

Chiral Discrimination in Hydrogen-Bonded [7]Helicenes

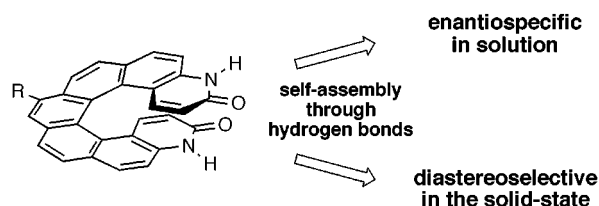
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ABSTRACT



A series of racemic [7]helicenes have been prepared and characterized both in solution and in the solid state. Despite the helicenes having the ability to self-assemble in a variety of stereochemical and topological relationships, they formed only enantiomerically pure dimers held together by two pairs of cooperative hydrogen bonds. The self-assembly process was enantiospecific in solution and diastereoselective in the crystal.

The design and synthesis of molecules that distinguish between stereoisomers can provide models to rationalize substrate–receptor selectivity, create chiral environments for asymmetric synthesis and separation, and supply building blocks for constructing supramolecular complexes having novel chemical and topological properties.¹ This last goal requires a great degree of stereocontrol and can be achieved by taking advantage of the appealing concept of autoselection where, through the interaction of molecular recognition elements, molecules sort themselves out into stereochemically pure assemblies based on their handedness.

Programming molecules to spontaneously and selectively assemble into stereochemically predictable architectures requires the consideration of two critical factors. First, the most appropriate functionality must be chosen to act as constructive recognition elements (hydrogen bonds, van der Waals' interactions, dative metal bonds, for example) and guide the self-assembly reaction along the desirable pathway. In this regard, the strength and directionality of hydrogen bonds are particularly useful. Second, undesirable assemblies

must be eliminated through the rational choice of a scaffold onto which the molecular recognition sites are fused. The twisted backbone in helicenes results in stereodiscrimination because they possess a high degree of structural integrity which minimizes conformational scrambling that would otherwise result in the possible recognition of more than one substrate stereoisomer. The high optical stability (often greater than 35 kcal mol⁻¹) of hexahelicene and larger [n]helicenes² and their use as metal ligands for enantioselective catalysis³ and as optically active crown ethers for chiral recognition⁴ is testament to this stability.

The above considerations make the combination of hydrogen bonding and helicenes ideally suited for supramolecular projects where stereocontrol is paramount.^{5,6}

In this Letter, we describe the synthesis and characterization of three novel racemic [7]helicenes **1a–c** bearing pyridinone hydrogen bond sites on the ends of the twisted

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(2) Janke, R. H.; Haufe, G.; Würthwein, E.-U.; Borkent, J. H. *J. Am. Chem. Soc.* **1996**, 118, 6031.

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(5) For a review on self-assembling helices, see: Rowan, A. E.; Nolte, R. J. M. *Angew. Chem., Int. Ed.* **1998**, 37, 63.

backbone. The self-complementary nature of these molecular recognition elements and their position on the helical scaffold allows for several possible stereochemical products of the self-assembly reaction. This reaction can follow two general pathways and generate two topologically distinct supra-molecular architectures as illustrated in Figure 1. One

