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TWISTED POLYAZA CLEFTS FOR THE COMPLEXATION OF CYCLOHEXANE-POLYOLS

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Abstract: A polyaza cleft was synthesized and shown to bind 1,2- and 1,3-cyclohexanediols and 1,3-2-cyclohexanetriol in chloroform.

Molecular recognition of polar compounds via hydrogen bonding in lipophilic solvents is a rapidly growing field due to its potential to mimic biological processes such as self replication[1] and enzyme-like catalysis.[2] Some biologically significant compounds such as amino acids[3] and nucleotide bases[4] have been successfully complexed. Carbohydrates, however, have received little attention. In 1988, Aoyama et. al. were able to bind aldopentoses such as ribose and arabinose by using a polyhydroxy macrocycle.[5] With an initial interest in complexing pyranoses, we herein introduce results using a twisted polyazacleft for the binding of cyclohexanediols and 1,3-2-cyclohexanetriol.[6]

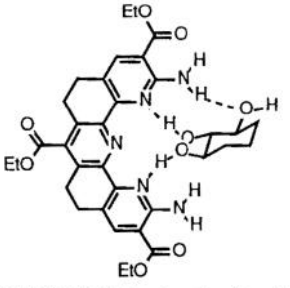


Figure 1: Possible complexation mode for host **1** and guest **13**.

Compound **1** is a polyaza cleft which consists of three pyridine rings fused via saturated ethanediyl linkers. The three pyridine nitrogens and the two ortho amino groups can act as hydrogen bond acceptors and donors respectively and are converged toward the interior of the cleft. Due to the saturation of the linkers, the molecule can exist in two forms, a d,l set or a meso form. Molecular mechanics calculations[7] show that the angle between the top and bottom pyridine rings is approximately 24° in the d,l set, and little energetic preference exists for either the d,l or meso forms. The twist in the d,l form diverges the top and bottom nitrogen pyridine lone pairs away

from each other, and could allow each to accept a different hydrogen bond on a polyhydroxylated substrate.

The synthesis of receptor **1** began from cyclohexanone. Two equilvalents of the pyrrolidine enamine[8] of cyclohexanone **2** were allowed to react with ethyl glyoxylate[9] at reflux in benzene for 16 hours, hydrolyzed via a water reflux, and purified by flash silica gel chromatography to give a 55% yield of **3**. Compound **3** was then stirred in a refluxing mixture of with NH_4OAc/HOAc for 3 hours, neutralized and purified by flash silica gel chromatography to afford an 62% yield of **4**. The reaction of **4** with 10 eqvs. of acetic anhydride and benzaldehyde at 180°C for 10 hours, followed by vacuum distillation of the excess reagents and crystallization of the residue from hexane/EtOAc furnished a 91% yield of **5**. Compound **5** was converted to diketone **6** by ozonolysis in a yield of 48%. Each of the synthetic steps up to this point are analogous to those reported by Thummel in the synthesis of other polypyridine compounds.[10] When **6** was treated with 9 equilvalents of neat N,N-dimethylformamide dimethylacetal at reflux for 1 hour followed by stirring with 0.1N HCl for 1 hr, the diformylated derivative **8** was formed in 82% yield. The reaction of **8** with the extremely good carbon nucleophile[11] **9** at room temperature in THF gave **1** in 45% yield after flash chromatography.[12] For comparison, compound **10** was also synthesized in a similar fashion starting from 2,3,-cyclohexenopyridine.[13]

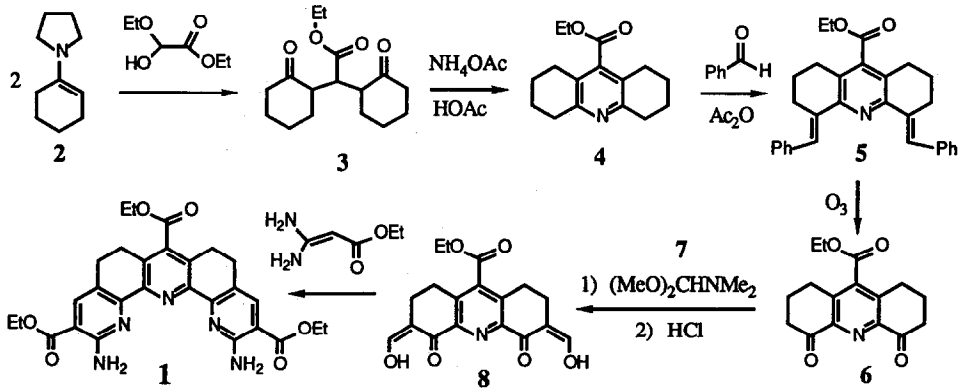
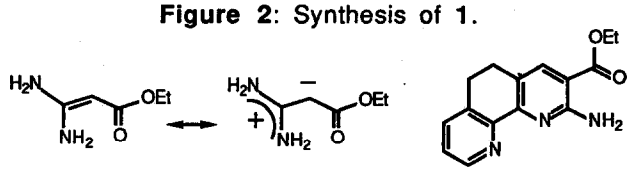


Figure 2: Synthesis of **1**.



