz, 2 H), 7.15 (t, J = 8.3 Hz, 1 H), 7.03 (br t, 1 H), 6.82 (dd, J = 2.0, 8.3 Hz, 2 H). ^{13}C NMR (150 MHz, DMS0-d_6) δ 147.8, 137.6, 134.8, 132.5, 131.1, 130.2, 129.9, 124.8, 116.2, 111.7. HRMS (ESI+) calcd for $C_{18}H_{13}N_4O_8S_2$ (M^+ − H) 477.0169, found 477.0171.

Synthesis of 13a. Diethyl azodicarboxylate (40% in toluene, 3.45 g, 7.93 mmol) was added to a solution of **12** (1.79 g, 3.74 mmol), (*S*)-**5** (1.29 g, 7.24 mmol), and triphenylphosphine (2.03 g, 7.74 mmol) in dry THF (30 mL) under Ar atmosphere at 0 °C. After stirring for 3 h at room temperature, the solvent was removed in vacuo. The residue was used for the next

reaction without further purification. **13a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 8 H), 7.27 (m, 3 H), 7.04 (s, 1 H), 3.54 (m, 22 H), 3.35 (s, 6 H), 1.12 (d, J = 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 140.0, 133.9, 131.9, 131.6, 131.5, 129.8, 129.7, 129.5, 123.9, 74.4, 72.1, 70.7, 70.7, 68.2, 59.2, 56.9, 17.7. HRMS (ESI+) calcd for $C_{34}H_{46}N_4NaO_{14}S_2$ (M^+ + Na) 821.2344, found 821.2366.

Synthesis of 14a. A solution of crude **13a** (1.06 g, 1.33 mmol) in acetonitrile (5 mL) was added to a solution of benzenethiol (0.3 mL, 2.4 equiv) and cesium carbonate (1.33 g, 3.1 equiv) in acetonitrile (5 mL), and the mixture was refluxed for 12 h. The reaction mixture was allowed to cool to room temperature, diluted with water, and extracted with ethyl acetate twice. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. After the solvent was removed in vacuo, the residue was purified by silica gel column chromatography (hexane/ethyl acetate 1:2, then ethyl acetate) to give **14a** (322 mg, 69% from **12**) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (t, J = 8.0 Hz, 1 H), 6.02 (dd, J = 2.0, 8.4 Hz, 2 H), 5.92 (s, 1 H), 3.77−3.64 (m, 18 H), 3.39 (s, 6 H), 3.19 (dd, J = 3.6, 12.4 Hz, 2 H), 3.03 (dd, J = 7.6, 12.4 Hz, 2 H), 1.21 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.6, 130.0, 103.5, 98.2, 74.5, 72.1, 70.9, 70.7, 68.1, 59.2, 49.4, 18.0. HRMS (ESI+) calcd for $C_{22}H_{41}N_2O_6$ (M^+ + H) 429.2959, found 429.2968.

Synthesis of 15. Phenyl isocyanate (7.4 mL, 68.3 mmol) was added to a solution of *m*-nitroaniline (9.33 g, 67.6 mmol) in THF at room temperature. After 1 h, the solvent was removed in vacuo. The residue was washed with ethyl acetate to afford *N*-phenyl-*N*′-(3-nitrophenyl)urea (16.2 g, 63.0 mmol, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1 H), 8.82 (s, 1 H), 8.55 (t, J = 2.2 Hz, 1 H), 7.81 (dd, J = 7.8, 2.4 Hz, 1 H), 7.70 (d, J = 6.8 Hz, 1 H), 7.56 (t, J = 8.2 Hz, 1 H), 7.47 (d, J = 7.5 Hz, 2 H), 7.29 (t, J = 8.0 Hz), 6.99 (t, J = 6.8 Hz, 1 H).

