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Control of Absolute Helicity in Single-Stranded Abiotic Metallofoldamers

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Metals play an important role in protein structure and function, and the use of metals as components of unnatural foldamers[1] holds promise for applications in catalysis and in materials science. Metalloenzymes derive exquisite selectivity from their global structure and not solely from the ligands that are directly associated with the metal.[2] Metals can also nucleate or template the secondary structures of single-stranded abiotic foldamers,[3] but little is known about controlling the absolute sense of folding of such structures.

We recently described a new class of salophen and salen ligands that fold into helices upon complexation of either Ni(II) or Cu(II) (e.g., **1** and **2**, Figure 1).[3a] Complex **2** derives asymmetry from the primary sphere of the metal; that is, a moiety in the immediate coordination sphere is inherently chiral. An alternative and biomimetic way to control the chiral environment of a metallofoldamer is via secondary sphere chirality,[2] through which remote stereocenters control the asymmetric environment about the metal.[4] By analogy to the crystallographically determined structure of **1**, we hypothesized that the enantiomerically pure ligand **3** would fold into the discrete conformation **4**(***P***) (Scheme 1) because the methyl groups on the peripheral benzofuran rings would point to the outside of the helix.[5] Enantiomerically pure **3** was synthesized (see Supporting Information) and combined with $Ni(OAc)_2$ to provide a crystalline product that was analyzed by X-ray diffraction. Although the product has a helical structure in the crystal that is controlled in the absolute sense by the stereocenters at the periphery, the configuration of the crystallized structure [**4**(***M***)] was the opposite of prediction (Scheme 1). A difference between the structures of **4**(***M***) and **1** is that the peripheral carbonyls of **4**(***M***) point to the interior of the helix, whereas those of **1** point toward the exterior.

The product from **3** and $Ni(OAc)_2$ was also analyzed in solution by variable temperature ^1H NMR (23 to −40 °C). Two species undergo chemical exchange (Scheme 1) with a barrier of ~13 kcal/mol. On the basis of the crystal structures of **1** and **4**, and the earlier observation that **1** racemizes rapidly at room temperature, we hypothesized that the two conformations that were detected at −40 °C were **4**(***M***) and **4**(***P***). Interconversion of **4**(***M***) and **4**(***P***) requires helix inversion and an ~180° rotation of the outermost arene-nitrogen bonds (Scheme 1). The small magnitudes of the specific rotation (−362°) and the CD spectrum (Figure 3) are consistent with the hypothesis that **4** is a mixture of conformers with opposite helicity.

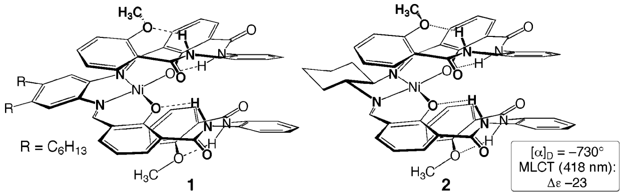
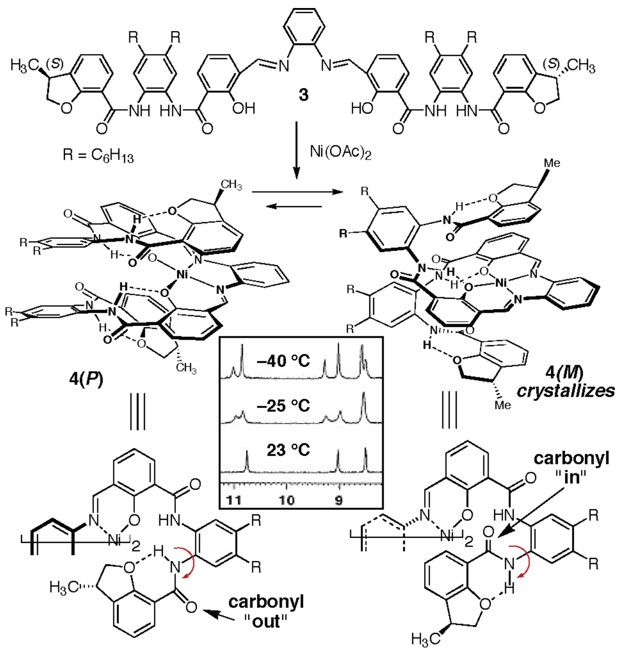


Figure 1. Previously reported metallofoldamers.

