Perylene Bisimide Atropisomers: Synthesis, Resolution, and Stereochemical Assignment

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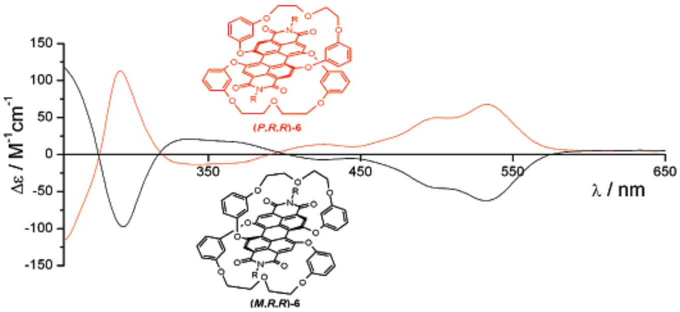

The macrocyclization of the tetra-hydroxyphenoxy-substituted perylene bisimide **4** bearing two (*R*)-configured 2-octyl substituents in the imide positions by etherification with diethylene glycol ditosylate afforded both the diagonally bridged (1,7- and 6,12-linkage) and laterally bridged (1,12- and 6,7-linkage) regioisomers **6** and **7**. The atropo-diastereomers of the diagonally bridged macrocycle **6** were separated by semipreparative HPLC on a chiral column, and their absolute configurations were determined by circular dichroism (CD) spectroscopy in combination with quantum chemical CD calculations. The isolated epimers (*P*,*R*,*R*)-**6** and (*M*,*R*,*R*)-**6** represent the first examples of diasteriomerically pure perylene bisimide atropisomers. The optical and chiroptical properties of these epimers were investigated by UV/vis, fluorescence, and CD spectroscopy, and their conformational properties have been explored by temperature-dependent ^{1}H NMR studies.

Introduction

Apart from the academic interest in chirality as a central topic of chemistry and biology, chiral molecules are widely applied in numerous fields such as chiral recognition (with particular importance in drug research)[1] and enantioselective catalysis,[2] as well as in nonlinear optics[3] and as molecular switches.[4] Furthermore, chiral polymeric emitters or chiral dopants in nematic liquid crystals show potential for application in photo and electroluminescence devices owing to their circularly polarized emission, which should enable stereoimaging.[5] Most prominent examples of chiral compounds with inherent chirality used in this context are biphenyl[6] and binaphthyl[7] derivatives, as well as helicenes and helicene-like systems.[8] In the latter case, the twisting of the π-conjugated molecule endows the

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chirality. It has been shown that twisting of π-systems can be enforced by attaching sterically demanding substituents in appropriate positions. Thus, by applying this principle, a large variety of functional chiral π-conjugated systems have been synthesized, among them, e.g., cyanines, phenanthrenes, triphenylenes, and also acene derivatives.[9] In general, such twisted aromatic systems are not conformationally stable, as in most cases dynamic racemization was observed at elevated temperature depending on the energy barriers for this process, which can vary significantly depending on the steric demand of the substituents.[10]

We are particularly interested in bay-substituted perylene bisimides, a class of fluorophores that has attracted a great deal of attention in the past years owing to their outstanding optical and light fastness properties and their high solubility in common organic solvents.[11] Perylene bisimides (PBIs) bearing substituents in the bay area (1,6,7,12-positions) possess a twisted π-system with a torsion angle between 4° and 36° depending on the number and size of the substituents.[11c,12] It has been recognized already some years ago that such twisted fluorophores might possess interesting chiroptical properties.[13] However, due to the low barriers for the interconversion of the two twisted enantiomeric conformers in solution, atropoisomerically pure perylene bisimides could not be isolated so far, and racemic material prevails in the crystalline state. In hydrogen-bonded co-aggregates of tetraphenoxy-substituted PBIs with oligo(phenylenevinylenes) (OPVs) bearing chiral side chains, we have previously observed a negative (non-bisignated) CD signal for the perylene bisimide chromophore indicative of an enrichment of one enantiomer of PBI in the aggregate.[14] In this case, the chirality is transferred from the optically active OPV units to PBI molecules to afford helical assemblies showing notable Cotton effects for the optical transition of PBI.

Recently, we have reported a strategy to restrict the dynamic racemization process of tetraphenoxy-substituted perylene bisimides by bridging the substituents at the bay positions with oligo(ethylene glycol) chains through macrocyclization.[15] By applying this approach, we herein present the synthesis of chiral macrocyclic PBIs containing two (*R*)-configured 2-octyl substituents in the imide positions and report on the resolution of pure PBI epimers that have allowed the elucidation of the chiroptical properties of twisted PBI fluorophores. The absolute configurations of the epimers have been determined by applying CD spectroscopy in combination with quantum chemical CD calculations.

Results and Discussion

Synthesis and Resolution of Atropisomerically Pure Macrocyclic Perylene Bisimides. The macrocyclic perylene bisimides **6** and **7** were synthesized in five steps starting with the tetrachloro-substituted perylene bisimide **1**[16] as outlined in Scheme 1. The nucleophilic substitution of the chlorine atoms in **1** by 3-methoxyphenol afforded the tetraphenoxy-substituted perylene bisimide **2** in 36% yield. Subsequent saponification of **2** with potassium hydroxide in isopropanol under reflux provided perylene bisanhydride **3** in 90% yield. The chiral substituents were then introduced by imidization of **3** with 2-(*R*)-octylamine in quinoline, employing zinc acetate as a catalyst. After column chromatography of the crude product on silica gel with dichloromethane as eluent, the chiral perylene bisimide **4** was isolated in 58% yield. Cleavage of the methyl ether groups in **4** with boron tribromide in anhydrous dichloromethane provided the resorcinol-functionalized PBI **5** as a synthetic key intermediate.

For the macrocyclization of the chiral perylene bisimide **5**, a similar procedure was applied as previously described for achiral derivatives.[15] A diethylene glycol linker was chosen as the bridging unit because it provides conformationally rigid macrocycles with reasonable yields.[15] Thus, the tetra-hydroxyphenoxy-substituted PBI **5** was treated with diethylene glycol ditosylate and cesium carbonate in dimethylsulfoxide at 120 °C under argon, and after column chromatographic purification of the crude product, both the diagonally bridged (1,7- and 6,12-linkage) macrocycle **6** and its laterally bridged (1,12- and 6,7-linkage) isomer **7** were obtained in 4% and 30% yields, respectively. In comparison to the previously reported macrocyclization of perylene bisimides bearing achiral imide groups,[15] a significantly higher yield for the laterally bridged isomer was observed in the present case.

