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Diastereomeric Recognition of Chiral Foldamer Receptors for Chiral Glucoses

Chuang Li, Gui-Tao Wang, Hui-Ping Yi, Xi-Kui Jiang, Zhan-Ting Li,* and Ren-Xiao Wang*

State Key Laboratory of Bio-Organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

ztli@mail.sioc.ac.cn; wangrx@mail.sioc.ac.cn

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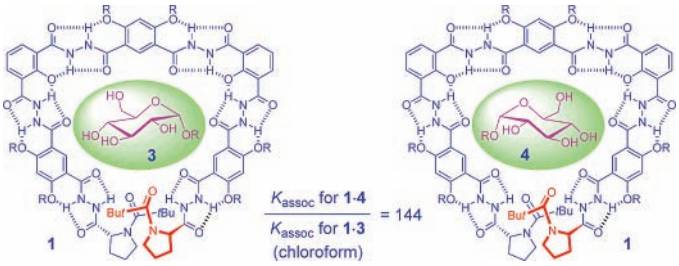
ABSTRACT



Three chiral aromatic hydrazide foldamers have been designed and synthesized, in which two *R*- or *S*-proline units were incorporated at the terminals of their backbones. The ^{1}H NMR, circular dichroism (CD), and fluorescent experiments and molecular dynamics simulations revealed that the foldamers adopted a chiral helical conformation and complexed alkylated glucoses in chloroform with a good diastereomeric selectivity.

The intriguing folded or helical conformation of peptides and proteins has always fascinated chemists. In the past decade, there has been considerable interest in developing foldamers, unnatural oligomers that are capable of folding into well-defined secondary conformations.[1] It has been expected that progress in this field will eventually lead to unnatural structures with sizes and functions of biomolecules such as proteins and DNA.[1b] One of the interesting functions of foldamers is their application in molecular recognition. Depending on the design, binding sites, and cavity size, foldamers may complex monoterpenes,[2] alkylated saccharides,[3,4] aliphatic ammoniums,[5] water,[6] metal ions,[7,8] anions,[9] and fullerenes.[10] However, examples of recognitions of chiral foldamers for chiral guests are very limited.[11] It was revealed that complexation of achiral foldamers for a chiral guest could cause significant chiral differentiation for the folded backbones.[2−5] In principle, if one or more chiral units are incorporated into a folded scaffold to generate an energeti-

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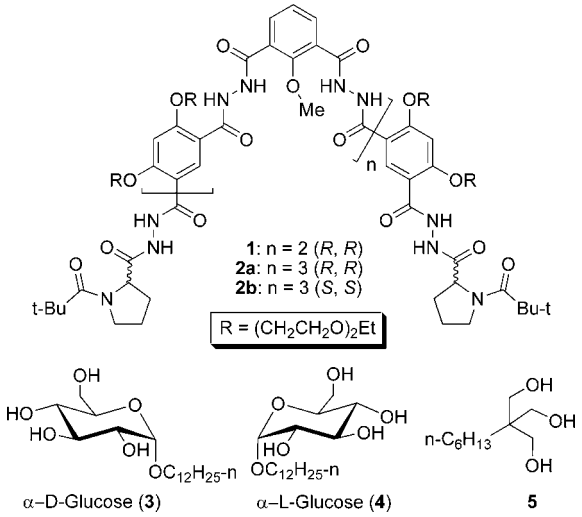
cally favorable chiral conformation, diastereomeric recognition for chiral guests may be achieved. We previously found that hydrazide-based foldamers efficiently complexed discrete saccharides in chloroform.[4a] By introducing two *R*- or *S*-proline units at the terminals of the backbones, we have designed three new chiral foldamers. We herein report that these chiral foldamers complex glucoses with a remarkable diastereomeric selectivity.[12,13]



Three oligomers **1**, **2a**, and **2b** have been synthesized, each of which bears two *R*- or *S*-proline units at the terminals of the backbone. **2a** and **2b** are enantiomers. CPK modeling showed that the backbones of all the molecules were long enough to form a helical conformation. It was envisaged that these molecules would produce helical differentiation in solution due to the introduction of the chiral prolines. Anomers α-D-glucose (**3**) and α-L-glucose (**4**) were chosen as chiral guest molecules because a previous study revealed that achiral hydrazide foldamers could complex discrete sacchrides in chloroform.[4a] For comparison, achiral triol **5** was also investigated as a guest.[4b] The syntheses for the oligomers are provided in the Supporting Information. All the oligomers are soluble in common organic solvents such as chloroform and dichloromethane and have been characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.

