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2,15-Dihydroxy-hexahelicene (HELIXOL): synthesis and use as an enantioselective fluorescent sensor

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Dedicated to Professor Henri Kagan, a pioneer in the stereochemistry of organic compounds

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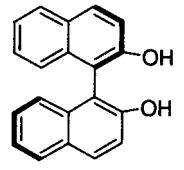
Abstract—The helical diol 2,15-dihydroxy-hexahelicene (HELIXOL) is an excellent fluorescence sensor for chiral amines and amino alcohols. The fluorescence of HELIXOL can be efficiently as well as enantioselectively quenched by the enantiomers of several chiral amines and amino alcohols. Its high fluorescence intensity and its ability to enantiodiscriminate effectively makes it potentially useful for high-throughput screening of *ee*. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

A wide variety of axially chiral 1,1′-binaphthyl-derived compounds have been prepared in enantiomerically pure form and used in many different applications,[1] BINOL (**1**)[2] and BINAP (**2**)[3] being two prominent examples. Metal complexes of **1** and **2** comprise catalysts for numerous reactions. A rather different application of **1** is its use as an enantioselective fluorescent sensor in the recognition of chiral amines,[4] although fluorescence intensity and degree of enantioselectivity are somewhat small. We are interested in the helical counterparts of **1** and **2** in the form of hexahelicene derivatives. 2,15-Dihydroxy-hexahelicene (HELIXOL; **3**) and 2,15-bis(diphenylphosphino)-hexahelicene (PHELIX; **4**)[5] are two obvious possibilities. We have already prepared **4** and used it as a ligand in Rh-catalyzed hydrogenation[5] and Pd-catalyzed allylic substitution.[6] In an independent study, Brunner et al. also described the synthesis of **4**,[7] although they did not report antipode separation or use in catalysis. We now describe the synthesis and antipode separation of HELIXOL (**3**) as well as its use as a highly efficient sensor in the enantioselective recognition of chiral amines and amino alcohols.



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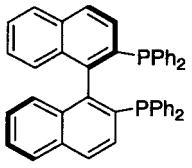

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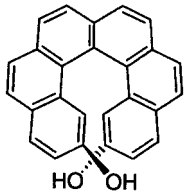

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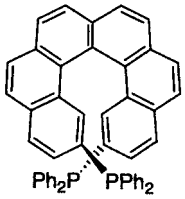

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2. Synthesis and antipode separation of HELIXOL

Although Newman first succeeded in preparing hexahelicene in 12 steps,[8] it was Martin, who in 1967 described an efficient and general strategy[9] for the preparation of the parent compound and of many different derivatives.[10] It is based on the photocyclization of appropriately substituted stilbene derivatives leading to initial photo-products which undergo I_2-promoted aromatization with formation of the hexahelicene derivatives. In our case, the synthetic route is shown in Scheme 1. Wittig reaction of the bis-ylide of the known phosphonium salt **5**[7] with dialdehyde **6**[11] affords the diene **7** which was photocyclized to compound **8**. Following antipode separation by HPLC, using a chiral stationary phase, deprotection was performed by BBr_3-promoted ether cleavage. *p*-Methoxybenzaldehyde can also be used in place of **6** leading to the O-methyl protected form of **3**.[12] However, the photocyclization step is less efficient and the antipode separation is difficult.[13a]

HELIXOL (**3**) is a light yellow crystalline compound, which was characterized by ^1H and ^{13}C NMR spectroscopy, mass

Keywords: enantioselection; fluorescence; helicenes; molecular recognition.

