Podand Sulfones. Enantioselective Receptors for Peptidic Ammonium Ions

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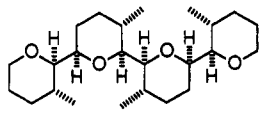
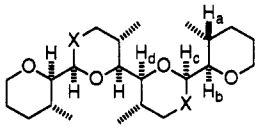
Summary: Sulfone analogues of previously prepared tetrahydropyranoid podand receptors bind C-terminal amides and esters of α-amino acids with enantioselectivity as high as 80% ee. X-ray structures of the free receptor and several of its complexes are reported.

Methylated podands such as 1 below form an important class of nonmacrocyclic hosts for cations which are conformationally homogeneous and bind simple chiral ammonium ions enantioselectively.[1] The enantioselection



1



2, X = O
3, X = S
4, X = SO_2

previously observed with the simple podand ether 1 is modest (up to 40% ee) and derives from the differing steric demands of the substituents at the guest chiral center. In this communication, we describe the more highly functionalized podands 2–4 which can distinguish guest substituents on other than steric grounds. These receptors are easy to prepare and have cation-binding properties which are very different from those of 1. In particular, we find that the sulfone podand 4 binds ammonium ions derived from naturally occurring α-amino acids with enantioselectivity[2] exceeding that of 1 by up to 1 kcal/mol.

Enantiomerically pure podands 2–4 were prepared as outlined in Scheme I. Starting material 5 is commercially available[3] and 6 is an intermediate in our previous synthesis[1b,d] of 1. While most of the transformations employ standard methods, we note that the highly electrophilic PhSeOTf[4] proved much more effective than common reagents such as PhSeCl at cyclizing 8. While acetalization of aldehyde 9 with tetrol 6 gave 2 (40%) among other diastereomeric acetals, thiol 10 formed the equatorial hemithioacetal stereochemistry almost exclusively to provide 3 in 61% yield. The stereochemical assignment at the newly created chiral centers followed from the C_2 symmetry of the product and a ~10% NOE between H_c and H_d. Oxone converted 3 to crystalline sulfone 4 (mp = 291–292 °C).

The ^1H NMR spectra of the new podands 2–4 were quite similar. The observed 1.3–1.9-Hz H_b/H_c coupling indicated a gauche relationship while the 9.6–10.2 Hz H_a/H_b coupling implied anti stereochemistry for the outside THP rings. The X-ray crystal structure[5a] of 4 (shown below in stereo, Chart I) indicates that 4 has essentially the same conformation as the parent podand 1. This and other crystal structures (see below) indicate that the conformational locking mechanism[1b] used to rigidify the receptor in the desired binding conformation is not undone by the sulfone functionality in spite of 1,3-syn oxygen/oxygen contacts.

To measure the enantioselective binding properties of podands 2–4, we extracted excess racemic organoammonium hexafluorophosphate guests from D_2O with $CDCl_3$ solutions of our podands.[2c,d] Since the resulting

Scheme I

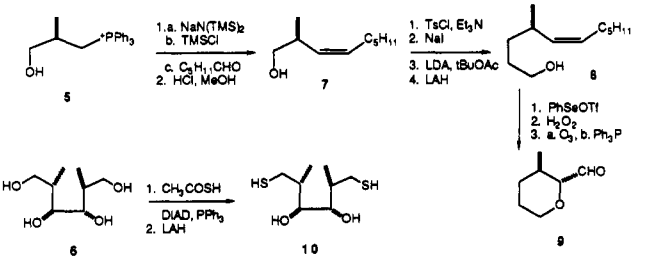
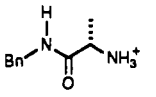
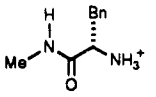
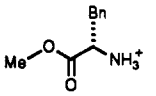
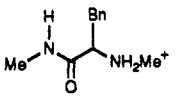
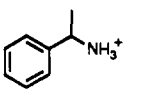
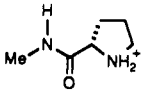
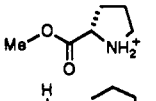
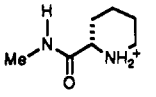


Table I. Enantioselective Binding with Podand 4 to Chiral Ammonium Hexafluorophosphates

	enantioselection[a] (% ee)	extraction[b] (%)
	40	40
	52	80
	60	95
	<5	67
	<5	99
	80	66
	78	99
	58	40

[a] Enantiomeric excess of indicated ammonium ion extracted from excess racemic ammonium PF_6^- (0.5 M) in D_2O by podand 4 (0.01 M) in $CDCl_3$ at 25 °C. [b] Percentage of podand which is bound to ammonium salt after extraction into $CDCl_3$.