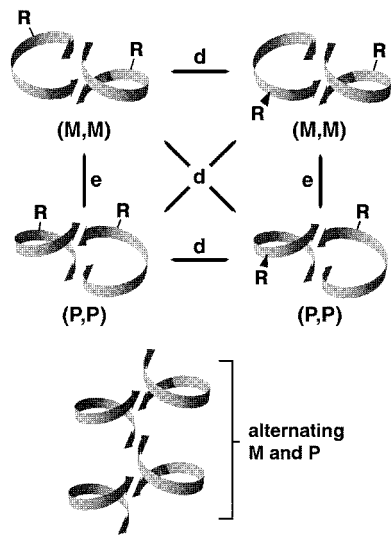
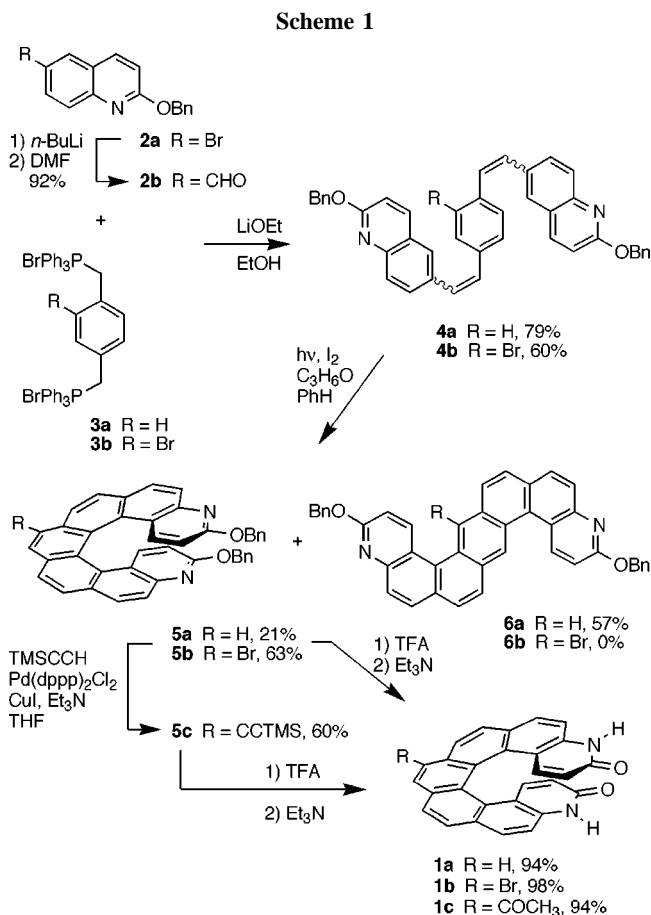


Figure 1. Schematic representations of all possible hydrogen-bonded assemblies of [7]helicenes **1b** and **1c**. Enantiomeric (e) and diastereomeric (d) relationships between the dimers are highlighted in the top set of architectures. For clarity, the positions of the side groups (R) in the stereochemically heterogeneous fiber are not shown (bottom architecture).

pathway leads to a fiber composed of alternating *M* and *P* stereoisomers as shown in the bottom of the figure.⁷ Alternatively, cooperative hydrogen bonding drives the building blocks into four stereochemically unique dimers with respect to the R-group as shown in the top of the figure. In this report we show that the self-assembly reaction takes the latter pathway both in solution and in the solid state. In

solution, helicenes **1b** and **1c** undergo a discrimination process that selects for only the dimeric topology. In the crystal, a second level of geometric discrimination occurs, resulting in only two of the four possible dimers illustrated in Figure 1.

All [7]helicenes were prepared as outlined in Scheme 1. The synthesis of parent helicene **1a** began with the conden-



sation of 2-benzoxy-6-quinolinecarboxaldehyde (**2b**)⁸ with *p*-xylenenebis(triphenylphosphonium bromide) (**3a**) to afford a mixture of *cis,cis*-, *cis,trans*-, and *trans,trans*-**4a**.⁹ Irradiation of this isomeric mixture in the presence of iodine as an oxidizing agent and propylene oxide as an HI scavenger generated the desired [7]helicene **5a** but in only minor amounts. Instead, the major product was the extended aromatic **6a**.¹⁰ Removal of the benzyl groups from **5a** with trifluoroacetic acid cleanly afforded pyridinone **1a** as a yellow solid. However, the insolubility of **1a** in all common solvents, as well as the large amounts of the undesirable *S*-isomer **6a**, forced us to pursue alternative functional [7]helicenes.

