To demonstrate the utility of the present new phosphite approach, heptadecamer, d-AGACTTCTCCTCAGGAG on a solid support was synthesized. The reaction was carried out on controlled pore glass (15 mg, 36 μmol/g) with a Biosearch Model 381 A DNA synthesizer. We showed the following elongation cycle to be effective: treatment with (1) washing [CH_3CN, 20 s], (2) 5′-unblocking [3% Cl_3CCOOH in CH_2Cl_2, 90 s], (3) washing [CH_3CN, 30 s], (4) coupling [19 μmol phosphite unit (**3**), 95 μmol MeIm in CH_3CN, 10 min], (5) washing [CH_3CN, 30 s], (6) hydrolysis [THF–pyridine–H_2O, 4:3:1, v/v, 2 min], (7) washing [CH_3CN, 30 s]. The extent of coupling in each cycle was monitored by the spectrophotometric assay of DMTr cations; it was estimated each averaged ca. 96%. When the assembly of the oligonucleotide chain was completed, the solid support was treated with 0.1 M I_2 in THF–pyridine–H_2O (4:3:3, v/v) for 15 min. After the usual deprotection, isolation of the desired oligomer, d-AGACTTCTCCTCAGGAG, was performed by TSKgel DEAE-2SW (Figure 1a). The main peak was found to be homogeneous by reversed phase ^{18}C HPLC (Figure 1b) and by gel electrophoresis. The proportions of four nucleosides were analyzed by reversed phase ^{18}C HPLC after hydrolysis with snake venom phosphodiesterase and alkaline phosphatase.

This result and those shown above clearly demonstrate that transesterification of a new type of phosphite unit (**3**) could prove to be very effective for the synthesis of deoxyribooligonucleotides on a solid support. They are readily activated by *N*-methylimidazole under very mild conditions. It is noteworthly that this operation involves a one-step reaction, which is an advantage over both the phosphite and H-phosphonate approaches. The syntheses of phosphorothioylated oligonucleotides and other modified DNA fragments are now in progress.

Podand Ionophores. A New Class of Nonmacrocyclic Yet Preorganized Hosts for Cations

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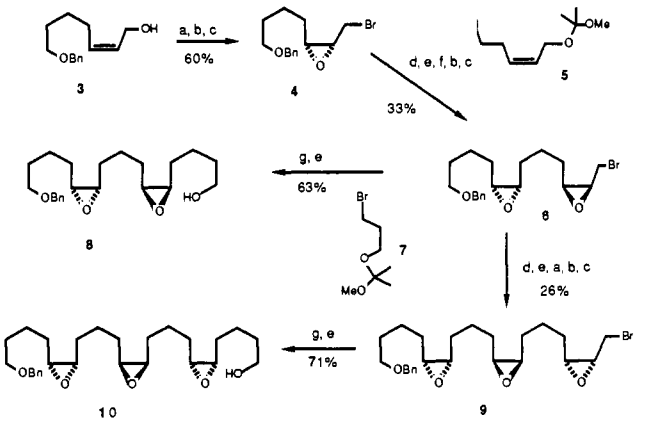
Nonmacrocyclic host molecules (podands) are traditionally regarded as poor ligands when compared with analogous monomacrocycles (coronands) and bridged polymacrocycles (cryptands).[1] The weak binding properties of the podands stem from the conformational freedom of their component acyclic chains. This freedom disfavors binding both entropically and enthalpically because effective binding conformations are usually both few in number and high in energy. On the other hand, the naturally occurring polyether antibiotics are podand-like structures which bind cations rather well. The cation-binding properties of these natural ionophores result in part from their incorporation of an anionic carboxylate and in part from the stereochemically reinforced preorganization of the array of ligating oxygens.[2] In this communication, we describe the synthesis and properties of two neutral podands which structurally resemble the poly-THF/THP substructures of the polyether antibiotics. These novel podands are preorganized by connectivity and stereochemistry into binding

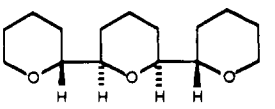
Scheme I[a]



[a] a. (L)-Diethyl tartrate, $Ti(OiPr)_4$, *t*-BuOOH, CH_2Cl_2; b. TsCl, Et_3N, DMAP, CH_2Cl_2; c. LiBr, acetone; d. **5** + *t*-BuLi/Et_2O; $MgBr_2$, Li_2CuCl_4, 4:1 THF–HMPA; e. Pyr·HOTs, MeOH; f. (D)-diethyl tartrate, $Ti(OiPr)_4$, *t*-BuOOH, CH_2Cl_2; g. **7** + Li/Et_2O, $MgBr_2$, Li_2CuCl_4, 4:1 THF–HMPA.

conformations and form molecular complexes with small, cationic guests.