Since the macrocyclic perylene bisimides **6** and **7** contain two (*R*)-configured chiral imide substituents and the perylene core possesses a chirality plane, the occurrence of diastereomers (more precisely, epimers) was to be expected for these compounds. Indeed, the epimers of the diagonally bridged macrocycle **6**, for which an interconversion of the twisted conformers (*P* and *M*) is not possible, proved to be separable by semipreparative HPLC on a chiral column (Reprosil 100 chiral-NR) using isopropanol/*n*-hexane (1:1) as the eluent (Figure 1). The absolute configurations of the first (**6′**) and the

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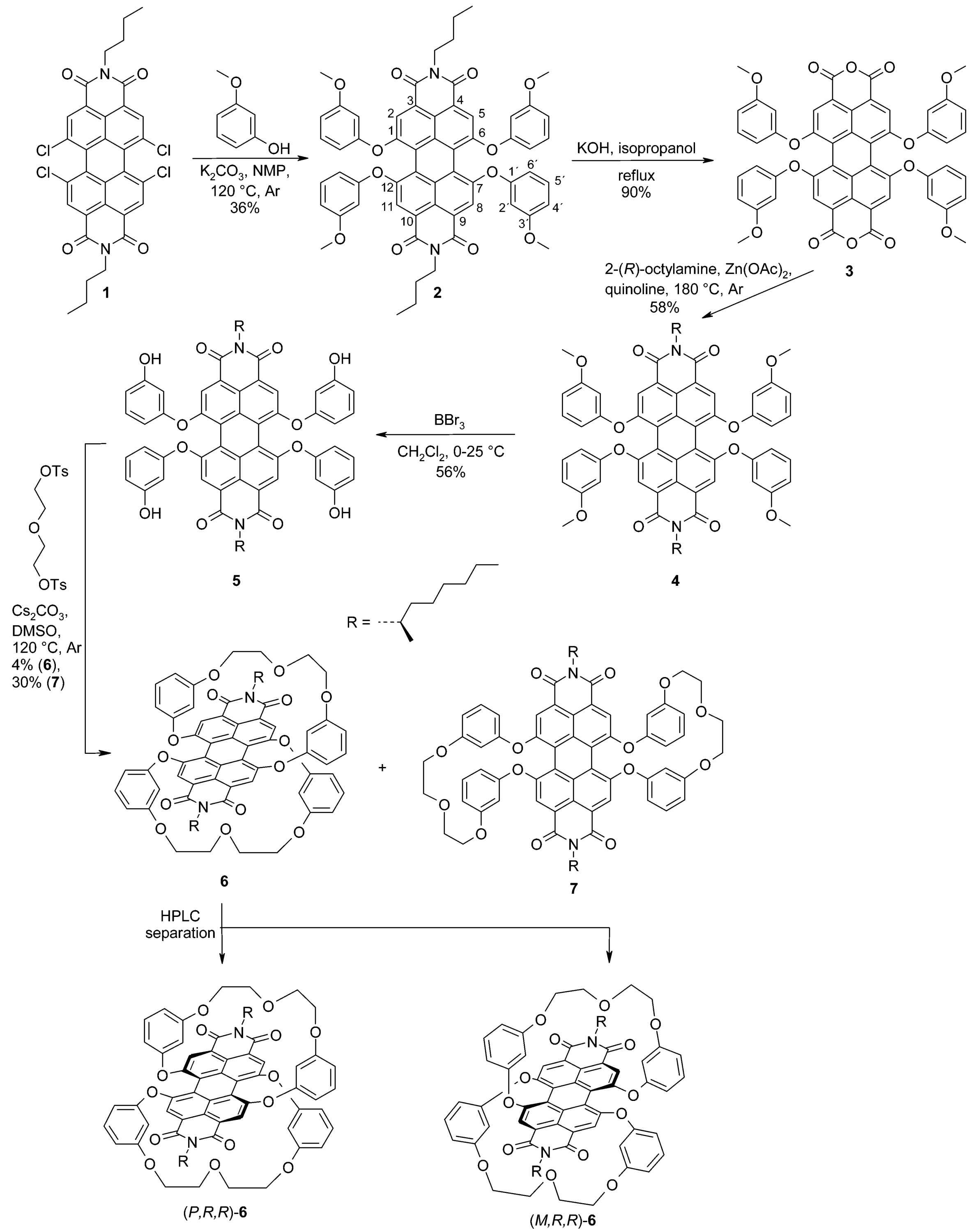
SCHEME 1. Synthesis of Regioisomeric Macrocyclic Perylene Bisimides 6 and 7 and Resolution of the Atropo-diastereomers of 6



second eluted (**6′′**) epimers (retention times 25 and 30 min) were determined as (*P*,*R*,*R*) and (*M*,*R*,*R*), respectively, by CD spectroscopy in combination with quantum chemical CD calculations (details are given in following sections). The epimers of the laterally bridged compound **7**, by contrast, could not be resolved, apparently as a result of its low isomerization ($M \rightleftarrows P$) barriers (vide infra).

The constitutions of the regioisomeric macrocyclic perylene bisimides **6** and **7** were unambiguously assigned by comparison of their ^{1}H NMR data with those of the previously reported similar macrocycles, whose structures were unequivocally determined by X-ray analysis.[15] Thus, for the diagonally bridged macrocycle **6** a characteristic upfield shift of the signal for the aromatic protons ($\delta = 5.6$ ppm) between the two oxygen atoms of the resorcin residues was observed (Figure 2), indicating that these protons are located above and below the aromatic perylene core. The respective protons of the laterally bridged isomer **7** were found to be shifted to lower field ($\delta = 6.7$ ppm), implying that in this regioisomer the phenoxy residues are oriented more in the plane of the perylene core.

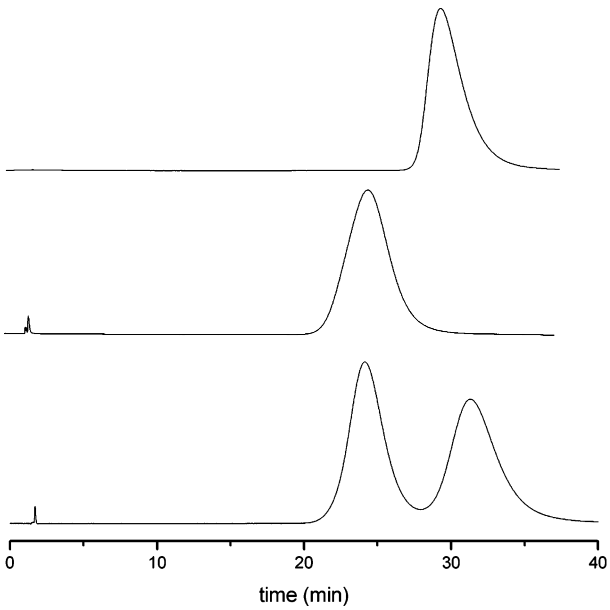


FIGURE 1. HPLC chromatograms before (bottom) and after separation of the epimers of **6** on a Trentec Reprosil 100 chiral-NR column at ambient conditions using isopropanol/*n*-hexane (1:1) as eluent (flow rate 2 mL/min).

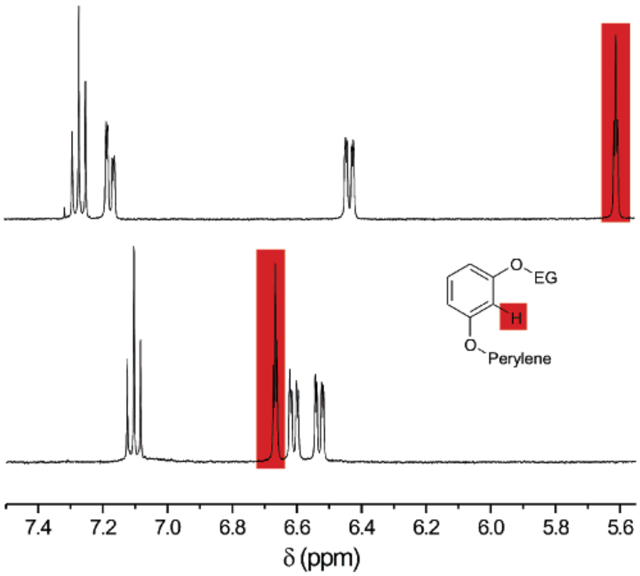


FIGURE 2. Aromatic region of the ^{1}H NMR spectra (400 MHz) of **6** (top) and **7** (bottom) in CD_2Cl_2 at 300 K. The signals of the protons situated between the two oxygen atoms of the resorcinol residues are highlighted in red. EG denotes ethylene glycol.