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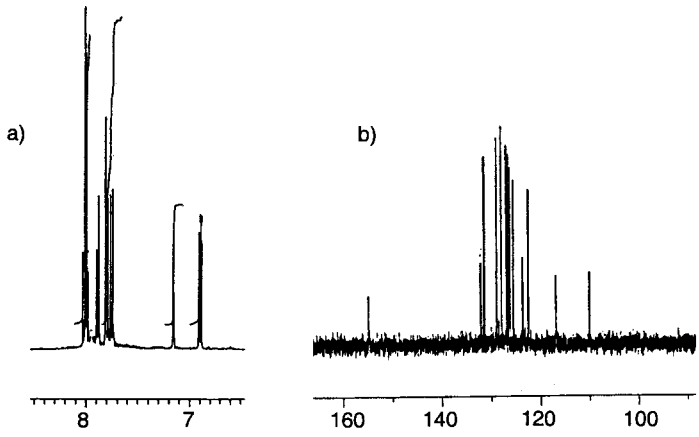
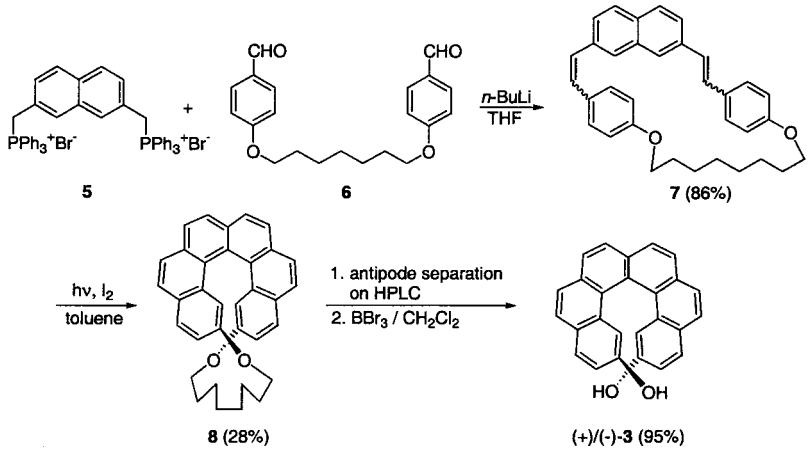


Figure 1. (a) ^{1}H NMR; (b) ^{13}C NMR spectra of HELIXOL (**3**) in d_6-acetone.



Scheme 1.

spectrometry (MS) and elemental analysis. Fig. 1 shows the two NMR spectra.

The optical rotations of (+)- and (−)-**3** were found to be $[\alpha_{589}{}^{21}]=+2530$ (*c* 0.26, CH_2Cl_2 and $[\alpha_{589}{}^{21}]=-2510$ (*c* 0.25, CH_2Cl_2), respectively. The chiroptical properties of HELIXOL in the form of the CD spectrum were also measured. Fig. 2 shows the results of this study. Presently, we do not know for certain the absolute configuration.

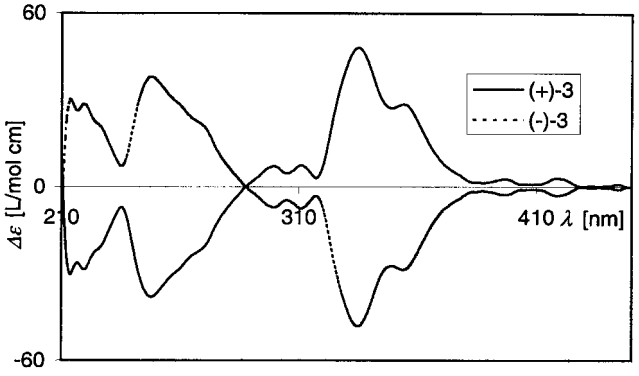


Figure 2. CD spectra of HELIXOL (**3**).

However, based on the CD spectra of **3** and other known hexahelicene derivatives, we are confident that the CD-characteristics are not influenced strongly by the substituents. We therefore conclude that the (−)-enantiomer of **3** has the *M*-configuration, whereas the (+)-enantiomer can be assigned to P-helicity.

3. Fluorescence studies

In initial experiments, we measured conventional fluorescence and phosphorescence spectra of **3** (Fig. 3). The intensity of fluorescence is dramatically higher than that of BINOL (**1**). Thus, the quantum yield of HELIXOL can be measured to be five times higher than in the case of BINOL.

