Molecular Recognition of Cyclitols by Neutral Polyaza-Hydrogen-Bonding Receptors: The Strength and Influence of Intramolecular Hydrogen Bonds between Vicinal Alcohols

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Abstract: Polyaza-clefts **1**, **2**, and **3** were investigated as receptors for cyclohexane diols and triols (**23**, **24**, **25**) in chloroform. The receptors were designed to form hydrogen bonds to the triols from above and below the cyclohexane rings. The synthesis of the receptors was accomplished by two different routes, beginning with either the central or the peripheral pyridine rings. Binding studies performed in chloroform gave only moderate binding constants of 2–110 M^{-1}. For the binding of **2** with **23**, $\Delta H = -4.5$ and $T\Delta S$ at 295 K $= -1.8$ kcal/mol. Molecular dynamics studies suggest that binding of the triols involves the formation of four intermolecular hydrogen bonds and the cleavage of one intramolecular cyclitol hydrogen bond. IR studies confirm that the diols and triols possess intramolecular hydrogen bonds under the experimental conditions for the binding studies. The strength of the *trans* intramolecular hydrogen bond in *trans*-1,2-cyclohexanediol is 1.93 ± 0.08 kcal/mol, as determined by examination of the conformational equilibrium of compound **29**. The strength of a *cis* intramolecular hydrogen bond was found to be 2.22 ± 0.16 to 2.51 ± 0.13 kcal/mol, as determined by measuring the equilibrium between the α and β anomers of **33** and **34**. When considering the strength of one intramolecular hydrogen bond, the binding constants correlate well with literature values for four hydrogen bonds in a host–guest complex. In addition, the differential strength of the *cis* and *trans* intramolecular hydrogen bonds correlates well with the selectivities of binding the triols with **1** and **2**. Future saccharide receptors in nonpolar organic solvent will need to effectively compete with or complement the intramolecular hydrogen bonds to achieve large association constants.

Introduction

Carbohydrates constitute the bulk of organic matter on Earth.[1] They play key roles in many biological functions such as structure formation, energy storage, and metabolism. During saccharide metabolism the sugars are transported through cellular membranes. Nature has evolved elaborate proteins for such transport. For example, L-arabinose-binding protein (ABP), found in the periplasm of gram-negative bacteria,[2] transports its guests across cell membranes and is involved in respiratory action, cell–cell communication, and chemotaxis. The crystal structure of ABP,[2] as well as other sugar transport proteins,[3] has been determined by Quiocho (Figure 1). A common feature of the protein–sugar complexes is that each of the sugar hydroxyls (except the anomeric hydroxyl) participates in one donor and one or more acceptor interactions. In addition, amino acids with planar side chains, such as arginine, asparagine, aspartic acid, and glutamic acid, are used to form hydrogen bonds. Mimicking these binding strategies of ABP may lead to successful artificial agents for saccharide transport.

Despite the importance of carbohydrates, only a limited number of hydrogen-bonding abiotic receptors have been targeted for saccharide complexation.[4-9] Also, few receptors for other hydroxy guests have been explored.[11] Unlike other potential biological targets, such as planar DNA bases, the three-dimensional shape of sugars suggests the use of a three-dimensional receptor. Therefore, macrocyclic receptor designs have been the most prevalent. For example, Aoyama has reported that a resorcinol–aldehyde cyclooligomer is capable of extracting D-ribose, but not D-glucose, from water into carbon tetrachloride.[4a] In continuing work, Aoyama studied the binding of this receptor with different cyclohexanediols in chloroform.[4b] Most recently, the ability of this macrocycle to bind sugars in water has been reported.[4c] In 1990, Davis and colleagues found that a cyclophane can bind a β-*n*-dodecyl-D-glucoside in chloroform.[5] This macrocycle bears six functional groups with hydrogen bond donor–acceptor properties: four hydroxyls and two secondary amides. The

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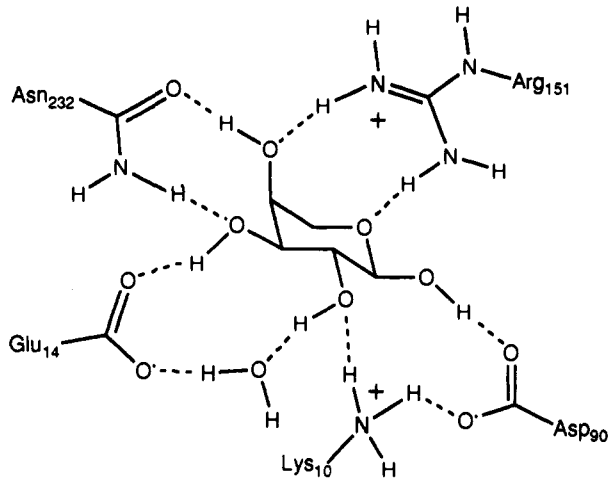
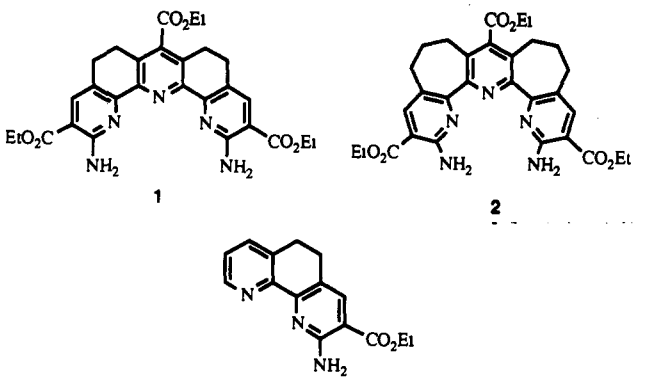


Figure 1. Binding site of ABP showing the two-point hydrogen bonding of ditopic amino acid side chains to 1,2-diols of sugar moieties and water.

receptor forms a 1:1 complex with a glucoside involving six proposed hydrogen bonds. A similar receptor based upon cholic acid has also been found by Burrows to bind saccharides.[6] In another macrocyclic approach, Still studied a C_3-symmetric receptor which can bind *N*-methylamides of α-amino acids with high selectivity,[7a] as well as octyl glucosides in chloroform.[7b] In higher dielectric media, Gellman has targeted amino sugars with macrocycles in chloroform–methanol mixtures,[8] and Penades and co-workers used a cyclophane, formed by the combination of saccharides and aromatic surfaces, to bind sugars in water.[9] Finally, in a nonmacrocyclic approach, Greenspoon studied the use of inverse micelles (sodium succinate surfactant aggregates in chloroform/cyclohexane) as a model for the binding site of carbohydrate binding proteins.[10]

Our initial efforts at saccharide complexation were focused on analyzing the energetics of cyclohexanediol and triol (cyclitol) recognition by polyaza-clefts in chloroform.[12a] The use of cyclitols instead of monosaccharides allows an energetic analysis that is not complicated by multiple host–guest geometries due to the reduced number of hydroxyls compared to pyranosides. The binding was found to be weak to moderate in magnitude, and in order to improve the binding, it was deemed important to delineate those factors that assist or impede saccharide complexation. On the basis of these early studies, we concluded that the complexation of cyclitols is strongly impeded by the intramolecular hydrogen bonds within the guests.[12b]

This manuscript describes studies supporting the hypothesis that breaking the intramolecular hydrogen bonds in the guests controls the selectivity and the magnitude of binding constants between cyclitols and polyaza-clefts **1**, **2**, and **3**. After a discussion of the design and synthesis of the receptors, the Gibbs free energy of binding of triols will be compared with diols. In addition, the Gibbs free energy of binding by "full receptors" (**1**, **2**) and "half receptor" (**3**) will be contrasted. The binding constants and the intermolecular hydrogen bond strengths are lower than may be predicted. Molecular modeling and IR studies are then presented which support the existence of intramolecular hydrogen bonds within cyclitols and the cleavage of one intramolecular hydrogen bond within the triols upon complexation with the receptors. In order to quantitate the influence of breaking intramolecular hydrogen bonds upon binding, a determination of the strengths of *cis* and *trans* intramolecular hydrogen bonds between vicinal diols is presented. Finally, the strengths of the intramolecular bonds are directly correlated to the selectivity of binding cyclitols and the magnitude of the binding constants. The data lead to the conclusion that intramolecular hydrogen bonds act to internally solvate saccharides in low-dielectric media and thus will deter hydrogen-bond-driven molecular recognition.



Results and Discussion

A. Design Criteria. As a starting point for the design of saccharide receptors, the binding site of ABP, as well as other transport proteins, was studied. The analysis revealed a common strategy of hydrogen-bonding molecular recognition of vicinal diols. This strategy was then incorporated into a cleft that could complement a cyclohexanetriol. As shown in Figure 1, ABP uses amino acid side chains that form two hydrogen bonds, one to each hydroxyl on adjacent alcohols. In order to mimic this pattern, we chose to use the 2-aminopyridine group, which resembles the asparagine side chain. The pyridine nitrogen can accept a hydrogen bond, while the amino group can donate. This moiety has been used extensively to bind amide[13] and carboxylic acid[14] functional groups. The 2-aminopyridine group can also bind a single hydroxyl, although the hydrogen bond angles in this motif are significantly less than 180°. The hydroxyl in the latter motif, however, benefits from the cooperative effect on hydrogen bonding.[15]

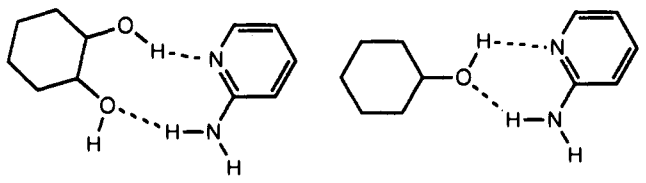


Figure 2 shows the approach for combining the 2-aminopyridine rings into a cleft complementary to a cyclohexanetriol. The cleft is V-shaped, the sides of which are located above and below the plane of a bound cyclohexane ring. Each side of the "V" binds to an alcohol from an opposing face of the cyclohexane ring. The 2-aminopyridine groups converge due to the terpyridine structural motif, and the V-shape is imparted by restricting the pyridine rotations.

Compounds **1** and **2** are the receptors discussed herein which conform to the V-shaped design and incorporate 2-aminopyridine

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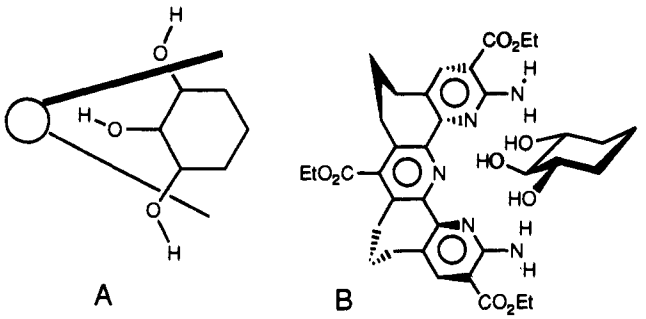


Figure 2. (A) V-shaped receptor design converges hydrogen bond donating and accepting groups from above and below the cyclohexane ring. (B) Schematic representation of how the twist in compound **2** spans a triol moiety.

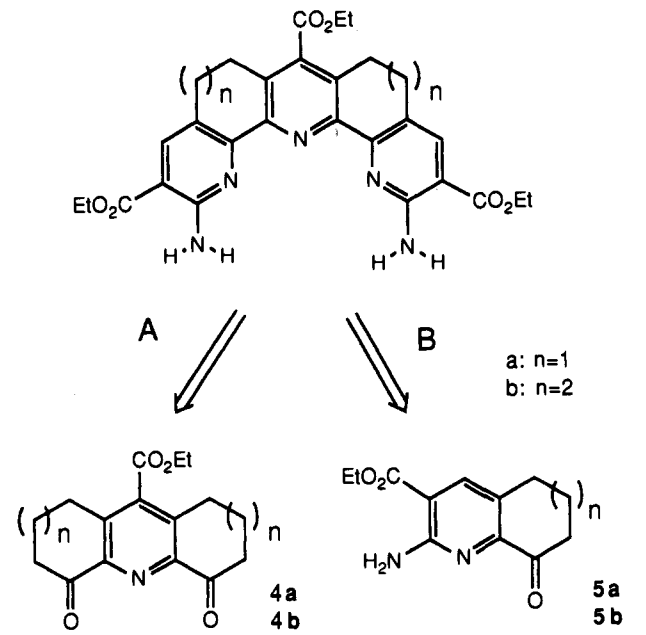


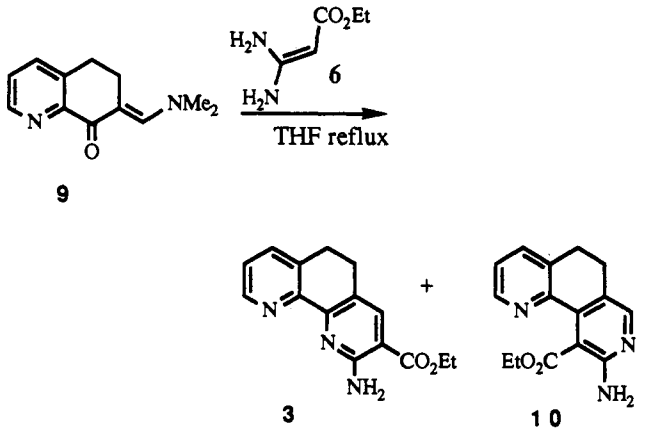
Figure 3. Two retrosynthetic approaches to **1** and **2**: (A) divergent approach; (B) convergent approach.

moieties. The V-shape has been confirmed by both molecular mechanics and crystal structures. To test the cooperativity between the C_2-symmetric halves of hosts **1** and **2**, compound **3** was also investigated. The three pyridine rings in **1** and **2** are fused with ethanediyl and propanediyl linkers to impart rigidity and preorganize the hydrogen-bonding groups.[16] These saturated hydrocarbon linkers cause the receptors to exist as *d*, *l*, or *meso* isomers. Although these isomers readily interconvert, molecular mechanics calculations on **1** and **2** predict that the *d,l* set has a lower energy by 1 and 2 kcal/mol, respectively.[17] The calculated dihedral angle between the two peripheral pyridine rings of the *d,l* set were found to be 24° and 80° for **1** and **2**, respectively.[17] The calculated structures match the crystal structures extremely well,[17] and therefore, molecular mechanics calculations can be used confidently to predict structures of these polyaza-clefts.

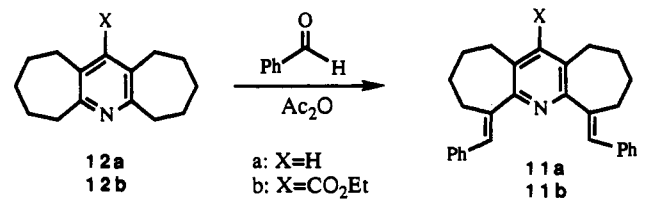
B. Synthesis. Retrosynthetic analysis of hosts **1** and **2** yields at least two general approaches to the synthesis of these compounds (Figure 3). One is divergent, synthesizing the center pyridine ring first (**4**) and the peripheral pyridines last. The other is a convergent synthesis, first constructing the peripheral pyridine rings (**5**) and then assembling the entire structure around the central pyridine. The synthesis of **4a** has been reported in detail previously[18] and will not be discussed here.