A solution of *N*-phenyl-*N*′-(3-nitrophenyl)urea (264 mg, 1.02 mmol) in THF (5 mL) was added to a suspension of sodium hydride (60%, 230 mg, 5.75 mmol, washed with hexane twice) in THF (3 mL) at 0 °C. After 30 min of stirring for at room temperature, 1-bromopropane (0.90 mL, 9.99 mmol) was added to the mixture at 0 °C, and the mixture was refluxed for 12 h. The solvent was removed in vacuo, poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. After evaporation, residue was purified by silica gel column chromatography (ethyl acetate/hexane 1:5) to give *N*,*N*′-di-*n*-propyl-*N*-phenyl-*N*′-(3-nitrophenyl)urea (66 mg, 0.194 mmol, 19%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 2.0, 8.4 Hz, 1 H), 7.52 (t, J = 2.0 Hz, 1 H), 7.17 (t, J = 8.4 Hz, 1 H), 7.06 (dd, J = 0.8, 7.2 Hz, 1 H), 7.00 (t, J = 8.0 Hz, 2 H), 6.89 (t, J = 7.2 Hz, 1 H), 6.89 (d, J = 7.2 Hz, 2 H), 3.56 (t, J = 8.0 Hz, 4 H), 1.61 (sextet, J = 8.0 Hz, 4 H), 0.90 (t, J = 7.6 Hz, 6 H).

A solution of *N*,*N*′-di-*n*-propyl-*N*-phenyl-*N*′-(3-nitrophenyl)-urea (7.87 g, 23.1 mmol) in methanol (50 mL) was hydrogenated with Pd−C (10%, 1.52 g) for 1.5 h at room temperature. The reaction mixture was filtered on Celite, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane 1:2) to give **15** (6.65 g, 21.4 mmol, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (t, J = 7.2 Hz, 2 H), 6.94 (t, J = 7.2 Hz, 1 H), 6.76 (t, J = 8.0 Hz, 1 H), 6.75 (d, J = 7.2 Hz, 2 H), 6.25 (dd, J = 2.0, 8.0 Hz, 1 H), 6.12 (dd, J = 2.0, 8.0 Hz, 1 H), 5.98 (t, J = 2.0 Hz, 1 H), 3.50 (t, J = 7.6 Hz, 2 H), 3.45 (t, J = 7.6 Hz, 2 H), 1.57 (sextet, J = 7.6 Hz, 2 H), 1.56 (sextet, J = 7.2 Hz, 2 H), 0.87 (t, J = 7.6 Hz, 3 H), 0.86 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.8, 146.7, 145.5, 144.5, 129.1, 128.4, 127.2, 124.8, 117.5, 113.9, 111.8, 53.5, 53.4, 21.7, 21.7, 11.6. HRMS (ESI+) calcd for $C_{19}H_{25}N_3NaO$ (M^+ + Na) 334.1890, found 334.1898.

Synthesis of 16a. Compound **15** (157 mg, 0.50 mmol) was added to a solution of triphosgene (49.9 mg, 0.33 equiv) in 1,2-dichloroethane (3.5 mL) at 0 °C. After 1 h, triethylamine (0.1 mL, 1.5 equiv) and then **13a** (106 mg, 0.25 mmol) were added to the reaction mixture at 0 °C, and the whole was stirred for 12 h at room temperature. After evaporation, the residue was diluted with ethyl acetate and filtered to remove triethylamine hydrochloride. The filtrate was purified by silica gel column chromatography (ethyl acetate/hexane 3:1) to give **16a** (139 mg, 0.13 mmol, 25%) as a colorless foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, J = 8.0 Hz, 1 H), 7.34−7.26 (m, 3 H), 7.00 (t, J = 7.6 Hz, 4 H), 6.89 (t, J = 7.6 Hz, 2 H), 6.86 (d, J = 6.4 Hz, 4 H), 6.82 (s, 2H), 6.74 (d, J = 7.6 Hz, 4 H), 6.36 (d, J = 6.4 Hz, 2 H), 3.84−3.44 (m, 32 H), 3.29 (s, 6 H), 1.58−1.52 (m, 6 H), 1.18 (d, J = 6.4 Hz, 6 H), 0.85 (t, J = 7.2 Hz, 6 H), 0.83 (t, J = 7.2 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 154.7, 144.7, 144.3, 144.2, 139.4, 130.4, 128.3, 128.3, 127.0, 126.4, 125.7, 124.5, 121.3, 117.9, 115.7, 77.2, 75.4, 71.9, 70.6, 70.4, 68.3, 59.0, 56.0, 53.4, 53.3, 21.6, 21.5, 17.3, 11.5, 11.5. HRMS (ESI+) calcd for $C_{62}H_{86}N_8NaO_{10}$ (M^+ + Na) 1125.6359, found 1125.6327.

