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Enantioselective Complexation with a Conformationally Homogeneous C_2 Podand Ionophore

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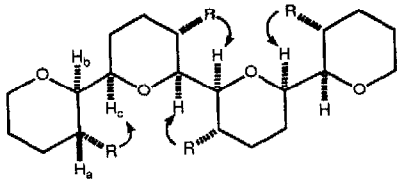
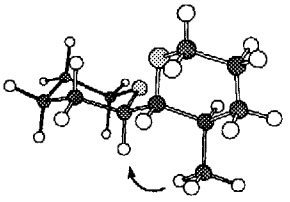
Summary: The podand tetraether **1b** has been prepared from (+)-diethyl tartrate. This ionophore is expected to have only one significantly populated conformation. It binds a variety of chiral organic ammonium cations with enantioselectivities corresponding to 34-42% ee.

Three-dimensional preorganization is characteristic of effective host molecules.[1] The most common approach to building preorganization into hosts is the incorporation of macrocyclic linkages which restrict conformational space and favor those conformers with geometries which are appropriate for binding. We recently described a different type of preorganized host, a podand constructed of linked tetrahydropyran rings (e.g. **1a**).[2] In contrast to the corresponding acyclic glyme ether which has approximately 10^3 conformations within 3 kcal/mol of the ground state, **1a** has only 25. In this letter we describe a related but less flexible THP-podand, the tetramethyl derivative **1b**. In this molecule, the only conformations which do not incur strain due to 1,3-syn C/C or C/O interactions are those having the single conformation of each interring bond which orients the 1,3 methyl and hydrogen substituents as shown in the ball-and-stick model. Thus the methyl substituents serve as conformational locks.[3] In the case of **1b**, they function to reduce conformational flexibility to an absolute minimum so that only one low energy conformation is possible.

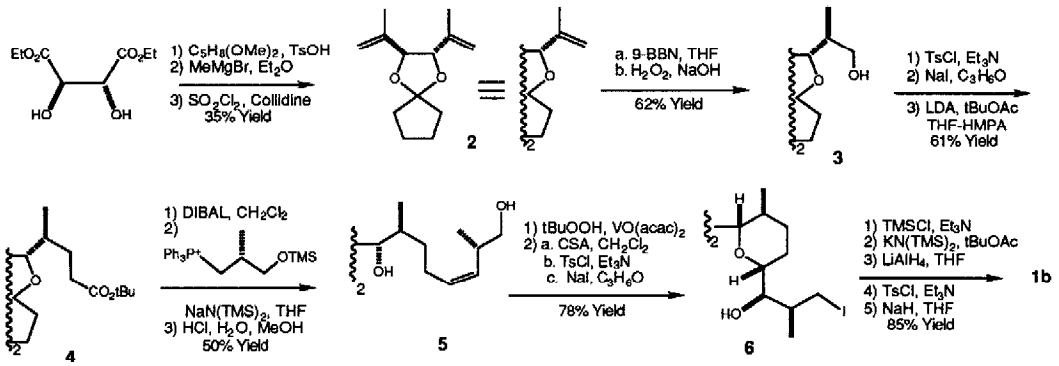




1a R = H
1b R = CH_3

The conformation into which **1b** is preorganized forms a cavity lined by the four oxygens resembling that found in crystal structures of the complexes of 18-crown-6. Podands **1a** and **1b** are both chiral and possess a C_2 axis. Whereas the crystal structures of **1a** show it in essentially planar conformations,[2] the sole low energy conformation of **1b** fixes the THP rings perpendicular to the plane of the ligating oxygens and forms a binding site having significant asymmetry.

While we might expect **1b** to be a better ionophore than **1a**, the differences should not be marked because many of the low energy conformations of **1a** are appropriate for binding. With respect to selectivity, however, **1a** and **1b** should be more distinct. Since only a single conformation of **1b** is available, it should display enhanced selectivity among similar substrates relative to **1a** whose properties reflect a dozen or more contributing conformations.



We synthesized **1b** starting from (+)-diethyl tartrate as summarized above. While most of the scheme is straightforward, the following details are worthy of note. In place of the more common acetonide, we chose the cyclopentylidene protecting group because of the relative ease of its removal. The double dehydration was carried out in a single operation but could be effected in higher yield by a stepwise procedure.[4] The hydroboration followed precedent[5] and afforded the desired isomer (**3**):other isomers in a 9:1 ratio. Stereoselection in the Wittig coupling of the (S) β-hydroxyisobutyrate-derived ylide was ~18:1 in favor of the Z-isomer leading to **5** (mp = 80-81 °C).[6] The epoxidation of **5** was directed by the homoallylic hydroxyl group[7] to yield the α-epoxy product (mp 121 °C) exclusively.

The final product **1b** crystallized in large, thin plates (mp 71-73 °C; α_D -22.5°, 1 mM in EtOH Although we could not obtain suitable crystals for an x-ray diffraction study, NMR analysis was consistent with the expected conformation. Thus we observed a large (9.6 hz) coupling constant fo diaxial H_a/H_b, and a smaller (1.9 hz) coupling for the gauche H_b/H_c pair.