Addition of the 2-aminopyridine rings to **4a** by a Friedlander condensation with 4-aminopyrimidine-5-carboxaldehyde followed by hydrolysis, as has been used extensively by Thummel[19] and Caluwe,[20] gave a low yield. A different approach involves the condensation of ethyl 2,2-diaminopropenoate (**6**) with α-formyl ketones to form substituted 2-aminopyridines.[21] In order to utilize this strategy, diketone **4a** was transformed into diformylated compound **7** (Scheme 1). Treatment of **4a** with *N,N*-dimethylformamide dimethyl acetal[22] forms **8** in good yield, and hydrolysis with HCl yields derivative **7** efficiently. The reaction of **7** with **6** at room temperature in THF gave **1** in 45% yield. Compound **3** was also synthesized in a similar fashion starting from 5,6,7,8-tetrahydro-8-quinolone.[23]

A more direct route to **1** is the treatment of **8** with **6**; however, a model study involving the condensation of **9** and **6** gave both regioisomers **3** and **10**, and therefore this route was not pursued.



A procedure similar to that presented in Scheme 1 was attempted in the synthesis of receptor **2**. Formation of the precursor (**11b**) to **4b** was difficult. Thummel has reported the synthesis of compound **11a** in 66% yield from **12a** in refluxing benzaldehyde and acetic anhydride.[23] An ester group on the central pyridine ring (**12b**) lowered the yield to only 5%. Receptor **2** was therefore synthesized via approach B in Figure 3. Although this synthetic approach is longer, it has allowed for the synthesis of unsymmetrical receptors.[24]



The synthesis of **2** is shown in Scheme 2. Cycloheptanone was allowed to react with 1 equiv of benzaldehyde and potassium hydroxide to give the aldol product **13** in 60% yield,[25] which was subsequently treated with *N,N*-dimethylformamide dimethyl acetal in refluxing DMF to yield **14**. Hydrolysis of **14** gave the formylated product **15** in 94% yield. The reaction of compound **15** with **16** gave **17** in 61% yield. Compound **16** is similar to

(16) Such preorganization has been shown to be critical in similar hosts. Zimmerman, S. C.; Mrksich, M.; Baloga, M. *J. Am. Chem. Soc.* **1989**, *111*, 8528–8530.

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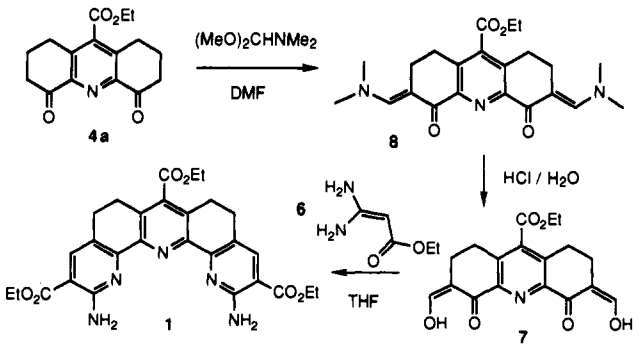
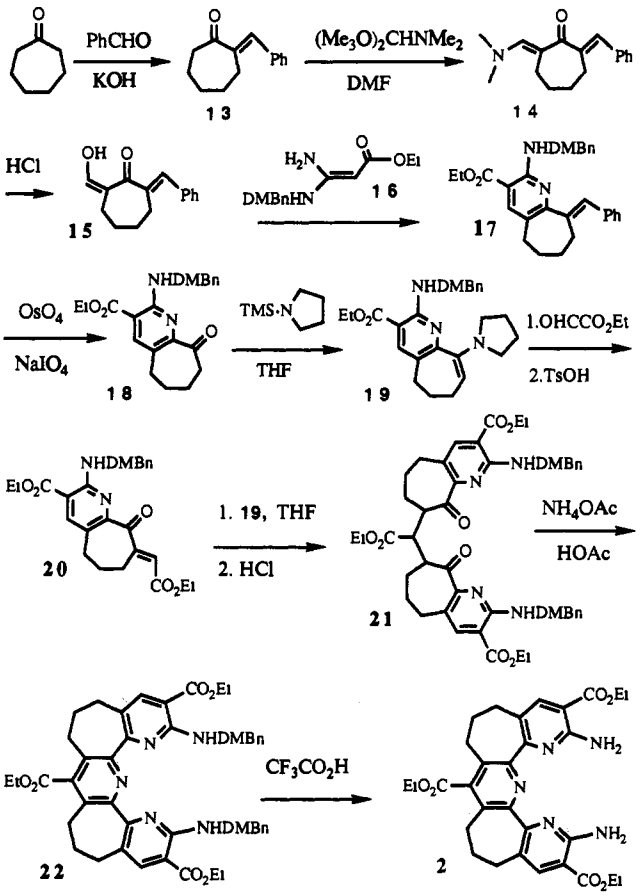
Scheme 1



Scheme 2



compound **6** except that one of the amines is protected with the 3,4-dimethoxybenzyl group. Other protecting groups were explored, but 3,4-dimethoxybenzyl resulted in better yields at the deprotection step. When compound **17** was treated with osmium tetroxide and sodium periodate, the ketone **18** was formed in 92% yield. In an attempt to form enamine **19**, compound **18** was allowed to reflux with pyrrolidine in benzene, but only decomposition of **18** was observed. Ketone **18** was therefore converted to enamine **19** by treatment with (trimethylsilyl)-pyrrolidine[26] followed by ethyl glyoxylate to give compound **20** in 73% overall yield from **18**. The ethyl glyoxylate used in this reaction was prepared from diethyl tartrate following Kelly's procedure.[27] As the oligomeric form of ethyl glyoxylate did not react efficiently with **19**, the glyoxylate was cracked and distilled directly into a solution of **19** in THF cooled to −78 °C. In this transformation the 2-amino group of the pyridine ring also reacts with ethyl glyoxylate if not protected with the 3,4-dimethoxybenzyl group. The reaction of compound **20** with enamine **19** in THF gave a mixture of isomeric forms of compound **21**. Compound **21** was cyclized by treatment with ammonium acetate and acetic acid to form **22** in moderate yield (50%). Deprotection of the 3,4-dimethoxybenzyl group to give receptor **2** was accomplished in 60% yield by treating the cyclized product with trifluoroacetic acid.[28]

C. Complexation Studies. a. Preliminary Considerations. In order for valid conclusions about the strengths and selectivity of cyclitol binding to be drawn from comparisons of relatively small binding constants, complications from oligomerizations and solvent impurities must be minimized. Oligomerization is common for cyclitols in low-dielectric media. To determine the concentration range in which the cyclitols are not aggregated, the guests were diluted until their ^{1}H NMR spectra showed no observable change in chemical shift. The IR spectra of the guests in chloroform at these concentrations also showed no intermolecular hydrogen bonding between the hydroxyls (found near 3400 cm^{-1}), further confirming that there was no guest oligomerization under these experimental conditions. Binding constant determinations were carried out in these concentration ranges. Similarly, at all host concentrations used in the NMR titration studies, no observable change in the ^{1}H NMR spectra was evident upon either dilution or concentration, thus indicating that no dimerization or aggregation of the host occurred. A host dimerization constant of 5 M^{-1} or above would have been detectable. If, however, this maximum dimerization constant is assumed, then at the highest equivalents of host used in a binding study less than 13% of the host would be dimerized if no guest was present. Under most experimental conditions, only 2–3% of the host would be dimerized if no guest was present. Accordingly, there are no corrections for these potential effects in the reported binding constants.

In addition, water has been shown to be a competitive inhibitor of hydrogen-bond-driven molecular recognition in low-dielectric media.[27] Hence the extent of water contamination in the binding studies was carefully controlled. Polyaza-clefts such as **1**, **2**, and **3** are tenacious water binders. However, the extent of water contamination in a binding study was easily monitored by examination of the ^{1}H NMR water resonance at 1.7 ppm in chloroform. A near complete elimination of this resonance in the stock solutions used to prepare the host–guest mixtures (see Experimental Section) was always found after drying the hosts over P_2O_5 and subliming the cyclitols over P_2O_5.

b. Results of Binding Studies. The interactions of receptors **1**, **2**, and **3** in chloroform-*d* with *cis*- and *trans*-1,2-cyclohexanediols, cyclohexanetriols **23**, **24**, and **25**, and β-dodecyl-D-glucopyranoside **26** were investigated by ^{1}H NMR. In each binding experiment, the guest concentration was held constant and the concentration of the host was incrementally increased. The host-to-guest ratio began at 0 and in general increased to 4, though some experiments were taken to 10. The ^{1}H NMR spectra obtained during binding experiments showed 2–3 ppm downfield shifts of the guest hydroxyl resonances from that of pure guest. This indicated hydrogen bond formation.[31] The broadening of these hydroxyl resonances, however, complicated their use in a binding isotherm. The C*H*OH protons of the guest usually shifted upfield by 0.2–0.5 ppm and remained sharp. The upfield shift likely reflects increasing negative charge on the alcohol oxygen due to the hydrogen bonding. These upfield chemical shift movements versus host concentration conformed to the typical

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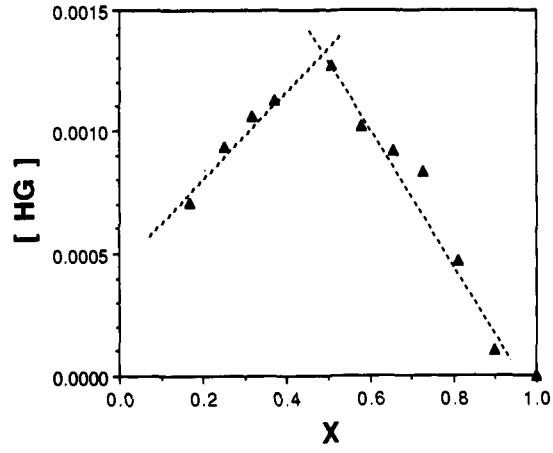


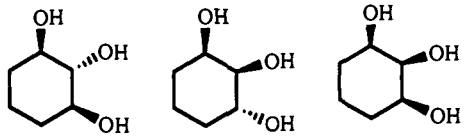
Figure 4. Job plot for the binding of **23** and **2**. X = mole fraction of **23**. Concentration of **23** + **2** was held constant at 1×10^{-2} M.

Table 1. Binding Constants K (M^{-1}) and ΔG (kcal/mol) for Complexation of Receptors **1**, **2**, and **3** with Diols and Triols[a]

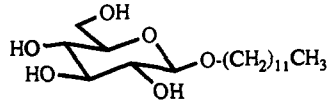
	hosts					
	1		2		3	
guests	K	ΔG	K	ΔG	K	ΔG
trans-1,2-diol	5 (22)	−0.96	17 (19)	−1.69	2 (17)	−0.44
cis-1,2-diol	7 (17)	−1.13	12 (16)	−1.48		
25	39 (21)	−2.16	39 (5)	−2.16	14 (11)	−1.56
24	35 (12)	−2.11	47 (18)	−2.27	12 (17)	−1.47
23	80 (13)	−2.59	110 (10)	−2.78	36 (10)	−2.11

[a] Percent errors are in parentheses and represent the standard deviation of the calculated binding constant and the experimentally determined binding constant for each point on the binding isotherms.

1:1 binding algorithm.[32] This stoichiometry was confirmed with a Job plot[33] for the complex between **2** and **23** (Figure 4).



23 **24** **25**



26

Table 1 lists all binding constants and corresponding free energy changes for the various receptors and cyclitols, and Figure 5 shows the ^{1}H NMR experimental isotherms for all three cyclohexanetriols with receptor **2**. The percent of saturation achieved for the triols was always near 70% or above, as recommended by Wilcox for reliable binding constants.[34] The size of the diol binding constants, however, is too small (2–17 M^{-1}) to be strictly reliable since only 30–40% saturation in these binding isotherms was achieved. One glucoside was also examined. When β-dodecyl-D-glucoside (**26**) was used as a guest to complex with receptor **2** in chloroform, the binding constant measured was 190 M^{-1} (22% error).

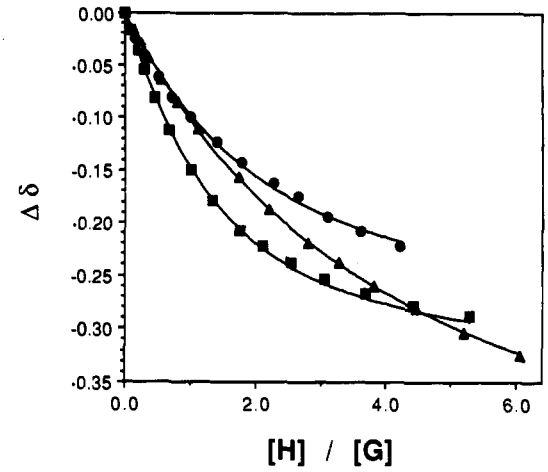


Figure 5. Experimental isotherms and theoretical lines for 1:1 binding of **23** (■), **24** (●), and **25** (▲) with **2**. The percent saturation achieved in the isotherms is 87, 73, and 64, respectively. Starting chemical shifts for **23**, **24**, and **25** were 3.22, 3.79, and 3.73 ppm, respectively. The calculated chemical shifts for the complex of **23**, **24**, and **25** with **2** were 2.88, 3.46, and 3.21. Concentrations of **23**, **24**, and **25** were 1.32×10^{-2}, 1.51×10^{-2}, and 9.69×10^{-3} M, respectively.

In addition to the measurement of Gibbs free energies of binding, the ΔH and ΔS of binding **23** by **2** was determined. Since the isotherm for **23** with **2** is known for the ^{1}H resonance on C-2 of **23** (Figure 5), this chemical shift at any temperature directly yields the percent of host–guest complex in solution.[35a] This analysis is valid only if the chemical shift of **23** is temperature independent.[35b] Warming a solution of 7.32×10^{-3} M **2** and 2.22×10^{-2} M **23** from 295 to 323 K gave a total downfield shift of 0.051 ppm, while the same temperature change gave an upfield shift of only 0.004 for **23** alone. Plotting R ln K_a versus $1/T$ (van't Hoff analysis) gave a straight line (supplementary material) and resulted in $\Delta H = -4.5$ kcal/mol and $T\Delta S$ at 295 K = −1.8 kcal/mol.

For conclusions to be drawn from the Gibbs free energies of binding, an estimate of the error associated with these measurements is required. The binding constants reported in Table 1 are given with errors that are the standard deviation of the binding constant values calculated for each point on the curve. The diol binding constants are not reliable due to their small size, but the triol binding constants were reproducible within 10%. Given these errors, comparisons between the full clefts **1** and **2** with the half cleft **3**, as well as comparisons of the diols and triols, are internally consistent. In other words, the binding constants from different hosts and guests lead to predictions which can be confirmed experimentally. For example, Figure 6 shows the energetic differences in the binding constants of diols and triols, with hosts **2** and **3**. Binding *trans*-1,2-cyclohexanediol with **2** has a −0.51 ± 0.10 kcal/mol advantage over that with **3**. Binding the all-*trans* triol **23** with **2** has a 1.09 ± 0.22 kcal/mol enhancement over binding *trans*-1,2-cyclohexanediol. In addition, there is a 0.67 ± 0.13 kcal/mol advantage when binding **23** with **2** over that with **3**. These numbers predict that the enhancement for binding **23** over *trans*-1,2-cyclohexanediol with **3** would be 0.94 kcal/mol. A 0.93 ± 0.19 kcal/mol advantage was experimentally determined. Similar good agreement is found when comparing the *cis*-1,2-cyclohexanediol with the all-*cis* triol **25** or comparing **1** with **3**.

c. Analysis of Binding Data. Inspection of Table 1 reveals four important points: (1) Hosts **1** and **2** bind cyclitols more strongly than **3**, indicating cooperativity[36c] between the C_2-

(32) Wilcox, C. S.; Cowart, M. D. *Tetrahedron Lett.* **1986**, *27*, 5563. H. W. Whitlock, Jr., kindly provided the program. Sheridan, R. E.; Whitlock, H. W. *J. Am. Chem. Soc.* **1986**, *108*, 7120 and ref 8.
(33) Job, A. *Ann. Chim. (10th Series)* **1928**, *9*, 113.
(34) Cowart, M. D.; Sucholeiki, I.; Bukownik, R. R.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 6204.
(35) (a) Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1090. (b) Stauffer, D. A.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Org. Chem.* **1990**, *55*, 2762.
(36) Here we are using the term "cooperativity" in a broad sense to point out the enhancement of binding from two parts of a host molecule.

