Enantioselective Complexation of the Alanine Dipeptide by a C_2 Host Molecule

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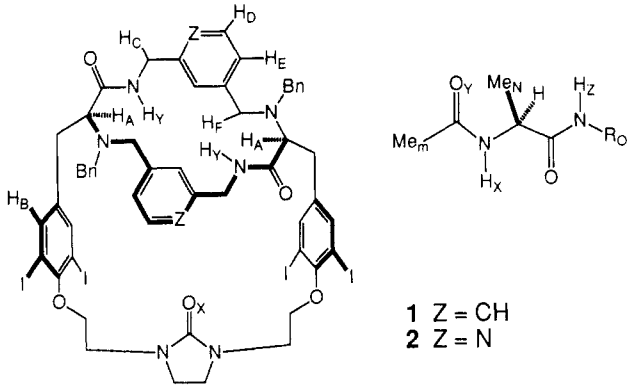
Summary: Starting from L-tyrosine, a chiral host molecule has been prepared which has an amide binding site and additional functionality which distinguishes guest chiral center substitutents based on steric and hydrogen bond donating properties. This molecule shows enantioselective binding ($\Delta\Delta G \sim 1$ kcal/mol) of acetyl-L-alanineamides.

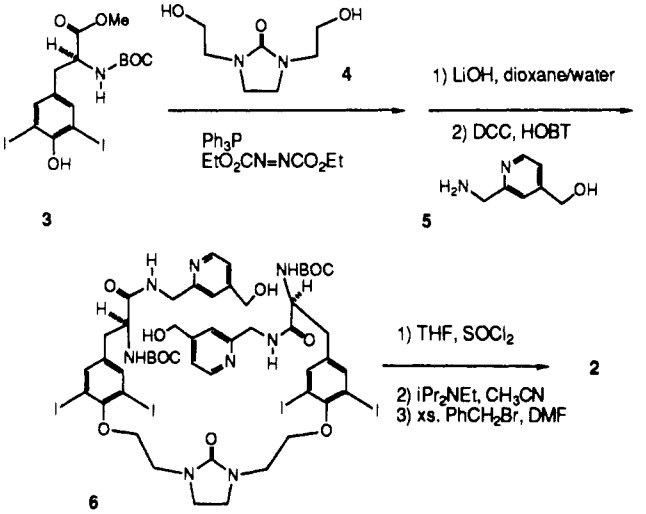
The rational design of enantioselective host molecules has been a major objective of workers in molecular recognition.[1] The objective is an important one not only because of potential applications in separation technology, but also because the simplified thermodynamics[1c,2] of enantioselection make calculations of selectivity feasible. Such calculations hold great promise for the design of new host molecules because they allow optimization of structures for desirable binding properties prior to synthesis. We recently described a receptor (1, Z = CH) for the amides of chiral amines which showed enantioselection corresponding to 20–40% ee. In this paper we replace Z = CH with nitrogen to produce a dipyridino analogue (2, Z = N) with enantioselectivity ~70% ee for L-enantiomers of the so-called alanine dipeptide shown below.



1 Z = CH
2 Z = N

In our previously described host molecule 1, amides were bound by hydrogen bonds H_X/O_X and O_Y/H_Y and enantioselectivity followed from the differing steric requirements of the other substituents at the chiral center. With our new host 2, an additional hydrogen bond (H_Z/Z) provides more effective distinction between the substituents and should lead to enhanced enantioselection for the L-alanine dipeptide in the C_5 conformation. The stereopair plot in Figure 1 illustrates what we expect the geometry of the most stable complex to be.

