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Highly Diastereoselective Templated Complexation of Dipyrromethenes

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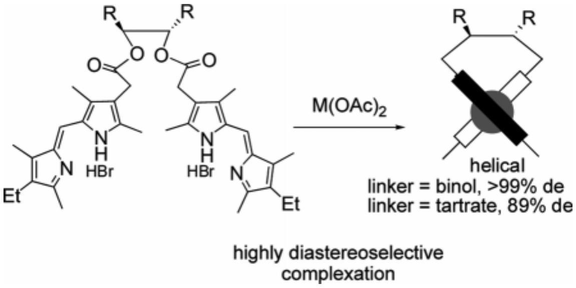
ABSTRACT



Bis(dipyrromethene)s with relatively long spacers (>5 atoms) form helical monomeric complexes as the two binding units of the bis(dipyrromethene) chelate around the same tetrahedrally coordinated metal ion. Herein we report the first highly diastereoselective mononuclear helicate-forming complexation reactions of bis(dipyrromethene)s using homochiral binol and tartrate motifs which serve as both linkers and asymmetric templates.

Dipyrromethenes (dipyrrins) give monoanionic ligands that form neutral complexes with various metal ions.[1,2] Bis(dipyrromethene)s with short linkers form helical double-stranded dinuclear complexes from the self-assembly of two bis(dipyrromethene)s and two tetrahedrally coordinated metal ions.[3−5] Conversely, bis(dipyrromethene)s with relatively long spacers (>5 atoms) form helical monomeric complexes as a result of the two binding units of the bis(dipyrromethene) chelating around the same tetrahedrally coordinated metal ion.[6] Chiral auxiliaries and templates have been reported to effect helical bias and enantioselectivity in supramolecular,[7] polymer,[8,9] and complexation chemistry.[10,11] The template directs the forming helicity by virtue of the stereochemical effects of its absolute configuration. For example, remote stereogenic centers have been shown to induce diastereoselective helix formation in bilirubins and zinc bilinones.[12−14] We have recently demonstrated the stereochemical stability of dinuclear double-helical bis(dipyrromethene)s zinc(II) complexes using novel ligands appended with homochiral amides, although the observed diastereoselectivity of complexation was very low (<10%).[15]

The first report[16] of single enantiomers of bis(dipyrromethene) complexes came from Bröring et al., who used MPLC to separate the two helicates of 2,2′-bis(dipyr-

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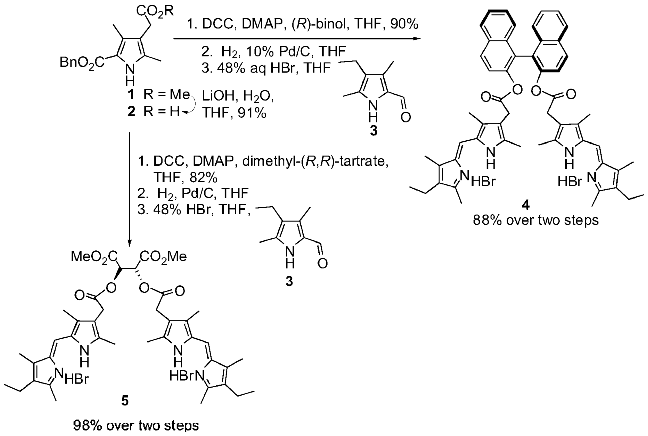
romethene) nickel(II) complexes. The resolved enantiomers showed complimentary Cotton effects in their CD spectra, and the *M* and *P* helices were thus assigned. Although dipyrromethenes bearing homochiral auxiliaries have been used to prepare optically active fluorescent dipyrromethene-BF_2 (BODIPY) dyes,[17,18] such ligands have not been used in the formation of helicates, apart from our own report.[15] Herein we report the first highly diastereoselective mononuclear helicate-forming complexation reactions of bis(dipyrromethene)s incorporating homochiral binol and tartrate motifs, which serve as both linkers and asymmetric templates.