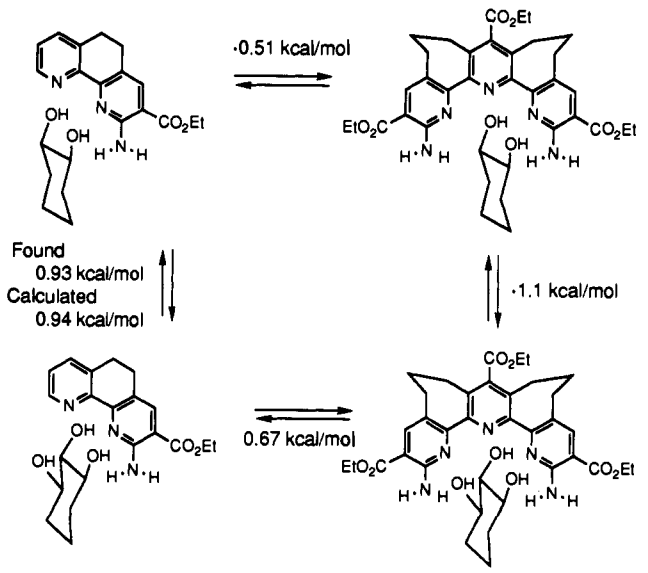


Figure 6. Analysis of the energetic differences between binding *trans*-1,2-cyclohexanediol and **23** with **2** and **3**. Reading clockwise starting in the upper left corner would predict the energetic difference between binding the diol and triol with **3** to be 0.94 kcal/mol, and experimentally 0.93 was found.

symmetric halves of **1**. (2) With the same host, the binding of triols is typically 4-fold better than that of diols. (3) Within a series of guests (diols or triols), *trans*-stereochemistry of hydroxyls yields larger binding constants than *cis*-stereochemistry. (4) The binding constants observed are lower than those of other systems which possess four hydrogen bonds.

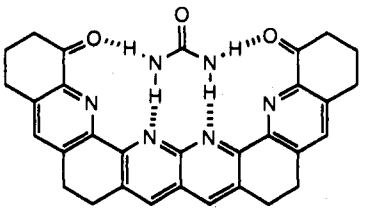
Point 1. To determine if the C_2-symmetric arms of **1** and **2** act together in complexing cyclitols, a comparison of the binding to **3** was made. There is a negligible energetic advantage to binding diols with the full clefts **1** and **2** over binding to **3** (0–0.5 kcal/mol), suggesting that the diols tend to associate with only one-half of the full clefts. The triols, however, consistently bind better to the full clefts than to **3**. The advantage in binding the triols with **1** over **3** is 0.5 ± 0.1 to 0.6 ± 0.12 kcal/mol, and the advantage with **2** over **3** is between 0.6 ± 0.12 and 0.8 ± 0.16 kcal/mol. This indicates that the full clefts **1** and **2** indeed form additional binding interactions with the triols that are not present with **3**.

Point 2. To determine if the receptors form additional hydrogen bonds to the triols that are not formed with the diols, a direct comparison of the diol and triol Gibbs free energy of binding was made. The free energy difference favoring triol binding over the diols ($\Delta\Delta G$) is near 1.0 kcal/mol for **3**, between 1.6 ± 0.32 and 1.0 ± 0.2 kcal/mol for **1**, and between 1.3 ± 0.26 and 0.5 ± 0.1 kcal/mol for **2** (Table 1). The magnitude of this increase in binding of the triols over the diols indicates that the third hydroxyl in the triols is forming extra interactions with the hosts.

Point 3. To gain insight into the selectivity of binding cyclitols, a study of the change in binding constants as a function of vicinal diol stereochemistry was performed. It was found that the binding constants of the triols become larger as the number of *trans* hydroxy interactions increase from 0 to 1 to 2. For example, in the complexation of **2** with triols, **23** (all *trans*) has the highest binding constant and **25** (all *cis*) has the lowest binding constant. The binding constant for **24** is between those of **23** and **25** due to one *cis* and one *trans* cyclitol hydrogen bond. The energetic difference between binding **23** and **25** by **2** is 0.60 ± 0.12 kcal/mol. The same trend is also found for hosts **1** and **3**. Although the binding constants for the diols are too small to be reliable, the trend that the *trans*-arrangement of hydroxyls gives the larger binding constant is still evident.

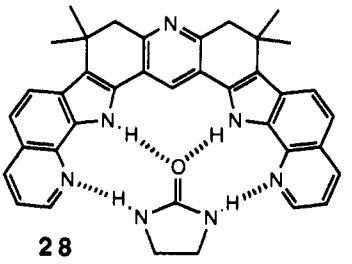
The selectivity among **23**, **24**, and **25** could arise from either complementarity differences with the receptors or the different strengths of the intramolecular hydrogen bonds with the cyclitols. On the basis of molecular dynamics calculations (section D), there appears to be little complementarity differences between the triols for receptor **2**. The strength of *cis* intramolecular hydrogen bonds, however, are higher than *trans*, and if these bonds within the cyclitols are weakened upon complexation, the binding of *trans* vicinal diols should be better than *cis* diols. If the hydrogen bonds within the cyclitols are completely broken upon complexation, the difference in the *cis*/*trans* strengths should correlate to the selectivity of binding. Indeed, such an energetic correlation exists (discussed in section G).

Point 4. In order to understand whether the magnitude of the binding constants in Table 1 is appropriate for the host–triol complexes, molecular dynamics (see section D) were performed and four intermolecular hydrogen bonds were predicted. This was followed by a comparison to similar host–guest complexes reported in the literature. Shown below are literature host–guest structures involving four hydrogen bonds that use hosts similar to **1** and **2**. Bell has reported the complexation of urea by a four point hydrogen bonding polyaza-cleft in chloroform (**27**) with a binding constant of at least 4×10^4 M^{-1}.[37a] Thummel has also used a polyaza-cleft to bind urea derivatives in chloroform, resulting in a binding constant of 1.3×10^4 M^{-1}.[37b] Other host–guest systems involving hosts not directly analogous to **1** and **2** but also with four hydrogen bonds have been reported.[37c–e] These binding constants are significantly greater than those given in Table 1 (30–110 M^{-1}).



27

$K = 4 * 10^4\ M^{-1}$



28

$K = 1.3 * 10^4\ M^{-1}$

Several reasons can be given as to why the binding constants with **27** and **28** are 2–3 orders of magnitude greater than those given for the triols in Table 1. First, these host–guest complexes do not involve hydrogen bonds to guests with hydroxyl groups, and thus the differences in donating and accepting ability could depress the cyclitol binding. The cyclitol hydroxyls, however, are more acidic than ureas and would tend to increase binding, not suppress binding.[11] Second, secondary hydrogen bonding may be playing an influential role, but as will be discussed in section D, secondary interactions in these systems do not seem to be large. Finally, a critical difference between the cyclitol guests and these literature examples is that ureas have a planar conformation, and all the hydrogen bond donors and acceptors

(37) (a) Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673. (b) Hegde, V.; Madhukar, P.; Madwa, J. D.; Thummel, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 4549. (c) Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549. (d) Kelly, T. R.; Bilodeau, M. T.; Bridger, G. J.; Zhao, C. *Tetrahedron Lett.* **1989**, *30*, 2485. (e) Chang, S.-K..; Engen, D. V.; Fan, E.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 7640.

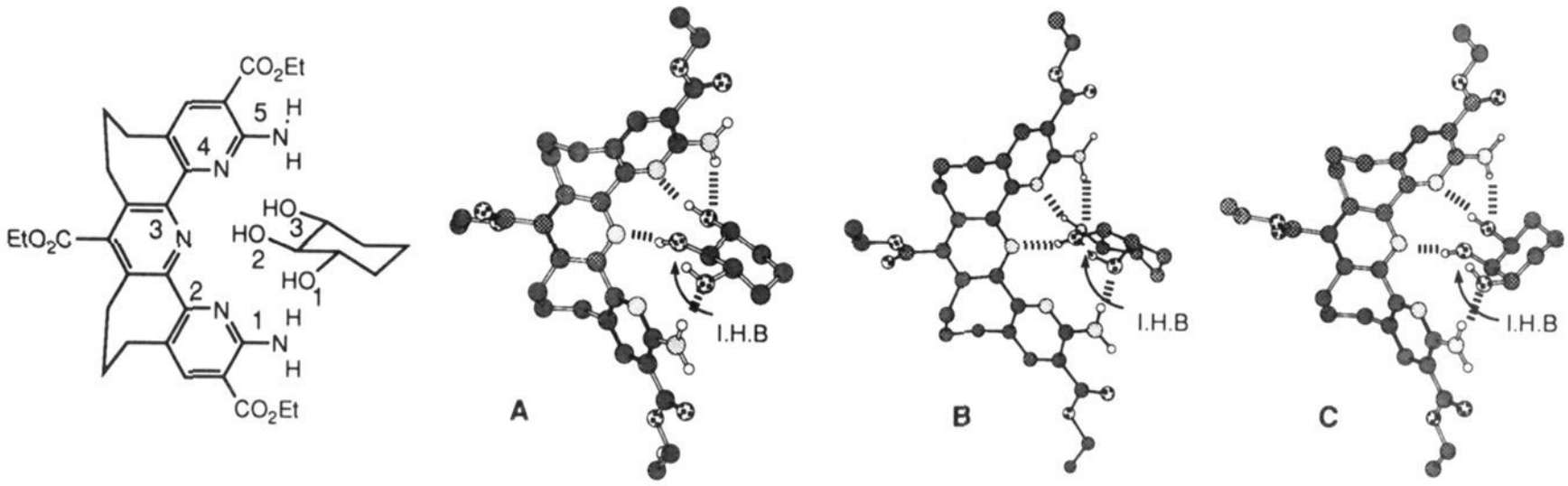


Figure 7. Molecular dynamics derived structures for the complexation of **23**, **24**, and **25** with **2**, along with the numbering scheme for Table 2. IHB = intramolecular hydrogen bond.

Table 2. Hydrogen Bond Angles (deg) and Bond Distances (Å) between Heteroatoms Derived from Molecular Dynamics Calculations of the Binding of **2** with **23**, **24**, and **25**

	23		**24**		**25**	
compd	distance	angle	distance	angle	distance	angle
N_1–H---O_1	2.91	159	2.82	165	2.91	156
N_3---H–O_2	2.90	164	2.92	151	2.94	155
N_4---H–O_3	2.87	165	2.83	155	2.93	154
N_5–H---O_3	2.90	132	2.94	134	2.89	131
O_1–H---O_2	2.24	142	2.10	151	2.11	152

are truly divergent. It is not possible for these guests to form intramolecular hydrogen bonds. In contrast, the three-dimensional arrangements of the hydroxyl groups of cyclitols and saccharides allow the formation of intramolecular hydrogen bonds. Breaking or weakening these intramolecular hydrogen bonds would cost energy in the complexation event, thus yielding binding constants below predicted values. Indeed, if the strengths of the cyclitol intramolecular hydrogen bonds are accounted for, then binding constants approaching those for **27** and **28** are obtained (see section G).

D. Molecular Modeling. In order to investigate a potential relationship of the low binding constants and the selectivity trend with the breaking of an intramolecular hydrogen bond, computer modeling was performed as a means of predicting the number of primary and secondary hydrogen bonds.[38] Figure 7 shows the dominant low-energy structures of the three triols and host **2**. Each of the two amino groups of the host donate one hydrogen bond to a hydroxyl oxygen, and two pyridine nitrogens (center and one peripheral ring) accept one proton from two different hydroxyls. In each structure a third hydroxyl of the cyclitol is involved in an intramolecular hydrogen bond to a neighboring hydroxyl oxygen. The molecular dynamics suggests that in all three cases of triol complexation, the cyclitols undergo a reorganization to break one intramolecular hydrogen bond and form four intermolecular bonds with the host. A confirmation of these results would be an X-ray crystal structure of a cyclitol–host complex. Unfortunately, repeated attempts to grow such crystals consistently resulted in separate crystals of the host and the cyclitol.

The molecular dynamics results not only predict the number of hydrogen bonds but also can be used to examine the source of triol-binding selectivity. The molecular dynamics calculations show few differences in the intermolecular interactions of all three triols and host **2**. Table 2 lists the distances and bond angles of the hydrogen bonds in the triol–**2** structures. The angles and distances for complexing the triols with **2** are all very similar. The distances between guest oxygens and host nitrogens are between 2.8 and 3.0 Å, within the usual hydrogen bond distance.[39] The intermolecular hydrogen bond angles are above 150°, except for the N5–H---O3 angles, which are between 130° and 135°. The remaining intramolecular hydrogen bond in each structure has an O---O distance between 2.1 and 2.2 Å and an O–H---O angle between 140° and 155°. The calculations consistently point to retention of the *cis* intramolecular hydrogen bond in **24**. This correlates well with the fact that *trans* bonds are weaker than the *cis* bonds.[40] Finally, the calculations suggest that the differences in binding constants among the triols are not due to significant changes in intermolecular or intramolecular hydrogen bond geometries. Since few complementarity differences are found for the triols with the receptors, the selectivity of binding is likely based upon other factors.

With a prediction of the placement of the primary intermolecular hydrogen bonds in the host–cyclitol complexes, it is now possible to determine whether secondary hydrogen bonds could be influencing the binding of the triols. It has been calculated,[41] and experimentally confirmed,[42] that complexes with three linear and parallel hydrogen bonds in chloroform have binding constants from as low as 150 to greater than 200 000 M^{-1} depending upon whether secondary hydrogen bonds act cooperatively. Increasing the number of adjacent donors (D) on a given host with the corresponding adjacent acceptors (A) on the guest (or vice versa) yields higher binding constants than alternating the donors and acceptors on either the individual host or guest.[41,42]

One can compare the host–guest geometries involving **2** (Figure 7) with host–guest complexes **27** and **28** to evaluate the importance of such secondary hydrogen bonds in these polyaza-clefts. The secondary interactions in the binding of the triols by **2** are schematically displayed below. The donor–acceptor pattern on host **2** is A-D-D-D-A, which is both constructive and destructive. Examination of **28** shows the hydrogen bond pattern on the host to be A-D-D-A, which is similar to the secondary interactions for triols with **2**, and the pattern on host **27** to be A-A-A-A, which is completely constructive. The binding constant for **27**, however, is only slightly greater than that of complex **28**. There are two possible explanations for the small difference in these binding constants compared to the large differences observed with three linear hydrogen bonds.[41,42] First, the increased distances between donors and acceptors would diminish the secondary attractions and repulsions. Second, the nonparallel nature of the hydrogen

(38) Still, C. *Macromodel*, version 3.5; Columbia University: New York. Both the AMBER and MM2 force fields gave slightly different bond lengths and angles, but an intramolecular hydrogen bond was always broken.

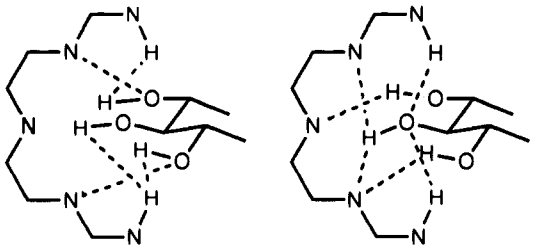
(39) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: New York, 1991.

