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Combinatorial Synthesis of Modular Chiral Cyclophanes

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Abstract: A new chiral cyclophane incorporating the 4,4'-bipyridinium dication and a dipeptide subunit forms complexes with amino acid derivatives and allows for the preparation of combinatorial libraries of hydrogen bonding, π-acidic chiral selectors.
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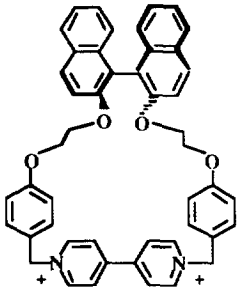
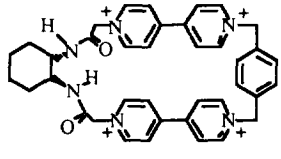
In the growing field of chiral separations, impressive successes have been realized with chiral host molecules (selectors) that are rationally designed to bind a particular analyte or class of analytes.[1-5] Immobilization of these selectors on solid supports, such as silica, provides a medium for chiral resolution or analysis. For example, one of the most widely used chiral chromatographic stationary phases is based on a selector designed by Pirkle and coworkers.[4] This molecule contains a 3,5-dinitrobenzoyl π-acceptor group and an amino acid fragment, and resolves a broad class of complementary π-donor, hydrogen bonding analytes. We have previously reported batchwise chiral separations using a related Pirkle-type selector intercalated into α-zirconium phosphate.[6,7] This system is interesting for preparative-scale chiral separations, because of the high selector loading inherent in the support, but suffers from host pre-organization effects that limit its utility as a chromatographic stationary phase. The rigid chiral cyclophane hosts **1** and **2**, which embody strongly π-accepting 4,4'-bipyridinium groups and a chiral barrier (1,1'-binaphthol or 1,2-diaminocyclohexane), were subsequently synthesized. These hosts contain a pre-organized binding pocket, which eliminates the expansion and contraction of the lamellar host upon complexation of π-donor analytes.[8] Preparative-scale preparations are possible, particularly with **2**, which does not self-associate significantly.

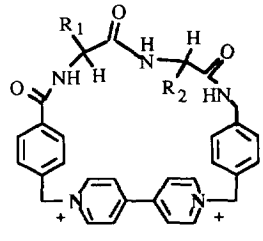
Hosts **1** and **2** represent a rational extension of previous work on chiral an achiral cyclophanes[9-17]. However, their utility is limited to a fairly narrow range of complementary analytes, because they are not easily adapted to combinatorial variation. In this paper, we describe the preparation of a new class of cyclo-



1



2

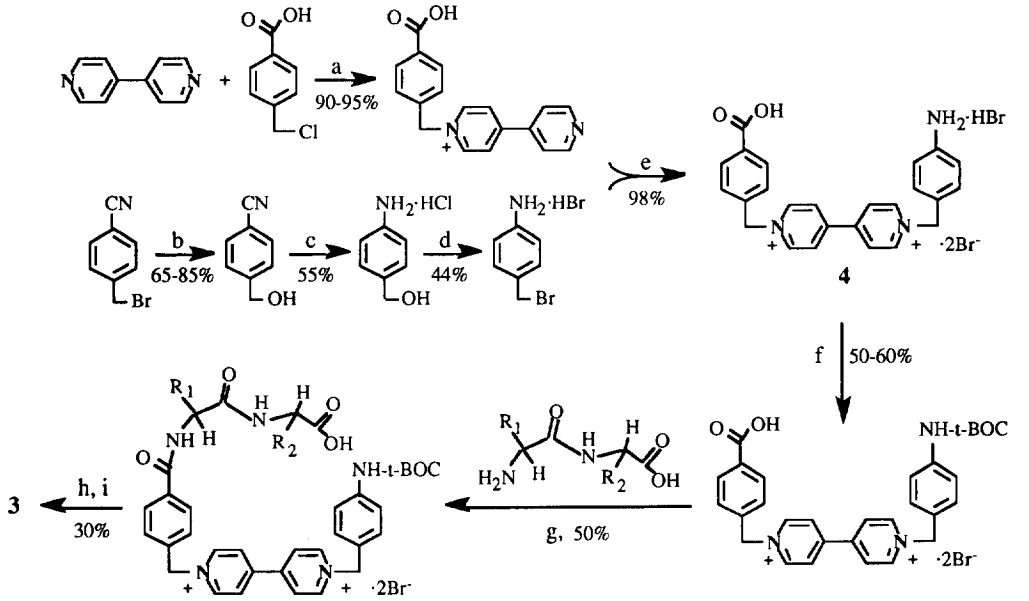


3

phane hosts **3**, which incorporate similar molecular recognition groups (4,4'-bipyridinium and a hydrogen-bonding dipeptide fragment), and which are additionally easily adapted to combinatorial synthesis. To our knowledge, this is the first example of a combinatorial library of chiral selectors. It should be noted that a parallel approach, in which a single cyclophane host distinguishes between members of a peptide library, has been explored by Still and coworkers. These hosts show very high selectivity for combinatorially identified analytes,[18,19] and have recently been incorporated into a chromatographic stationary phase.[20]

Cyclophanes **3** are made from a common backbone **4** (Scheme 1)[21] by adding the dipeptide subunit.[22,23] The cyclophane backbone was chosen to have the same functionality as an amino acid, in order to allow standard peptide protection and coupling reactions to be used.

