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Diastereoselective Encapsulation of Tartaric Acid by a Helical Aromatic Oligoamide

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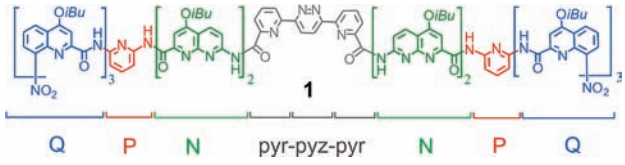
Helical molecules strongly express chirality and as a result may provide confined environments suited to recognizing chiral guests with high enantioselectivity.[1] Here we present the encapsulation (i.e., the complete surrounding and isolation from the solvent) of a cornerstone of molecular chirality,[2] namely, tartaric acid, in a helically folded aromatic oligoamide. Very high affinities, guest selectivities, and diastereoselectivities have been observed that bode well for extensions of this approach to larger and more complex guests.

The folding of molecular strands into compact architectures is the method selected by nature to elaborate well-defined asymmetrical environments for molecular recognition. Inspired by this, chemists have designed artificial receptors based on helically folded oligomers possessing a hollow cavity.[1,3,4] As an extension of this concept, it was shown that a decrease in the helix diameter at each end of the sequence closes the cavity, which becomes insulated from the surrounding medium.[4] In such helical capsules, the binding and release of guests to and from the cavity require a local unfolding of the helix. On the basis of this design, aromatic oligoamide **1** (Chart 1) was proposed to encapsulate chiral carboxylic acids. The long **pyr**−**pyz**−**pyr** linear segment[5] was introduced to substantially enlarge the diameter at the center of the cavity in comparison with previous designs[4] in order to accommodate stereogenic centers. The recently developed naphthyridine amino acid units[6] were selected for their ability to hydrogen bond to carboxylic acids.[7] The convergent synthesis of **1** involves the coupling of a $\mathbf{Q}_3$ acid chloride with the amine of H_2N−$\mathbf{PN}_2$−Boc to yield $\mathbf{Q}_3\mathbf{PN}_2$−Boc, which after Boc cleavage was coupled to the diacid chloride of the **pyr**−**pyz**−**pyr** unit to give **1** (see the Supporting Information).

Chart 1. Formula of **1** and Abbreviations Used for Its Subunits



A first titration of **1** by D/L-tartaric acid was carried out in $CDCl_3$ using 1% DMSO-d_6 to dissolve the guest in the stock solution. NMR monitoring showed changes consistent with the emergence of a host−guest complex in slow exchange with the free host on the NMR time scale (Figure 1A). Upon addition of 1 equiv of guest, the signals of the free host completely disappeared. This saturation is indicative of very strong binding: K_a was actually too high for accurate determination but was certainly greater than 10^6 L mol^{-1} and even larger in pure $CDCl_3$. Furthermore, the complex emerged as a single set of sharp signals, suggesting that it existed in a single diastereomeric form (de > 99%): each of the tartaric acid enantiomers was encapsulated by a helix having a unique handedness. The diastereoselectivity was qualitatively illustrated by the circular dichroism (CD) titration of **1** with either pure L- or pure D-tartaric acid (Figure 1B). When a single enantiomer was introduced, an intense induced CD was observed, showing that the equilibrium between the *M* and *P* forms of the helix was shifted in one direction because of the associated stabilization of that form by tartaric acid binding. Thus, control over the absolute helix handedness[8] of **1** would produce a receptor that binds one enantiomer of tartaric acid and not the other.

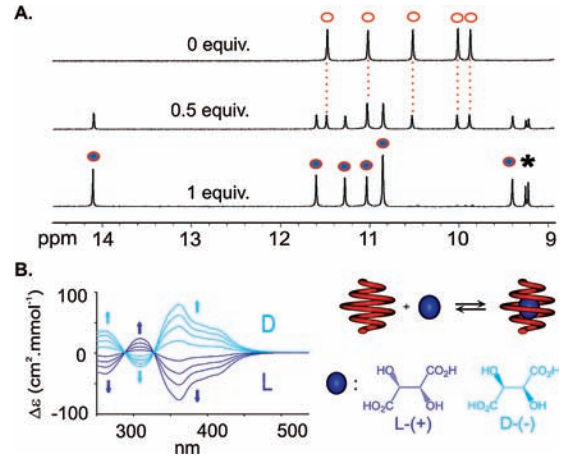


Figure 1. (A) Part of the 300 MHz ^{1}H NMR spectra of **1** (2 mM in 99:1 (v/v) $CDCl_3$/DMSO-d_6) at 298 K in the presence of 0, 0.5, and 1 equiv of D/L-tartaric acid. Signals of the empty host and of the host−guest complex are marked with open red and blue-in-red circles, respectively. * indicates an aromatic proton resonance. (B) CD spectra of **1** (40 μM in 99:1 (v/v) $CHCl_3$/DMSO) at 298 K titrated with 0.3, 0.5, 0.7, and 1 equiv of either D- or L-tartaric acid.