Because the chiral prolines in the oligomers are located at the ends of the hydrazide backbones, it is reasonable to assume that, like their proline-free analogues,[4a] the hydrazide backbones in these oligomers are also induced by hydrogen bonding to adopt a folded conformation. Actually, their ^{1}H NMR spectra in $CDCl_3$ showed that the NH signals of all the oligomers appeared at the downfield area (10.05−11.54 ppm), supporting the existence of intramolecular hydrogen bonding. As expected, the spectra of **2a** and **2b** are identical to each other. To further explore the influence of the chiral prolines on the conformation of the hydrazide backbone, compound **6** was also prepared. The X-ray diffraction analysis revealed that in the solid-state its hydrazide moiety adopted a rigidified planar conformation, and the methoxyl oxygen atom was involved in intramolecular hydrogen bonding (Figure 1). All these results suggested that the proline-incorporated hydrazide oligomers possessed a rigidified helical conformation.

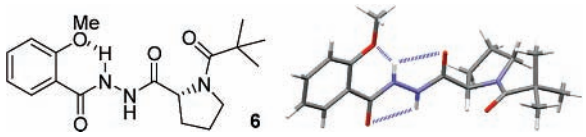


Figure 1. Compound **6** and its solid-state structure.

Conformations of methyl-substituted analogues of oligomers **1** and **2a** were also explored through molecular dynamics simulations (see the Supporting Information). Their conformations of the lowest energy are provided in Figure 2, both of which corresponded to the left-handed (*R*,*R*-M) helical conformers. Their right-handed (*R*,*R*-P) helical diastereomers were also analyzed. They were, however, energetically unfavorable by 12∼15 kcal/mol as compared to the two conformations shown in Figure 2. These results also suggest that introduction of two chiral proline units to the terminals of the hydrazide oligomers leads to important differentiation of their possible helical conformations. The ^{1}H NMR spectra of both compounds in $CDCl_3$ (see the Supporting Information) exhibit one set of signals, suggesting that the M and P helices in solution exchange quickly on the ^{1}H NMR time scale.

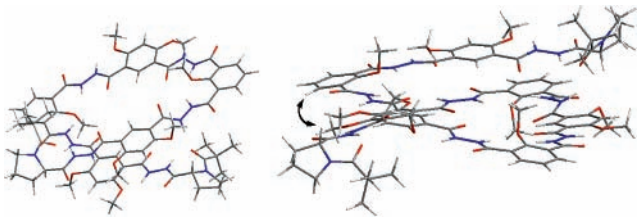


Figure 2. Energy-minimized conformation of **1** (left) and **2a** (right). The octyl chains were replaced with methyl groups for modeling. An NOE connection is shown for **2a**.

2D ^{1}H NMR NOESY experiments (5 mM, 400 MHz) revealed an NOE connection between the proton at the chiral carbon atom and one of the aromatic protons of **2a** or **2b**, as shown in Figure 2. Because no similar result was observed for **1** or **6** of identical concentration, this NOE should be

(12) Chiral aromatic amide or urea foldamers have been reported. See: (a) Dolain, C.; Jiang, H.; Leger, J.-M.; Guionneau, P.; Huc, I. *J. Am. Chem. Soc.* **2005**, *127*, 12943. (b) Sinkeldam, R. W.; Hoeben, F. J. M.; Pouderoijen, M. J.; De Cat, I.; Zhang, J.; Furukawa, S.; De Feyter, S.; Vekemans, J. A. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 16113. (c) Dong, Z.; Karpowicz, R. J., Jr.; Bai, S.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 14242.

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ascribed to cross-ring approach of the two protons. This result further supported the helical conformation of the oligomer shown in Figure 2.