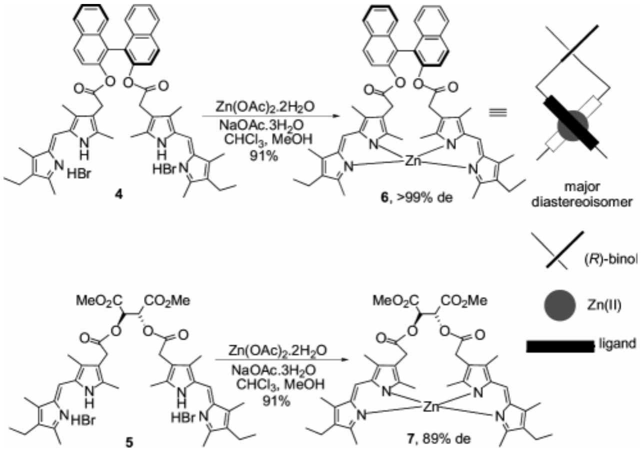
To examine the potential for diastereoselective mononuclear bis(dipyrromethene) helicate formation, bis(dipyrromethene)s containing homochiral binol[19−21] and tartrate linkers were prepared (Scheme 1). Hydrolysis of methyl ester 1,[22] followed by coupling of 2 equiv of the resultant carboxylic acid **2** with (*R*)-binol using DCC and DMAP gave the corresponding (*R*)-binol-linked bis(pyrrole). Hydrogenolysis of the benzyl esters, followed by treatment with 2 equiv of 4-ethyl-2-formyl-3,5-dimethylpyrrole (**3**) gave the required bis(dipyrromethene) **4** in 72% over four steps. Similarly, the (*R*,*R*)-tartrate-linked bis(dipyrromethene) **5** was prepared in 73% over four steps.

Scheme 1. Synthesis of **4** and **5**



Bis(dipyrromethene) hydrobromide salts **4** and **5** were reacted with an excess of zinc acetate under standard complexation conditions[15] in the presence of sodium acetate (Scheme 2). In both cases, excellent yields were obtained and the use of mass spectrometry confirmed the formation of mononuclear complexes, rather than dimers or oligomers. According to ^1H NMR spectroscopic analysis excellent diastereoselectivities were observed for the complexation reactions; only a single diastereoisomer of **6** had formed and two diastereoisomers of **7** had formed in a 9:1 ratio (determined by integration of the signals corresponding to the diastereotopic CH_2 group). These are the first examples of helical mononuclear dipyrromethene complexes formed in a stereoselective manner, and the first efficient diastereoselective dipyrromethene complexation reactions.

Scheme 2. Diastereoselective Synthesis of **6** and **7**



The two reaction mixtures containing **6** and **7** were analyzed by chiral HPLC.[23] Using a Pirkle column, Bröring has previously separated nickel(II) helicates of 2,2′-bis(dipyrromethene)s meso-substituted with aryl groups, exploiting stereocontrolled aryl−aryl interactions to enable resolution of the two helical enantiomers. The dipyrromethenes reported herein are not meso-substituted, and resolution of diastereoisomers was not observed when using a wide range[24] of Pirkle-type columns. As reported previously[15] CHIRALPAK columns give satisfactory resolution of dinuclear double-helicate bis(dipyrromethene) complexes. It was gratifying to discover that excellent resolution was observed for **6** and **7** with CHIRALPAK IA (amylose tris(3,5-dimethylphenylcarbamate) immobilized on 5 μm silica gel). Thus, the reaction mixture containing **7** showed a diastereomeric excess of 89% by chiral HPLC and that containing **6** showed only trace quantities of the minor diastereoisomer (Supporting Information), confirming our conclusions drawn from NMR spectroscopy.

Figure 1 shows the CD spectra of the ligand **4** and complex **6**. As expected, the binol moiety dominates the CD spectra in the <250 nm region, and the dipyrromethene conjugate absorbs in the 400−600 nm region. The signs of the Cotton effects at 470 and 510 nm confirm the *M* helix to be the diastereoisomer formed.[16] The CD spectrum of the mixture

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[23] Chiralpak IA column (25 × 4.6 mm^2), $CHCl_3$:MeOH (98:2), 0.5 mL/min.

[24] Whelk-O 1, ULMO, DACH, β-Gem, α-Burke 2, Pirkle 1-J, Phenylglycine, Leucine.

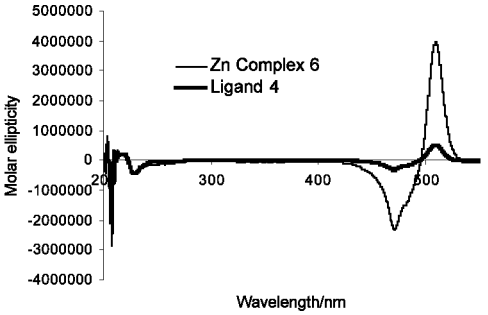

Figure 1. CD spectra for ligand **4** and zinc complex **6**.