We then studied fluorescence quenching by the addition of amines. By adding cyclohexylethyl amine (**9**) sequentially to **3** and measuring fluorescence, the spectra shown in Fig. 4 were obtained. In doing so, an excess of amine was used, which is normally the case in such studies.[4,14] It can be seen that the amine quenches fluorescence of **3** very efficiently.

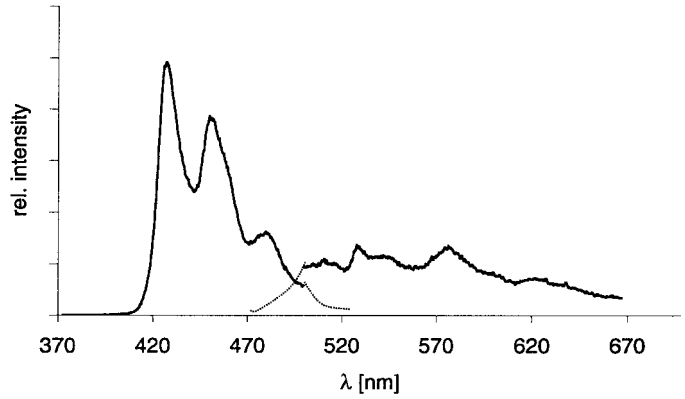


Figure 3. Fluorescence and phosphorescence emission spectra of HELIXOL (**3**).

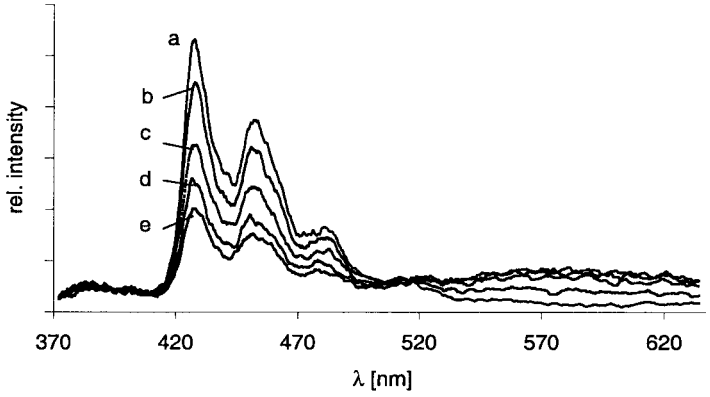
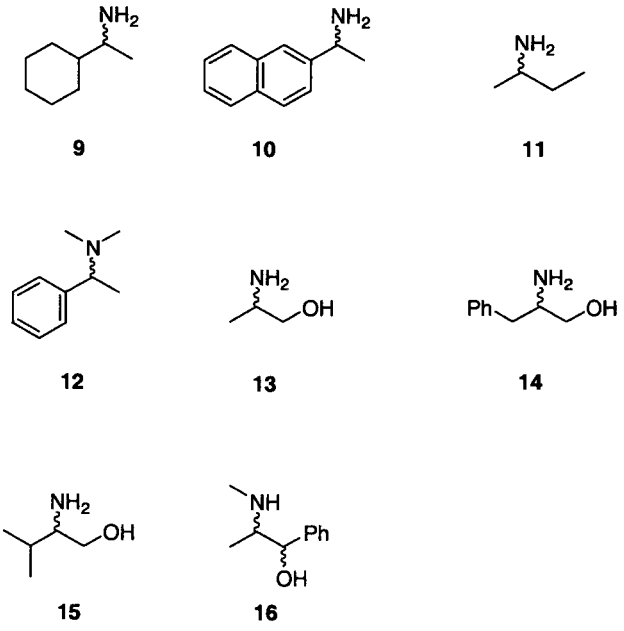


Figure 4. Fluorescence emission spectra of **3** in the presence of various concentrations of cyclohexylethylamine (**9**) (a–e: 0; 1.40; 3.67; 6.21; 8.57 mM in methylene chloride).