The nature of the hydrazide backbones enables circular dichroism (CD) studies for both the oligomers and their mixture solution with **3** and **4**. As expected, the solutions of all the oligomers in chloroform are CD active (Figure 3, top).

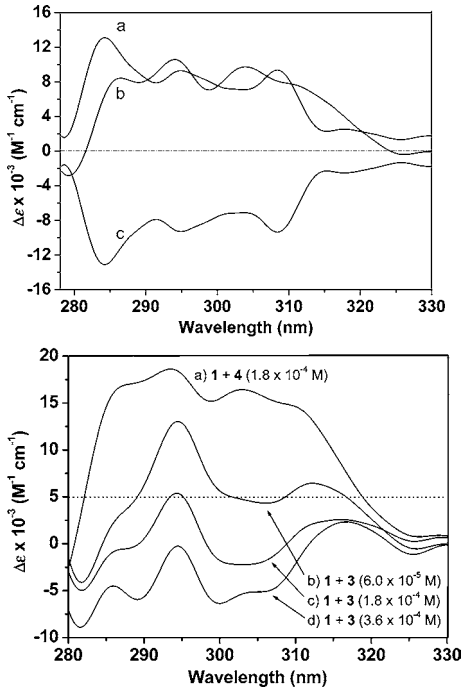

Figure 3. Top: CD spectra of (a) **2a**, (b) **1**, and (c) **2b** in chloroform (6.0×10^{-5} M) at 25 °C. Bottom: CD spectra of the mixture solution of **1** (6.0×10^{-5} M) and **3** and **4** in chloroform at 25 °C.

Because the solution of chiral hydrazide **6** in chloroform is CD silent, the signals displayed in Figure 3 must be generated due to the formation of the chiral helical conformation for their hydrazide skeletons. The spectra of **2a** and **2b** of identical concentration are of mirror shape, reflecting the feature of two symmetric chiral helicates of identical stability. These observations are consistent with the above results of ^{1}H NMR observations and molecular modeling.[14]

Adding **3** or **4** to the solution of **1** in chloroform caused an important change for the CD spectra of **1**. The representative results are shown in Figure 3 (bottom). As expected, the CD change was increased with the increase of the guest (Figure 3b−d). The spectra produced upon addition of **3** and **4** of identical concentration are opposite in direction but not of mirror symmetry (Figure 3a,c).

CD variations were also observed for the solution of **2a** and **2b** in chloroform with the addition of **3** or **4** (Figure 4).

(14) The results do not mean that the favorable helical conformer existed exclusively but that reasonably it was the major form of the helical structures.

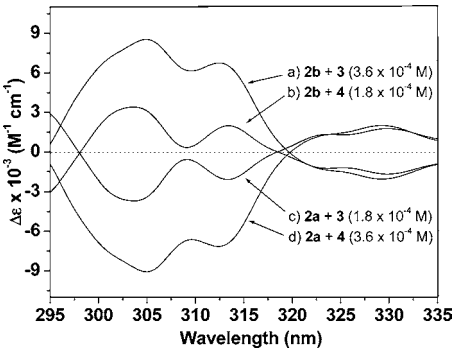

Figure 4. CD spectra of the mixture solution of **2a** and **2b** (5.1×10^{-5} M) with **3** and **4** in chloroform at 25 °C

Mirror symmetry was observed for the spectrum of the two pairs of complexes of the identical mixture concentration: **2a** + **4** vs **2b** + **3** and **2a** + **3** vs **2b** + **4** (Figure 4a vs e and b vs d). This observation clearly illustrates the "enantiomeric" feature of the two pairs of complexes and is in accordance with the quantitative fluorescent binding studies (vide infra).