(1) (a) Iimori, T.; Still, W. C.; Rheingold, A. L.; Staley, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 3439. (b) Iimori, T.; Erickson, S. D.; Rheingold, A. L.; Still, W. C. *Tetrahedron Lett.* **1989**, *30*, 6947. (c) Erickson, S. D.; Still, W. C. *Tetrahedron Lett.* **1990**, *31*, 4253. (d) Wang, X.; Erickson, S. D.; Iimori, T.; Still, W. C. *J. Am. Chem. Soc.*, submitted for publication.

(2) Cf. (a) Kyba, E. B.; Koga, K.; Sousa, L. S.; Siegel, M. G.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2692. (b) Helgeson, R. C.; Timko, J. M.; Moreau, P.; Peacock, S. C.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 6762. (c) Kyba, E. B.; Timko, J. M.; Kaplan, L. J.; de Jong, F.; Gokel, G. W.; Cram, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 4555. (d) Peacock, S. C.; Domeier, L. A.; Gaeta, F. C. A.; Helgeson, R. C.; Timko, T. M.; Cram, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 8190. (e) Huszthy, P.; Bradshaw, J. S.; Zhu, C. Y.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1991**, *56*, 3330. (f) Davidson, R. B.; Bradshaw, J. S.; Jones, B. A.; Dauey, N. K.; Christensen, J. J.; Izatt, R. M.; Morin, F. G.; Grant, D. M. *J. Org. Chem.* **1984**, *49*, 353.

(3) Available from Aldrich Chemical Co.

(4) Murata, S.; Suzuki, T. *Chem. Lett.* **1987**, 849.

(5) Crystal structures determined by (a) Michael Chang, Washington University, or (b) John C. Dewan, New York University.

0022-3263/91/1956-6964$02.50/0

Chart I. X-ray Structure of 4

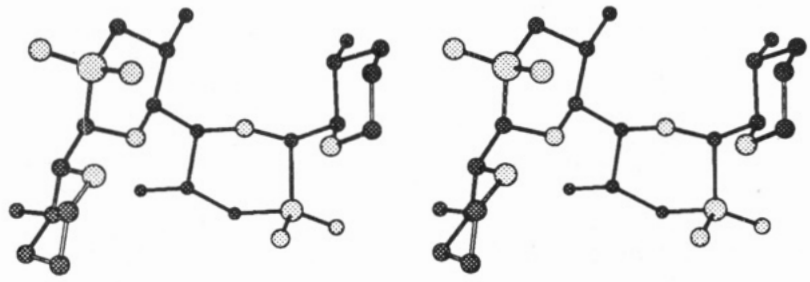


Chart II. X-ray Structure of 4/(*S*)-α-Phenethylammonium Perchlorate[5b]

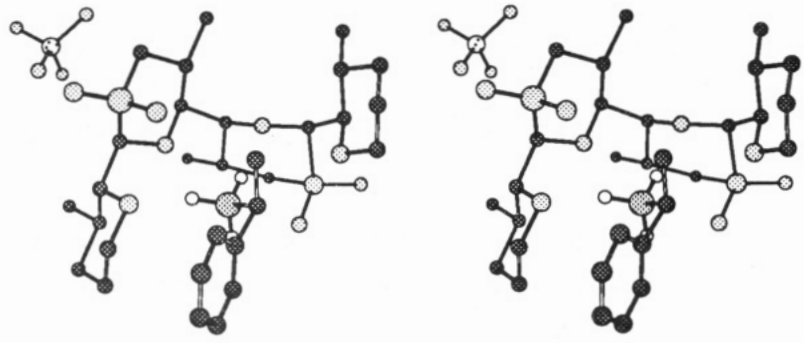


Chart III. X-ray Structure of 4/L-Proline Methyl Ester Perchlorate[5a]