The substances we have prepared (**1** and **2**) are shown below and are derivatives of the acyclic ethers diglyme and triglyme



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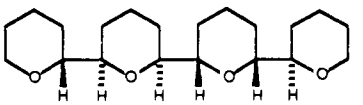

2

dimethyl ether. Compared with the corresponding acyclic glyme ethers, however, **1** and **2** have substantially fewer low-energy conformations (see below). This reduction in the number of possible conformations is analogous to the restriction in conformational space which is effected by the macrocyclization of the glyme ethers to form the ionophoric crown ethers. In our podands, decreased conformational freedom follows from the highly restricted conformational nature of all bonds except those linking the chairlike tetrahydropyran[3] rings. The three-dimensional properties of the low-energy conformations of **1** and **2** depend critically upon the stereochemistry at the ring junctures, and different diastereomers will favor different geometrical arrangements of the cation-ligating oxygens. We therefore expect binding properties to vary with the diastereomer studied. We chose the stereochemistry shown above because, according to molecular mechanics, it preorganizes the podands into low-energy conformers resembling parts of the potassium-binding conformation of 18-crown-6.[4]

The synthesis of **1** and **2** was planned around a polyepoxide cyclization[5] and is summarized in Scheme I. The stereochemistry of the product is controlled by a combination of stereoselective olefin formations and enantioselective[6] epoxidations. Here, in-

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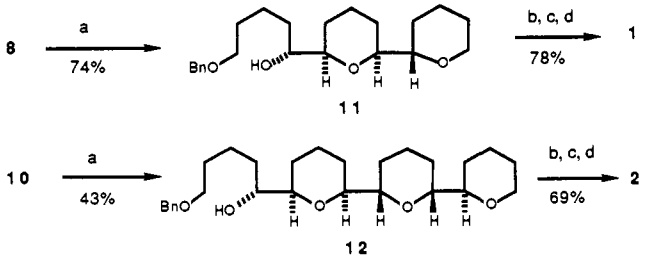
Scheme II[a]



[a] a. Camphorsulfonic acid, CH_2Cl_2; b. H_2, Pd/C, MeOH; c. TsCl, Et_3N, DMAP, CH_2Cl_2; d. NaH, THF.

Table I. Association Constants of Ionophores and Alkali Metal Cations by the Picrate Extraction Method[a]

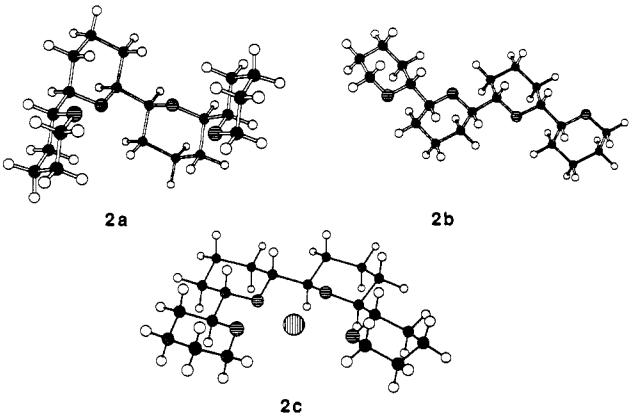
compd	Li^+	Na^+	K^+
1	6.8×10^4	9.3×10^3 [b]	$<5.0 \times 10^3$ [b]
$MeO(CH_2CH_2O)_2Me$	$<5.0 \times 10^3$ [b]	$<5.0 \times 10^3$ [b]	$<5.0 \times 10^3$ [b]
2	3.0×10^5	4.3×10^5	2.9×10^4
$MeO(CH_2CH_2O)_3Me$	1.2×10^4	$<5.0 \times 10^3$ [b]	$<5.0 \times 10^3$ [b]
12-crown-4	1.6×10^4	7.3×10^3 [b]	$<5.0 \times 10^3$ [b]
15-crown-5	1.0×10^5	4.1×10^6	7.7×10^5
18-crown-6(dicyclohexyl)	3.0×10^5	2.5×10^6	1.6×10^8

