(Lilly Research Laboratories) for a gift of natural hikizimycin.

Supplementary Material Available: IR, ^1H and ^{13}C NMR, and mass spectral and analytical data for **1–6**, **8**, **9**, **11**, **12**, **14**, and hikizimycin and ^1H NMR spectra of natural and synthetic hikizimycin (8 pages). Ordering information is given on any current masthead page.

Strong Binding of Ditopic Substrates by a Doubly Linked Occlusive C_1 "Clamshell" as Distinguished from an Aversive C_2 "Loveseat" Cyclodextrin

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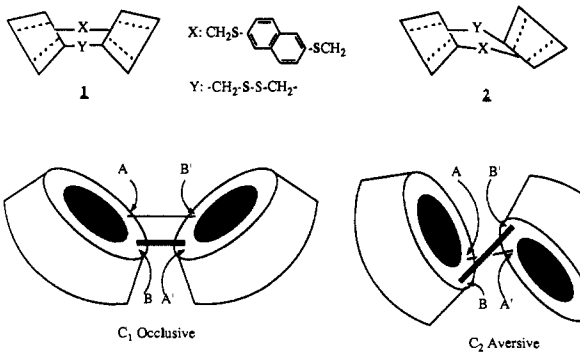
We[1] and others[2,3] have described various dimers of β-cyclodextrin linked at the C-6 carbon. With some of them, and appropriate rigid ditopic substrates, we saw[1] binding constants in water up to 7×10^8 M^{-1}, into the region of many antigen–antibody binding constants. One would expect even stronger binding with dimers having better defined optimal geometry. We have now prepared two cyclodextrin dimers doubly linked at adjacent sugar residues, converting the previous flexible linkage into a hinge. As hoped, the isomer **1** with occlusive geometry can close on a ditopic



substrate like a clamshell, leading to very strong binding. The isomer **2** with aversive geometry aims the two cyclodextrin rings away from each other and shows no cooperative binding of ditopic substrates.

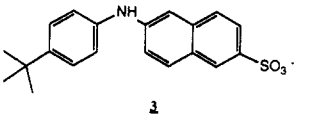
Reaction of β-cyclodextrin 6A,6B diiodide[4] with naphthalene-2,6-dithiol afforded a mixture of iodocyclodextrin dimers linked A–A′, A–B′, and B–B′. This mixture was directly converted to the bisthioacetate esters by displacement with potassium thioacetate, which were then hydrolyzed to the dithiol and air oxidized to the disulfide. The major dimeric product from this, isolated by repeated chromatography, was the aversive isomer **2**, whose C_2 symmetry was revealed in its H NMR spectrum, with three 2-proton naphthalene signals.[5] It had the expected FAB-MS peak at M + 1 = 2455. Strikingly, one of the two possible C_2 isomers predominated, to which we tentatively assign the structure **2**, with the naphthalene ring linking B and B′ positions. The 6A and 6B positions are diastereomeric, and molecular models suggest that C-6A could be strongly shielded by the iodine on C-6B. Only weak signals were seen from the other C_2 isomer, to which we assign the A–naphthalene–A′ structure.

Table I. Binding Constants in H_2O at 25 °C

host	substrate	K_f, M^{-1}
1 (occlusive)	BNS **3**	4×10^6
1 (occlusive)	**4**	$(4.0 \pm 0.2) \times 10^8$
1 (occlusive)	**5**	$(1.0 \pm 0.1) \times 10^{10}$
2 (aversive)	BNS **3**	2×10^5
2 (aversive)	di-*p*-*tert*-butylphenyl phosphate	1×10^5
2 (aversive)	4,4′-di-*tert*-butylphenyl benzoate	$<5 \times 10^4$
β-cyclodextrin-6,6′-disulfide	BNS **3**	5×10^6 [1]

Because one of the two positions in the diiodide is more reactive than the other, the A–naphthalene–B′-linked dimer **1** was formed in lower yield than was **2**, but it could be isolated by selective precipitation and chromatography. It showed six 1-proton signals for the naphthalene hydrogens in the H NMR[6] and also had the expected FAB-MS peak at M + 1 = 2455. The structure assignments to **1** and **2** were confirmed by their binding properties.

The aversive dimer **2** cannot bind a simple ditopic substrate using both its cavities simultaneously. The binding constant of the fluorescent ditopic substrate BNS **3** (Table I) is only slightly



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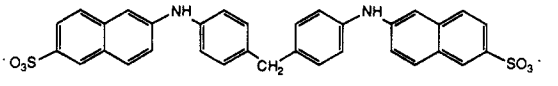
higher than that for β-cyclodextrin itself, presumably because of some extra hydrophobic interaction with the naphthalene linker. However, **1** binds BNS more strongly, even though BNS is a little short to occupy both cavities of **1** well. Ditopic substrates with appropriate length bind very strongly, and fluorescence competition techniques were needed to determine the binding constant. The fluorescent dimer **4** was prepared by Bucherer reaction[1,7] of



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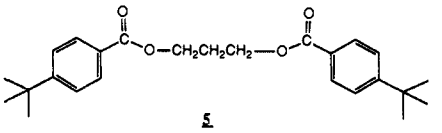
bis-*p*-anilinomethane with 2-aminonaphthalene-6-sulfonic acid. Substrate **4** is fluorescent when bound to **1**, but the fluorescence is quenched in free H_2O solution. The binding constant of **4** to **1** was determined by dilution; the value, 4×10^8 M^{-1}, is listed in Table I. Then an excess of **4** was allowed to compete for **1** with the long flexible substrate **5**, and from this competition the binding



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constant of **5** to **1** was determined. The value of 1×10^{10} M^{-1} puts it in the range of very strong antigen–antibody complexes.