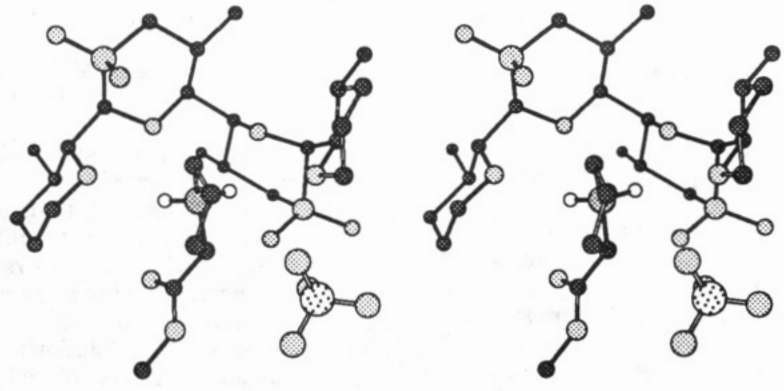
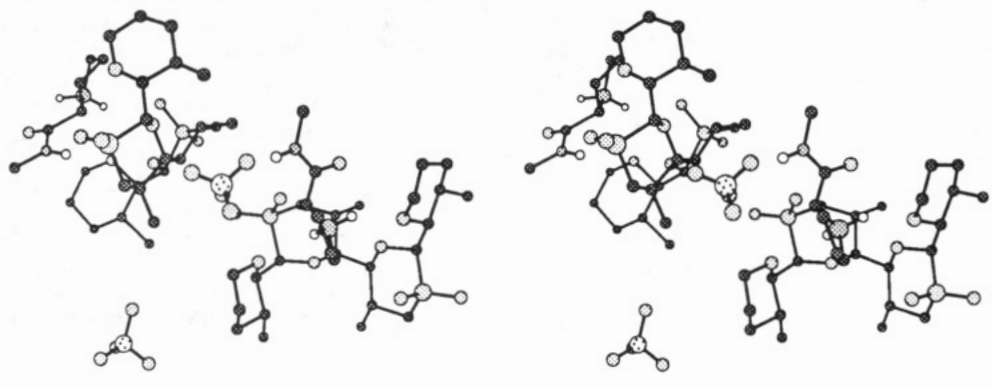


Chart IV. X-ray Structure of 4/L-Proline *N*-MethylAmide Perchlorate[5b]



diastereomeric complexes were distinct by ^{1}H NMR, integration of resolved guest peaks gave enantioselectivity directly. The results are shown in Table I.

While podands **2** and **3** showed negligible enantioselectivity with all chiral ammonium salts tested, salts of simple α-amino acid esters and amides bound to the sulfone podand **4** with enantiomeric excesses as high as 80%. The diminished selectivity with **2** and **3** relative to the parent **1** may be due to the increased number of hydrogen bond accepting atoms (six vs four) which give rise to more binding modes and consequently less selectivity. With **4**, on the other hand, the two sulfone oxygens which project into the ion-binding cavity may dominate over the four ethereal oxygens in ligating cations. Thus, the hydrogen bond accepting sites appear to be more localized in **4** than they are in **2** or **3**.

By cocrystallizing podand **4** and certain chiral ammonium perchlorates from CH_2Cl_2/hexane, we obtained crystals and solved x-ray structures of a number of the complexes.[5] With (*S*)-α-phenethylammonium (see below, Chart II), all three of the ammonium hydrogens form hydrogen bonds with podand oxygens. With the (*R*)-α-

phenethylammonium complex, a similar X-ray structure was found except that the positions of methyl and phenyl substituents were switched. With the L-proline ester perchlorate (Chart III), 4 forms a complex having the ammonium ion at the center of the binding site and the ester group placed in an electrostatically favorable location relative to nearby tetrahydropyranyl ether and sulfonyl dipoles. The L-proline amide complex (Chart IV) has two forms in the crystal, one similar to the ester complex and one having simultaneous ammonium NH and amide NH hydrogen bonding to the two sulfone groups. All of these structures have spatially separated ammonium and perchlorate ions and differ qualitatively from the X-ray structures of the corresponding complexes of 1 which show contact ion pairing. The absence of ion contact in the X-ray structures of five distinct complexes of 4 probably reflects the large electrical polarization of the sulfone S=O bond which makes 4 a better ligand than 1 for cations. Experimentally, we find that 4 is the most effective podand we have studied at extracting ammonium ions from water.