(40) Tichý, M. The Determination of Intramolecular Hydrogen Bonding by Infrared Spectroscopy In *Advances in Organic Chemistry: Methods and Results*; Parhael, R. A., Taylor, E. C., Wynberg, H., Eds.; John Wiley: New York, 1965; Vol. 5, p 115. Kuhn, L. P. *J. Am. Chem. Soc.* **1954**, *76*, 4324. Kuhn, L. P. *J. Am. Chem. Soc.* **1952**, *74*, 2492.

(41) Jorgenson, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008.

(42) Murray, T. J.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 4010–4011

bonds with polyaza-clefts **2**, **27**, and **28** would further diminish the impact of the secondary hydrogen bonds. Therefore, the low magnitude of the binding constants between **2** and the triols, in comparison to **27** and **28**, is likely caused by a factor other than just destructive secondary hydrogen bonds.



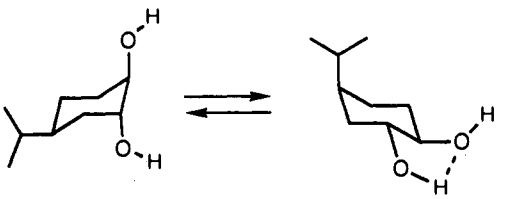
Destructive Constructive

E. IR Studies. In order to confirm that the selectivity (point 3) and the weak binding (point 4) could arise from competition between intramolecular hydrogen bonds in the guests and intermolecular hydrogen bonds formed with the hosts, IR spectra of the guests were recorded. IR spectroscopy has a time scale that allows for the direct observation of free and intramolecular hydrogen-bonded hydroxyl stretches and is a common method for determining the extent of both intramolecular and intermolecular hydrogen bonding.[43,44]

It has been reported that *cis*-1,2-hydroxyls form stronger intramolecular hydrogen bonds than *trans*-1,2-hydroxyls in carbon tetrachloride.[40] A similar situation was found for chloroform (Figure 8A,B). For *cis*-1,2-cyclohexanediol, a stretch at 3615 cm^{-1} appeared for the free OH, and the intramolecular hydrogen-bonded hydroxyl stretch appeared at 3580 cm^{-1}. The corresponding stretches in the spectrum of *trans*-1,2-cyclohexanediol appeared at 3620 and 3593 cm^{-1}. The larger frequency difference between the *cis* hydroxyl stretches compared to the *trans* confirmed that the *cis* intramolecular hydrogen bond is stronger than the *trans* intramolecular hydrogen bond in chloroform. For cyclohexanetriols, IR spectra were similar to those of the diols in the region 3615–3580 cm^{-1} (Figure 8C,D,E). Complete resolution of the hydroxyl stretches was not observed. The peak widths, however, still indicate the relative strengths of the intramolecular hydrogen bonds. The widths were largest for **24** and **25**, which possess *cis* hydrogen bonds, whereas the peak width for **23** (with only *trans* bonds) was quite narrow. As expected, the same trend of intramolecular hydrogen bond strengths was found for both the diols and the triols.

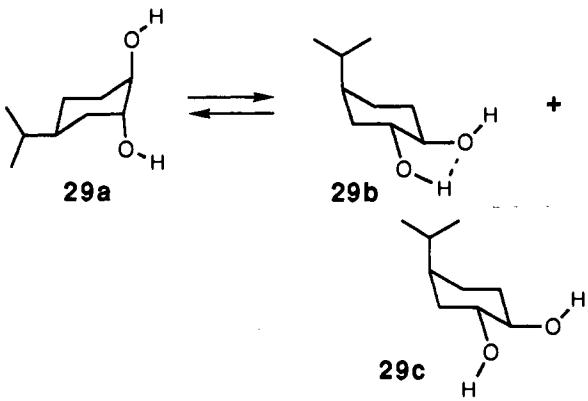
F. Determination of Intramolecular Hydrogen Bond Strengths. Determination of the strength of intramolecular H---OH bonds is valuable as a means of estimating the amount of energy that must be paid if these bonds are to be broken upon complexation.[45] As mentioned earlier, *cis* hydrogen bonds are stronger than *trans*, but the actual strength differences have not been reported. The reason for the difference in strength derives from the conformational strain introduced into the cyclohexane ring by the formation of such bonds. As discussed in detail by Kuhn,[40] the *cis* intramolecular hydrogen bond causes flattening of the cyclohexane chair conformation, whereas the *trans* bond causes a puckering of the cyclohexane ring. Puckering is more sterically demanding than flattening due to increased 1,3-interactions. Hence, the vicinal OH groups will approach each other more closely in the *cis* isomer.

a. *Trans*-Strength. In 1963, Tichý reported a determination of the intramolecular hydrogen bond strength in *trans*-1,2-cyclohexanediol in tetrachloroethylene.[46] We used a similar but modified procedure in chloroform. He examined the IR spectrum of the equilibrium mixture of the conformations shown in eq 1. Tichý used eq 2 (ΔG_H is the free energy of the intramolecular hydrogen bond) to measure the hydrogen bond strength. He used an A value for hydroxyl (0.8 kcal/mol) measured in acetic acid, and thus the size was overestimated. In addition, the equilibrium is better represented by eq 3, where some percentage of the diequatorial compound is in the free hydroxyl form (**29c**). Our procedure uses an A value for hydroxyl = 0.35 kcal/mol (measured in chloroform)[47] and an A value for isopropyl = 2.1 kcal/mol[47] and assumes the equilibrium in eq 3.



(1)

$$\Delta G_{eq} = A_{ipr} + \Delta G_H - 2A_{OH} \quad (2)$$



29a **29b** **29c** (3)

To measure hydrogen bond strengths by this IR method, conformationally restricted analogs of each isomer are used as models to determine the concentration of each conformation in the equilibrium mixture. The extinction coefficient of the hydroxyl stretch of a structural analog which lacks intramolecular hydrogen bonds is used as a model for the free hydroxyls in the equilibrium. In addition, an estimation of the extinction coefficient for the bonded hydroxyl must be made. This is complicated by the high sensitivity of an intramolecular hydrogen bond to local geometry;[48] however, we used a model for the hydrogen bond stretch in **29b** that is essentially identical (**31a**). In the

(43) For other hydrogen bonds studies by IR see: Khot, M. S.; Smith, D. A.; McMillan, G. R.; Sukenik, C. N. *J. Org. Chem.* **1992**, *57*, 3799. Gellman, S. H.; Dado, G. P.; Liang, G.-B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164–1173. Landmannm B.; Hoffman, R. W. *Chem. Ber.* **1987**, *120*, 331. Auerbach, R. A.; Kingsbury, C. A. *Tetrahedron* **1971**, *27*, 2069. Kingsbury, C. A. *J. Org. Chem.* **1970**, *35*, 1319. Naobumi, O.; Coetzee, J. F. *J. Am. Chem. Soc.* **1969**, *91*, 2478. Bodot, H.; Fediere, J.; Pouzard, G.; Pujol, L. *Bull. Soc. Chim. Fr.* **1968**, 3260. Baker, A. W.; Shulgin, A. T. *J. Am. Chem. Soc.* **1958**, *80*, 5358. NMR has also been found to be a useful tool for delineating the extent of intramolecular hydrogen bonding.[44]

(44) Beeson, C.; Dix, T. A. *J. Chem. Soc., Perkins Trans. 2* **1991**, 1913. Landmann, B.; Hoffman, R. W. *Chem. Ber.* **1987**, *120*, 331–333. Abraham, R. J.; Griffiths, L. *Tetrahedron* **1981**, *37*, 575–583. Allan, E. A.; Reeves, L. W. *J. Phys. Chem.* **1962**, 613.

(45) For some measurements of hydrogen bond strengths see: Cox, J. P.; Nicholls, I.A.; Williams, D. H. *J. Chem. Soc.* **1991**, 1295. Aoyama, Y.; Asakawa, M.; Yamagishi, A.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1990**, *112*, 3145. Fersht, A. R.; Shi, J.-P.; Knill-Jones, J.; Lowe, D. M.; Wilkinson, A. J.; Blow, D. M.; Brick, P.; Carter, P.; Waye, M. M. Y.; Winter, G. *Nature* **1985**, *214*, 235. Guidry, R. M.; Drago, R. S. *J. Phys. Chem.* **1974**, *78*, 454. Sherry, A. D.; Purcell, K. F. *J. Am. Chem. Soc.* **1972**, *94*, 1853. Christian, S. D.; Johnson, J. R.; Affsprung, H. E.; Kilpatrick, P.J. *J. Phys. Chem.* **1966**, *70*, 3376. Allerhand, A.; Schleyer, P. R. *J. Am. Chem. Soc.* **1963**, *85*, 371. Beeson, C.; Pham, N.; Shipps, G.; Dix, T. A. *J. Am. Chem. Soc.* **1993**, *115*, 6803–6812. Davies, M.; Thomas, D. K. *J. Phys. Chem.* **1956**, *60*, 767.

(46) Pitha, J.; Sicher, J.; Sipos, F.; Tichy, M.; Vasickova, S. *Proc. Chem. Soc.* **1963**, 301.

(47) (a) Hirsch, J. A. Table of Conformational Energies. *Topics in Stereochem.* **1967**, *1*, 199. (b) Eliel, E. L. *J. Chem. Educ.* **1960**, *37*, 126.

(48) Aaron, H. S. *Top. Stereochem.* **1980**, *11*, 1.

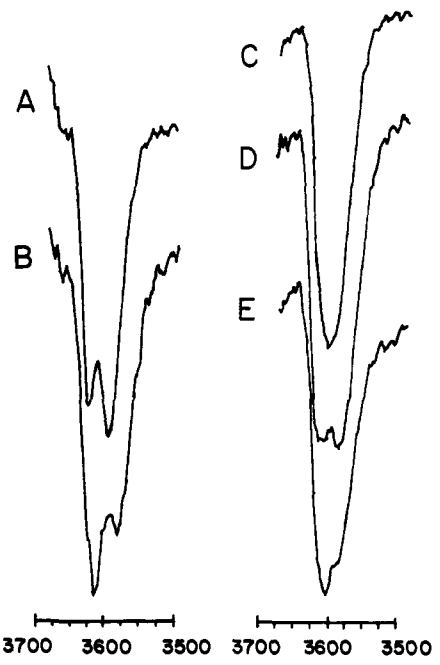


Figure 8. IR spectra of the O–H stretching region of the cyclitols: (A) *trans*-1,2-cyclohexanediol; (B) *cis*-1,2-cyclohexanediol; (C) **23**; (D) **24**; (E) **25**.

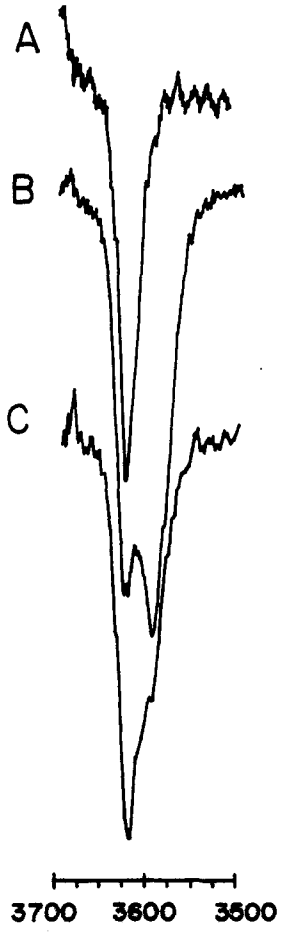
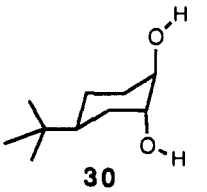
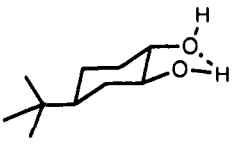


Figure 9. IR spectra for the analysis of the *trans*-1,2-cyclohexanediol intramolecular hydrogen bond strength: (A) **30**; (B) **31**; (C) **29**.

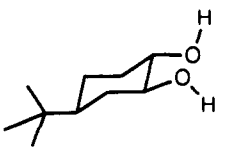
present study, the conformations in eq 3 were modeled by the conformationally homogeneous 4-*t*ert-butyl-substituted diols **30** and **31**. The IR spectrum of compound **30** showed a single stretch at 3618 cm^{-1} (Figure 9A). Absorbance of the ν_{OH} of **30** at 3618 cm^{-1} (3.6–10.5 mM) gave a linear response with concentration, and using Beer's Law an extinction coefficient of 1196 $M^{-1}cm^{-1}$ (ϵ_{aa}) was calculated.



30



31a



31b

A complication arises in modeling the intramolecular hydrogen bond absorptivity of **29** by **31** since they both have two possible forms, one with a hydrogen bond (**31a** and **29b**) and one without (**31b** and **29c**). In order to determine the extent of intramolecular hydrogen bonding in **31**, the percent of **31a** must be measured. This was performed by measuring the free OH stretch, the absorbance of which should follow eq 4,

$$A_T = 0.5\epsilon_{aa}b\chi C_T + \epsilon_{aa}b(1-\chi)C_T \quad (4)$$

where A_T is the observed absorbance, C_T is the total concentration of **31**, b is the pathlength, ϵ_{aa} is the absorptivity measured for the free OH groups of compound **30**, χ is the mole fraction of **31a**, and $(1-\chi)$ is the mole fraction of conformation **31b**. Since **31a** has only one free OH, a factor of 0.5 is multiplied by ϵ_{aa}. Two bands appeared in the spectrum of compound **31**, one at 3618 cm^{-1} and another at 3590 cm^{-1} (Figure 9B). The absorption at 3618 cm^{-1} was a combination of free OH stretches in conformations **31a** and **31b**. Using the measured absorbance at 3618 cm^{-1} and ϵ_{aa} in eq 4, $\chi = 0.88$, and $(1-\chi) = 0.12$. Therefore, 88% of compound **31** is in the hydrogen-bonded conformation **31a**, and 12% is in conformation **31b**. This knowledge allows for a measurement of the extinction coefficient of the intramolecular hydrogen bond stretch.

A linear relationship of the intramolecular hydrogen bond absorbance at 3590 cm^{-1} versus concentration of **31** was observed over the range 3.8–11.3 mM. Using a modified version of Beer's Law that accounts for the 88% population in the hydrogen-bonded state (eq 5) yields the extinction coefficient (ϵ_H) of 795 M^{-1} cm^{-1} for compound **31a**.

$$\epsilon_H = A_T/(0.88C_T)b \quad (5)$$

With the parameters ϵ_{aa}, ϵ_H, and χ solved, the population of the three conformations of **29** can be calculated using eqs 6–8, where $[\mathbf{29}]_t$ is the total concentration of **29**.

$$[\mathbf{29b}] = A_{3590}/b\epsilon_H \quad (6)$$

$$[\mathbf{29c}] = (0.12/0.88)[\mathbf{29b}] \quad (7)$$

$$[\mathbf{29a}] = [\mathbf{29}]_t - [\mathbf{29b}] - [\mathbf{29b}] \quad (8)$$

The IR spectrum of **29** (Figure 9C) showed a broad band, the result of superposition of spectra of **29a**, **29b**, and **29c**. The absorption of the intramolecular hydrogen bond stretch at 3590 cm^{-1} and ϵ_H were used to calculate the concentration of compound **29b** (eq 6). Accordingly, the concentration of compounds **29c** and **29a** were calculated (eqs 7 and 8). The free energy difference between compound **29a** and **29b** (ΔG_{eq}) was then calculated. This was then used in eq 2 to calculate the strength of the *trans*-intramolecular hydrogen bond (ΔG_H). Table 3 shows four values

Table 3. Calculated Concentrations (mM) of **29a**, **29b**, and **29c** from Eqs 6–8 with Four Different Total Concentrations of **29**[a]

$[29]_t$	[29a]	[29b]	[29c]	ΔG_{eq}	ΔG_H
10.13	2.58	6.64	0.91	−0.56	−1.96
8.78	2.42	5.60	0.76	−0.50	−1.90
7.02	1.80	4.59	0.63	−0.55	−1.95
5.85	1.63	3.71	0.51	−0.49	−1.89

[a] ΔG_{eq} = thermodynamic difference (kcal/mol) between **29a** and **29b**, and ΔG_H = *trans* intramolecular hydrogen bond strength (kcal/mol).

for ΔG_H obtained at different concentrations of **29**. The average of these values is −1.93 ± 0.08 kcal/mol.

