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Two-Point Binding in Podand Acetals Favors Enantioselective Complexation.

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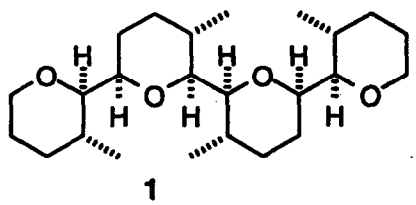
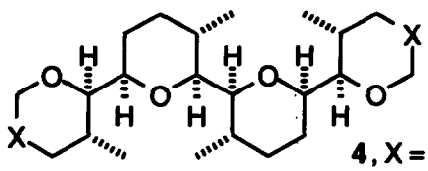
Abstract: Judicious substitution of methylene by oxygen or sulfur in podand **1** gives new ionophores **4** and **5** which selectively bind α-amino acid esters of the L configuration and amides of the D configuration.

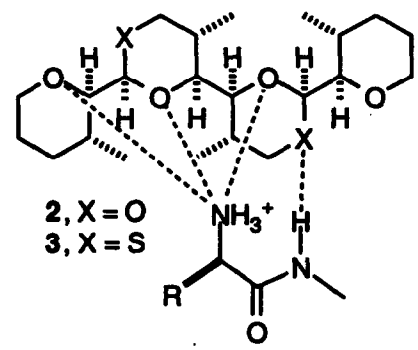
In previous studies of conformationally homogeneous podand ionophore hosts, we noted that enantioselective complexation is generally favored by systems in which the host/guest complex exists in one conformation. The simple podand **1** is a conformationally homogeneous host having a single functional group binding site. This host selectively binds primary ammonium ions having adjacent chiral centers of the S configuration. However, its complexes have several low energy conformations and its enantioselectivity is only moderate (30-40% ee).[1] By adding further functionality to the host which associates with specific guest functional groups, new structural constraints are introduced which can result in a more conformationally homogeneous complex and thus enhanced selectivity.[2] Interestingly, the podand acetals **2** and **3** which could associate with certain α-amino acid derivatives by such two-point binding as shown below failed to give significant enantioselection with such guests.[2a] One rationale suggested by molecular modeling is that two-point binding[3] is geometrically difficult to attain with **2** or **3** but would be more favorable if the acetals were moved from the inner to the outer THP rings. In this communication, we test this hypothesis by preparing and studying the binding properties of the new podand acetals **4** and **5**.



1

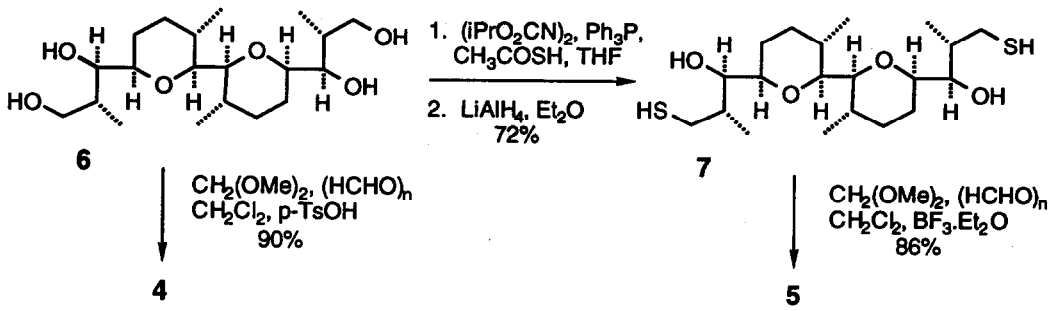


4, X = O
5, X = S

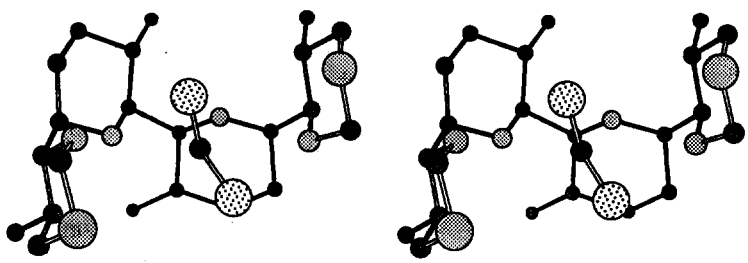


2, X = O
3, X = S

As shown below, synthesis of the new receptors **4** and **5** was straightforward from the previously described[1] tetraol **6**, an intermediate in the synthesis of **1**:



The most significant property of podands related to **1** is their stereochemically-enforced conformational homogeneity. Given the structural similarity of **1**, **4** and **5**, it is not surprising that all appear to have similar conformations according to ^1H nmr coupling constant analysis. Indeed, x-ray crystallography finds these three receptors to have the same conformation which possesses an open, oxygen-lined cation binding site as shown in the x-ray structure of **5**/CH_2Cl_2:



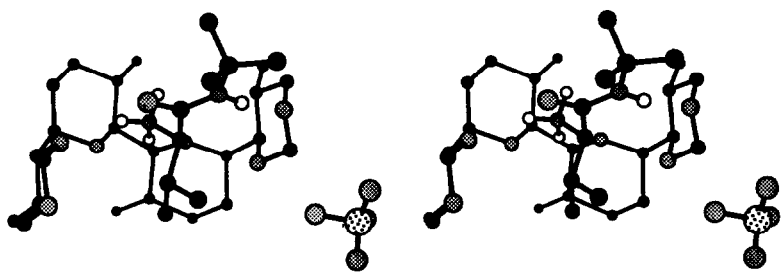
Enantioselective binding properties of the new podand acetals **4** and **5** were measured by extraction of D_2O solutions of excess racemic ammonium hexafluorophosphate with $CDCl_3$ solutions of podand.[4] The results are given in the Table along with previously reported[1] data for **1**. In marked contrast to the previously described podand acetals **2** and **3** which showed no measurable enantioselectivity in binding amino acid amides, acetals **4** and **5** displayed enantioselectivities up to 0.5 and 1.2 kcal/mol respectively. Another striking finding is that α-amino acid amides of the D configuration are bound selectively by podands **4** and **5**, whereas the corresponding esters are preferentially bound as the L configuration where selectivity is observed. Furthermore, enantioselectivity is generally higher with the amide guests, a result which is compatible with the 2-point binding proposal given in the introduction.

Table. Enantioselective Extractions of α-Amino Acid Derivatives by Podands.*

Guests	Podand Ionophore Hosts		
Amino Acid *Esters*:	1	4	5
Me Phenylglycine	L, 40% ee (82%)	<5% ee (85%)	L, 51% ee (82%)
Me Phenylalanine	L, 36% ee (97%)	<5% ee (90%)	L, 23% ee (90%)
Me Alanine	L, 40% ee (39%)	<5% ee (17%)	L, 20% ee (18%)
Me Valine	L, 34% ee (38%)	<5% ee (32%)	L, 20% ee (21%)
Amino Acid *Amides*:			
Bn Phenylglycine	L, 20% ee (20%)	D, 25% ee (70%)	D, 26% ee (45%)
Me Phenylalanine	-	D, 35% ee (33%)	D, 50% ee (35%)
Bn Alanine	-	D, 42% ee (56%)	D, 45% ee (50%)
Bn Valine	-	D, 35% ee (53%)	D, 78% ee (45%)
tBu Valine	-	D, 30% ee (60%)	D, 70% ee (42%)

*Extractions of excess PF_6 salt of racemic guest (0.5M) in D_2O with $CDCl_3$ solution of host (10 mM) at 25 °C. Table entries give the absolute configuration of the preferentially extracted guest, % enantiomeric excess of extracted guest, and (% of host bound by extracted guest).

In the crystal state, the complex of **4** and (D)-valine *tert*-butyl amide perchlorate also shows 2-point binding as revealed in the crystal structure below in stereo:



The shortest ether/ammonium hydrogen bonds range in length from 2.1 to 2.4Å while the secondary amide/ether hydrogen bond is 2.2Å.

Without two-point binding, enantioselectivity based on simple steric effects seems to play little role in the binding properties of our new podands: both enantiomers of α-phenethylammonium are bound by **4** and **5** to nearly the same extent. While the hemithioacetal host **5** is generally more enantioselective than acetal **4**, it is also a slightly poorer ionophore as measured by extraction ability. The novel binding properties of **5** in particular may be related to the highly polarizable nature of sulfur. Thus, thioether functionality may function not only as a hydrogen bond acceptor (thus binding D-amides), but may also associate with other polar functional groups in some different orientation by dipole/induced-

dipole interactions (thus conceivably binding L-esters). Polarization effects have been implicated previously as being important in host/guest association.[5]

While the 2-point binding model provides a qualitative rationale for the binding properties of **4** and **5**, insight sufficient to allow realistic *predictions* of binding selectivity with such molecules will likely require sophisticated molecular modeling. As found here and implicit in several previous reports,[6] significant (enantio)selectivity can originate from effects which are difficult to visualize with physical molecular models. It is likely that many of the qualitative descriptions commonly given to rationalize selectivity are only crudely related to the actual physical situation, especially when the complexes involved are conformationally heterogeneous. Similar conclusions will apply to complexes involved in the transition states of chemical reactions.[7]

Notes and References.

1. X. Wang, S.D. Erickson, T. Iimori and W.C. Still, *J. Am. Chem. Soc.*, **114**, 4128 (1992) and references therein.

2. Examples: a. G. Li and W.C. Still, *J. Org. Chem.*, **56**, 6964 (1991); b. A. Armstrong and W.C. Still, *J. Org. Chem.*, submitted (1992).

3. W.H. Pirkle and T.C. Pochapsky, *Chem. Rev.*, **89**, 347 (1989); W.H. Pirkle, K.C. Deming and J.A. Burke, *Chirality*, **3**, 183 (1991).

4. a. E.B. Kyba, J.M. Timko, L.J. Kaplan, F. de Jong, G.W. Gokel and D.J. Cram, *J. Am. Chem. Soc.*, **100**, 4555 (1978); b. S.C. Peacock, L.A. Domeier, F.C.A. Gaeta, R.C. Helgeson, T.M. Timko and D.J. Cram, *J. Am. Chem. Soc.*, **100**, 8190 (1978).

5. D.A. Stauffer, R.E. Barrans, Jr., and D.A. Dougherty, *J. Org. Chem.*, **55**, 2762 (1990); S.K. Burley and G.A. Petsko, *Adv. Prot. Chem.*, **39**, 125 (1988); and references therein.

6. Examples: P.P. Castro, T.M. Georgiadis and F. Diederich, *J. Org. Chem.*, **54**, 5834 (1989); D.B. Smithrud, E. Sanford, I. Chao, S.B. Ferguson, D.R. Carcanague, J.D. Evanseck, K.N. Houk and F. Diederich, *Pure and Appl. Chem.*, **62**, 2221 (1990); ref 2a.

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