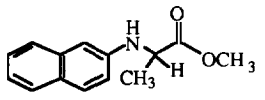
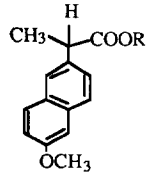
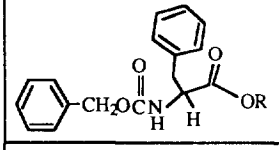
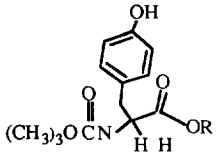
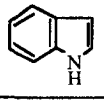
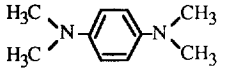
Scheme 1



(a) CH_3CN reflux, 1 day; (b) $BaCO_3$, 2 equiv, H_2O reflux, 3 h; (c) $LiAlH_4$ reduction in dry ether; (d) reflux in conc. aq. HBr 3 h; (e) CH_3CN reflux, 2 days; (f) BOC-ON, 1.5 equiv., add Et_3N to pH 7.5 in dioxane/water (50/50); (g) 1 equiv. N-methyl morpholine (NMM), 1 equiv. isobutylchloroformate, 1 equiv. Et_3N, THF/DMF (30/70) -5°C 30 min. then ambient temperature 24 h; (h) 25% TFA in $CHCl_3$ 30 min; (i) 1 equiv. NMM, 1 equiv. isobutylchloroformate, 1 equiv. Et_3N in DMF, -5°C 30 min. then ambient temperature 72-96 h.

Table 1 shows binding constants determined by variable concentration NMR for the model cyclophane **3** (L-Phe-L-Leu) and several analytes, both neutral and anionic.[24] The self-association constant for this cyclophane is 6-10 M^{-1}, which is sufficiently low to allow accurate measurements of complexation constants with π-donor analytes. Of the analytes evaluated, the potassium salt of naproxen showed the strongest binding. Several amino acid derivatives were also evaluated and showed varying degrees of binding in the 10^0-10^1 M-1 range in water-polar solvent mixtures. Little enantioselectivity was seen, consistent with weak host-guest hydrogen bonding interactions in these solvent mixtures. The low solubility of the host in non-hydrogen

Table 1. Association constants of several analytes with the L-Phe-L-Leu model cyclophane **3**.

Analyte	Enantiomer		K_a (M^{-1})[a]	Solvent
	±		10±1[a]	acetone-d_6: D_2O 9:4
	±	R= CH_3	6±1[a]	dmso-d_6
	±	R= K	29±4[b]	acetone-d_6: D_2O 3:2
	+	R= H	20±2[a]	
	-	R= H	17±2[a]	
	DL-	R= H	19±5[a]	acetone-d_6: D_2O:MeOH-d_4 6.5:7:6
	D-	R= H	7±3[b]	
	L-	R= H	13±4[a]	
	DL-	R= Na	8±2[a]	CD_3CN: D_2O 1:1
	DL-	R= Na	7±2[a]	CD_3CN: D_2O 1:1
			2±0[c]	CD_3CN
			7±1[c]	CD_3CN

NMR titrations were done using (a) bromide, (b) chloride, and (c) hexafluorophosphate salts of the cyclophane. Association constants shown represent the average of two (or more) different proton chemical shifts.

bonding solvents precluded the search for enantioselectivity in those media. When the solvent is changed to DMSO (which often gives very specific solvation effects[25]) the binding constant with N-(2-naphthyl) alanine methyl ester changes only slightly, from 10±1 to 8±2 M^{-1}.

A second model cyclophane **3** was synthesized, containing the less bulky L-Leu-L-Ala dipeptide. This host exhibits slightly higher association constants than the Phe-Leu compound, implying that a much improved host might emerge by screening a larger selection of cyclophanes. In order to check the viability of the combinatorial approach in this case, a small orthogonal library was prepared. A random set of dipeptides was synthesized using standard solid-phase techniques[26-28] and the split bead method.[29-32] The library

contained 20 L-dipeptide members prepared from two amino acid groups. Group A contained Trp, Ala, Phe, Gln and Leu, and was coupled first; Group B contained Val, Trp, Ile and Lys. Amino acid analysis of the library before coupling and after incorporation into the cyclophane showed all residues to be present and no evidence of kinetic resolution in reactions (g)-(i) (Scheme 1). Future studies will focus on the identification of optimized hosts from this and similar cyclophane libraries using affinity chromatographic techniques.

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