Following these exploratory experiments, we set out to test potential enantiodiscrimination of HELIXOL (**3**) with respect to chiral amines (*R*)/(*S*)-cyclohexylethylamine (**9**), (*R*)/(*S*)-naphthylethylamine (**10**), (*R*)/(*S*)-*sec*-butylamine (**11**), (*R*)/(*S*)-*N*,*N*-dimethylphenylethylamine (**12**) and amino alcohols (*R*)/(*S*)-2-amino-1-propanol (D/L-alaninol, **13**), (*R*)/(*S*)-2-amino-3-phenylpropanol (D/L-phenylalaninol, **14**), (*R*)/(*S*)-2-amino-3-methyl-1-butanol (D/L-valinol, **15**) and (1*R*,2*R*)-(−)/(1*S*,2*S*)-(+)-pseudoephedrin (**16**).



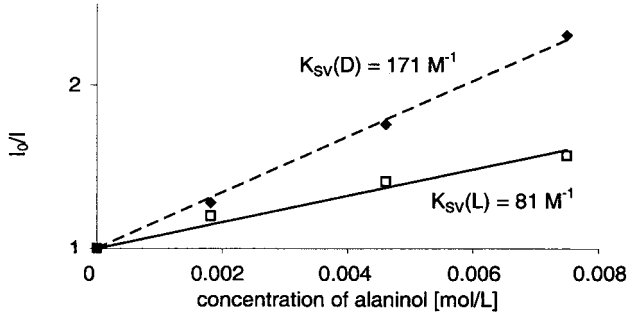


Figure 5. Comparison of the Stern–Volmer plots for quenching of (−)-HELIXOL (**3**) by (*R*)- and (*S*)-alaninol (**13**).

It was therefore necessary to obtain Stern–Volmer quenching plots of (−)-**3** in the presence of the (*R*)- and (*S*)-forms of the amines. For example, in the case of **13**, the corresponding plots are shown in Fig. 5.

Table 1. Fluorescence quenching rates of (−)-HELIXOL by various amines and amino alcohols

Amine/amino alcohol	ΔK_{SV} (M^{-1})	$K_{SV}(R)/K_{SV}(S)$
9	50	1.24
10	134	0.72
11	56	1.25
12	23	1.50
13	90	2.10
14	14	1.16
15	31	1.40
16	8	1.14

It is immediately obvious that a pronounced degree of chiral recognition is operating. The so-called Stern–Volmer constant K_{SV} amounts to 171 M^{-1} [$K_{SV}(R)$] in the presence of (+)-**3** and 81 M^{-1} [$K_{SV}(S)$] in the presence of (−)-**3**. Consequently, $[K_{SV}(R)-K_{SV}(S)]=90\ M^{-1}$ which results in the following measure of enantiodiscrimination:

$$\frac{K_{SV}(R)}{K_{SV}(S)} = 2.1.$$

When (−)-**3** was treated with mixtures of *R*- and *S*-enantiomers, the value of K_{SV} can be correlated linearly with *ee* of the amino alcohol **13**. This demonstrates the possibility to determine the *ee* of a chiral molecule using HELIXOL as a fluorescence sensor. In previous work, Mattay et al. studied the quenching of the fluorescence of BINOL (**1**) and observed a very small degree of enantioselectivity in a related case.[4a] They speculated that amines interact with BINOL (**1**) via hydrogen bonding in which the phenolic-type hydroxy moieties are involved.[4a] It is likely that in our case a similar phenomenon is operating, although it was not possible to prove such molecular recognition in the ground state by NMR studies.[13a] However, a control experiment using the O-protected form **8** showed essentially no chiral recognition. Clearly, the phenolic hydroxy moieties of **3** are intimately involved.