Characteristic aromatic shielding effects were also observed for protons of the bridging ethylene glycol units. For the laterally bridged regioisomer **7**, the resonances of these protons appear at 3.8−4.8 ppm, whereas the corresponding protons of the diagonally bridged analog **6** show resonances at considerably higher field (3.5−3.9 ppm). Thus, the bridging units in **6** experience a deshielding due to the aromatic perylene core that is only given for this diagonally bridged macrocycle.

Optical Properties. The optical properties of the epimeric perylene bisimides **6** and **7** were investigated by UV/vis and fluorescence (steady-state and time-resolved) spectroscopy. The absorption and emission spectra of **6** and **7** in dichloromethane (Figure 3) reveal the characteristic transitions for PBIs, i.e., a S_0-S_1 transition at ~550 nm and a S_0-S_2 transition at 450 nm.

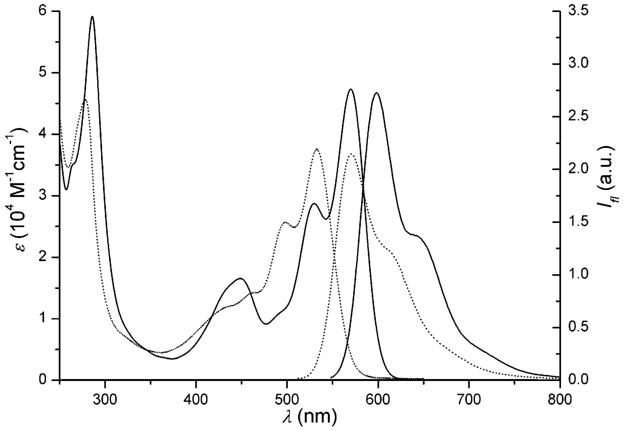


FIGURE 3. UV/vis absorption and emission spectra of **6** (dotted line) and **7** (solid line) in dichloromethane at 25 °C.

TABLE 1. Fluorescence Properties of Perylene Bisimides 6 and 7

	solvent	λ_{max} (nm)	Φ_{fl}[a]	τ_{fl} (ns)[b]	k_r (s^{-1})[c]	k_{nr} (s^{-1})[d]
6	dichloromethane	570	0.22	2.2	1.0×10^8	3.6×10^8
	diethylether	560	0.73	6.2	1.2×10^8	4.4×10^7
7	dichloromethane	598	0.95	6.9	1.4×10^8	7.3×10^6

[a] $\Phi_{fl} \pm 0.03$. [b] $\tau_{fl} \pm 0.5$ ns. [c] $k_r = \Phi_{fl}/\tau_{fl}$. [d] $k_{nr} = (1 - \Phi_{fl})/\tau_{fl}$.

The UV/vis absorption spectrum of the diagonally bridged isomer **6** shows a hypsochromic shift of the absorption maximum of the S_0-S_1 transition by 38 nm in comparison to that of **7**, accompanied by a pronounced hypochromicity. Moreover, **6** exhibits a significantly less intense S_0-S_2 transition compared to that of **7**. These spectral features are typical of diagonally bridged PBI macrocycles[15] and thus further confirm the structural assignment based on characteristic ^{1}H NMR data.

The fluorescence properties of **6** and **7** in dichloromethane, as summarized in Table 1, reveal that the diagonally bridged isomer **6** is only weakly fluorescent in dichloromethane with a fluorescent quantum yield of 22%. The corresponding fluorescence lifetime was determined as 2.2 ns. These results indicate that the rate constant for the nonradiative processes is increased in comparison to laterally bridged macrocycle **7** (see Table 1).[15] Moreover, for the diagonally bridged isomer **6** a Stokes shift of 38 nm was observed, which is 10 nm larger than that of the laterally bridged macrocycle **7**, implying a more pronounced change of the geometry between the ground and the excited states of **6**. By decreasing the solvent polarity, an increase of the quantum yield was observed. Thus, **6** exhibits a fluorescence quantum yield of 73% in diethylether, accompanied by an increase of the fluorescence lifetime to 6.2 ns. In contrast to **6**, the fluorescence properties of the laterally bridged perylene bisimide **7** properly corroborate those observed for conformationally flexible open-chained, phenoxy-substituted perylene bisimides such as **4** (Φ_{fl} = 94%), as for regioisomer **7** a fluorescence quantum yield of 95% was observed in dichloromethane. It is noteworthy that the fluorescence quantum yields of the macrocycles **6** and **7** are slightly higher (by 10−15%) than those of the previously reported macrocycles bearing aryl substituents in the imide position.[15]

Stereochemical Assignment and Chiroptical Properties of Atropisomerically Pure Perylene Bisimides. The absolute configurations of the isolated epimers (**6′** and **6″**) of the

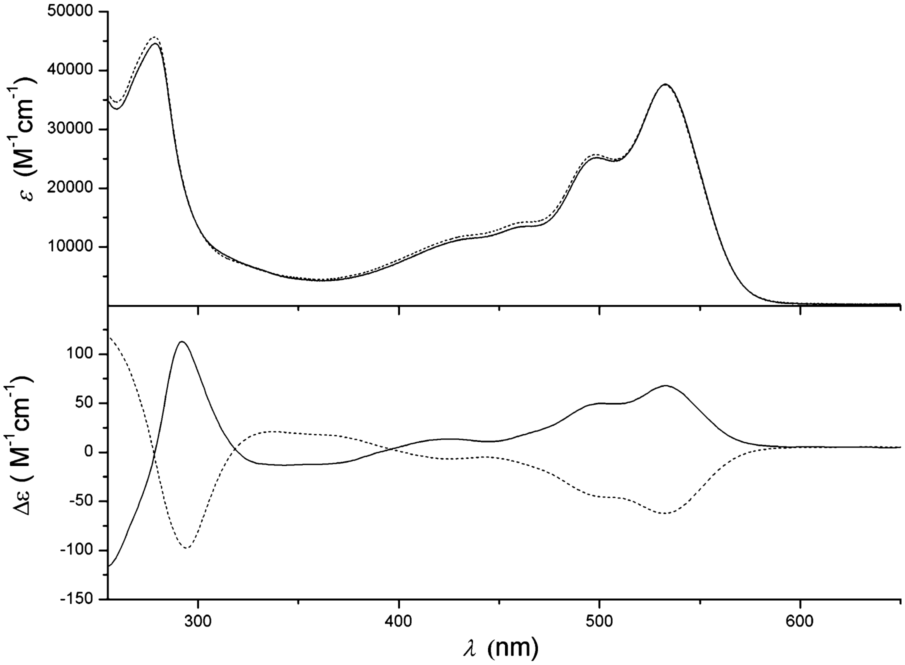


FIGURE 4. UV/vis absorption (top) and CD spectra (bottom) of the first (**6′**, solid line) and the second eluted (**6″**, dotted line) epimers of **6** in dichloromethane at 20 °C.

macrocyclic perylene bisimide **6** were determined by CD spectroscopy in combination with quantum chemical calculations. For this purpose, the chiroptical properties of these epimers were explored beforehand.