The particular linkages selected in **1** hold the two cyclodextrin rings at an angle, so **1** should more readily bind bent substrates than linear ones. Indeed, we find that the rigid nonlinear substrate **6** has a K_f with **1** even higher than that of **5**, while binding of the linear analogue **7** is considerably weaker. Thus, **1** is a good candidate to use some of its very large binding energy for rate

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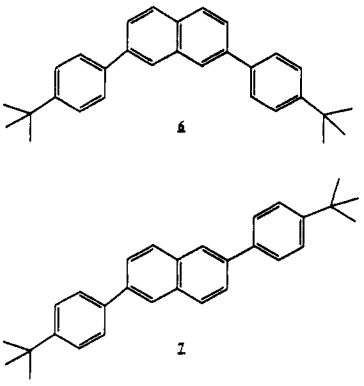

acceleration, by binding a bent transition state more readily than it binds a linear starting material. If this can be achieved, the resulting catalysis will put cyclodextrin dimers even more clearly into close resemblance to antibodies.

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Synthesis and Reactions of Enantiomerically Pure Molybdenum π-Complexes of 2*H*-Pyran. A General Approach to the Enantiospecific Synthesis of *cis*-2,5-Disubstituted 5,6-Dihydro-2*H*-pyrans and *cis*-2,6-Disubstituted Tetrahydropyrans

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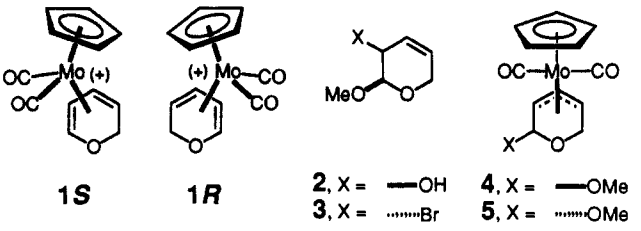
Although transition-metal π-complexes of unsaturated hydrocarbons have been investigated extensively for their applications to organic synthesis, there have been surprisingly few studies of the synthetic potential of isolated transition-metal π-complexes of unsaturated heterocycles.[2-6] Transient palladium species have been utilized in a variety of carbohydrate synthesis applications.[7-13] We describe herein the enantiospecific synthesis of both enantiomers of (η^5-cyclopentadienyl)(dicarbonyl)(η^4-2*H*-pyran)molybdenum tetrafluoroborate (**1S** and **1R**)[14] from D- and L-arabinose, respectively, and the use of these reactive electrophiles in an enantiospecific synthesis of *cis*-2,6-disubstituted tetrahydropyrans and *cis*-2,5-disubstituted 5,6-dihydro-2*H*-pyrans.



1S **1R** **2**, X = —OH **3**, X = ····Br **4**, X = —OMe **5**, X = ····OMe

(5*S*,6*R*)-5-Hydroxy-6-methoxy-5,6-dihydro-2*H*-pyran (**2**), readily available on a large scale from D-arabinose,[15] was converted into the allylic bromide **3** on reaction with $PPh_3/CBr_4/R_4NBr$ (92% yield, four isomeric allylic bromides formed, 91% selectivity for **3**). Following precedent established by Faller and Pearson,[16,17] **3** was converted into (η^5-cyclopentadienyl)(dicarbonyl)-[(2*R*,3*R*)-(3,4,5-η)-2-methoxy-5,6-dihydro-2*H*-pyran-5-yl]molybdenum (**4**) in 72% yield by treatment with $Mo(CH_3CN)_3(CO)_3$ in acetonitrile followed by LiC_5H_5. Treatment of **4** with HBF_4 in diethyl ether led to a low yield of the desired cation **1S**; however, prior epimerization of **4** to the exo isomer **5** (cat. *p*-TSA, CH_2Cl_2, MeOH) followed by ionization with HBF_4 in ether gave **1S** in 88% yield.[18] The enantiomeric molybdenum complex **1R** was prepared in an identical fashion from L-arabinose.

The enantiomerically pure cationic molybdenum complexes **1S** and **1R**, although stable and handled without special precautions, were potent electrophiles and reacted with a wide range of nucleophiles exclusively at the terminus of the coordinated diene adjacent to the oxygen (Table I). Nuclear Overhauser enhancement experiments allowed assignment of nucleophile stereochemistry as anti to the metal. The range of carbon nucleophiles that participated in efficient reaction is particularly noteworthy. In addition to high-yield carbon–carbon bond formation with a stabilized carbanion such as sodio malonate, good yields of products were obtained with unstabilized enolates of simple esters and keto imines and from simple organometallics such as Grignard reagents and lithium organometallics. All three levels of carbon hybridization were accommodated in the nucleophilic addition. The products (**6**) were formed with a minimum of 96% enantiomeric excess.[19]

The value of the enantiomerically pure molybdenum cations **1S** and **1R** in enantiospecific synthesis was demonstrated in two ways. The preparation of both enantiomers of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**7**) is shown in Scheme I, the *S,S* isomer being a component of the scent gland secretion of *Viverra civetta*.[9,20-29] Allyl molybdenum complex **6b** (Table I, entry 2) was converted into cationic diene complex **8**, which underwent high-yield addition of $LiCH_2COOMe$ leading to formation of the cis-disubstituted molybdenum allyl **9a**. After hydrolysis of the methyl ester **9a** to the carboxylic acid **9b**, demetalation produced an approximate 1:1 mixture of olefin re-

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