The fact that enantio discrimination using HELIXOL (**3**) is much more pronounced than in the case of BINOL (**1**) is not easily explained. Coupled with the intrinsic property of high intensity flourescence, our compound appears to be an ideal candidate as a sensor for chiral amines. For this reason, the rest of the chiral amino alcohols and amines were also studied. Table 1 shows that for most substrates high levels of enantioselectivity are observed. Highest enantioselectivity was observed in the case of **13**. It is interesting to note that the sense of enantiodiscrimination in the case of the naphthyl derivative **10** is opposite to that of the other compounds. The source of this effect is currently unclear.

4. Conclusion

We have prepared in optically active form and characterized the first di-hydroxy-hexahelicene. Substitution at the 2,15-positions makes HELIXOL (**3**) a particularly interesting compound. It has an unusually high fluorescent intensity. Moreover, it is capable of chiral discrimination between enantiomeric forms of amines and amino alcohols as detected by fluorescence quenching, the high degree of recognition having no precedence in the literature.[4,15] Thus, one of the potential applications of HELIXOL (**3**) is its use as an enantioselective sensor. Since the effects are so pronounced, it is conceivable that a high-throughput *ee*-screening system can be devised for use in the formation of combinatorially produced chiral transition metal catalysts and/or enantioselective enzymes created by directed evolution.[16] We are currently studying this possibility.[3b]

5. Experimental

5.1. General

$^1H/^{13}C$ NMR: Bruker AMX 300, DMX 400; TMS int. standard. MS: Finnigan MAT 8400; direct inlet (EI: 70 eV). Column chromatography: Merck Silica Gel 60. Optical rotations (CH_2Cl_2): JASCO DIP-360. CD-spectra: JASCO J-715. Fluorescence spectra: Spex Fluorolog (PDP 11/34). Elemental analyses: Mikroanalytisches Laboratorium H. Kolbe, Mülheim/Ruhr.

5.1.1. Synthesis of 5,14-dioxa-4,5(1,4)-dibenzena-1(2,7)-naphthalena-cycloheptadecaphane-2,10-diene (7).[17] To a solution of 4.22 g (5 mmol) **5** in 2 L of absolute THF is added dropwise 6.25 mL (10 mmol) of a 1.6 M *n*-butyllithium-solution in hexane resulting in a red solution. The mixture is stirred for 1 h at 0°C. Then 1.77 g (5 mmol) of dialdehyde **6** are added in one portion. The mixture is stirred overnight and hydrolyzed with 100 mL of water. The THF is removed in vacuum and the suspension is extracted three times with 100 mL toluene. After extraction, the product is isolated using a silica column (SiO_2, 15×5 cm, $CHCl_3$/hexane=2:1). Removal of the solvent leads to a mixture of the three isomers of **4** (70%). Spectroscopic data of the mixture of isomers: ^1H NMR (300.1 MHz, $CDCl_3$): δ 7.9–6.4 (m, 18H, H–Ph/H–Nap), 4.3–3.3 (m, 4H, O–CH_2–alkyl), 1.9–0.8 (m, 12H, –$(CH_2)_6$–). MS (EI, 70 eV): 474 (100, $[M]^+$), 364 (21, $[M-C_8H_{14}]^+$), 269 (5), 107 (5). Anal. calcd for $C_{34}H_{34}O_2$: C, 86.04; H, 7.22. Found: C, 85.88; H, 7.24.