The CD spectra of the isolated epimers **6′** and **6″** show a clear mirror image relation as depicted in Figure 4 (bottom). In the visible region (400−650 nm) of the CD spectra a broad monosignated peak with a maximum at 536 nm can be seen, which properly correlates with the absorption maximum at 532 nm (Figure 4, top). The absolute $\Delta\epsilon$ values for the longest wavelength transition (536 nm) of the two epimers of **6** are +67 (**6′**) and −63 M^{-1} cm^{-1} (**6″**), giving an absorption dissymmetry factor $g = \Delta\epsilon/\epsilon$ of 0.0018. This is in accordance with the values observed for related chiral twisted π-systems, e.g., hypericin derivatives, which in their 1,6-dioxo form show a *g*-factor of 0.0014 for the longest wavelength transition.[17] Moreover, in the visible part of the CD spectra (400−650 nm) of the epimers, two optical transitions are located, i.e., the S_0−S_1 (536 and 495 nm) and the S_0−S_2 transitions (450 nm), whose transition dipole moments are polarized along the long and the short axes of the perylene bisimide, respectively. Since these transitions can be attributed to the whole chromophore, the monosignated CD signal represents the chirality of the whole molecule. These observations are characteristic for molecular chirality and differ from those arising from excitonic coupling.[18]

On the other hand, for the naphthalene-related optical transitions in the UV region (250−400 nm) of the CD spectra, an asymmetric bisignated signal was observed, with a positive first Cotton effect and a negative second one for the first eluted epimer **6′** and vice versa for the second eluted diastereomer **6″**. In both cases the peak maxima of the first Cotton effects are located at 292 nm ($\Delta\epsilon$ values are +113 and −100) and those of the second ones are found at about 250 nm with a crossover point at 276 nm. This zero transition corresponds very well to the maximum at 278 nm observed in the UV/vis absorption spectra (Figure 4, top). The observation of an exciton couplet at about 280 nm can be attributed to the excitonic interaction of the two twisted naphthalene imide units of the perylene bisimide core (phenoxy residues absorb at lower wavelengths). Therefore, the exciton chirality method[18] was applied for a first tentative assignment of the absolute configurations of the epimers of **6**. Since the first eluted stereoisomer **6′** shows a first positive Cotton effect (at 278 nm), it should be (*P*)-configured and, accordingly, the second eluted epimer **6″** should have the (*M*)-configuration, leading to the full absolute stereostructure of (*P*,*R*,*R*) for **6′** and of (*M*,*R*,*R*) for **6″**. Since both imide substituents of **6** are (*R*)-configured, the absolute configuration of the first eluted epimer, **6′**, can be assigned as (*P*,*R*,*R*) and that of the second one **6″** as (*M*,*R*,*R*). The mirror-image relation of the two CD spectra indicates the pseudo-enantiomeric character of these diastereomers, i.e., the chiral alkyl substituents do not contribute to the optical activity in the visible wavelength range. Additionally, the optical rotation values $[\alpha]^{20}_{D}$ for (*P*,*R*,*R*)-**6** and (*M*,*R*,*R*)-**6** were determined at 20 °C in dichloromethane to be +6600 ($c = 0.007$) and −6600 ($c = 0.006$), respectively. Optical rotations of such large sizes had been previously observed only for twisted π-systems such as helicenes.[8i] However, in our case a pronounced dispersion enhancement is present, since the detection wavelength ($\lambda = 589$ nm) is close to the absorption maximum of **6**. The identical absolute values of the optical rotations, yet with opposite signs, confirm the pseudo-enantiomeric behavior of these perylene bisimide dyes. Such a pseudo-enantiomeric behavior had been previously demonstrated for related hypericin derivatives, for which the observed chirality emanates from the inherently chiral chromophore.[17]

As mentioned above, the absolute configurations of the epimers of **6** can be tentatively attributed by applying the exciton chirality method. For a more reliable configurational assignment

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of the epimers, quantum chemical calculations of the CD spectra were performed, with subsequent comparison of the simulated spectra with the measured ones.[19]

In a first step, the conformational space of (*P*,*R*,*R*)-**6** was investigated by means of PM3,[20] resulting in 24 minimum geometries within an energy range of 3 kcal/mol.[21] For each single geometry thus obtained, a CD spectrum was calculated using the semiempirical OM2[22] Hamiltonian. These individual spectra were then added up weighted following the Boltzmann statistics, i.e., according to the corresponding heats of formation, to give the overall simulated CD curve, which was then UV-corrected.[23] Comparison with the experimental CD spectrum of the fast eluted epimer **6′** revealed an acceptable agreement for (*P*,*R*,*R*)-**6** and a reversed behavior for (*M*,*S*,*S*)-**6** (Figure 5a),[24] suggesting that the first eluted epimer is (*P*)-configured, and consequently, the second eluted one, **6″**, is (*M*).

In order to confirm these stereochemical assignments and in view of the molecular flexibility of **6**, further CD calculations for (*P*,*R*,*R*)-**6** were performed, now based on a molecular dynamics (MD) simulation using the TRIPOS[25] force field at a virtual temperature of 800 K. For the geometries extracted from the trajectory of motion, single CD spectra were computed again by means of OM2.[21] Subsequent summation of these curves and UV correction[23] delivered the overall simulated CD spectrum, which now corresponded very well with the experimental spectrum of the first eluted epimer, **6′**, while the spectrum predicted for (*M*,*S*,*S*)-**6** was found to be perfectly opposite (Figure 5b). Consequently, the first eluted epimer is unambiguously confirmed to have the (*P*)-configuration, whereas the second one is (*M*)-configured.

Conformational Properties of Perylene Bisimides 4, 6, and 7. In contrast to the diagonally bridged regioisomer **6**, an interconversion of the epimers (*P*,*R*,*R* and *M*,*R*,*R*) of the laterally bridged regioisomer **7** and of the chiral, non-macrocyclic PBI **4** is possible. To gain insight into the equilibrium process ($M \rightleftarrows P$) for the given pseudo-enantiomeric PBIs, **4** and **7**, and to assess whether any additional dynamic processes are involved, temperature-dependent ^{1}H NMR spectroscopic studies were performed for the open-chained tetraphenoxy-substituted PBI **4** and for the macrocycles **6** and **7**. Figure 6 shows the resonances for the perylene core protons in temperature-dependent ^{1}H NMR spectra of **4** and **6**.