The incorporation of a bromine atom onto the central benzene ring of the [7]helicene as reported by Katz¹¹ conveniently addressed these critical issues. Here, the bromine plays two roles: (1) it minimizes the photoinduced cyclization to form structure **6** and (2) it provides a site to introduce solubilizing functional groups. Brominated

(6) For other studies that use rigid polyazaclefts, helicopodands, or bifunctional helicenes for hydrogen-bonding recognition, see: (a) Perreault, D. M.; Chen, X.; Anslyn, E. V. *Tetrahedron* **1995**, *51*, 353. (b) Huang, C.-Y.; Lynch, V.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1244. (c) Owens, L.; Thilgen, C.; Diederich, F.; Knobler, C. B. *Helv. Chim. Acta* **1993**, *76*, 2757. (d) Tanaka, K.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1998**, 1141. (e) Tanaka, K.; Shogase, Y.; Osuga, H.; Suzuke, H.; Nakanishi, W.; Nakamura, K.; Kawai, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1873. (f) Tanaka, K.; Kitahara, Y.; Suzuki, H.; Osuga, H.; Kawai, Y. *Tetrahedron Lett.* **1996**, *37*, 5925.

(7) For a description of *M* and *P* nomenclature and how it is used to describe the stereochemistry of helicenes, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 14, pp 1121, 1163–1166.

(8) The precursor to **2b** was prepared as described for the methyl ether: Osborne, A. G.; Miller, L. A. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 181.

(9) The structures of all new compounds were verified by ¹H and ¹³C NMR spectroscopy, infrared spectroscopy, and mass spectrometry.

(10) ¹H NMR of **4a** (R = H) shows a resonance peak at 9.22 ppm, characteristic of the *S*-isomer. Katz, T. J.; Sudhakar, A.; Teasley, M. F.; Gilbert, A. M.; Geiger, W. E.; Robben, M. P.; Wuensch, M.; Ward, M. D. *J. Am. Chem. Soc.* **1993**, *115*, 3182.

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[7]helicene **1b** was synthesized starting from bis(phosphonium salt) **3b** in a manner analogous to that of **1a** (Scheme 1). It was immediately found that the bromine atom greatly improved the solubility of the helicene in typical organic solvents such as chloroform, DMSO, and THF, allowing the stereodiscrimination process to be assessed in solution.

All of the signals in the ^1H NMR spectrum of **1b** in CDCl_3 were assigned on the basis of chemical shifts, coupling constants, and G-COSY experiments. These experiments allowed the broad singlet at 13.70 ppm to be unambiguously identified as that corresponding to the N–H protons. It is significant that this signal resides downfield ($\Delta\delta = 1.5$ ppm) from where it appears in the ^1H NMR spectrum in the more competitive solvent $\text{DMSO}-d_6$. This downfield shift can only be a result of the presence of strong noncovalent interactions between [7]helicenes and suggests the presence of cooperative hydrogen bonding. The significant upfield shift ($\Delta\delta = -0.97$ ppm, 6×10^{-3} M) of the signal corresponding to the N–H proton of 2-quinolinone **7**, which can be considered to represent one of the hydrogen bond surfaces in **1b**, when the solvent is changed from $\text{DMSO}-d_6$ to CDCl_3 supports the involvement of cooperative hydrogen bonds in the association of **1b**.

^1H NMR studies of **1b** in CDCl_3 and $\text{THF}-d_8$ show the N–H resonance to be concentration independent ($\Delta\delta$ is unchanging over a 10^{-4} – 10^{-1} M range). Changing to a solvent such as pyridine- d_5 that competes more effectively for hydrogen bonds shows the N–H resonance to be concentration dependent. The data from the dilution experiment correlate well with calculated curves using a dimer binding model (although, as expected, it fits equally well to a polymer binding model), giving an association constant (K_a) of 207 M^{-1} (Figure 2). This value of K_a is much higher than would be expected if the two recognition surfaces are acting independently. More importantly, the association