Crystals of the complex were obtained from the diffusion of hexane in a titration solution, and its structure in the solid state was resolved (Figure 2A,B). The structure fully validates the encapsulation process: tartaric acid is completely surrounded by the helix backbone and isolated from the surrounding medium. A pseudo-C_2 symmetry axis perpendicular to the helix axis applies to both the host and the guest. Tartaric acid lies flat in the cavity and adopts a typical conformation with trans acid groups and gauche hydroxy groups. Each carboxylic acid moiety is doubly hydrogen bonded ($d_{OH\cdots N}$ = 2.74 Å, $d_{NH\cdots OC}$ = 3.08 Å) to a neighboring 7-aminonaphthyridine unit (Figure 2C). Two additional hydrogen

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bonds involve the tartaric acid hydroxy oxygen atoms and amide protons belonging to pyridine units ($d_{NH\cdots O} = 3.24$ Å). The crystal structure also provides an unambiguous attribution of the matching stereochemistry: the natural L-tartaric acid is bound by the *M* helix of **1** and D-tartaric acid by the *P* helix. A full structural assignment of the NMR spectra using COSY, HMQC, HMBC, and ROESY experiments showed that the complex structure in solution is the same as in the solid state (see the Supporting Information). The sharp signal at 14.1 ppm is that of the hydrogen-bonded acid protons (Figure 1A). Five unambiguous intermolecular NOEs confirm the positioning of the guest in the cavity, the most significant being a correlation between the pyridazine protons and the tartaric acid C*H* protons.

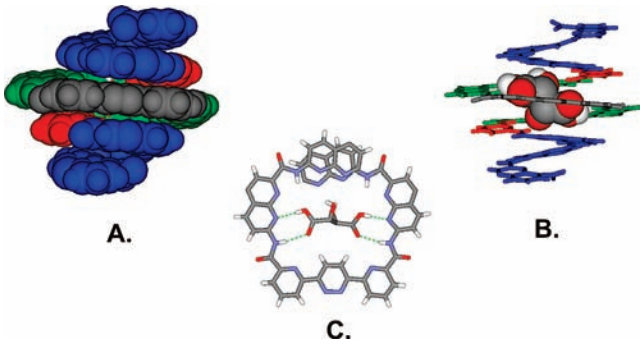

Figure 2. (A) CPK and (B) stick representations of the solid-state structure of L-tartaric acid in the cavity of *M*-**1**. Units are color-coded as in Chart 1. Isobutoxy groups and solvent molecules are not shown. (C) Top view of the central part of the same complex, showing tartaric acid hydrogen-bonded to $\mathbf{N_2-pyr-pyz-pyr-N_2}$.

To assess the binding selectivity, **1** was titrated with a series of guests structurally related to tartaric acid (Table 1 and the Supporting Information). A more competitive solvent was used (10% DMSO-d_6 in $CDCl_3$) to decrease the binding constants to a level at which ^{1}H NMR titrations are accurate. In this solvent, the K_a value for D/L-tartaric acid was 5300 L mol^{-1}. Changing the orientation of a single OH group (in *meso*-tartaric acid) reduced K_a by a factor of 13. NMR spectra showed that both the host and the guest lost their C_2 symmetry, and it appeared that only one carboxylic acid was hydrogen bonded. Mismatching interactions of OH groups with the capsule inner wall are thus detrimental to binding, in agreement with the diastereoselective recognition of tartaric acid: when the orientation of both hydroxy groups was changed, binding became very weak for the mismatched helix (but strong for the other helix handedness). Removing an OH group (in D/L-malic acid) reduced K_a by 2 orders of magnitude. The de of the complex decreased substantially, but the matching handedness remained the same as for tartaric acid (Figure S6 in the Supporting Information). NMR spectra indicated that both carboxylic acid groups were hydrogen-bonded, albeit with broader and less upfield-shifted resonances. Threitol, a tetraol analogue, also featured weak binding, weak de, and the same matching stereochemistry. Finally, mono- and diacids structurally more remote from tartaric acid, such as succinic, malonic, and lactic acids, showed even weaker binding, and any guest too large to fit in the cavity was not bound at all.

The perfectly defined complex geometry and the observed high K_a, high selectivity, and diastereoselectivity of **1** for tartaric acid make it an outstanding receptor in comparison with previously described hydrogen-bond-based,[7a,9] boronate ester-based, or salt-bridge-based hosts.[10] This may arise from the complete surrounding of the guest, which allows interactions to take place from all directions simultaneously. Potential future developments rest on the high modularity of such folded oligomer receptors. Indeed, each monomer in the sequence may be replaced by another unit to achieve a predictable change in binding properties, thus providing fine-tuning of host−guest interactions. Our current efforts are targeting the control of guest binding and release rates and will be reported in due time.

Table 1. Binding Constants of Different Guests to **1** in $CDCl_3$/DMSO-d_6 Solutions As Measured by ^{1}H NMR Titrations at 298 K

entry	guest[a]	K_a (L mol^{-1})[b]	de (%)[c]
1	D/L-tartaric acid	>10^6 [d]	>99
2	D/L-tartaric acid	5300	>99
3	*meso*-tartaric acid	400	−
4	D/L-malic acid	70	52
5	succinic acid	<1	−
6	L-threitol	250	70
7	malonic acid	22	−
8	L-lactic acid	<1	n.d.[e]

[a] See the Supporting Information for structures. [b] Measured in 90:10 (v/v) $CDCl_3$/DMSO-d_6, except for entry 1. [c] Diastereomeric excess measured by integration of amide peaks. [d] In 99:1 (v/v) $CDCl_3$/DMSO-d_6. [e] Not determined.

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Supporting Information Available: Experimental details, spectroscopic data, and crystallographic data for **1**⊃D/L-tartaric acid (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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