Scheme 1. Conformational Equilibrium of **4**[a]



[a] VT-NMR is shown in the inset.

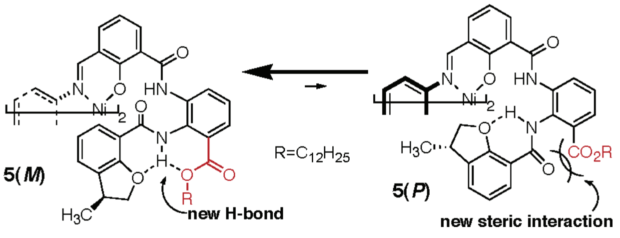


Figure 2. Design of foldamer **5** to bias the absolute sense of helicity.

To bias the absolute sense of helicity at equilibrium, we considered structure **5** shown in Figure 2. The design was to add ester functions that would stabilize the (*M*)-helix by a three-center hydrogen bond[6] and destabilize the (*P*)-helix through steric interference with the amide carbonyl. Accordingly, we synthesized **5** from salophen **6** (Figure 3). Although the chiroptical properties of **6** are unremarkable ($[\alpha]_D = 11^\circ$), those of Ni-complex **5** are large and consistent with a structure of (*M*)-helicity (Figure 3). The magnitudes of the specific rotation ($[\alpha]_D = -1040^\circ$) and the CD spectrum are both larger than those of **2** (Figure 1). The solution structure does not appear to be altered by the addition of methanol. Thus, the CD spectra of **5** are similar in pure CH_2Cl_2 and in 1:1 CH_2Cl_2/MeOH, and the ^1H NMR spectrum is not altered significantly by addition of 10% CD_3OD to **5** in $CDCl_3$. The failure of methanol to alter the spectroscopic properties suggests that the steric destabilization of **5**(***P***) (Figure 2) has an important role in biasing the equilibrium toward **5**(***M***).

Crystals of Ni-complex **5** were grown from CH_2Cl_2/EtOH and were analyzed by X-ray diffraction (Figure 4). As predicted, crystalline **5** folds into the "carbonyl-in" conformation as an (*M*)-helix. Evidence that the solution structure of **5** is helical was supported by chemical shift anisotropy. As compared to its

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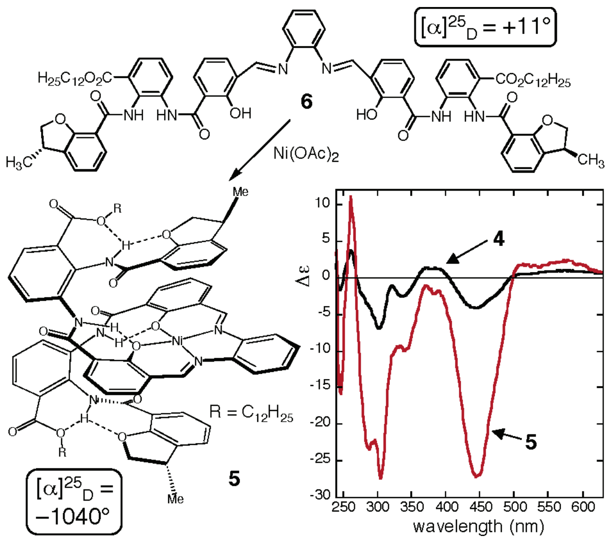


Figure 3. Synthesis and chiroptical properties of foldamer **5**.