These and other studies support the notion that host/guest selectivity is a function not only by host preorganization but also of the number and flexibility of the conformations of the complex itself. In general, selectivity between guests should be best when the complexes as well as hosts have single well-defined conformations. One way to create such recognition systems is to build specific host/guest functional group interactions into the complex.[6]

(6) This work was supported by NIH Grant HL25634.

Subtle Effects in the Asymmetric Epoxidation: Dependence of Kinetic Resolution Efficiency on the Monodentate Alkoxide Ligands of the Bystander Titanium Center

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Summary: Complexes of diisopropyl tartrate and Ti(O^tBu)$_4$ were found to catalyze the kinetic resolution of racemic, secondary allylic alcohols with surprisingly low efficiency relative to those generated from Ti(O^iPr)$_4$. This effect is documented and its implications are discussed.

In the course of our studies on the mechanism of the asymmetric epoxidation we have, on occasion, employed a ligand variation approach.[1] Along these lines, both singly and doubly[2,3] linked tartrate ligands were synthesized and assayed for their performance in the asymmetric epoxidation of prochiral and racemic allylic alcohols. Asymmetric epoxidation of the latter lead to kinetic resolution.[4] Singly linked tartrate ligands gave complexes with Ti(O^tBu)$_4$ which efficiently catalyzed asymmetric epoxidation of allylic alcohols, whereas they were not capable of affecting satisfactory kinetic resolution of racemic, secondary allylic alcohols. We concluded that this effect was the result of stereochemical restrictions imposed by the linked tartrate on the loaded catalyst,[2] but a key control experiment, overlooked in the original study,[2] now reveals that this conclusion was wrong. As seen in entry 2 of Table I, an ineffective catalyst system is generated from Ti(O^tBu)$_4$ *even* when using the conventional, unlinked tartrate ligand, diisopropyl tartrate. This report presents evidence tying this lack of efficient kinetic resolution to the steric influence of the monodentate (nontartrate) alkoxide on the bystander titanium center of the dimeric catalyst.

As is well-known and shown in Table I, "standard" asymmetric epoxidation catalysts generated from titanium isopropoxide are very efficient at kinetic resolution. Simply changing the alkoxide from isopropoxide to *tert*-butoxide greatly reduces the ability of the complex to perform kinetic resolution. Kinetic resolution efficiency is often described in terms of k_f/k_s, k_f and k_s being the rate constants for epoxidation for the faster and slower reacting enantiomers, respectively. Useful levels of enantiomeric excess in the unreacted allylic alcohol may be obtained with a k_f/k_s of 5 or more.[4]

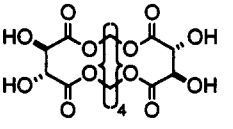
The existence of this subtle effect is easily demonstrated, but its cause is obscured by the difficulties of knowing the catalyst composition in these rapidly exchanging early transition metal alkoxide systems. The differences between the two systems lead us to believe that in Ti(O^iPr)$_4$-based kinetic resolution catalysts, bulky secondary allylic alcohols (such as cyclohexylpropenylcarbinol) do not to a significant extent displace the spectator isopropoxide ligands. If they did, the Ti(O^tBu)$_4$- and Ti(O^iPr)$_4$-based catalysts would be identical. Although exchange may be rapid, the equilibrium mixture will be dominated by complexes having isopropoxide as the bystander ligand. In Ti(O^tBu)$_4$-based catalysts, however, the *tert*-butoxide and the bulky secondary allylic alcohol have more similar steric

† Address correspondence to this author at Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, CA 92037.

(1) (a) Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 4016. (b) Burns, C. J.; Martin, C. A.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2826.

(2) See ref 1a.

(3) Kalantar, T. H., Ph.D. Thesis, Massachusetts Institute of Technology, 1990. The doubly linked tartrate ligand was of the structure shown below.



(4) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamado, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(5) This number is obtained from the equation

$$\frac{k_f}{k_s} = \frac{\ln (A/A_o)}{\ln (B/B_o)} = \frac{\ln [(1-c)(1-ee)]}{\ln [(1-c)(1+ee)]}$$

where c is the fraction of consumption of racemate and ee is % ee/100.

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