To assess the relative binding properties of **1b**, we used Cram's picrate extraction method[8] with three alkali metals. The results are summarized along with those for three other tetraethers in Table 1. As shown, there is a significant shift in ion selectivity upon going from **1a** to **1b**. Thus the restriction in the conformational space available to **1** is associated with order of magnitude decreases in binding for lithium and sodium, while the affinity for potassium increases three-fold.

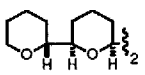
Table 1. Partition constants of tetraethers with alkali metal cations by picrate extraction.

Ionophore	Li^+	Na^+	K^+
$MeO(CH_2CH_2O)_3Me$	12,000	<5,000	<5,000
12-crown-4	16,000	7,300	<5,000
1a	300,000	430,000	29,000
1b	13,000	30,000	91,000

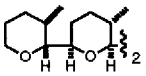
Table 2 summarizes the enantioselective binding properties of podands **1a** and **1b** with various ammonium salts. For comparison, we have included results described by Cram some year

ago which still provide some of the most highly enantioselective examples of binding which use synthetic hosts yet reported.[9] Our binding results were obtained by extracting an aqueous solution of alkylammonium hexafluorophosphate with a $CDCl_3$ solution of podand and by measuring the guest enantiomeric excess using ^1H NMR. This measurement could be carried out directly because the podand acted as a chiral shift reagent for certain guest protons (most notably the methine attached to nitrogen). The NMR indicated that 42-97% of the host was bound in the examples shown.

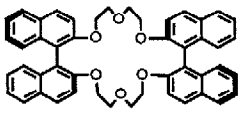
Table 2. Enantioselective binding of synthetic ionophores with chiral ammonium salts including α-aminoacid methyl esters.



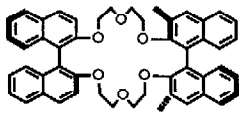
1a



1b



7a

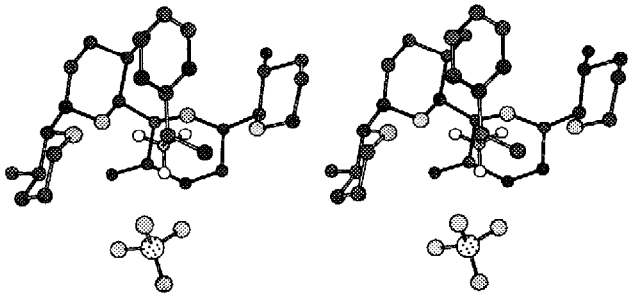


7b

Ammonium Guest:	**1a**	**1b**	**7a**	**7b**
α-Phenylethyl	20% ee (R)	42% ee (S)	24% ee (S)	-
Alanine	-	40% ee (S)	-	-
Methionine	-	36% ee (S)	26% ee (R)	38% ee (S)
Phenylalanine	-	36% ee (S)	28% ee (R)	56% ee (S)
Valine	-	34% ee (S)	20% ee (R)	68% ee (S)
Phenylglycine	13% ee (S)	40% ee (S)	48% ee (S)	90-94% ee (S)

As expected, **1b** is significantly more enantioselective than its more flexible sibling **1a**. Thus on going from **1a** to **1b** with the phenylethyl ammonium guest, enantioselection not only doubled but also changed from R-selectivity to S-selectivity. Little or no enantioselectivity was observed with **1a** and aminoacid esters, but **1b** preferentially bound the S enantiomer of every amino acid methyl ester examined with a selectivity corresponding to 35-40% ee. Such enantiomeric excesses are equivalent to $\Delta\Delta G^*$ ~0.5 kcal/mol. It is interesting that methylation of both our podand and Cram's coronand markedly increased enantioselection. With **7**, the effect was attributed to the addition of steric barriers.[9] With **1b**, however, the substituent effect is clearly indirect. The methyls enforce the shape of the binding site but do not themselves interact with the guest.

The mode of binding of **1b** and (S)-phenylethyl ammonium perchlorate was determined by x-ray crystallography and the structure is shown in stereo on the next page:



According to molecular mechanics with the OPLS/AMBER force field,[10] the geometry of the (S)-phenylethyl ammonium complex found in the crystal is more stable than any other by ~1.5 kcal/mol. This geometry was found prior to the x-ray structure determination by a Monte Carlo conformational search during which (S)-phenylethyl ammonium was moved by translation and rotation within the binding site of **1b**.[11] The calculation further shows that the most stable geometry of the less stable (R)-complex differs from the x-ray structure above primarily by an interchange of H and Me substituents at the alkylammonium chiral center. Thus phenyl is predicted to occupy the same site in both complexes. The steric similarity of the podand atoms in the vicinity of the guest H and Me substituents most likely accounts for the only moderate enantioselection observed with **1b**. It also suggests that structural modifications at the two termini of the podand could result in major enhancements in enantioselectivity. Such studies will be reported in due course.[12]

Notes and References.

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