Our preparation of 2 begins with L-BOC-diiodotyrosine methyl ester (3). A double Minsunobu[3] coupling with diol 4 began the bidirectional construction of the C_2-symmetric 2. Ester hydrolysis and DCC-promoted amide formation with 5[4] then lead to the cyclization precursor (52% overall). Thionyl chloride both converted the benzylic alcohols to chlorides and removed the BOC protecting groups. Macrocyclization was then carried out as a double intramolecular amine alkylation by syringe pump addition of the amine hydrochloride salt to refluxing CH_3CN containing excess iPr_2NEt and LiBr. Benzylation finally led to 2 (15% overall yield from 6). A major reason for the poor yield was competitive alkylation of the pyridines by benzyl bromide in the final step.



Upon standing as a concentrated solution in EtOAc/CH_2Cl_2, 2 crystallized as large orthorhombic prisms (mp 191–195 °C). Its X-ray crystal structure is shown in the stereopair diagram in Figure 2. As shown, 2 binds a molecule of EtOAc in an orientation much like that proposed[1c] for the amide complexes. The conformation shown must be quite stable for macrotricyclic systems like 1 and 2 since it is closely related to the conformations found in X-ray structures of 1 and its derivatives. In particular, the meta-substituted aromatic rings fold over the binding site and the tyrosine α-hydrogens point inward in all crystals structures we have determined thus far. All of these structures incorporate large, solvent-filled internal cavities.

We evaluated the amide-binding properties of 2 by the standard NMR titration method using a nonlinear least-squares data treatment. The results are summarized in Table I. In comparing the properties of 2 with 1, we find that 2 has a significantly greater affinity for amides. In both $CDCl_3$ and C_6D_6 for example, *N*-methylacetamide binds to 2 ~2 kcal/mol more tightly than to 1. The origin of the enhanced binding may involve stabilization of the host hydrogen bond donor atoms in the binding conformation by the basic pyridine nitrogens.

The table also shows that diamides of L-alanine are bound preferentially with enhanced enantioselectivity as anticipated. Thus while both 1 and 2 bind enantiomeric acetyl alanine esters with ~0.5 kcal/mol distinction (entries 6–9), 2 shows 1.0–1.1 kcal/mol enantioselection with

(1) Previous examples of enantioselective complexation of neutral organic guest molecules: (a) Caneill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1985**, *107*, 6993. (b) Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 5947 (see also ref 2). (c) Sanderson, P. E. J.; Kilburn, J. D.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 8314. (d) Castro, P. P.; Georgiadis, T. M.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5834.

(2) Dappen, R.; Karfunkel, H. R.; Leusen, F. J. J. *J. Comput. Chem.* **1990**, *11*, 181.

(3) Mitsunobu, O. *Synthesis*, 1. (1981).

(4) Prepared from 2-cyanoisonicotinic acid methyl ester (Tani, H. *Yakugaku Zasshi* **1960**, *80*, 1418; *Chem. Abstr.* **1961**, *55*, 6477g) by (1) H_2/Pd–C, HOAc, 91%; (2) $(BOC)_2O$, Et_3N, CH_2Cl_2 70%; (3) $LiAlH_4$, Et_2O, 67%; and (4) TFA, CH_2Cl_2, 86%.

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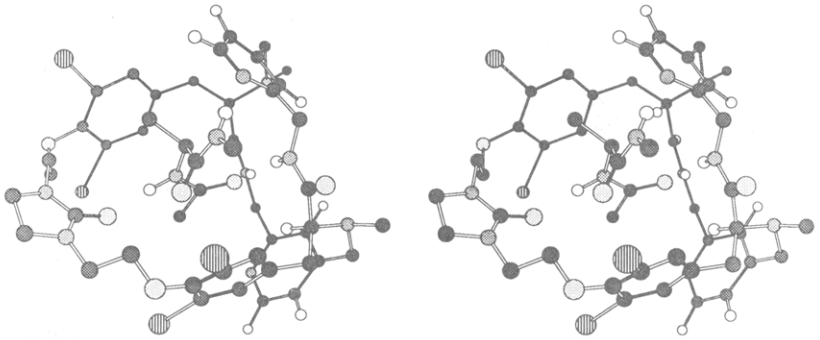

Figure 1.