Synthesis of 4a. A solution of **16a** (134 mg, 0.12 mmol) in DMF (2.5 mL) was added to a suspension of sodium hydride (22.4 mg, 4.7 equiv, washed with hexane twice) in DMF (1.5 mL) at 0 °C, and the mixture was stirred at room temperature for 20 min. 1-Bromopropane (0.1 mL, 9.3 equiv) was added to the mixture at room temperature, and the whole was stirred for 12 h. After removal of the solvent in vacuo, the residue was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. After evaporation, the residue was purified by preparative thin-layer chromatography to give **4a** (16 mg, 0.013 mmol, 11%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (t, J = 7.6 Hz, 4 H), 6.85 (t, J = 7.6 Hz, 2 H), 6.65 (t, J = 7.6 Hz, 2 H), 6.60 (d, J = 8.0 Hz, 4 H), 6.51 (t, J = 7.6 Hz, 1 H), 6.39 (br d, J = 7.6 Hz, 2 H), 6.28 (br s, 1 H), 6.27 (d, J = 7.6 Hz, 4 H), 5.90 (s, 2 H), 3.7−3.54 (m, 20 H), 3.47−3.30 (m, 6 H), 3.39 (s, 6 H), 3.20−3.10 (m, 8 H), 1.52−1.35 (m, 12 H), 1.10 (t, J = 6.0 Hz, 6 H), 0.87 (t, J = 7.6 Hz, 6 H), 0.84 (t, J = 7.6 Hz, 6 H), 0.82 (t, J = 7.6 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 159.2, 145.8, 144.9, 144.3, 144.2, 128.3, 127.8, 126.5, 124.8, 123.6, 123.3, 123.3, 123.2, 122.2, 73.8, 72.0, 70.8, 70.6, 67.7, 59.0, 57.5, 53.4, 21.59, 21.56, 21.51, 17.8, 11.4, 11.4, 11.3. HRMS (ESI+) calcd for $C_{68}H_{98}N_8NaO_{10}$ (M^+ + Na) 1209.7298, found 1209.7252.

Compound **4b** was prepared similarly by the synthetic methods of **4a** from **12** using (*R*)-**5**.

Computational Details. All computations were performed using Gaussian 03 package of programs.[32] Geometry optimizations of *N*-methylated oligo(phenylurea) (**3**) and 1,3-diaminobenzene were carried out with constrained C_2 and C_{2v} symmetry. B3LYP hybrid functional was used with the 6-31G** basis sets. NMR properties were calculated using the GIAO-B3LYP/6-31G** method. The calculated chemical shifts were analyzed by subtracting the isotropic shift for each hydrogen atom from the corresponding shift for TMS calculated using the same method (31.7551 ppm). The semiempirical ZINDO/S calculations were performed to obtain the excitation energies, oscillator strengths, and rotatory strengths. The transition velocity form was used to calculate rotatory strengths. Calculated absorption and CD curves were generated by superimposing Gaussian bands with a half-bandwidth of 3000 cm^{-1} for each transition. The IR and VCD spectra were calculated according to the magnetic field perturbation (MFP) theory.

VCD Spectra. The VCD spectra were recorded with a spectrometer PRESTO-S-2007 (JASCO, Japan). The absorption signals were detected using a liquid nitrogen cooled MCT infrared detector equipped with ZnSe windows. Spectra were recorded at

(32) Frisch, M. J. et al. *Gaussian 03, revision E.01*; Gaussian, Inc.: Wallingford, CT, 2004.

4 cm^{-1} resolution. Signals were accumulated for 10^4 scans in about 2 h. The FT-IR absorbance was adjusted below 1.0 in order to attain the optimal signal-to-noise ratio in the VCD measurements. A film sample for VCD measurements was prepared in the following way: first the weighed amount (ca. 5 mg) of the enantiomeric sample was dissolved in $CDCl_3$ (ca. 200 μL) . Thereafter about 40 μL of the solution was cast on a CaF_2 plate to prepare a transparent thin film with an area of ca. 2 cm^2.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **4** and **10**−**17**, temperature-dependent ^1H NMR of **4** and **17**, UV and CD spectra of compound **17**, calculated structure of **3**, calculated UV/CD spectra for the X-ray structure of **3**, IR/VCD spectra of **4** in solution, and calculated IR/VCD spectra of a derivative of **3** with chiral substituents. This material is available free of charge via the Internet at http://pubs.acs.org.