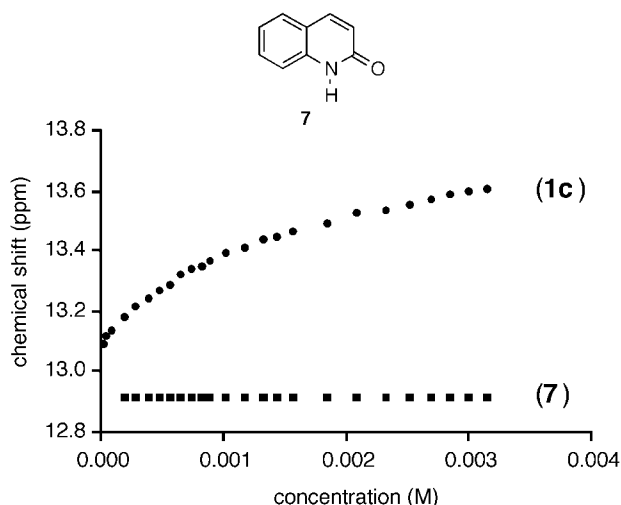


Figure 2. Concentration dependency of the chemical shift for the N–H proton in the ^1H NMR spectrum of [7]helicene **1b** and quinolinone **7** in pyridine- d_5 .

constant is also significantly higher than that calculated for the analogous dilution titration of 2-quinolinone **7** ($K_a < 1$). The position of the N–H resonance in the ^1H NMR spectrum ($\delta = 12.91$ ppm) for **7** is unchanging over a 10^{-4} – 10^{-2} M range and close to the chemical shift recorded for the most dilute solution of helicene **1b** ($\delta = 13.09$ ppm at $<10^{-5}$ M). The large discrepancy between the chemical shifts and the values of K_a for **1b** compared to **7** clearly indicates that cooperativity is the driving force for self-assembly.

These experimental observations would only result if **1b** exists as a dimer sewn together by four noncovalent bonding interactions. Molecular modeling shows that in order for **1b** to exist in this form, the building blocks within each dimer must be of the same helicity (*M* with *M* and/or *P* with *P*). This implies that there is enantiospecificity with respect to the building blocks and the possibility that the racemic fiber exists in solution can be eliminated. These observations, however, do not imply stereoselectivity, and any of the proposed dimers in Figure 1 are reasonable under these conditions.

X-ray crystallographic structure determination could not be accomplished as crystals of **1b** showed twinning, rendering this particular helicene inappropriate for investigating the stereodiscrimination in the solid state. We, therefore, focused our attention on replacing the bromine in helicene **1b** with a more utilitarian side group. Palladium- and CuI-cocatalyzed coupling of TMS-acetylene with **5b** yielded the ethynyl helicene **5c** (Scheme 1). Treatment of **5c** with trifluoroacetic acid cleanly liberated the pyridinone hydrogen bond sites and simultaneously deprotected the TMS-acetylene moiety, generating methyl ketone derivative **1c** in nearly quantitative yield.

X-ray quality single crystals of **1c** were isolated by slowly diffusing pentane into a chloroform solution of the [7]helicene. The crystal structure reveals what was already observed in the solution experiments of **1b**, analogue **1c** exists solely as a dimer (Figure 3). What is more significant is that a diastereoselective recognition process has taken place and only homochiral dimers where the R-groups exist exclusively

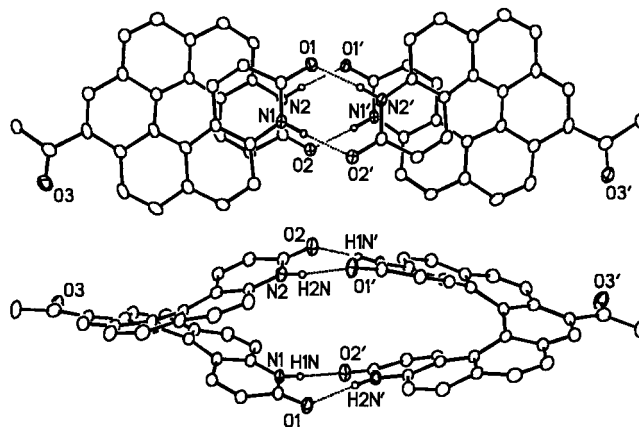


Figure 3. Two views of the X-ray diagram of one of the enantiomerically pure hydrogen-bonded dimers.