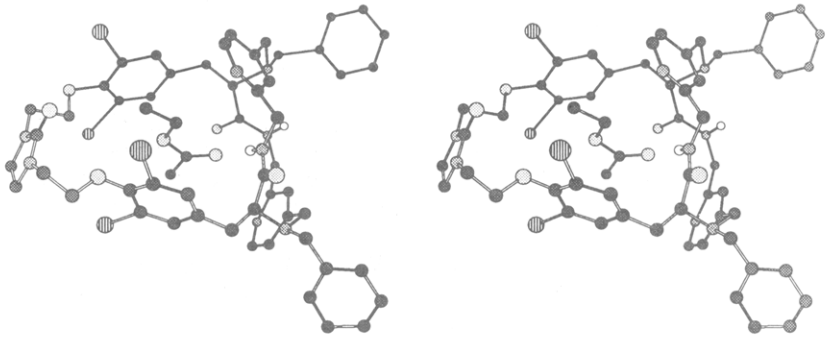

Figure 2.

Table I. Binding Data for Host 2 and Various Amides Measured by NMR Titration[a]

entry	guest	solvent	% saturation[b]	ΔG^c	$\Delta\Delta G^{*d}$
1	*N*-methylacetamide	$CDCl_3$	76	−3.33	
2	Ac-L-Ala-NHBn	$CDCl_3$	69	−2.36	−1.0
3	Ac-D-Ala-NHBn	$CDCl_3$	54	−1.36	
4	PhAc-L-Ala-NHMe	$CDCl_3$	53	−2.02	−0.1
5	PhAc-D-Ala-NHMe	$CDCl_3$	48	−1.91	
6	Ac-L-Ala-OBn	$CDCl_3$	40	−1.27	(−0.4)
7	Ac-D-Ala-OBn	$CDCl_3$	25	−0.86	
8	Ac-L-Ala-OBn	C_6D_6	79	−3.46	−0.5
9	Ac-D-Ala-OBn	C_6D_6	75	−2.93	
10	Ac-L-Ala-L-Ala-OBn	$CDCl_3$	78	−2.57	−0.9
11	Ac-D-Ala-L-Ala-OBn	$CDCl_3$	47	−1.67	
12	Ac-L-Ala-D-Ala-OBn	$CDCl_3$	69	−2.24	−0.8
13	Ac-D-Ala-D-Ala-OBn	$CDCl_3$	44	−1.48	
14	*N*-*tert*-butylacetamide	$CDCl_3$	53	−1.49	
15	Ac-L-Ala-NH-*tert*-butyl	$CDCl_3$	86	−2.35	(−1.3)
16	Ac-D-Ala-NH-*tert*-butyl	$CDCl_3$	39	−1.04	
17	Ac-L-Ala-NH-*tert*-butyl	C_6D_6	94	−4.38	−1.1
18	Ac-D-Ala-NH-*tert*-butyl	C_6D_6	64	−3.31	

[a] NMR titrations were carried out at 25 °C by adding the indicated guest to the host at 1–2 mM in the indicated solvent. [b] Percentage of total saturation achieved by the end of the titration. [c] Free energy of association in kilocalories/mole. [d] Stereoselectivity (ΔGL-ΔGD) in kilocalories/mole, parentheses indicate uncertainty due to low extent of saturation achieved in the titration.

acetylalanineamides (entries 2, 3, 10–13, 15–18). In $CDCl_3$, the *R*-alanine derivatives bound so weakly that we had difficulty in measuring the binding energies accurately (entries 7, 16), and certain of the studies below were repeated in C_6D_6 solvent where the binding energies were larger.