5.1.2. Synthesis of 2,11-dioxa-1(2,15)-hexahelicena-cycloundecaphane 8.[17] For carrying out the photoreaction in a 1 L photoreactor (Pyrex®) equipped with a high-pressure mercury immersion lamp [Heraeus®, TQ 718], the flushed is floated with argon in order to eliminated traces of oxygen and water. For the reaction 900 mg (1.9 mmol) 5,14-dioxa-4,5(1,4)-dibenzena-1(2,7)-naphthalena-cycloheptadeca-2,10-dien (**7**) and 1.05 g (4.18 mmol) iodine are solved in 1 L of toluene. 10 mL (appr. 100 equiv.) of propylene oxide as HI scavenger are added at once. The mixture is stirred vigorously and irradiated for 6 h (700 W) while keeping the reaction chamber under slight argon pressure. Afterwards, the excess of propylene oxide is removed by bubbling argon through the solution for 15 min. The mixture is reduced to 50 mL and filtered through silica. The product is eluted with 500 mL toluene, dried with $MgSO_4$, resulting in a crude product after several hours in high vacuum. After purification using column-chromatography (SiO_2, 15×6 cm, toluene/hexane=2:1), a mixture of the helicene **8** and a side product (only one styrene

function is photocyclized) is obtained. HPLC-chromatographic separation leads to 250 mg (0.53 mmol) of pure **8** (28% yield) as light-yellow crystals (mp 280°C). ^{1}H NMR (300.1 MHz, CD_2Cl_2): δ 7.93 (d, ^3J=8.5 Hz, 2H, H-8/H-9), 7.90 (d, ^3J=8.5 Hz, 2H, H-7/H-10), 7.85 (d, ^3J=9.9 Hz, H-5/H-12), 7.82 (d, ^3J=9.7 Hz, 2H, H-6/H-11), 7.70 (d, ^3J=8.7 Hz, 2H, H-4/H-13), 7.26 (d, ^4J=2.3 Hz, 2H, H-1/H-16), 6.97 (dd, ^3J=8.7 Hz, ^4J=2.4 Hz, 2H, H-3/H-14), 3.63 (m, OCH_aH), 2.77 (m, $OCHH_b$), 1.35 (m, H-2′/H-7′), 1.18 (m, H-4′/H-5′), 0.90 (m, H-3′/H-6′). ^{13}C NMR (75.5 MHz, CD_2Cl_2): δ 156.4 (s, C-2/C-15), 132.7 (s), 131.9 (s), 127.7 (d, C-4/C-13), 126.3 (d, C-7/C-10), 126.1 (d, C-5/C-12), 125.7 (d, C-8/C-9), 125.9 (s), 125.6 (s), 123.3 (d, C-6/C-11), 117.7 (d, C-3/C-14), 112.5 (d, C-1/C-16), 68.5 (t, OCH_2), 26.7 (t), 25.8 (t), 22.5 (t). MS (EI, 70 eV): 470 (100, $[M]^+$), 360 (18, $[M-C_8H_{14}]^+$), 340 (8), 313 (12), 300 (20). Anal. calcd for $C_{34}H_{30}O_2$: C, 86.78; H, 6.43. Found: C, 86.70; H, 6.48.

5.1.3. Preparative separation of the product mixture 8 with HPLC. Analytical HPLC-system: apparatus: HP 1090; column: 125 mm Nucleosil 100-5-C_{18}/A; 2.0 mm i.d.; mobile phase acetonitrile; temperature: 313 K; velocity: 0.2 mL/min; pressure: 4.6 MPa; detection: DAD, 254 nm. Preparative HPLC-system: apparatus: Shimadzu LC-8A, Gilson M 202; column: 250 mm Dynamax Microsorb C_{18}, 21 mm i.d., L9 10052; mobile phase: acetonitrile; temperature: 313 K; velocity: 20 mL/min; pressure: 4.9 MPa; detection: UV, 320 nm, E=1.28.

5.1.4. Preparative separation of the enantiomers 8 with HPLC. Analytical HPLC-system: apparatus: Shimadzu LC-10; column: 250 mm Chiralcel OD-H; 4.6 mm i.d.; mobile phase: *n*-heptane/2-propanol=80:20; temperature: 298 K; velocity: 0.5 mL/min; pressure: 3.2 MPa; detection: UV, 254 nm. Preparative HPLC-system: apparatus: Shimadzu LC-6A/Gilson 233 XL; column: 250 mm Chiralcel OD; 20 mm i.d.; mobile phase: *n*-heptane/2-propanol=90:10; temperature: 308 K; velocity: 9.9 mL/min; pressure: 2.3 MPa; detection: UV, 254 nm, E=0.64.