Other factors may perturb the equilibrium shown in eq 3 and will influence the measured strength of the *trans* intramolecular hydrogen bond. One factor not considered is the dipole cancellation in structure **29a**, which may be stabilizing in a low-dielectric solvent. To whatever extent this factor is influencing the equilibria, it would cause an underestimation of the strength of the intramolecular hydrogen bond.

c. *Cis* Strength. As a means of measuring the strength of a *cis* intramolecular hydrogen bond, an experiment was designed to determine the equilibrium between *trans* and *cis* bonds that interconvert via mutarotation. 2-Oxy sugars possess intramolecular hydrogen bonds involving the anomeric hydroxyl which would influence the equilibrium population of α and β anomers, whereas 2-deoxy sugars have no such hydrogen bonds. Therefore, the 2-deoxy sugar can be used to measure the intrinsic thermodynamic difference between α and β anomers. The 2-oxy α anomers have *cis* hydrogen bonds, and the β anomers have *trans* bonds. In an equilibrium between α and β anomers, the population of the α anomer should be larger in 2-oxy sugars than in 2-deoxy sugars due to the greater strength of the *cis* intramolecular hydrogen bond. The free energy favoring the α anomer in the 2-oxy over that in 2-deoxy sugars gives a thermodynamic value for the increased strength of a *cis* intramolecular hydrogen bond compared to *trans*. Once the difference in strength of the *cis* and *trans* intramolecular hydrogen bonds is known, it can be added to the *trans* intramolecular hydrogen bond strength to yield the strength of the *cis* bond.

Factors other than intramolecular hydrogen bonding may also influence the equilibria. Such factors would include different solvation of the α and β anomers in the 2-oxy and 2-deoxy sugars, different dipole interactions within the 2-oxy and 2-deoxy sugars, and differences in the exo anomeric effect on hydrogen bonding between α and β anomers (discussed below). The experiment relies on the assumption that the 2-deoxy sugar equilibrium between α and β anomers corrects for all these preferences unrelated to the differential *cis/trans* hydrogen bond strength.

The chemical equilibria for which the ΔG_{eq} values were determined are shown in Figure 10. The equilibrium between α and β anomers was measured in the 2-oxy and 2-deoxy forms of a chloroform-*d* soluble glucoside by ^{1}H NMR. The carbohydrates are known (except for **34**), but such measurements have not been previously made. The mutarotation reaction was catalyzed by addition of 2-hydroxypyridine, as reported by Swain and Brown[49] for the saccharide 2,3,4,6-tetramethyl-D-glucose.

Compound **34** has not been synthesized before, but its synthesis was a relatively straightforward application of well-precedented steps (Scheme 3).[50] Allyl was chosen for protecting positions 2 and 3 in addition to the anomeric position. Formation of 2,3-di-*O*-allyl glucoside **35** was accomplished by treatment of allyl-4,6-*O*-benzylideneglucopyranoside[51] with potassium hydroxide and allyl bromide in refluxing toluene, affording 62% of product.

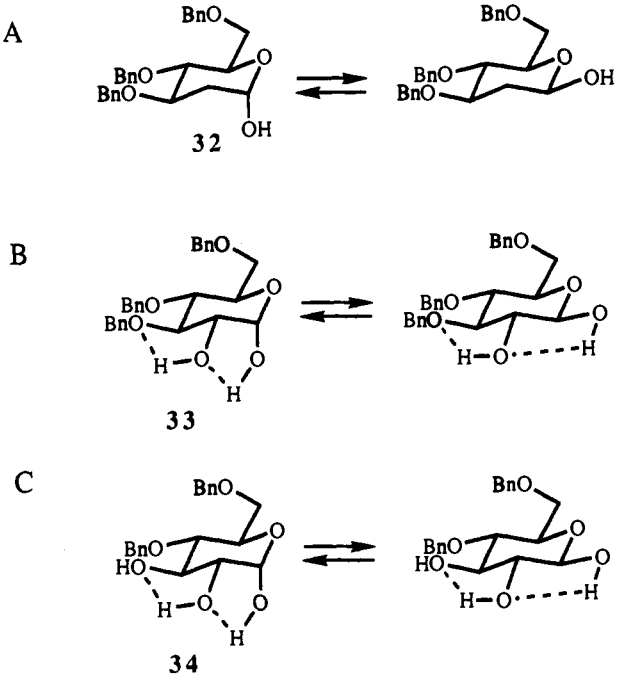
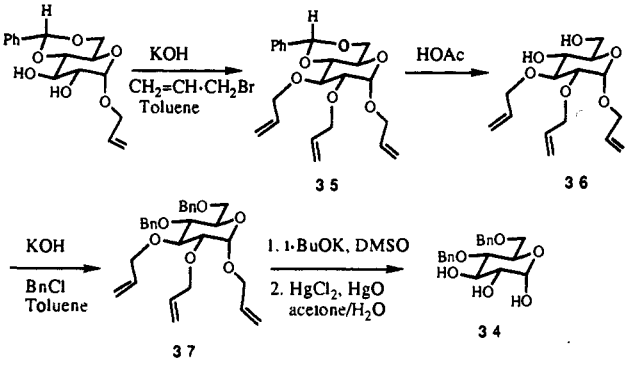


Figure 10. Mutarotation equilibria measured for the analysis of the *cis* intramolecular hydrogen bond strength.

Scheme 3



The benzylidene group was then removed by acetic acid (80%), in which the allyl ether was stable. The resulting compound **36** was converted to its benzyl derivative **37** in 85% yield by treatment with potassium hydroxide and benzyl chloride in refluxing toluene. Isomerization of the allyl groups of compound **37** to prop-1-enyl groups was carried out at 100 °C using potassium *tert*-butoxide in dry DMSO.[52] The crude product was then hydrolyzed by mercuric chloride in the presence of mercuric oxide[53] to give the title compound **34** in 55% yield from **37**.

Each ^{1}H NMR experiment to determine ΔG_{eq} was performed twice, and the results are listed in Table 4. The population of the species in the equilibria shown in Figure 10 was determined by integration of the anomeric protons. As expected, the 2-oxy sugars consistently had a higher fraction of the α anomer at equilibrium than the 2-deoxy sugars. The free energy advantage of the α anomers of **33** and **34** over **32**, which represents the differential *cis/trans* strength, was calculated to be 0.29 ± 0.08 and 0.58 ± 0.05 kcal/mol, respectively. As discussed in the last section, the strength of the *trans* intramolecular hydrogen bond was determined to be 1.93 ± 0.08 kcal/mol. Thus, the *cis* intramolecular hydrogen bond strengths are 2.22 ± 0.16 and 2.51 ± 0.13 kcal/mol for **33** and **34**, respectively.

If there is any non-hydrogen-bonded anomeric hydroxyl existing in the equilibrium, then the thermodynamic values resulting from

(49) Swain, C. C.; Brown, J. F. *J. Am. Chem. Soc.* **1952**, *74*, 2534.
(50) Khan, S. H.; Abbas, S. A.; Matta, K. L. *Carbohydr. Res.* **1989**, *193*, 125.
(51) (a) Talley, E. A.; Vale, M. D.; Yanovsky, E. *J. Am. Chem. Soc.* **1945**, *67*, 2037. (b) Gigg, J.; Gigg, R. *J. Chem. Soc. C* **1966**, 82. (c) Cunningham, J.; Gigg, R. *J. Chem. Soc.* **1965**, 2968.
(52) Price, G. C.; Whiting, M. C. *Chem. Ind.* **1963**, 775.
(53) Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1968**, 1903.

Table 4. Equilibrium Ratio of α and β Anomers of **32**, **33**, and **34**[a]

compd	α:β	ΔG_{ave}	$\Delta G_{cis} - \Delta G_{trans}$	ΔG_H
32	15:8 15.5:8	0.38		
33	8:2.5 15:5	0.67	0.29(0.08)	-2.22(0.16)
34	5:1 22:4.5	0.95	0.58(0.05)	-2.51(0.13)

[a] ΔG_{ave} = average thermodynamic difference (kcal/mol) from the two experimental runs. $\Delta G_{cis} - \Delta G_{trans}$ = thermodynamic difference between *cis* and *trans* intramolecular hydrogen bond strength. ΔG_H = *cis* intramolecular hydrogen bond strength (kcal/mol). The standard deviations are in parentheses.

our experiment do not represent the full difference between the strength of *cis* and *trans* intramolecular hydrogen bonds. Instead, they represent a lower limit. To determine the extent of intramolecular hydrogen bonds involving the anomeric hydroxyls of **33** and **34**, the IR spectra of these sugars were recorded. For 2-deoxy sugar **32**, a single hydroxyl stretch appeared at 3615 cm^{-1}, representing the free hydroxyl. In contrast, the IR spectra of sugars **33** and **34** showed a broad unsymmetrical band between 3598 cm^{-1} and 3570 cm^{-1}, indicating little or no free hydroxyl.

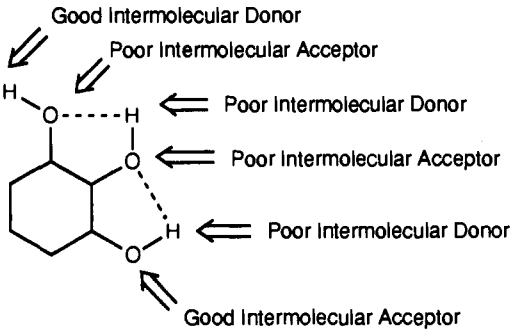
One assumption in the above analysis is that there is little or no difference in the exo anomeric effect between the α and β anomers. This anomeric effect causes the anomeric hydroxyl to be a better hydrogen bond donor, but a worse hydrogen bond acceptor. The enhanced donating and decreased accepting ability has, however, been shown to be similar for both α and β anomers.[54] There is good evidence for this from the bond distances measured by neutron and X-ray diffraction studies on simple carbohydrates.[15,54] Thus, the exo anomeric effect should affect the hydrogen bond strengths similarly for both the α and β anomers.

G. Intramolecular Hydrogen Bond Strengths and the Binding Constants. Now that the strengths of the intramolecular hydrogen bonds have been determined, they can be compared to the binding constants to see if they support the arguments given in points 3 and 4 (section C). In this discussion, we compare the difference in *cis* and *trans* intramolecular hydrogen bond ΔG's to the difference in the ΔG's of binding **23**, **24**, and **25** with **2**. In addition, we add ΔG's of the intramolecular hydrogen bonds to the ΔG's of binding as a means of estimating the overall ΔG of complexation. These analyses should be viewed as first estimates since direct addition or subtraction of these ΔG's involves changes in entropies of hydrogen bonds which may not be strickly additive. The approach, however, is similar to that which has been used to measure hydrogen bond strengths at enzyme active sites[55] and does give results that match experimentally measured ΔG's remarkably well.

Point 3. The increased binding with *trans* vicinal hydroxyls was explained by the breaking of weaker intramolecular hydrogen bonds. In fact, the differential strength of the *cis* and *trans* intramolecular hydrogen bonds (between 0.3 and 0.6 kcal/mol) is similar to the free energy difference favoring binding **23** versus **25** (0.43 ± 0.07 kcal/mol with **1**; 0.62 ± 0.12 kcal/mol with **2**). This correlation supports the hypothesis of breaking an intramolecular hydrogen bond because the selectivity difference can be explained by the difference in the intramolecular hydrogen bond strengths.

Point 4. If an intramolecular hydrogen bond is broken upon complexation of triols with **2**, then the addition of the hydrogen bond strength to the free energy of binding of the triols gives the total free energy of the intermolecular interactions. When such an addition is performed and the total free energy is converted to binding constants, one obtains values near 3×10^3 M^{-1}. These predicted binding constants are closer to those found for other complexes involving four hydrogen bonds (**27** and **28**).

Finally, even if the intramolecular hydrogen bonds are not fully broken upon complexation, the binding constants of saccharides and cyclitols with synthetic receptors could still be expected to be weaker than those of similar complexes with divergent hydrogen bond donors and acceptors. There is a destructive effect of internal solvation of the guest hydroxyls that participate in both a donor and acceptor intramolecular hydrogen bond. For instance, intermolecular hydrogen bond donation from a hydroxyl involved in an intramolecular bond will be weaker than normal. Similarly, a hydroxyl already involved in accepting an intramolecular hydrogen bond will be a weaker acceptor toward intermolecular hydrogen bonds. Despite these destructive effects, hydrogen bonding can be strengthened by the cooperative effect.[15] The cooperative effect, however, already exists between adjacent hydroxyls in the guest, and only the 1- and 3-hydroxyl of triols would benefit from a further cooperative effect as a result of intermolecular hydrogen bonding.



Conclusion

While only an X-ray structure would provide direct evidence for the breaking of an intramolecular hydrogen bond upon complexation of the triols with the receptors, a large amount of indirect evidence supports this conclusion. First, the magnitude of the binding constants and the observed selectivity supports a structure–energy relationship where one intramolecular hydrogen bond is broken. *Trans* intramolecular hydrogen bonds are weaker, giving rise to higher intermolecular binding constants. Second, molecular dynamics suggests that one intramolecular hydrogen bond is broken when a triol binds to receptor **2**. Third, IR evidence indicates the existence of intramolecular hydrogen bonds in the uncomplexed guests. Finally, the strength of the intramolecular hydrogen bonds and the differential strength between the *cis* and *trans* bonds correlate well with the binding constants reported in the literature and with the selectivity. The future design of receptors for carbohydrates will need to include strategies for competing with or complementing the intramolecular hydrogen bonds in order to achieve large association constants and yield controllable selectivities.

Experimental Section

A. General Considerations. Instrumentation. ^{1}HNMR and ^{13}CNMR spectra were obtained using a General Electric QE-300 or Bruker AC-250 spectrometer. Low-resolution mass spectra in the EI mode were recorded using a Bell and Howell Model 21-491 spectrometer at 70 eV and those in the CI mode using a Finnigan-MAT 4023 GC/MS with methane. High-resolution mass spectra were recorded with a CEC 21-110B instrument in the EI mode or in the CI mode. Only *m/z* values greater than or equal to 40% of the base peak and *m/z* values greater than or equal to 90 amu are reported. Melting points were measured with a Hoover Uni-Melt capillary melting-point apparatus. Elemental analyses were obtained from Galbraith Laboratories, Inc., in Knoxville, TN. Compounds and solvents were dried and stored in a Vacuum Atmosphere drybox MO-20. IR spectra were obtained in dry chloroform using a Nicolet FT-IR 730 spectrophotometer. Molecular mechanics calculations were performed on a Silicon Graphics Indigo workstation using the

(54) Jeffery, G. A.; Takagi, S. *Acc. Chem. Res.* **1978**, *11*, 264.
(55) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw Hill: New York, 1969. Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4046. Bartlett, P. A.; Marlowe, C. K. *Science* **1987**, *235*, 569.