The perylene core protons were chosen to monitor the atropisomeric interconversion, which in this case is not a racemization but an epimerization, since the atropisomeric PBIs **4**, **6**, and **7** contain two (*R*)-configured substituents. The process was investigated upon cooling to a temperature at which the epimerization occurs in the same time scale as the proton spin relaxation (NMR time scale). At even lower temperatures, where the spin relaxation is faster than the epimerization process, two sets of signals are expected due to the presence of two epimers (*P*,*R*,*R* and *M*,*R*,*R*). However, as can be seen from Figure 6b (middle), eight signals are observed for the epimeric mixture of **6** at low temperature (213 K). At 295 K, these signals merge into a singlet, again indicating the pseudo-enantiomeric character of the diastereomers. Since for the pure epimer (*M*,*R*,*R*)-**6** (Figure 6b, bottom) only four signals are observed at low temperature (213 K), the eight signals that appear in the respective low-temperature ^{1}H NMR spectrum of **6** can be unambiguously assigned to the two respective epimers. The occurrence of four signals for each epimer, instead of the expected one singlet, can be explained either by a self-dimerization[26] or by an intramolecular dynamic process that is frozen on the NMR time scale at lower temperature. Since both π-faces of the perylene core in **6** are surrounded and thus shielded by the bridging units, a dimerization of this PBI derivative through $\pi-\pi$ interactions is not feasible. Thus, the

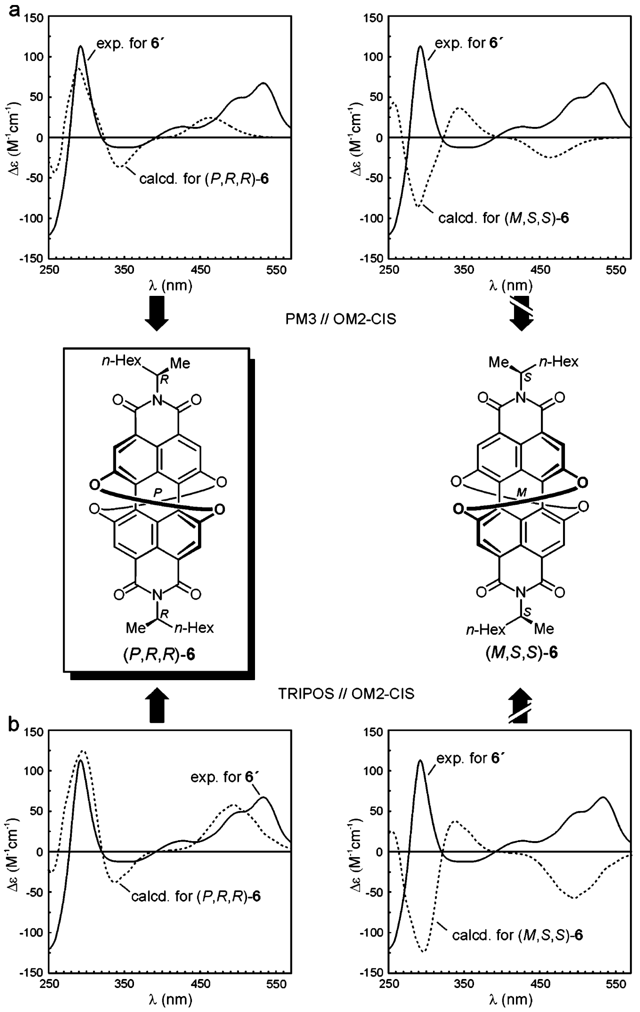

FIGURE 5. Assignment of the absolute configuration of the first eluted epimer of **6** by comparison of its experimental CD curve (solid lines) with the spectra calculated for (*P*,*R*,*R*)-**6** and (*M*,*S*,*S*)-**6**[24] using (a) the PM3-Boltzmann approach and (b) the TRIPOS-MD method, followed in both cases by OM2-CIS-CD calculations (dotted lines).

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[19] (a) Bringmann, G.; Gulder, T.; Reichert, M.; Meyer, F. *Org. Lett.* **2006**, *8*, 1037−1040. (b) Bringmann, G.; Mühlbacher, J.; Reichert, M.; Dreyer, M.; Kolz, J.; Speicher, A. *J. Am. Chem. Soc.* **2004**, *126*, 9283−9290. (c) Muranaka, A.; Asano, Y.; Tsuda, A.; Osuka, A.; Kobayashi, N. *ChemPhysChem* **2006**, *7*, 1235−1240.

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[21] The contribution of the CD spectra of those structures that lie energetically higher than 3 kcal/mol above the found global minimum to the overall CD curve is negligible.

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[23] Bringmann, G.; Busemann, S. In *Natural Product Analysis*; Schreier, P., Herderich, M., Humpf, H. U., Schwab, W., Eds.; Vieweg: Wiesbaden, 1998; pp 195−212.

[24] Given the extreme dominance of the chiroptical contributions of the chiral axis vs the two stereogenic centers, as proven by the inverse experimental CD spectra of the two epimers of **6** (Figure 4), additional calculations for (*M*,*R*,*R*)-**6** appeared unnecessary.

[25] *SYBYL*; Tripos, Inc.: 1699 South Hanley Road, St. Louis, MO 63144, U.S.A.

[26] Chen, Z.; Baumeister, U.; Tschierske, C.; Würthner, F. *Chem. Eur. J.* **2007**, *13*, 450−465.

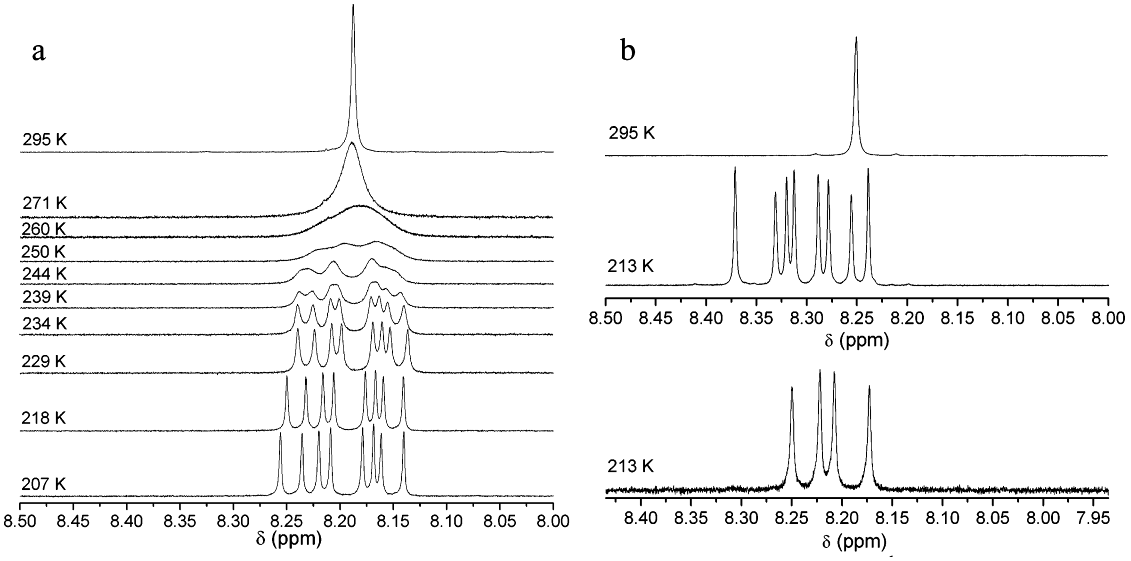

FIGURE 6. (a) Sections of the temperature-dependent (295−207 K) ^{1}H NMR (600.13 MHz) spectra of phenoxy-substituted PBI **4** in $CDCl_3$ and (b) sections of the ^{1}H NMR spectra (500.13 MHz) of diagonally bridged PBI **6** at 295 K (top) and 213 K (middle) in $CDCl_3$ and of epimerically pure (*M*,*R*,*R*)-**6** in CD_2Cl_2 at 213 K (bottom). Only the resonances of the perylene core protons (H2, H5, H8, and H11) are shown.