in a *cis*-relationship appear in the crystal. These enantiomerically pure dimers are held together by four strong intermolecular hydrogen bonds (N...O distance of 2.740 and 2.829 Å) between the two pyridinone residues. The dimers are similar in nature to one previously observed by Tanaka and coauthors.^{6d-f} These authors describe a bifunctional [7]helicene that contains a terminus hydroxythiophene ring and a terminus pyridine ring. The crystal structure reveals a pair of intermolecular hydrogen bonds between the hydroxy group of one helicene to the pyridine nitrogen atom of an adjacent molecule. Here, the crystals were enantiomerically pure because the starting solution was also enantiomerically pure.

The bond lengths, bond torsional angles, and intermolecular distances of **1c** closely resemble those found in crystal structures of other [7]helicenes.^{6c,12} Significant C,C-bond alternation is observed in the helicene. The outer bonds (C(9)–C(10), C(6)–C(7), C(15)–C(16), and C(18)–C(19)) are shortened to 1.340–1.352 Å while the inner bonds (C(24)–C(28) and C(28)–C(1)) are lengthened to 1.427–1.458 Å. These variations from standard aromatic bond lengths (1.39 Å for benzene) indicate that strain is localized in the inner aromatic rings. The torsional angles along the inner helical rim, which vary from 20.8(16)° for C(2)–C(1)–C(28)–C(27) to 27.9(16)° for C(25)–C(26)–C(27)–C(28), are in accordance with that observed in other heptahelicenes. The overlapping terminal rings in **1c** are separated by greater than van der Waal's half-radii of an aromatic ring on the outside of the helicene (C(22)–C(5) = 3.807(15) Å; C(20)–C(3) = 3.859(15) Å) but come into close contact on the interior of the helicene (C(23)–C(1) = 3.149(15) Å; C(24)–C(2) = 3.185(15) Å).

The packing diagram of **1c** shows that the homochiral dimers arrange into offset racemic columns where the

benzene rings of the *P* and *M* diastereomers are orientated in a face-to-face type orientation with an average distance of 3.64 Å between aromatic rings (Figure 4). The fact that

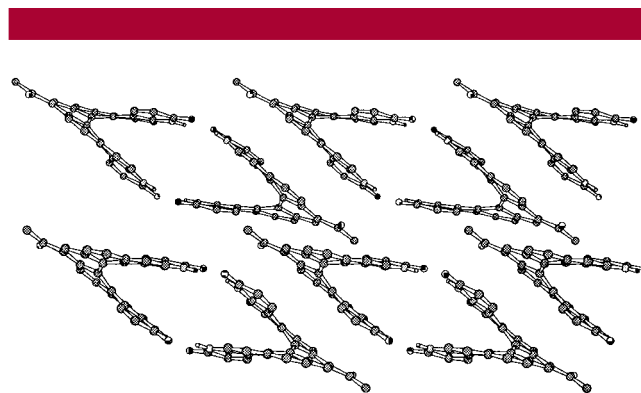


Figure 4. Packing diagram of [7]helicene **1c**.

the crystal is composed of racemic dimers reveals that the stereodiscrimination occurs at the molecular and not at the macroscopic level.

We have shown that although [7]helicene **1b** may associate into a variety of hydrogen-bonded assemblies, they initially self-assemble into dimers composed of the same helicity. These optically pure dimers then pack to form racemic columns, maximizing π -stacking interactions. Optimization, resolution, and applications in the areas of substrate selectivity and catalysis are in progress.

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Supporting Information Available: Experimental procedures for preparation of compounds **1–6** and X-ray crystallographic data for **1c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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