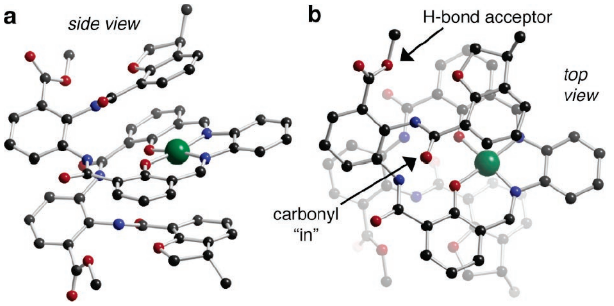
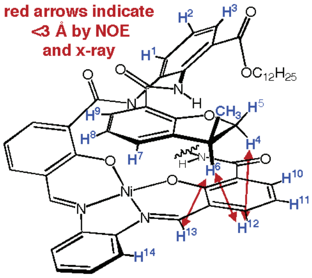
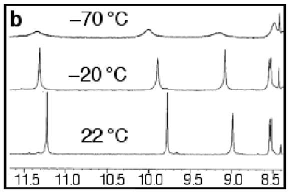


Figure 4. Molecular diagrams of **5** from crystallographic coordinates.



a Upfield chemical shifts in **5**

H^1	$\Delta\delta=0.67$	H^6	$\Delta\delta=0.55$
H^2	$\Delta\delta=0.44$	H^7	$\Delta\delta=0.66$
H^3	$\Delta\delta=0.31$	H^8	$\Delta\delta=0.74$
H^4	$\Delta\delta=1.09$	H^9	$\Delta\delta=0.40$
H^5	$\Delta\delta=0.55$	CH_3	$\Delta\delta=0.31$



c

proton pair	distance by: NOE (Å)	x-ray (Å)
H^4-H^{12}	2.95	2.88
H^4-H^{11}	3.45	3.11
H^4-H^{10}	3.87	4.03
H^6-H^{12}	2.95	2.83
H^6-H^{13}	2.90	2.91
H^6-H^{14}	3.88	4.06
H^7-H^{13}	3.83	4.00
H^8-H^{13}	3.57	4.90
H^9-H^{12}	3.76	5.47

Figure 5. (a) Upfield chemical shifts in **5**, as compared to its salicyladehyde precursor; (b) VT-NMR spectra of **5**; (c) the internuclear distances of Ni-complex **5** from NOESY and X-ray crystallography.

salicylaldehyde precursor, substantial shifts to higher field are observed for all of the hydrogens highlighted in Figure 5a. The largest $\Delta\delta$ is observed for H4, which is positioned directly above (∼2.7 Å) an aromatic ring in the crystal structure. VT-NMR was also used to study **5**. Whereas all of the aromatic resonances of **4** coalesce at −25 °C or above, the ^1H NMR spectrum of **5** is only slightly broadened at −20 °C (Figure 5b). Although further broadening is observed with cooling, none of the resonances coalesced even at −70 °C. While this broadening indicates a conformational equilibrium for **5**, it is unlikely that the equilibrium involves conformer **5**(***P***), as the new hydrogen bonding interaction in **5** (Figure 2) should only raise the barrier to helix inversion.

The NOESY spectrum of **5** provided further evidence that **5**(***M***) is a significant conformation in solution. The *trans*-helix internuclear distances that were measured to be less than 4 Å by NOE are displayed in Figure 5c, along with the analogous distances as measured by X-ray diffraction. A close correlation between the X-ray and NOE measurements was observed for 7 of the 9 internuclear distances, including three very close (<3 Å) measurements between the terminus and the core of the helix. For the last two entries in Figure 5c, the distances measured by NOE were shorter than those measured by X-ray diffraction. In the context of the VT-NMR data, it seems likely that these peaks arise from another conformation that is in equilbrium with **5**(***M***). As an NOE was not observed between H8 and H12, it is unlikely that this conformer is **5**(***P***). Crystalline **1** is isostructural to **5**(***P***), and the analogous distance in **1** was measured to be <4 Å both by X-ray diffraction and by NOESY. At this time, we cannot estimate the percentage of conformer **5**(***M***), but given the large chemical shift anisotropy and significant chiroptical properties, it can be reasoned either that **5**(***M***) is the major conformation in solution or that the undetermined conformer also has *M*-helicity.

In summary, peripheral stereocenters effectively control the absolute sense of helicity in Ni-salophen derived foldamers. Future studies will examine the applications of metallofoldamers in asymmetric catalysis and materials science.

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Supporting Information Available: Full experimental details, ^1H,^{13}C, and VT-NMR spectra, and cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

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