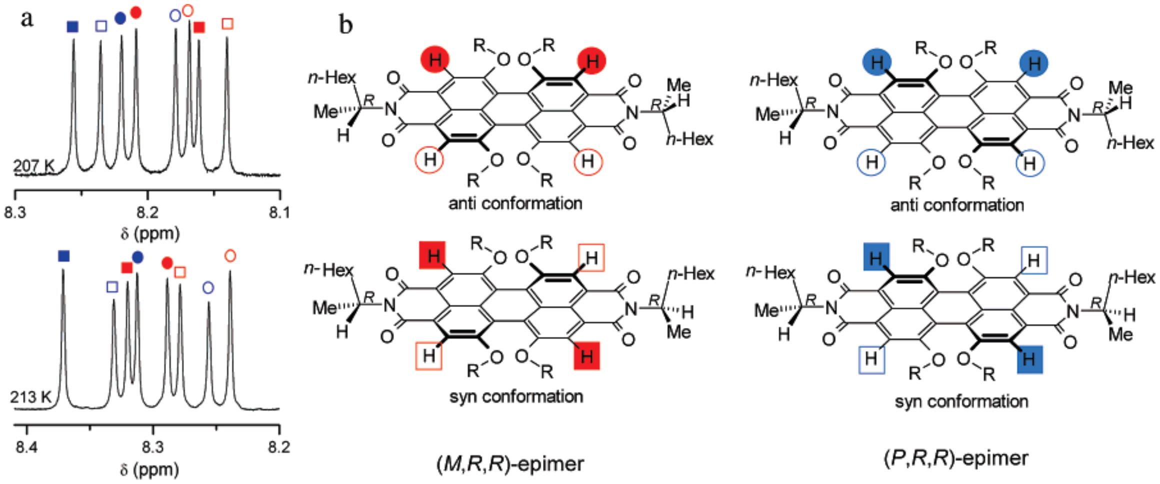

FIGURE 7. (a) Assignment of the NMR signal pattern of **4** (top) and of **6** (bottom) at low temperature and (b) anti (top) and syn (bottom) conformations of the (*M*,*R*,*R*)- and (*P*,*R*,*R*)-epimers. The blue symbols represent the resonances of the perylene core protons of the (*P*,*R*,*R*)-epimer and the red ones represent those of (*M*,*R*,*R*) (for **4**, the assignment is analogous to **6**). The circles and squares symbolize the resonances of two rotamers (tentatively assigned), and the filled and empty symbols denote the chemically equivalent core protons.

appearance of eight signals for **6** at 213 K can be ascribed to an intramolecular dynamic process. The observed four signals most probably result from a hindered rotation about the imide C−N bond, because rotational barriers for C−N bonds of structurally similar compounds were reported to be about 51 kJ/mol at 228 K.[27]

For a hindered rotation about the C−N bonds of the perylene bisimides **4** and **6**, the preferred conformations at low temperatures are syn and anti, as shown in Figure 7b.[28] Such conformational features have been reported by Shimizu et al. for unsubstituted perylene bisimide derivatives bearing aryl substituents in the imide positions.[28d] In both conformations only a C_2 axis remains as a symmetry element, resulting in two singlets for the perylene core protons for each of the two rotamers, syn and anti, Figure 7b. Therefore, the observed four signals for each epimer of **6** can be ascribed to the presence of both rotamers at low temperature. The signal pattern for the rotamers and epimers of **6** are marked in Figure 7a (bottom). The two singlets of one rotamer (marked with red or blue circles) are separated by 24 Hz, whereas for the other rotamer (red or blue squares) a lower distance of 21 Hz was found. Therefore, the signal pattern observed in the ^{1}H NMR spectrum of **6** at low temperature (213 K) is due to the presence of two epimers, whose signals are further split into four signals owing to the presence of syn and anti rotamers.

The temperature-dependent spectral changes for the phenoxy-substituted non-macrocyclic PBI **4** are shown in Figure 6a. Upon

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[28] (a) Degenhardt, C. F., III; Lavin, J. M.; Smith, M. D.; Shimizu, K. D. *Org. Lett.* **2005**, *7*, 4079−4081. (b) Degenhardt, C. F., III; Smith, M. D.; Shimizu, K. D. *Org. Lett.* **2002**, *4*, 723−726. (c) Degenhardt, C. F., III; Shortell, D. B.; Adams, R. D.; Shimizu, K. D. *Chem. Commun.* **2000**, 929−930. (d) Shimizu, K. D.; Dewey, T. M.; Rebek, Jr., J. *J. Am. Chem. Soc.* **1994**, *116*, 5145−5149.

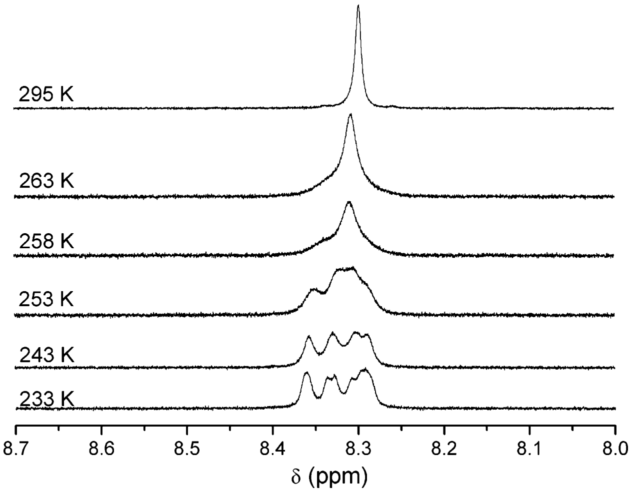

FIGURE 8. Sections of the temperature-dependent ^{1}H NMR spectra of **7** (500.13 MHz) in $CDCl_3$. Only the resonances of the perylene core protons are shown.

cooling, the singlet observed for the perylene core protons at room temperature (295 K) gets broadened and at temperatures below 230 K it splits into eight signals, as in the case of **6**. Therefore, the signal pattern of **4** at low temperatures can again be ascribed to the presence of two epimers combined with the occurrence of two rotamers each as in the case of **6** (Figure 7a). In the signal pattern, two corresponding singlets for each rotamer are found that are separated by 24 and 12 Hz, and the chemical shift of each rotamer results from the mean value of these two singlets. The chemical shifts of the epimers can be assessed as the center of the calculated chemical shift of the two respective rotamers (Figure 7) and are located at 8.22 and 8.17 ppm. Thus, the difference $\Delta\upsilon$ in chemical shift of the epimers, which is necessary for the calculation of $\Delta G^{\ddagger}$, was determined as 31.7 Hz (0.0528 ppm at 600 MHz). The coalescence temperature for the epimerization process was estimated to be 255 K from the line broadening. By using the coalescence method,[29] the barrier for the epimerization of **4** was estimated to be 53 ± 3 kJ/mol. Additionally, based on the resonances of the methoxy groups of **4** at 3.5 ppm (not shown in spectra), the coalescence temperature was determined as 244 K, and with a $\Delta\upsilon$ value of 7.7 Hz an epimerization barrier of 54 ± 3 kJ/mol was found.

Figure 8 displays the temperature-dependent ^{1}H NMR spectral changes for the core protons of the laterally bridged macrocycle **7** in $CDCl_3$. Similar changes for the resonances of the perylene core protons as in the case of **4** are observed upon cooling to 233 K, although eight individual signals could not be clearly seen for **7**, because upon cooling below 233 K further broadening of the signals occurred, which might be ascribed to an additional dynamic process. In this case, the coalescence temperature was estimated to be 256 K. Thus, compound **7** may have a similar activation barrier as **4**, although absolute values cannot be given because the low-temperature spectra are not properly resolved. The results of the temperature-dependent NMR studies reveal that the barrier for the $M \rightleftarrows P$ racemization in **4** and **7** is not significantly influenced by the presence of a diethylene glycol linker, while the chiral centers in the imide positions of perylene bisimide do not affect the dynamics of these dyes. Furthermore, the epimers are present in equal amounts as the integrated intensities of their NMR signals are identical, implying that the chiral substituents do not have any effect on the stability of (*P*)- and (*M*)-atropo-diastereomers.