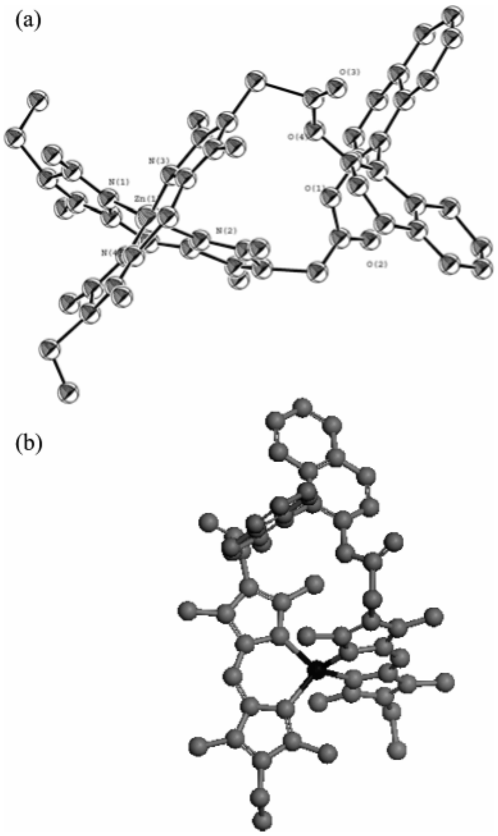

Figure 2. (a) ORTEP diagram of **6** (hydrogen atoms omitted). (b) Minimized structure of **6** (hydrogen atoms omitted).

containing **7** (89% de) shows that the *M* helix of **7** dominates, as a consequence of the (*R*,*R*)-tartrate asymmetric linker (Supporting Information). For both series, the ligands and the complexes exhibit significant molar ellipticity, with the same sense, and the values for the complexes are much greater than those for the ligands. It is assumed that the activity exhibited by the ligands arises from a preferred helical conformation as the asymmetric linkers interact with the dipyrromethene moieties; this preferred conformation is then locked in place upon complexation. The molar ellipticity determined for the essentially pure *M* helix **6** will be useful in estimating the diastereomeric excess of future mononuclear bis(dipyrromethene) complexes by analysis of CD spectra.

Further verification of the helical sense and structure of **6** was provided by an X-ray structure (Figure 2a and Supporting Information) of a crystal grown from a solution of chloroform layered with methanol. Although refinement was unsatisfactory, the absolute configuration of *R*-binol was confirmed and *M* helicity was observed for the dipyrromethene complex. Conformational analysis of the *M* and *P* helices of **6**[25] predicted the *M* helix to be 25 kJ mol^{-1} more stable than the corresponding *P* helix, supporting the observed >99% diastereoselectivity in favor of the *M* helix. The energy-minimized structure is shown in Figure 2b and reveals a distorted tetrahedral zinc(II) center, presumably necessary to accommodate planarity in both the binol and dipyrromethene conjugated systems; this is also observed in the X-ray structure.

In summary we have developed the first efficient diastereoselective complexation of dipyrromethenes, forming mononuclear bis(dipyrromethene) helicates. The asymmetry is induced by a homochiral auxiliary that acts as both linker and stereochemical template. The observed diastereoselectivity is excellent with the binol-linked bis(dipyrromethene) giving rise to highly diastereomerically pure dipyrromethene helicate. This is the first report of a synthesis of highly diastereomerically, and optically, pure dipyrromethene helicates. The synthesis is amenable to scale-up and all starting materials are readily available. The molar ellipticity for a helically pure mononuclear dipyrromethene complex has been established, and chiral HPLC conditions suitable for the resolution of mononuclear dipyrromethene complexes have been determined. Our current research is directed toward examining the scope of the binol and tartrate skeletons as asymmetric linkers in other dipyrromethene complexes, and extending the work to include oligomeric and polymeric helicates.

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Supporting Information Available: Preparative procedures and characterization data for **2** and **4**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[25] Accelrys MS Modeling 3.0 geometric optimization with GGA-BYLP/dzdp.