5.1.5. Synthesis of 2,15-dihydroxyhexahelicene 3 (HELIXOL). A solution of 41.9 mg (0.09 mmol) 2,11-dioxa-1(2,15)-hexahelicena-cyclononane **5** in 5.0 mL of methylene chloride is treated dropwise with 0.27 mL (0.27 mmol) of a 1 M solution of BBr_3 in methylene chloride at 0°C. The mixture is stirred for 30 min at 0°C and afterwards allowed to warm up to room temperature. After stirring for additional 3 h, the mixture is hydrolyzed using a small amount of water and extracted with methylene chloride, dried over $MgSO_4$ and purified by chromatography (SiO_2, 10×1 cm, hexane/ethylacetate=3:1) yielding 30.9 mg (0.086 mmol) of the 2,15-dihydroxyhexahelicene **3** (95%) as light-yellow crystals. ^{1}H NMR (400.1 MHz, d_6-Aceton): δ 8.08 (d, ^3J=8.3 Hz, 2H, H-8/H-9), 7.99 (d, ^3J=8.2 Hz, 2H, H-7/H-10), 7.94 (s(br), 2H, OH), 7.89 (d, ^3J=8.5 Hz, 2H, H-5/H-12), 7.80 (d, ^3J=8.5 Hz, 2H, H-6/H-11), 7.75 (d, ^3J=8.6 Hz, 2H, H-4/H-13), 7.15 (d, ^4J=2.4 Hz, 2H, H-1/H-16), 6.90 (dd, ^3J=8.6 Hz, ^4J=2.4 Hz, 2H, H-3/H-14). ^{13}C NMR (75.5 MHz, d_6-Aceton): δ 155.9* (s, C-2/C-15), 133.5 (s, C-8a), 132.8 (s, C-16a/C-16c), 132.7 (s, C-6a/C-10a), 130.0 (d, C-4/C-13), 128.8 (d, C-5/C-12), 127.9 (d, C-7/C-10), 127.7 (s), 127.5 (d, C-8/C-9), 127.2 (s), 125.2 (s, C-16c), 123.7 (d, C-6/C-11), 117.5* (d, C-3/C-14), 111.3* (d, C-1/C-16). [*=Splitting in two signals with Δ ppm=0.1.] MS (EI, 70 eV): 360 (100, $[M]^+$), 340 (6), 313 (13), 300 (21), 171 (7), 150 (12). Anal. calcd for $C_{26}H_{16}O_2$: C, 86.65; H, 4.47. Found: C, 86.59; H, 4.42.

5.1.6. Procedure for the fluorescence measurements. Corrected fluorescence emission and excitation spectra were recorded on a computer-controlled Spex Fluorolog spectrofluorimeter. An RCA C31034 photomultiplier with a gallium–arsenide photocathode was used as the detector in the photon-counting mode. The wavelength dependency of the sensitivity of the detector system was corrected with reference to a calibrated tungsten lamp. In order to avoid self-absorption, the samples were diluted to an absorbance in the scale of $\leq$0.2. Therefore, 10^{-8} M stock solutions of the helicenes in methylene chloride were prepared. 2.0 mL of the helicene stock solutions were charged in a 1.0 cm norm cell and treated with amine stock solutions (about 10^{-3} M), followed each time by measuring the fluorescence emission spectra in the range 360–650 nm (excitation at the UV maxima of 318 nm). By comparing the intensities of the first two maxima in the spectra (479 and 425 nm), the degree of fluorescence quenching could be determined with high precision. The uncertainty in the determination of the Stern–Volmer constants K_{SV} amounts to $\pm$5% on the bases of multiple titrations.

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