Conclusion

Our results have shown that pure stereoisomers of perylene bisimides with a (*P*) or (*M*) helically twisted perylene core can be isolated if the interconversion process ($M \rightleftarrows P$) is prevented by appropriate bridging of the substituents in the 1,7- and 6,12-positions as demonstrated here for PBI **6**. Since the racemization process for non-macrocyclic 1,6,7,12-tetraphenoxy-substituted PBIs is fairly fast at ambient temperature, owing to an activation energy of only about 54 kJ/mol (as estimated for open-chained PBI **4** and laterally bridged macrocyclic PBI **7**), diagonal bridging through macrocyclization has been the method of choice for the synthesis of atropisomerically pure perylene bisimides. The availability of chiral, conformationally stable perylene bisimide dyes could expand the possible application of this very important class of fluorophores to enantioselective recognition and other processes requiring chiral information.

Experimental Section

Synthesis and Characterization of Macrocyclic Perylene Bisimides.

***N,N′*-Di(*n*-butyl)-1,6,7,12-tetra(3-methoxyphenoxy)perylene-3,4:9,10-tetracarboxylic Acid Bisimide (2).** *N,N′*-Di(*n*-butyl)-1,6,7,12-tetrachloroperylene-3,4:9,10-tetracarboxylic acid bisimide (**1**)[16] (2.50 g, 3.90 mmol), 3-methoxyphenol (2.42 g, 19.5 mmol), and dry potassium carbonate (1.35 g, 9.76 mmol) were suspended under argon in 35 mL of NMP and heated for 42 h at 120 °C. After being cooled to room temperature, the reaction mixture was added dropwise to 150 mL of 0.66 M hydrochloric acid and stirred for additional 2 h. The resulting precipitate was collected by filtration and dried in vacuo. The crude product was chromatographed on silica gel with dichloromethane/*n*-pentane (3/2) as the eluent, dissolved in dichloromethane, precipitated by addition of methanol, and dried in vacuo (10^{-3} mbar) at 60 °C to afford 1.40 g (1.41 mmol, 36%) of **2** as a red solid: mp 309−311 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.20 (s, 4H), 7.17 (t, $J = 8.2$ Hz, 4H), 6.68 (ddd, $J = 8.3$, $J = 2.4$, and $J = 0.9$ Hz, 4H), 6.56 (ddd, $J = 8.1$, $J = 2.3$, and $J = 0.8$ Hz, 4H), 6.50 (t, $J = 2.3$ Hz, 4H), 4.12 (t, $J = 7.5$ Hz, 4H), 3.67 (s, 12H), 1.65 (m, 4H), 1.38 (m, 4H), 0.94 (t, $J = 7.4$ Hz, 6H). MS (FAB, 3-nitrophenyloctylether) *m/z*: 990.3 $[M]^+$ (calcd 990.3). Anal. Calcd for $C_{60}H_{50}N_2O_{12}$: C, 72.72; H, 5.09; N, 2.83. Found: C, 72.32; H, 5.17; N, 2.75. UV/vis (CH_2Cl_2): λ_{max}/nm (ϵ_{max}/$M^{-1}cm^{-1}$) = 573 (43500), 536 (27600), 450 (16200), 289 (55900). Fluorescence (CH_2Cl_2): $\lambda_{max} = 599$ nm, fluorescence quantum yield $\Phi_{fl} = 0.89$.

1,6,7,12-Tetra(3-methoxyphenoxy)perylene-3,4:9,10-tetracarboxylic Acid Bisanhydride (3). Perylene bisimide **2** (500 mg, 0.50 mmol) and potassium hydroxide (3.00 g, 53.5 mmol) were suspended under argon in 25 mL of isopropanol and heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was dropped into 90 mL of glacial acetic acid and heated to 50 °C for 30 min. The resulting red precipitate was collected by filtration, washed with water (100 mL), and dried in vacuo (10^{-3} mbar) at 60 °C to give 396 mg (0.45 mmol) **3** in 90% yield. The product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.20 (s, 4H), 7.20 (t, $J = 8.2$ Hz, 4H), 6.73 (ddd, $J = 8.4$, $J = 2.4$, and $J = 0.8$ Hz, 4H), 6.57 (ddd, $J = 8.1$, $J = 2.3$, and $J = 0.9$ Hz, 4H), 6.49 (t, $J = 2.3$ Hz, 4H), 3.68 (s, 12H). MS (FAB, 3-nitrobenzylalcohol) *m/z*: 880.1 $[M + H]^+$ (calcd 879.2). Anal. Calcd for $C_{52}H_{32}0_{14}$: C, 70.91; H, 3.66. Found: C, 70.44; H, 4.09.

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***N,N′*-Di(2-(*R*)-octyl)-1,6,7,12-tetra(3-methoxyphenoxy)perylene-3,4:9,10-tetracarboxylic Acid Bisimide (4).** Perylene bisanhydride **3** (0.90 g, 1.02 mmol), 2-(*R*)-octylamine (0.69 mL, 0.53 g, 4.09 mmol), and catalyic amounts of zinc acetate were dissolved under argon in 25 mL of quinoline and heated for 8 h at 180 °C. The reaction mixture was cooled to ambient conditions and slowly dropped into 50 mL of 0.4 M hydrochloric acid. After addition of 30 mL of methanol, the resulting precipitate was collected by vacuum filtration and dried in vacuo. Purification by silica gel column chromatography with dichloromethane/*n*-hexane (4/1), precipitation with methanol from dichloromethane solution, and drying in vacuo (10^{-3} mbar) at 60 °C afforded 660 mg (0.60 mmol, 58%) of **4** as a red solid: mp 279−281 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.18 (s, 4H), 7.17 (t, $J = 8.2$ Hz, 4H), 6.67 (ddd, $J = 8.3$, $J = 2.5$, and $J = 0.8$ Hz, 4H), 6.57 (ddd, $J = 8.1$, $J = 2.3$, and $J = 0.9$ Hz, 4H), 6.50 (t, $J = 2.4$ Hz, 4H), 5.18 (m, 2H), 3.67 (s, 12H), 2.11 (m, 2H), 1.82 (m, 2H), 1.49 (d, $J = 6.8$ Hz, 6H), 1.23 (m, 16H), 0.82 (t, $J = 7.0$ Hz, 6H). MS (MALDI-TOF, DCTB) *m/z*: 1102.5 $[M]^+$ (calcd 1102.5). Anal. Calcd for $C_{68}H_{66}N_2O_{12}$: C, 74.03; H, 6.03; N, 2.54. Found: C, 73.99; H, 6.06; N, 2.50. UV/vis (CH_2Cl_2): λ_{max}/nm (ϵ_{max}/M^{-1}cm^{-1}) = 568 (45100), 530 (28500), 445 (16500), 285 (57100). Fluorescence (CH_2Cl_2): $\lambda_{max} = 603$ nm, fluorescence quantum yield $\Phi_{fl} = 0.94$.