Macromodel program.[38] The calculations were performed from 0 to 300 K with 1.5-fs step sizes, a path length of 100 ps, chloroform as solvent, and the OPLS force field.[38] Random structures generated after multiple 4-ps intervals at 300 K were minimized.

Materials. Ether and THF were distilled from sodium benzophenone ketyl radical. Dichloromethane and chloroform were refluxed and distilled from calcium hydride. DMF was stirred with calcium sulfate, filtered, and distilled from calcium hydride. Triethylamine and pyridine were distilled from sodium. All column chromatography was carried out with Silica Gel 40 microns from Scientific Adsorbents Inc. Ozone was generated by a Welsbach T-816 at 90 V (1–2 L/min).

Compounds. 5,6,7,8-Tetrahydro-8-quinolone was synthesized following Thummel's procedure.[23] Ethyl 3,3-diaminopropenoate (**6**) was prepared in two steps from ethyl cyanoacetate.[21] 2-Benzylidenecycloheptanone was synthesized from cycloheptanone following Baltzly's procedure.[25] Ethyl glyoxylate was prepared from diethyl tartrate following Kelly's procedure.[27] Compounds **30** and **31** were prepared following the Davey and McGinnis procedure starting with 4-*tert*-butylcyclohexanol and 4-*tert*-butylcyclohexanone, respectively.[56a] Compound **29** was prepared in a manner similar to compound **30** except that 4-isopropylcyclohexanol was not commercially available. 4-Isopropylcyclohexanol was prepared from 4-isopropylphenol using a modified procedure developed by Januszklewica and Alper for phase-transfer-catalyzed hydrogenation.[56b] Compound **33** was synthesized following Ekborg and Lindberg's procedure starting from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide.[56c] Allyl-4,6-*O*-benzylideneglucopyranoside was synthesized from glucose in two steps following Khan's procedure.[51] The synthesis of the triols followed literature procedures.[57] The starting material for all syntheses was purchased from either Aldrich or Lancaster Chemical Companies.

B. Analytical Studies. Binding Studies. All binding studies were performed on a Bruker AC-250 NMR spectrometer. Chloroform-*d* was first dried with $CaSO_4$ and then stirred with CaH_2 under nitrogen before distillation. The solvent was then stored in the drybox. The dichloromethane used as internal reference for quantitating the concentration of triol was similarly dried. Hosts were recrystallized from dichloromethane and ethyl acetate several times and then dried in a drying pistol over P_2O_5 with boiling ethyl acetate for at least 24 h. *cis*-1,2-Cyclohexanediol and *trans*-1,2-cyclohexanediol were purchased from Aldrich and were sublimed at 80 °C in the presence of P_2O_5. Triols were sublimed at 100 °C in the presence of P_2O_5.

In a binding study, a stock solution (usually 5 mL) of the guest in $CDCl_3$ was prepared. One NMR tube containing 0.7 mL of stock solution was prepared (tube 1). To a weighed amount of pure host in another NMR tube, 0.7 mL of the stock solution was added. This gave a host–guest mixture (tube 2) with the guest concentration the same as that of tube 1 and stock. All the above solutions were prepared in the drybox. The ^1H NMR spectra of both tube 1 and tube 2 were recorded, thus giving a pure guest spectrum and the first host–guest complex spectrum. The extent of water contamination was checked by examination of the intensity of the ^1H NMR 1.7 ppm resonance. A certain volume (e.g. v mL) of solution was taken from tube 2 with a Hamilton syringe and then replaced with the same volume of stock 1 solution. This gave a new host–guest solution in which the guest concentration was kept constant, whereas the host concentration became $(0.7 - v)/0.7$ of the original. The ^1H NMR spectrum of this solution was recorded, and the above dilution procedure was repeated to create another host–guest mixture. By repeating the dilution procedure and taking the ^1H NMR spectrum of each solution, a set of spectra were collected in which the guest concentration was a constant and the host concentration was continuously decreased. The chemical shift changes of guests recorded in these spectra were modeled with a computer program using the traditional 1:1 algorithm.[32]

Since the solubilities of the triols are much less than those of the diols, one cannot determine an accurate concentration of the triol solution by weighing the sample. Instead, a saturated solution of a triol was prepared in the drybox in a Kontes valve sealed flask. The solution was sonicated for half an hour and then shaken for 48 h to ensure saturation. The saturated solution was then filtered (in the drybox) and used to prepare stock solutions as described above. In order to determine the concentration of the triol solutions, 2.5 μL of dry dichloromethane was added to the stock solution. The integration of the ^1H resonances of the guest against the internal standard was used to determine the concentration of the triols.

IR Studies. Spectrophotometric grade chloroform containing no ethanol was purchased from Aldrich. This chloroform was dried by standing with $CaCl_2$ for several hours and stirred with CaH_2, followed by distillation. The dry chloroform was stored in the drybox. Each cyclitol solution for an IR study was prepared in the drybox with the dry solvent and kept under an Ar atmosphere during the course of the study. During the study, the IR spectrometer sample chamber was continuously purged with a stream of nitrogen.

***Cis* Intramolecular Hydrogen Bond Strength.** Experiments for determining the equilibrium ratio of α and β anomers for **32**, **33**, and **34** were performed by preparing a stock solution of 2-hydroxypyridine in dry chloroform-*d* with a concentration of 2.1×10^{-4} M. This stock solution was then used to prepare each sugar solution with a concentration of 9.0×10^{-3} M, which in the IR spectra showed no intermolecular hydrogen bonds. The different sugar solutions were then added to 5-mm NMR tubes, and the NMR tubes were flame sealed and heated at 40 °C for 2 days, sonicated for 1 h, and shaken continuously at 25 °C for several days. During this period, the ^1H NMR spectra were taken periodically. After a week, no further change in the spectra was evident.

C. Synthesis. 5,6,7,8-Tetrahydro-7-[(dimethylamino)methylidene]-8-quinolone (9). 5,6,7,8-Tetrahydro-8-quinolone (1.47 g, 10 mmol) was mixed with 20 mL of *N,N*-dimethylformamide dimethyl acetal (67 mmol) and heated slowly to reflux for 2 h. The residue was poured over ice and extracted with CH_2Cl_2 (4 × 200 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. The residue was dried overnight to give 2.9 g of a brown-yellow solid, yield 99%. The product was not purified prior to use in the next step. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.66 (d, J = 4.2 Hz, CH-2, 1 H), 7.82 (s, Me_2N=CH, 1 H), 7.49 (d, J = 5.4 Hz, CH-4, 1 H), 7.24 (m, CH-3, 1 H), 3.14 (s, NMe_2, 6 H), 2.91 (t, J = 6.6 Hz, CH_2-5, 2 H), 2.85 (t, J = 6.6 Hz, CH_2-6, 2 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 149.4 (2 C's), 148.3, 146.7, 136.1, 137.6, 124.6, 115.3, 38.1, 34.9, 30.7. MS-CI: m/z 203 (M^+ + H).

5,6,7,8-Tetrahydro-7-(hydroxymethylidene)-8-quinolone. Compound **9** (1 g, 5.3 mmol) was dissolved in 40 mL of 2 N HCl and stirred for 2 h. The solution was neutralized with $NaHCO_3$ and extracted with dichloromethane (50 mL × 3). The organic layer was dried over Na_2SO_4 and evaporated. After drying under vacuum for 2 h, 825 mg of product was collected, yield 89%. Mp: 101–102.5 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.45 (br, C=CHO*H*, 1 H), 8.48 (d, J = 4.2 Hz, CH-2, 1 H), 7.51 (d, J = 7.5 Hz, CH-4, 1 H), 7.25 (dd, J = 7.5, 4.2 Hz, CH-3, 1 H), 2.86 (t, J = 7.5 Hz, CH_2-5, 2 H), 2.56 (t, J = 7.5 Hz, CH_2-6, 2 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 186.3 (broad, 2 C's), 147.6, 147.2, 136.0, 135.9, 125.7, 111.0, 26.7, 19.4. MS-CI: m/z 176 (M^+ + H). HRMS-CI calcd for $C_{10}H_{10}N_1O_2$: 176.0711. Found: 176.0713. Anal. Calcd for $C_{10}H_{10}NO_2$: C, 68.11; H, 5.73; N, 7.95. Found: C, 68.32; H, 5.24; N, 7.95.

2-Amino-5,6-dihydro-1,10-phenanthroline-3-carboxylic Acid, Ethyl Ester (3). The 3,3-diaminopropenoate HCl salt (179 mg, 1.07 mmol) was dissolved in a stirred solution of 0.5 mL of ice water saturated with K_2CO_3 and 1.5 mL of EtOAc and was then shaken vigorously. The aqueous layer was washed with EtOAc. The combined EtOAc layer was dried with Na_2SO_4 and reduced to an oil. The oil was dissolved in 1 mL of dry THF and added dropwise to a stirred solution of 150 mg of 5,6,7,8-tetrahydro-7-(hydroxymethylidene)-8-quinolone in 3 mL of dry THF. The mixture was stirred under a N_2 atmosphere overnight. The THF was removed under reduced pressure and EtOAc added to precipitate the product. The precipitate was filtered, washed with EtOAc, and dried to give 140 mg of product, yield 61%. Mp: 242–243 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.71 (dd, J = 4.5, 1.2 Hz, 1 H), 8.05 (s, 1 H), 7.56 (d, J = 7.5 Hz, 1 H), 7.25 (dd, J = 7.5, 4.5 Hz, 1 H), 6.55 (br, 2 H), 4.36 (q, J = 7.2 Hz, 2 H), 2.95 (t, J = 7.2 Hz, 2 H), 2.89 (t, J = 7.2 Hz, 2 H), 1.40 (t, J = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) : δ 166.5, 158.5, 154.2, 150.7, 148.5, 139.5, 135.7, 135.0, 123.7, 122.1, 105.9, 60.6, 27.6, 25.9, 14.1. MS-EI: m/z 269 (M^+). Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.91; H, 5.58; N, 15.61. Found: C, 66.78; H, 5.53; N, 15.60.

3,6-Bis-[(dimethylamino)methylidene]-4,5-dioxo-1,2,3,4,5,6,7,8-octahydro-9-acridinecarboxylic Acid, Ethyl Ester (8). Diketone **4a** (1.15g, 4.0 mmol) was dissolved in 5 mL of dry DMF at room temperature under

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a N_2 atmosphere, and 7 mL of *N,N*-dimethylformamide dimethyl acetal (23 mmol) was added. The mixture was heated at 110 °C for 1 h. The mixture was poured over ice and extracted with CH_2Cl_2 several times. The combined CH_2Cl_2 layers were washed with water and dried over Na_2SO_4. After removing the solvent under reduced pressure, the resulting liquid was dried overnight to give an orange slurry. The residue was then crystallized from ether/EtOAc to give 1.1 g of an orange precipitate, yield 70%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (s, C*H*NMe$_2$, 2 H), 4.40 (q, J = 7.2 Hz, OC*H*$_2$CH$_3$, 2 H), 3.12 (s, 2 NMe$_2$, 12 H), 2.87 (t, J = 6.0 Hz, CH$_2$-1,8, 4 H), 2.82 (t, J = 6.0 Hz, CH$_2$-2,7, 4 H), 1.37 (t, J = 7.2 Hz, OCH$_2$C*H*$_3$, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 183.3, 166.8, 150.1, 139.0, 135.3, 103.2, 61.8, 42.5, 26.1, 22.7, 14.2. This compound was characterized no further but instead used immediately.

3,6-Bis-(hydroxymethylidene)-4,5-dioxo-1,2,3,4,5,6,7,8-octahydro-9-acridinecarboxylic Acid, Ethyl Ester (7). Compound **8** (1.05 g, 2.65 mmol) was dissolved in 50 mL of 0.1 N HCl and stirred for 1 h. The reaction mixture was extracted with CH_2Cl_2 (50 mL × 4), and the combined CH_2Cl_2 layer was washed with water, dried over Na_2SO_4, and evaporated to give 0.832 g of yellow solid, 92% yield. Mp: 202–206 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.72 (br, 2 O=CH, 2 H), 4.48 (q, J = 7.2 Hz, OC*H*$_2$CH$_3$, 2 H), 2.94 (m, CH$_2$-1,8, CH-3,6, 6 H), 2.63 (t, J = 15 Hz, CH$_2$-2,7, 4 H), 1.43 (t, J = 7.2 Hz, OCH$_2$C*H*$_3$, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 300 MHz): δ 187.0 (broad, 2 C's), 166.0, 146.3, 140.7, 134.8, 111.8, 62.4, 24.7, 18.7, 14.2. MS-EI: m/z 343 (M^+). HRMS-EI calcd for $C_{18}H_{17}NO_6$: 343.3328. Found: 343.3354.

Bispyrido[3′,2′:5,6]cyclohexa[1,2-*b*:2′,1′-*e*]pyridine-3,7,11-tricarboxylic Acid, 2,12-Diamino-5,6,8,9-tetrahydro-, triethyl Ester (1). Compound **7** (832 mg, 2.42 mmol) was dissolved in 60 mL of dry THF under N_2, and 2.3 equiv of 3,3-diaminopropenoate (**6**) in 10 mL of dry THF was added. The mixture was stirred at 25 °C under a N_2 atmosphere overnight and the solvent removed under reduced pressure. The residue was purified via silica gel chromatography with eluent EtOAc (1 L), 10% MeOH in EtOAc (1 L), and 20% MeOH in EtOAc (1 L). Collecting the second band gave 0.507 g of **1**. A mixture of the first and second band was evaporated to an oil and crystallized from EtOAc to give another 79 mg of **1**. Total yield: 46%. Mp: 225 °C (decomposed). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.03 (s, 2 H), 6.75 (br, NH$_2$, 4 H), 4.48 (q, J = 7.2 Hz, OC*H*$_2$CH$_3$, 2 H), 4.36 (m, OC*H*$_2$CH$_3$, 4 H), 2.87 (t, J = 4.5 Hz, 4 H), 2.81 (t, J = 4.5 Hz, 4 H), 1.38 (t, J = 7.2 Hz, OCH$_2$C*H*$_3$, 3 H), 1.34 (t, J = 7.2 Hz, OCH$_2$C*H*$_3$, 6 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 167.0, 166.1, 159.0, 152.1, 149.0, 141.0, 140.3, 131.9, 120.9, 107.2, 62.2, 60.9, 25.0, 24.7, 14.2 (2 C's). MS-CI: m/z 532 (M^+ + H). HRMS-CI calcd for $C_{28}H_{29}N_5O_6$: 531.2118. Found: 531.2118. Anal. Calcd for $C_{28}H_{29}N_5O_7 \cdot H_2O$: C, 61.18; H, 5.89; N, 12.75. Found: C, 61.28; H, 5.73; N, 12.09.

2-Benzylidene-7-[(dimethylamino)methylidene]cycloheptanone (14). A mixture of compound **13** (31.4 g, 157 mmol), 146 mL of *N,N*-dimethylformamide dimethyl acetal (490 mmol), and 50 mL of DMF was stirred at reflux under a N_2 atmosphere for 60 h. The mixture was poured over ice and extracted with CH_2Cl_2 (200 mL × 4). The combined organic layers were reduced to 200 mL and washed with brine (150 mL × 2). The organic layer was then dried (Na_2SO_4), evaporated, and dried in vacuo at 50 °C to remove DMF. A total of 37.5 g of an orange-red oil was collected, yield 94%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55 (s, PhCH=C, 1 H), 7.44 (d, J = 7.8 Hz, C$_6$H$_5$, 2 H), 7.36 (t, J = 7.8 Hz, C$_6$H$_5$, 2 H), 7.26 (t, J = 7.8 Hz, C$_6$H$_5$, 1 H), 6.95 (s, Me$_2$NCH=C, 1 H), 3.09 (s, 2 NMe$_2$, 6 H), 2.66 (t, J = 5.1 Hz, CH$_2$-3, 2 H), 2.60 (t, J = 6.0 Hz, CH$_2$-6, 2 H), 1.87 (m, CH$_2$-4, 2 H), 1.70 (m, CH$_2$-5, 2 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 198.1, 149.0, 146.1, 136.9, 130.3, 129.2, 127.9, 126.9, 105.2, 43.1, 29.1, 28.6, 25.5, 24.1. MS-CI: m/z 256 (M^+ + H). HRMS-CI m/z calcd for $C_{17}H_{21}NO$: 255.1623. Found: 255.1617.