Binding constants were measured by following the ^1H NMR chemical shift change of guests upon incremental increases in host concentration. The experimental data was then fit by the nonlinear least square method[14] to give the binding constants (Table 1). From the ^1H NMR spectra, we observe that the hydroxyl resonances of the guests move to lower field upon addition of host and the aliphatic resonances typically move to higher field.

The binding constant between **11** and **1** is about 30 fold larger than the binding constant between **11** and **10**. We conclude that this increase in binding is caused by a cooperativity of the top and bottom amidines in **1**. The cooperativity can be either due to an increase in the number of hydrogen bonds between host and guest, or is due to a chelate effect which allows for the trapping of the guest as it begins to depart from the cleft by an identical set of hydrogen bond donors and acceptors on the other half of the cleft. This phenomenon has recently been suggested in the case of Rebek's ditopic receptors.[15]

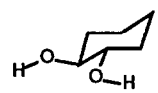
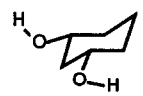
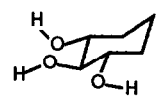
Guest \ Host	**10**	**1**
11 	$1.9\ M^{-1}$	$58\ M^{-1}$
12 	$2.1\ M^{-1}$	$20\ M^{-1}$
13 	$35\ M^{-1}$	$1.5{\cdot}10^2\ M^{-1}$

Table 1: Binding Constants: The values reported are averages of the binding constants found for each proton resonance in each individual guest. Estimated error ± 20%.[16]

The complexation between **13** and **1** could involve three hydrogen bonds whereas the complex between **11** or **12** with **1** could involve only two hydrogen bonds. The ratios of binding constants of **13** and **1** to the binding constants of **11** and **12** with **1** are 2.6 and 7.4 respectively. The free energy difference favoring triol binding over the diols is thus between 0.55 and 1.18±0.2 Kcal/mol. Since the majority of the translational and rotational entropy costs in binding should be included in the binding constants of the 1,2-diols, we expected to observe the binding constant of the triol to increase significantly if a strong third hydrogen bond was formed.[17] The approximate 1Kcal/mol increase is significant and could indicate a weak third H-bond. We are

continuing to study the complexation of **1** with cyclohexane polyols, but we are also examining a similar host with propanediyl linkers which should impart a larger twist between the amidine groups.

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7. Complete conformational space searching on **1** revealed the d,l and meso forms possess an energy separation of less than 1 kcal/mol favoring the d,l set. Searching was performed using the torsion bond driving option in the program MACROMODEL Ver. 2.5 with the OPLSA force field.
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12. **1**: ^{1}H NMR ($CDCl_3$) d 1.35 (m,9H), 2.81(t,4H), 2.87(t,4H), 4.29(q,4H), 4.42(q,2H), 6.7(bs,4H), 7.97(s,2H). ^{13}C $\{^{1}H\}$ NMR ($CDCl_3$) d 14.2, 24.7, 25.0, 60.9, 62.2, 107.2, 120.9, 131.9, 140.3, 141.1, 148.9, 152.1, 158.9, 166.1, 166.9. Anal. Calcd. for $C_{28}H_{29}N_5O_6$: C, 63.28; H, 5.46. Found: C, 60.52; H, 5.35
13. **10**: ^{1}H NMR ($CDCl_3$) d 1.33 (t,3H), 2.81 (t,2H), 2.88 (t,2H), 4.29 (q,2H), 6.50 (bs,2H), 7.17 (t,1H), 7.49 (d,1H), 7.97 (s,1H), 8.63 (d,1H). ^{13}C $\{^{1}H\}$ NMR ($CDCl_3$) d 14.1, 25.9, 27.6, 60.55, 105.9, 122.1, 123.7, 135.0, 135.7, 139.5, 148.5,. 150.7, 154.2, 158.5, 166.5. Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.91; H, 5.58. Found: C, 66.78; H, 5.53
14. A set of programs called K12 and KP was kindly provided by Professor Whitlock at the University of Wisconsin at Madison. For a reference to a similar procedure and formula, see Wilcox, C.S.; Cowart, M.D.; *Tet. Lett.*, **1986**, *27*, 5563-5566
15. The ratio of binding constants for the complexation of **11** by **10** and **1** of 30 is similar to the 12 fold ratio between pyridine and pyrazine in Rebek's diacid. The 12 fold difference was shown not to be due to an extra H-bond. Jorgensen, W.L.; Boudon, S.; Nguyen, T.B.; *J. Am. Chem. Soc.*, **1989**, *111*, 755-757 and reference 4 therein.
16. Since we only reached 19% and 35% saturation for **12** and **11** with **10** respectively, an estimated error of 20% is probably too low for these binding constants.
17. The binding constant of the diols are of the correct magnitude for the formation of two H-bonds between relatively nonbasic and nonacidic groups. For several examples of binding due to two H-bonds and three H-bonds, see (a.) Dobashi, Y.; Dobashi, A.; Ochiai, H.; Hara, S.; *J. Am. Chem. Soc.*, **1990**, *112*, 6121-6123 (b.) Kilburn, J.D.; MacKenzie, A.R.; Still, W.C.; *J. Am. Chem. Soc.*, **1988**, *110*, 1307-1308 (c.) Jorgensen, W.L.; Pranata, J.; *J. Am. Chem. Soc.*, **1990**, *112*, 2008-2010

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