***N,N′*-Di(2-(*R*)-octyl)-1,6,7,12-tetra(3-hydroxyphenoxy)perylene-3,4:9,10-tetracarboxylic Acid Bisimide (5).** Perylene bisimide **4** (0.60 g, 0.54 mmol) was dissolved in 20 mL of dry dichloromethane and cooled to 0 °C. Over a period of 30 min a solution of 0.83 mL (2.18 g, 8.70 mmol) of boron tribromide in 40 mL of dry dichloromethane was added dropwise and stirred at 0 °C for 1 h and for an additional 3 h at room temperature. The solvent was removed by distillation, and a mixture of water (48 mL) and methanol (12 mL) was added to the residue under ice cooling and treated for 30 min in a ultrasonic bath. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo. Column chromatographic purification on silica gel with dichloromethane/methanol (97/3) yielded 314 mg (0.30 mmol, 56%) of **5** as a wine-red solid: mp 311−315 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.68 (s, 4H), 7.88 (s, 4H), 7.16 (t, $J = 8.0$ Hz, 4H), 6.62 (ddd, $J = 8.2$, $J = 2.1$, and $J = 0.8$ Hz, 4H), 6.60−6.42 (m, 8H), 5.03 (m, 2H), 2.03 (m, 2H), 1.73 (m, 2H), 1.40 (d, $J = 7.0$ Hz, 6H), 1.16 (m, 16H), 0.77 (t, $J = 6.9$ Hz, 6H). MS (MALDI-TOF, DCTB) *m/z*: 1046.3 $[M]^+$ (calcd 1046.4). Anal. Calcd for $C_{64}H_{58}N_2O_{12}$: C, 73.41; H, 5.36; N, 2.68. Found: C, 72.76; H, 5.58; N, 2.52.

Macrocyclic Perylene Bisimides 6 and 7. Perylene bisimide **5** (300 mg, 0.29 mmol), diethylene glycol ditosylate (712 mg, 1.72 mmol), and cesium carbonate (1.23 g, 3.44 mmol) were suspended under argon in 45 mL of dry DMSO and heated for 6 h at 120 °C. The reaction mixture was cooled to room temperature and dropped slowly into 75 mL of 0.33 M hydrochloric acid under stirring. The resulting precipitate was collected by vacuum filtration and dried in vacuo. The two regioisomeric macrocycles formed in the reaction were separated by column chromatography with dichloromethane as the eluent, and each of the fractions was subjected to an additional column chromatographic purification with dichloromethane as eluent to yield 15.1 mg (12.7 μmol, 4%) of **6** as orange crystals and 106 mg (0.09 mmol, 30%) of **7** as red solid.

Data for 6: mp 249−251 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 4H), 7.25 (m, 4H), 7.15 (m 4H), 6.42 (m, 4H), 5.58 (m, 4H), 5.21 (m, 2H), 3.84−3.76 (m, 4H), 3.67−3.58 (m, 8H), 3.56−3.49 (m, 4H), 2.23−2.11 (m, 2H), 1.91−1.79 (m, 2H), 1.54 (m, 6H), 1.37−1.18 (m, 16H), 0.83 (m, 6H). HRMS (ESI, dichloromethane/acetonitrile = 1:1): *m/z* calcd for $C_{72}H_{70}N_2O_{14}Na$ $[M + Na]^+$ 1209.4719, found 1209.4713 $[M + Na]^+$. UV/vis (CH_2Cl_2): λ_{max}/nm (ϵ_{max}/M^{-1}cm^{-1}) 532 (37600), 498 (25600), 460 (sh), 438 (sh), 279 (45600). Fluorescence: (CH_2Cl_2) $\lambda_{max} = 570$ nm, fluorescence quantum yield $\Phi_{fl} = 0.22$, fluorescence lifetime $\tau_{fl} = 2.2$ ns; (Et_2O) $\lambda_{max} = 560$ nm, fluorescence quantum yield $\Phi_{fl} = 0.73$, fluorescence lifetime $\tau_{fl} = 6.2$ ns.

Data for 7: mp 317−320 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.29 (s, 4H), 7.07 (t, $J = 8.2$ Hz, 4H), 6.68 (t, $J = 2.3$ Hz, 4H), 6.59 (dd, $J = 8.2$, and $J = 1.9$ Hz, 4H), 6.54 (dd, $J = 8.2$, $J = 1.7$ Hz, 4H), 5.19 (m, 2H), 4.20 (bs, 8H), 4.00−3.70 (m, 8H), 2.20−2.05 (m, 2H), 1.90−1.70 (m, 2H), 1.50 (d, $J = 6.8$ Hz, 6H), 1.35−1.15 (m, 16H), 0.82 (t, $J = 6.8$ Hz, 6H). HRMS (ESI, dichloromethane/acetonitrile = 1:1) *m/z*: calcd for $C_{72}H_{71}N_2O_{14}$ $[M + H]^+$ 1187.4900, found 1187.4876. Anal. Calcd for $C_{72}H_{70}N_2O_{14}$: C, 72.83; H, 5.94; N, 2.36. Found: C, 72.77; H, 5.94; N, 2.36. UV/vis (CH_2Cl_2): λ_{max}/nm (ϵ_{max}/M^{-1}cm^{-1}) 570 (47800), 530 (29100), 450 (16700), 286 (59600). Fluorescence (CH_2Cl_2): $\lambda_{max} = 598$ nm, fluorescence quantum yield $\Phi_{fl} = 0.95$, fluorescence lifetime $\tau_{fl} = 6.9$ ns.

Separation of Epimers (*P,R,R*)-(+)-6 and (*M,R,R*)-(−)-6. Separation of the epimers of **6** was accomplished by HPLC on a semipreparative chiral column (Trentec Reprosil 100 chiral-NR, Ø = 2 cm) with isopropanol/*n*-hexane (1/1) as eluent (flow rate 10 mL/min). Owing to the low solubility of **6** in the eluent, a dichloromethane solution of **6** was used for injection. The separation was performed on a scale of 8 mg. **(*P,R,R*)-(+)-6:** retention time (Trentec Reprosil 100 chiral-NR, Ø = 0.8 cm, isopropanol/*n*-hexane (1/1), flow 2 mL/min): 24.7 min; $[\alpha]^{20}_D$ (CH_2Cl_2, $c = 0.007$) +6600. CD (CH_2Cl_2) λ_{max}/nm ($\Delta\epsilon$/M^{-1} cm^{-1}) = 536 (67), 499 (49), 425 (13), 337 (−13), 292 (113). **(*M,R,R*)-(−)-6:** retention time (Trentec Reprosil 100 chiral-NR, Ø = 0.8 cm, isopropanol/*n*-hexane (1/1), flow 2 mL/min): 29.6 min; $[\alpha]^{20}_D$ (CH_2Cl_2, $c = 0.006$) −6600. CD (CH_2Cl_2) λ_{max}/nm ($\Delta\epsilon$/M^{-1} cm^{-1}) = 536 (−63), 499 (−45), 425 (−6), 337 (21), 292 (−97).

Acknowledgment. Financial support of our work by the Fonds der Chemischen Industrie is greatly appreciated. We thank Mrs. M.-L. Schäfer and Mrs. E. Ruckdeschel for their help in measuring temperature-dependent ^{1}H NMR spectra.

Supporting Information Available: General experimental methods and ^{1}H NMR spectra of **2**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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