2-Benzylidene-7-(hydroxymethylidene)cycloheptanone (15). To 37.5 g of compound **14** (147 mmol) was added 220 mL of 2 N HCl, and the mixture was stirred vigorously for 2.5 h. After extraction with CH_2Cl_2 (200 mL × 3), the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The resulting orange oil was further dried under vacuum overnight to give 33.0 g of product, yield 97%. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 15.36 (d, J = 5.7 Hz, C=CHO*H*, 1 H), 8.29 (d, J = 4.3 Hz, C=C*H*OH, 1 H), 7.39 (m, C$_6$H$_5$CH=C, 6 H), 2.65 (t, J = 4.3 Hz, CH$_2$-3, 2 H), 2.42 (t, J = 4.3 Hz, CH$_2$-6, 2 H), 1.81 (br, CH$_2$-4,5, 4 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 188.9, 181.1, 139.3, 135.9, 135.2, 129.4, 128.3, 128.0, 112.4, 27.2, 26.9, 26.1, 25.7. MS-CI: m/z 229 (M^+ + H). HRMS-CI m/z calcd for $C_{15}H_{17}O_2$ (M^+ + H): 229.1228. Found: 229.1229.

3-[[(3,4-Dimethoxyphenyl)methyl]amino]-3-aminopropenoic Acid, Ethyl Ester (16). Ethyl 3-ethoxy-3-aminopropenoate (19.45 g, 99.5 mmol) was dissolved in 100 mL of absolute ethanol, and 15 mL of 3,4-dimethoxybenzylamine (99.5 mmol) was added under nitrogen. A white precipitate (NaCl) formed. Another 50 mL of absolute EtOH was added, and the mixture was stirred vigorously. A solution of 2.3 g of Na in 35 mL of absolute EtOH was added dropwise through an addition funnel. The mixture was stirred overnight and then filtered through Celite to remove NaCl. The filtrate was evaporated to remove EtOH and then partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated. The residue was purified via silica gel chromatography with 50% EtOAc in hexane (1 L) and EtOAc (2 L). An orange syrup was collected, which solidified after drying in vacuo, yield 11.1 g, 40%. Mp: 86–87 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.79 (br, C$_6$H$_3$(OMe)$_2$, 3 H), 6.27 (br, NH-benzyl, 1 H), 4.77 (br, *H*N=CCH$_2$-CO$_2$Et, 0.625 H), 4.27 (br, *H*$_2$NC=CHCO$_2$Et, 0.75 H), 4.17 (br, HNC*H*$_2$C$_6$H$_3$(OMe)$_2$, 2 H), 4.10 (q, J = 7.2 Hz, CO$_2$C*H*$_2$CH$_3$, 2 H), 4.04 (br, H$_2$NC=C*H*CO$_2$Et, 0.375 H), 3.84 (s, OCH$_3$, 6 H), 2.02 (s, HN=CC*H*$_2$CO$_2$Et, 1.25 H), 1.23 (t, J = 7.2 Hz, CO$_2$CH$_2$C*H*$_3$, 3 H). ^{13}C NMR, mixture of interconverting *cis* and *trans* isomers ($CDCl_3$, 75 MHz): δ 171.2, 171.1, 161.2, 149.1, 148.4, 130.0, 119.6, 111.2, 110.5, 63.8, 60.3, 57.9, 55.8, 55.7, 45.8, 20.9, 14.6, 14.1. MS-CI: m/z 281 (M^+ + H).

5*H*-Cyclohepta[*b*]pyridine-3-carboxylic Acid, 2-[[(3,4-Dimethoxyphenyl)methyl]amino]-6,7,8,9-tetrahydro-9-benzylidene-, Ethyl Ester (17). Compound **15** (1.02 g, 4.46 mmol) was dissolved in 2 of mL dry THF under a N_2 atmosphere, and 1.25 g (4.46 mmol) of compound **16** in 5 mL of dry THF was added dropwise. The mixture was allowed to stir at room temperature for 20 h. After the THF was removed, the residue was purified via silica gel chromatography with 20% EtOAc in hexane (0.75 L) and 33% EtOAc in hexane (0.3 L). The late fraction was collected to give 1.28 g of yellow solid, yield 61%. Mp: 98.5–100 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 (br, HN-benzyl, 1 H), 7.88 (s, para H, 1 H), 7.34–7.44 (m, C$_6$H$_5$, 5 H), 7.20 (s, C$_6$H$_5$C*H*=C, 1 H), 7.01 (s, H-2 of C$_6$H$_3$(OMe)$_2$, 1 H), 6.99 (d, J = 8.1 Hz, C$_6$H$_3$(OMe)$_2$, 1 H), 6.83 (d, J = 8.1 Hz, C$_6$H$_3$(OMe)$_2$, 1 H), 4.77 (d, J = 5.1 Hz, HNC*H*$_2$C$_6$H$_3$-(OMe)$_2$, 2 H), 4.31 (q, J = 7.2 Hz, CO$_2$C*H*$_2$CH$_3$, 2 H), 3.85 (s, OCH$_3$, 3 H), 3.82 (s, OCH$_3$, 3 H), 2.71 (t, J = 5.4 Hz, CCH$_2$, 4 H), 1.83 (m, CCH$_2$C*H*$_2$, 4 H), 1.38 (t, J = 7.2 Hz, CO$_2$CH$_2$C*H*$_3$, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 167.5, 163.5, 156.4, 148.9, 142.5, 141.1, 137.5, 133.1, 132.4, 129.2, 128.2, 126.9, 122.4, 119.9, 111.3, 111.1, 104.2, 60.5, 55.8, 55.7, 44.8, 31.8, 28.9, 27.0, 26.8, 14.3. MS-CI: m/z 473 (M^+ + H). HRMS-CI m/z calcd for $C_{29}H_{32}N_2O_4$: 472.2362. Found: 472.2363.

5*H*-Cyclohepta[*b*]pyridine-3-carboxylic Acid, 2-[[(3,4-dimethoxyphenyl)methyl]amino]-6,7,8,9-tetrahydro-9-oxo-, Ethyl Ester (18). Compound **17** (1.28 g, 2.7 mmol) was dissolved in 10 mL of H_2O and 30 mL THF, to which was added 627 μL of an OsO_4 solution (2.5% in 2-methylpropanol). After stirring for 10 min, the solution had turned black and 2.14 g of sodium periodate (10.7 mmol) was added slowly by spatula. After stirring for 30 h, the osmium was quenched with sodium bisulfite solution and the THF was removed under reduced pressure. The aqueous solution was then extracted with CH_2Cl_2 (25 mL × 4). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified via silica gel chromatography with eluent 20% EtOAc in hexane (0.5 L) and 50% EtOAc (1 L). Product (0.92 g) was collected, 92% yield. Mp: 65–66 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09 (t, J = 4.5 Hz, HN-benzyl, 1 H), 7.98 (s, para H, 1 H), 7.04 (s, H-2 of C$_6$H$_3$(OMe)$_2$, 1 H), 6.93 (d, J = 8.1 Hz, C$_6$H$_3$(OMe)$_2$, 1 H), 6.81 (d, J = 8.1 Hz, C$_6$H$_3$(OMe)$_2$, 1 H), 4.66 (d, J = 4.5 Hz, HNC*H*$_2$C$_6$H$_3$-(OMe)$_2$, 2 H), 4.30 (q, J = 7.2 Hz, CO$_2$C*H*$_2$CH$_3$, 2 H), 3.87 (s, OCH$_3$, 3 H), 3.84 (s, OCH$_3$, 3 H), 2.73 (m, CCH$_2$, 4 H), 1.85 (m, CCH$_2$C*H*$_2$, 4 H), 1.35 (t, J = 7.2 Hz, CO$_2$CH$_2$C*H*$_3$, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 205.4, 166.7, 157.7, 156.8, 148.8, 148.0, 141.8, 132.1, 122.1, 120.1, 111.8, 111.1, 107.7, 60.9, 60.4, 55.8, 55.7, 44.8, 40.7, 29.9, 25.6, 22.1, 14.1. MS-CI: m/z 399 (M^+ + H), 385. HRMS-CI calcd for $C_{22}H_{26}N_2O_5$: 398.1842 (M^+). Found: 398.1835.

5*H*-Cyclohepta[*b*]pyridine-3-carboxylic Acid, 2-[[(3,4-dimethoxyphenyl)methyl]amino]-6-dihydro-9-(1-pyrrolidinyl), Ethyl Ester (19). To a solution of compound **18** (1.6 g, 4 mmol) in 10 mL of dry THF under a N_2 atmosphere were added 250 mg of TsOH and 2.1 mL (12 mmol) of (trimethylsilyl)pyrrolidine. The mixture was stirred at 50 °C overnight. The THF and excess pyrrolidine were removed under reduced pressure to afford a quantitative yield of the enamine. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.03 (t, J = 5.7 Hz, HN-benzyl, 1 H), 7.88 (s, para H, 1 H), 6.87 (s, H-2 of C$_6$H$_3$(OMe)$_2$, 1 H), 6.82 (d, J = 8.4 Hz, C$_6$H$_3$(OMe)$_2$,

1 H), 6.71 (d, J = 8.4 Hz, $C_6H_3(OMe)_2$, 1 H), 4.79 (t, J = 7.2 Hz, NC=CH, 1 H), 4.62 (d, J = 5.7 Hz, $HNCH_2C_6H_3(OMe)_2$, 2 H), 4.24 (q, J = 7.2 Hz, $CO_2CH_2CH_3$, 2 H), 3.77 (s, OCH_3, 3 H), 3.76 (s, OCH_3, 3 H), 2.88 (m, CH_2NCH_2, 4 H), 2.37 (t, J = 6.3 Hz, CCH_2, 2 H), 1.76 (m, $CCH_2CH_2CH_2CH$=C, 4 H), 1.70 (m, $N(CH_2CH_2)_2$, 4 H), 1.30 (t, J = 7.2 Hz, $CO_2CH_2CH_3$, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 62.5 MHz): δ 167.3, 160.0, 156.4, 148.7, 147.7, 146.8, 140.1, 132.7, 124.4, 119.3, 111.0, 103.7, 100.2, 67.7, 60.6, 55.7, 55.6, 51.4, 45.5, 33.4, 29.3, 25.4, 24.3, 14.2. MS-CI: m/z 452 (M^+ + H).

5*H*-Cyclohepta[*b*]pyridine-3-carboxylic Acid, 2-[[(3,4-Dimethoxyphenyl)methyl]amino]-8-(2-ethoxy-2-oxoethylidene)-6,7,8,9-tetrahydro-9-oxo-, Ethyl Ester (20). The enamine **19** (1.8 g, 4.0 mmol) was dissolved in 10 mL of dry THF under a N_2 atmosphere and cooled to −78 °C. The ethyl glyoxylate (570 mg, 5.6 mmol) was then cracked and distilled directly into the solution of enamine. The mixture was stirred under a N_2 atmosphere and allowed to warm slowly to room temperature. After 36 h, 15 mL of HCl (pH = 3) was added and the mixture was stirred for another 6 h. $NaHCO_3$ solution (10 mL) was then added, and the THF was evaporated under reduced pressure. The resulting aqueous solution was then extracted with CH_2Cl_2 (25 × 3 mL). The combined organic layers were dried over Na_2SO_4 and filtered. After evaporation, the residue was purified via silica gel chromatography with 25% EtOAc in hexane (1.0 L), 33% EtOAc in hexane (0.5 L), and 50% EtOAc in hexane (1.0 L) to give 1.08 g of a dark orange oil, yield 54%. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.14 (t, J = 5.4 Hz, HN-benzyl, 1 H), 7.98 (s, para H, 1 H), 7.05 (s, H-2 of $C_6H_3(OMe)_2$, 1 H), 6.93 (d, J = 8.1 Hz, $C_6H_3(OMe)_2$, 1 H), 6.79 (d, J = 8.1 Hz, $C_6H_3(OMe)_2$, 1 H), 4.67 (d, J = 5.4 Hz, $HNCH_2C_6H_3(OMe)_2$, 2 H), 4.29 (q, J = 7.2 Hz, $CO_2CH_2CH_3$, 2 H), 4.23 (q, J = 7.2 Hz, $CO_2CH_2CH_3$, 2 H), 3.88 (s, OCH_3, 3 H), 3.86 (s, OCH_3, 3 H), 2.87 (t, J = 6.6 Hz, CCH_2, 2 H), 2.64 (t, J = 6.6 Hz, CCH_2, 2 H), 1.97 (m, J = 6.6 Hz, CCH_2CH_2, 2 H), 1.34 (t, J = 7.2 Hz, $CO_2CH_2CH_3$, 3 H), 1.30 (t, J = 7.2 Hz, $CO_2CH_2CH_3$, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 194.5, 166.5, 165.7, 157.1, 154.9, 150.6, 148.7, 147.9, 141.5, 131.9, 125.5, 122.1, 120.1, 111.8, 111.0, 108.7, 60.9, 60.5, 55.7, 55.6, 44.7, 28.1, 25.0, 24.5, 14.0, 13.9. MS-CI: m/z 483 (M^+ + H), 333. HRMS-CI calcd for $C_{26}H_{30}N_2O_7$: 482.2053 (M^+). Found: 482.2051.