[a] Association constants from partitioning between aqueous 0.015 M picrate and $CDCl_3$ containing 0.015 M host, corrected for slight water solubility of hosts. [b] Association constants on the order of 10^3 or less are subject to considerable uncertainty.

termediates having alternating (*R*)- and (*S*)-*cis*-epoxides give the desired stereoisomers of the products. The construction of the desired polyepoxide is iterative with an overall yield of ~30% per homologation. Fragment crosscoupling was accomplished with a copper-catalyzed Grignard reaction[8] in ~70% yield using bromoepoxides **4**, **6**, and **9**. Cyclization of the epoxides **8** and **10** proceeded cleanly with camphorsulfonic acid in methylene chloride to give **11** and **12** in 74% and 43% yields, respectively, after purification on silica gel. The modest yields resulted primarily from the accumulation of diastereomers which resulted in turn from the less than perfect enantioselectivity of the cis-allylic alcohol epoxidations (~80% ee each). After closure of the final rings using base with the primary tosylate derivatives of **11** and **12**, we isolated podands **1** and **2** (mp = 103–104 °C).

As noted above, **1** and **2** are conformationally less heterogeneous than the corresponding acyclic glyme ethers. Using the MacroModel united atom AMBER force field[9] and an internal coordinate Monte Carlo conformational search,[10] we established that **1** and **2** have 10 and 25 conformers, respectively, within 3 kcal/mol of the ground state, whereas the corresponding dimethyl ethers of diglyme and triglyme have 80 and >750 conformers within the same energetic bounds. Thus the number of low-energy conformations of the linked tetrahydropyrans increases by a factor of ~2 with each additional ring, whereas the number of conformations of the ethylene glycol oligomers increases by a factor of ~10 with each added monomer unit.

Among the lowest energy conformations of **1** and **2** were several structures which resembled a segment of 18-crown-6 in its binding conformation. Conformer **2a** shown here is one such structure,



and it is preorganized for cation binding. It lies +0.1 kcal/mol above the global minimum according to MM2. Conformer **2b** was located by the conformational search at +1.7 kcal/mol and is the conformer found in the X-ray crystal structure of free **2**. Structure **2c** shows the X-ray structure of the sodium complex of **2** (thiocyanate counterion not shown). Its free ligand conformation was also found by the search and is +3.0 kcal/mol above the global minimum. Much of the relative strain of **2b** and **2c** originates from three *gauche*-butane substructures at the ring junctures. This strain may be offset by favorable packing of the relatively planar conformations within the crystal lattice.

The binding properties of **1**, **2**, the corresponding ethylene glycol oligomers, and several crown ethers were measured using Cram's picrate extraction method.[11] Comparing ligands having the same number of oxygens, **1** and **2** form stronger complexes with alkali metal cations than do the other hosts. As shown in Table I, triether **1** associates with lithium approximately 1 order of magnitude more tightly than does diglyme dimethyl ether, and **2** binds the alkali metals we examined at least 10^1–10^2 times more tightly than does triglyme dimethyl ether. Tetraether **2** binds the alkali metals approximately an order of magnitude better than does triether **1**. Ligand **2** is comparable in ionophoric properties to the crown ethers 15-crown-5 and dicyclohexyl-18-crown-6 for lithium and 1 order of magnitude weaker for sodium. Triether **1** is a more selective and 4-fold tighter binder of lithium than the lithium-selective tetraether 12-crown-4.

In conclusion, the podands **1** and **2** are preorganized into ion-binding conformations and exhibit ionophoric properties exceeding those of the other ligands examined which have the same number of oxygens. These linked tetrahydropyrans may have significant advantages over simple podands and crown ethers for selective recognition of cationic guests due to their more restricted conformational nature and their incorporation of conformation-regulating arrays of chiral centers. It is possible to reduce even further the conformational heterogeneity of the tetrahydropyranoid podands described here and thus presumably to enhance both selectivity and host/guest affinity. It is also possible to utilize the highly chiral nature of the binding sites of certain conformations (e.g., **2a**) of our enantiomerically pure **2** for recognition of chiral organic cations. Such studies will be reported in due course.[12]

Supplementary Material Available: Spectral data (IR, ^1H NMR, ^{13}C NMR, MS, and R_f) for all compounds including a listing of X-ray crystallographic data for **2** and its sodium thiocyanate complex (5 pages). Ordering information is given on any current masthead page.

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