Because of overlapping with the OCH_2 signals of the oligomers, ^{1}H NMR spectra did not provide useful information for the shifting of the hydroxyl signals caused by intermolecular hydrogen bonding.[4a] Therefore, the complexation behavior was investigated with fluorescent spectroscopy. Adding a glucose guest to the solution of the foldamers in chloroform caused significant emission increase of the oligomers. On the basis of studies of Job's plots (Figure 5),[15]

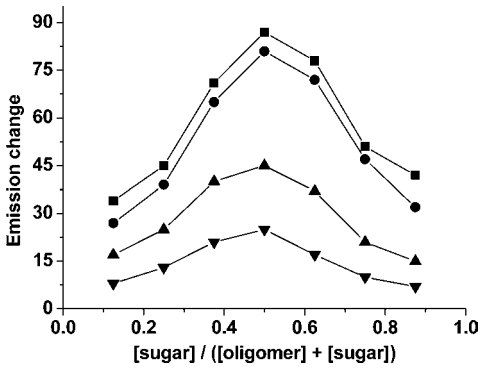

Figure 5. Job's plots for the solutions of **2a** and **3** (■), **2a** and **4** (●), **1** and **3** (▲), and **1** and **4** (▼) in chloroform at 25 °C (the emission change at 408 nm as the probe). The total concentration is 2.0×10^{-5} M for the former two systems and 1.0×10^{-5} M for the latter two systems.

we could establish a 1:1 stoichiometry for the investigated complexes. Fluorescent titrations were then carried out by incremental addition of the glucoses to the solution of the oligomers of fixed concentration in chloroform.[4a] Association

(15) Job, P. *Ann. Chim. Ser. 10* **1928**, *9*, 113.

constants were derived from the titration data and are listed in Table 1.[16]

Table 1. Association Constants of Complexes Among **1**, **2a** and **2b**, Glucoses **3** and **4**, and Triol **5** in $CHCl_3$ at 25 °C[a]

complex	K_{assoc} (M^{-1})	ΔG (kcal/mol)	complex	K_{assoc} (M^{-1})	ΔG (kcal/mol)
1·3	1.8×10^3	−4.4	**2a·5**	1.1×10^2	−2.8
1·4	2.6×10^5	−7.4	**2b·3**	1.3×10^4	−5.6
1·5	5.0×10^2	−3.7	**2b·4**	3.1×10^2	−3.4
2a·3	3.0×10^2	−3.4	**2b·5**	1.3×10^2	−2.9
2a·4	1.2×10^4	−5.6			

[a] The results are average values of two titration experiments, and the error is generally <15%.

Complex **1·4** gave rise to the largest association constant, which was about 144 times higher than that of **1·3**. A previous study revealed that hydrazide foldamers complexed saccharide guests with their cavity by intermolecular hydrogen bonding.[4a] Considering that the new chiral oligomers also adopted a folded conformation and formed 1:1 complexes with the glucoses, it should be reasonable to propose that similar binding patterns exist for the new complexes. Similar binding differentiation was also observed for **2a** toward **4** over **3** and for **2b** toward **3** over **4**, with a ratio of the association constants being approximately 40 and 42, respectively. These results suggest that the oligomers with *R*-proline units were able to complex chiral guest **4** more efficiently, whereas *S*-proline-incorporated oligomers preferred to bind its enantiomer **3**. As expected, the association constants of the complexes of enantiomeric symmetry, i.e., **2a·3** vs **2b·4** and **2a·4** vs **2b·3**, are very close. This result is consistent with the above CD observations. By using the identical method, association constants of the complexes between the foldamers and achiral triol **5** were also obtained and listed in Table 1. The values are generally small, although the value of **1·5** is notably higher than those of **2a·5** and **2b·5**.

In conclusion, a new series of hydrogen bonding driven chiral hydrazide foldamers have been constructed, in which two *R*- or *S*-proline units are introduced at the terminals of their backbone. The foldamers are induced by the chiral proline units to display chiral helical differentiation in solution. The resulting chiral helicates efficiently bind enantiomeric alklyated glucoses in chloroform. Quantitative fluorescent investigations revealed a good binding differentiation for the diastereomeric complexes. The results well demonstrate that, by introducing rationally designed chiral groups, foldamers can be induced to form a chiral cavity for selective complexation of chiral guests. Future studies will include the utility of the chiral cavity for membrane transportation of chiral species and the construction of foldamer-appended or incorporated polymers for chirality transfer or amplification.

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Supporting Information Available: Full experimental and characterization data for **1**, **2a**, **2b**, and **6**; methods and results of molecular dynamics simulations; ^1H NMR spectra of new compounds and NOESY spectrum of **2a**; typical fluorescent titration spectra; CIF file of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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