α-Bis-[2-[[(3,4-dimethoxyphenyl)methyl]amino]-3-(ethoxycarbonyl)-6,7,8,9-tetrahydro-9-oxo-8-(5*H*)-pyrido[*b*]cycloheptyl]acetic Acid, Ethyl Ester (21). To a solution of 4.24 g (8.79 mmol) of compound **20** in 15 mL of dry THF was added enamine **19** (made from 3.5 g (8.79 mmol) ketone **18**) in 15 mL of dry THF. The mixture was allowed to reflux under nitrogen for 24 h and then cooled to room temperature, and 15 mL of HCl solution (pH = 3) was added. The mixture was stirred overnight and evaporated to remove THF. The resulting aqueous solution was extracted with CH_2Cl_2 (100 mL × 3). The combined CH_2Cl_2 solution was dried (Na_2SO_4) and evaporated. The residue was purified via silica gel chromatography with 30% EtOAc in hexane (1.0 L), 40% EtOAc in hexane (1.0 L), and 50% EtOAc in hexane (1.0 L). A brown oil (2.93 g) was collected, 40% yield. The ^1H and ^{13}C NMR spectra showed that the oil contained several isomers. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.09 (t, J = 5.4 Hz, HN-benzyl, 0.8 H), 7.99 (t, J = 5.4 Hz, HN-benzyl, 0.8 H), 7.96 (s, para H, 0.4 H), 7.88 (t, J = 5.4 Hz, 0.4 H), 7.85 (s, para H, 0.8 H), 7.82 (s, para H, 0.8 H), 7.03 (s, H-2 of $C_6H_3(OMe)_2$, 0.6 H), 6.97–6.86 (m, 2.2 H), 6.77 (d, J = 8.1 Hz, $C_6H_3(OMe)_2$, 0.8 H), 6.70 (d, J = 8.1 Hz, $C_6H_3(OMe)_2$, 0.8 H), 6.60 (d, J = 8.4 Hz, $C_6H_3(OMe)_2$, 0.6 H), 6.51 (d, J = 8.4 Hz, $C_6H_3(OMe)_2$, 0.6 H), 6.35 (s, 0.4 H), 5.06 (d, J = 6.0 Hz, $HNCH_2C_6H_3(OMe)_2$, 0.2 H), 5.01 (d, J = 6.3 Hz, $HNCH_2C_6H_3(OMe)_2$, 0.2 H), 4.76 (d, J = 6.3 Hz, $HNCH_2C_6H_3(OMe)_2$, 0.2 H), 4.70 (d, J = 6.3 Hz, $HNCH_2C_6H_3(OMe)_2$, 0.6 H), 4.64 (d, J = 5.4 Hz, $HNCH_2C_6H_3(OMe)_2$, 1.6 H), 4.51 (d, J = 5.4 Hz, $HNCH_2C_6H_3(OMe)_2$, 0.4 H), 4.45 (d, J = 5.4 Hz, $HNCH_2C_6H_3(OMe)_2$, 0.4 H), 4.38 (d, J = 5.4 Hz, $HNCH_2C_6H_3(OMe)_2$, 0.4 H), 4.26 (m, $CO_2CH_2CH_3$, 4 H), 4.10 (m, $CO_2CH_2CH_3$, 2 H), 3.85 (s, OCH_3, 2.2 H), 3.79 (s, OCH_3, 3 H), 3.77 (two s, OCH_3, 3.2 H), 3.73 (s, OCH_3, 1.8 H), 3.65 (s, OCH_3, 1.8 H), 3.22 (t, J = 12.9 Hz, EtO_2CCH, 0.6 H), 2.89 –2.42 (m, 6.4 H), 1.79 –1.61 (br, CCH_2CH_2, 8 H), 1.32 (t, J = 7.2 Hz, $CO_2CH_2CH_3$, 6 H), 1.21 (m, $CO_2CH_2CH_3$, 3 H). $^{13}C\{^1H\}$ NMR, several isomers ($CDCl_3$, 75 MHz): δ 205.1, 173.9, 167.2, 166.5, 161.1, 157.9, 157.6, 156.7, 156.4, 155.5, 148.8, 148.6, 148.5, 148.4, 147.8, 147.6, 147.1, 141.6, 140.1, 133.0, 132.9, 131.9, 124.3, 122.9, 121.9, 120.0, 119.9, 117.8, 111.6, 111.1, 110.5, 110.9, 110.4, 109.7, 107.4, 103.8, 103.6, 95.1, 60.7, 60.6, 60.4, 60.2, 60.0, 55.6, 55.5, 55.3, 47.8, 45.0, 44.6, 44.1, 43.6, 41.1, 40.5, 33.3, 33.2, 30.2, 29.7, 28.1, 25.6, 25.4, 25.3, 24.3, 22.7, 22.0, 14.1, 14.0, 13.9. Characterized no further.

Bispyrido[3′,2′:6,7]cyclohepta[1,2-*b*:2′,1′-*e*]pyridine-3,8,13-tricarboxylic Acid, 2,14-Bis[[(3,4-dimethoxyphenyl)methyl]amino]-5,6,7,9,10,11-hexahydro-, Triethyl Ester (22). Compound **21** (2.9 g, 3.33 mmol) was dissolved in 15 mL of acetic acid, and 512 mg of ammonium acetate (6.6 mmol) was added. The mixture was heated to reflux for 10 h and neutralized with $NaHCO_3$. The solution was extracted with CH_2Cl_2 (100 mL × 4). The combined CH_2Cl_2 fraction was dried (Na_2SO_4) and evaporated. The residue was purified by a silica gel column (2 × 7 in.) with eluent 25% EtOAc in hexane (1.0 L), 33% EtOAc in hexane (0.5 L), and 50% EtOAc in hexane (1.0 L). The product was an orange oil, which solidified when dried in vacuo (yield 50%). Mp: 250 °C (decomposed). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.05 (t, J = 5.1 Hz, HN-benzyl, 2 H), 8.00 (s, para H, 2 H), 6.89 (s, H-2 of $C_6H_3(OMe)_2$, 2 H), 6.82 (d, J = 8.1 Hz, $C_6H_3(OMe)_2$, 2 H), 6.66 (d, J = 8.1 Hz, $C_6H_3(OMe)_2$, 2 H), 4.74 (d, J = 5.1 Hz, $HNCH_2C_6H_3(OMe)_2$, 4 H), 4.47 (q, J = 7.2 Hz, $CO_2CH_2CH_3$, 2 H), 4.30 (q, J = 7.2 Hz, $CO_2CH_2CH_3$, 4 H), 3.80 (s, OCH_3, 6 H), 3.61 (s, OCH_3, 6 H), 2.54 (m, CCH_2, 8 H), 2.19 (m, CCH_2CH_2, 4 H), 1.41 (t, J = 7.2 Hz, $CO_2CH_2CH_3$, 3 H), 1.36 (t, J = 7.2 Hz, $CO_2CH_2CH_3$, 6 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 167.8, 167.3, 159.6, 157.5, 155.6, 148.6, 147.8, 141.1, 140.2, 132.1, 131.0, 122.2, 120.3, 111.8, 110.9, 105.6, 61.7, 60.6, 55.7, 55.4, 45.1, 31.8, 28.3, 27.0, 14.3 (3 C's). MS-CI: m/z 860 (M^+ + H). HRMS-CI calcd for $C_{48}H_{54}N_5O_{10}$: 860.9821. Found: 860.9802.

Bispyrido[3′,2′:6,7]cyclohepta[1,2-b:2′,1′-e]pyridine-3,8,13-tricarboxylic Acid, 2,14-Diamino-5,6,7,9,10,11-hexahydro-, Triethyl Ester (2). Compound **22** (1.1 g, 1.28 mmol) was dissolved in 20 mL of trifluoroacetic acid under nitrogen, and 556 μL of anisole (5.12 mmol) was added, followed by 1.1 mL of concentrated H_2SO_4. The mixture was stirred at room temperature for 22 h and then adjusted to pH 8 with 2.5 N NaOH. The solution was extracted with CH_2Cl_2 (100 mL × 4), and the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified via silica gel chromatography with eluent of variant ratio from 33% EtOAc in hexane to 10% MeOH in EtOAc to give 0.7 g of yellow powder in 60% total yield. Further purification can be achieved by recrystallization from ethyl acetate. Mp: 350 °C (decomposed). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.99 (s, para H, 2 H), 6.59 (br, NH_2, 4 H), 4.46 (q, J = 7.2 Hz, $CO_2CH_2CH_3$, 2 H), 4.34 (q, J = 7.2 Hz, $CO_2CH_2CH_3$, 4 H), 2.48 (m, CCH_2, 8 H), 2.18 (m, CCH_2CH_2, 4 H), 1.43 (t, J = 7.2 Hz, $CO_2CH_2CH_3$, 3 H), 1.41 (t, J = 7.2 Hz, $CO_2CH_2CH_3$, 6 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 62.5 MHz): δ 167.3, 166.3, 158.0, 154.2, 148.9, 142.1, 141.7, 132.2, 123.8, 106.9, 62.0, 61.1, 31.9, 28.4, 27.3, 14.3 (3 C's). MS-CI: m/z 560 (M^+ + H), 154. HRMS-CI calcd $C_{30}H_{34}N_5O_6$ (M^+ + H): 560.2451. Found: 560.2509. Anal. Calcd for $C_{30}H_{33}N_5O_6$: C, 64.40; H, 5.90; N, 12.52. Found: C, 63.64: H, 5.95; N, 12.46.

Allyl-2,3-*O*-diallyl-4,6-*O*-benzylideneglucopyranoside (35). To a stirred milky solution of 3.54 g of allyl-4,6-*O*-benzylideneglucopyranoside (11.5 mmol) in 65 mL of dry toluene under nitrogen was added 3 g of powdered KOH (53.6 mmol). The mixture turned clear slowly. Allyl bromide (3.8 mL, 44 mmol) was added dropwise to the mixture through an addition funnel. A white precipitate formed slowly. The mixture was stirred at reflux under nitrogen for 8 h. After cooling, the mixture was washed twice with water to remove the precipitate, and the organic layers were dried under vacuum to remove toluene. The residue was purified via silica gel chromatography (20% EtOAc in hexane) to give 2.77 g of a white solid (62%). Mp: 61–62 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.48–7.35 (m, C_6H_5, 5 H), 5.93 (m, 3 H_2C=C$H$$CH_2O$, 3 H), 5.54 (s, $PhCH(O)_2$, 1 H), 5.37–5.12 (m, 3 H_2C=CHCH_2O, 6 H), 4.94 (d, J = 3.6 Hz, CHeq-1, 5/6 H), 4.46 (d, J = 7.5 Hz, 1/6 H), 4.40–4.05 (m, 3 H_2C=CHCH_2O, CH-2, 7 H), 3.87 (m, CH-3,4, 2 H), 3.71 (m, 1 H), 3.57 (m, CH-5, 1 H), 3.46 (m, CHax-6, 1 H). $^{13}C\{^1H\}$ NMR, α and β anomers ($CDCl_3$, 75 MHz): δ 137.4, 135.2, 134.8, 133.7, 133.6, 128.8, 128.2, 126.0, 118.2, 117.4, 117.3, 116.6, 101.2, 101.1, 96.8, 82.1, 81.6, 81.2, 79.0, 78.0, 74.1, 73.9, 72.8, 69.0, 68.4, 62.5. MS-CI: m/z 389 (M^+ + H), 331, 225. HRMS-CI calcd for $C_{22}H_{29}O_6$: 389.1964 (M^+ + H). Found: 389.1955. Two later fractions from the column (0.26 and 0.7 g, respectively) were identified as monoallylation products.

Allyl-2,3-*O*-diallylglucopyranoside (36). Compound **35** (2.76 g, 7.1 mmol) was dissolved in 30 mL of 75% acetic acid and heated at 80 °C for 3 h. The mixture was dried under vacuum to remove acetic acid. The residue was purified via silica gel chromatography with 33% hexane in EtOAc as eluent to give 1.7 g of a clear oil, yield 80%. NMR spectra showed the product contained both anomers (α:β = 5:1). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.93 (m, 3 H_2C=C$H$$CH_2O$, 3 H), 5.35–5.17 (m, 3 H_2C=CHCH_2O, 6 H), 4.94 (d, J = 2.7 Hz, CHeq-1, 5/6 H), 4.42–4.05 (m, CHax-1, 3 H_2C=CHCH_2O, CH-2, 7+ 1/6 H), 3.80 (m, CH-

3,4, 2 H), 3.67 -3.32 (m, CH-5, CH_2-6, 3 H). $^{13}C\{^1H\}$ NMR, α and β anomers ($CDCl_3$, 75 MHz): δ 135.1, 134.9, 134.8, 134.6, 133.6, 118.2, 117.5, 117.3, 117.0, 102.5, 95.7, 83.6, 81.5, 80.9, 79.5, 74.8, 74.1, 73.5, 71.9, 70.9, 70.5, 70.4, 70.3, 68.2, 62.6, 62.4. MS-CI: m/z 301 (M^+ + H), 243, 185. HRMS-CI calcd for $C_{15}H_{25}O_6$: 301.1651 (M^+ + H). Found: 301.1640.

Allyl-2,3-*O*-diallyl-4,6-*O*-dibenzylglucopyranoside (37). Compound **36** (1.7 g, 5.7 mmol), powdered KOH (3.17 g, 57 mmol), and 10 mL of dry toluene were stirred under nitrogen. To this mixture was added 5.2 mL of benzyl chloride (45.3 mmol) dropwise through an addition funnel. The mixture was stirred at reflux for 12 h. The mixture was cooled and partitioned between water and CH_2Cl_2 (100 mL/100 mL). The aqueous layers were washed with CH_2Cl_2 (100 mL × 2). The combined organic layer was dried (Na_2SO_4), evaporated, and vacuum distilled to remove toluene, benzyl chloride, and benzyl alcohol. The residue was purified via silica gel chromatography with 15% EtOAc in hexane to give 2.3 g of a yellow liquid, yield 85%. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.14 (m, 2 C_6H_5, 10 H), 5.89 (m, 3 H_2C=C$H$$CH_2O$, 3 H), 5.23 (m, 3 H_2C=CHCH_2O, 6 H), 4.93 (d, J = 3.6 Hz, CH-1, 1 H), 4.80 (m, CH-2, 1 H), 4.62–4.05 (m, 2 $PhCH_2$, 3 H_2C=CHCH_2O, 10 H), 3.78–3.56 (m, CH-3,4, CH_2-6, 4 H), 4.20 (m, CH-5, 1 H). $^{13}C\{^1H\}$ NMR, α and β anomers ($CDCl_3$, 75 MHz): δ 138.2, 138.1, 137.9, 135.3, 135.2, 135.0, 134.8, 133.7, 128.3, 127.9, 127.8, 127.6, 127.5, 127.4, 117.9, 117.4, 116.4, 116.7, 116.6, 116.4, 102.4, 95.7, 84.3, 81.6, 79.5, 77.6, 77.5, 75.0, 74.9, 74.7, 74.4, 74.2, 73.5, 73.4, 72.2, 72.0, 70.1, 70.0, 68.9, 68.4, 68.0. MS-CI: m/z 479 (M^+ – H), 423, 365.

4,6-*O*-Dibenzylglucopyranose (34). A stirred solution of compound **37** (2.2 g, 4.6 mmol) and *t*-BuOK in 50 mL of dry DMSO was heated at 100 °C for 1 h. The mixture was cooled and diluted with 100 mL of water and then extracted with ethyl ether (100 mL × 3). The combined organic layers were dried (Na_2SO_4), evaporated, and further dried in vacuum overnight. The residue was dissolved in acetone/water (10:1, 50 mL), together with 2.4 g of mercuric oxide. To this solution was added a solution of mercuric chloride (2.4 g, 8.8 mmol) in acetone/water (10:1, 15 mL) dropwise with stirring over 10 min. When the addition was complete, the mixture was stirred for another 30 min. The mercuric oxide was removed by filtration through Celite, the acetone was evaporated, and ether was added to the residue. The ether layer was washed with an aqueous solution of potassium iodide (20 mL), dried (Na_2SO_4), and evaporated. Crystallization of the residue from methanol and methylene chloride give 0.65 g of a white solid, yield 55%. Mp: 154–155 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30–7.23 (m, C_6H_5, 10 H), 5.14 (d, J = 3.9 Hz, CH_{eq}-1, 6 H), 4.87–4.44 (m, $PhCH_2$, CH_{ax}-1, 4 H), 3.96–3.32 (m, C-2,3,4,5-H, CH_2-6, 6 H). $^{13}C\{^1H\}$ NMR, α and β anomers ($CDCl_3$, 75 MHz): δ 139.5, 139.0, 129.1, 129.0, 128.8, 128.5, 128.4, 128.3, 97.6, 93.3, 79.2, 78.9, 75.9, 75.4, 75.3, 74.0, 73.5, 70.6, 70.0, 70.1. MS-CI: m/z 361 (M^+ + H), 129. HRMS-CI calcd for $C_{20}H_{24}O_6$: 360.1573 (M^+ + H). Found: 360.1553.

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Supplementary Material Available: Molecular mechanics optimized structures of compounds **23**, **24**, and **25**, van't Hoff plot for determining ΔH and ΔS of binding between **2** and **23** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.