The significance of these findings lies not in the enantioselectivity itself, but in its connection with a structure for the complex, which rationalizes selectivity for the L-alanine dipeptide. In this context, we carried out a series of experiments which show that the *N*-acetylamide is most intimately involved in the enantioselective complexation. First, moving the bulky phenyl from the C-terminal to the N-terminal end of the alaninediamide eliminates enantioselection altogether (entries 2–5). Second, as shown in entries 1 and 14, replacing the *N*-methyl of *N*-methylacetamide with a *tert*-butyl results in a large decrease in binding with **2**. If the C-terminal amide of an alaninediamide were bound within the cavity of **2**, then a related substitution would be expected to give a major change in enantioselectivity and binding energy. Yet, entries 15–18 show that acetyl *N*-tert-butylalanineamide retains its enantioselective binding with **2**. Third, entries 10–13 establish that **2** binds stereoisomeric acetyldialanines with selectivity dependent only on the stereochemistry of the N-terminal amino acid.

Further evidence for the proposed structure of acetyl-L-alanine *tert*-butyl amide/**2** complex comes from difference NOE measurements. Under fast exchange conditions where **2** was ~90% bound, we observed the following intermolecular NOE signals:

alanine acetyl methyl (H_M)	H_A, H_B, H_D
alanine sidechain methyl (H_N)	H_A, H_B, H_D, H_E, H_F
alanine *tert*-butyl (H_O)	H_B, H_C, H_D

The proximities of H_N with $H_D/H_E/H_F$ and of H_O with

H_C/H_D locate the alanine sidechain and the C-terminal amide substituent essentially as shown in the stereopair diagram of the proposed complex. While H_z shifts downfield (~0.5 ppm) as expected for hydrogen bond formation upon complexation, the control experiment using 1 could not be carried out due to 1's weak association with the alanine dipeptide.

Macrocycle 2 provides one of the few examples of an enantioselective host whose binding properties follow clearly from its structure. Knowing the detailed structure of the complex, we should now be able to improve enantioselectivity in a rational way. We will describe such studies in the near future.[5]

(5) This work was supported by Grant Number CHE89-11008 from the National Science Foundation.

Mild Periodinane Oxidation of Protected Nucleosides To Give 2'- and 3'-Ketonucleosides. The First Isolation of a Purine 2'-Deoxy-3'-ketonucleoside Derivative[1,29]

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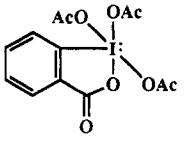
Summary: Oxidation of 3',5'- or 2',5'-bis-*O*-silyl-protected nucleosides with the Dess-Martin 12-I-5 periodinane reagent, 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (I), in dichloromethane gives 2'- or 3'-ketonucleoside derivatives, respectively. Isolation of the first purine 2'-deoxy-3'-ketonucleoside derivative (**2d**) has been accomplished by periodinane oxidation of 5'-*O*-(*tert*-butyldiphenylsilyl)-2'-deoxyadenosine (**1d**).

Ketonucleoside derivatives are useful synthetic intermediates whose synthesis has attracted considerable attention.[2] The instability of pentofuranulosyl nucleosides, especially under basic conditions, was noted in the first attempted oxidation of 5'-*O*-tritylthymidine with CrO_3/pyridine which resulted in spontaneous β-elimination of thymine.[3] Loss of thymine also occurred during the mild Pfitzner-Moffatt (DMSO/DCC) oxidation of 5'-*O*-acetylthymidine.[4] Moffatt and co-workers oxidized 3',5'- and 2',5'-di-*O*-trityluridine[5] and cytidine[6] derivatives with DMSO/DCC to obtain the first reported furanosyl 2'- and 3'-ketonucleosides. Rosenthal et al. oxidized 9-(3,5-*O*-isopropylidene-β-D-xylofuranosyl)adenine with RuO_4 to give a protected purine 2'-ketonucleoside.[7] Antonakis and co-workers prepared theophylline hexopyranosyl 2'- and 4'-ketonucleosides with Cr(VI) and DMSO/DCC oxidants.[8] Sasaki et al. have obtained furanosylpyrimidine 2'-ketonucleosides from elimination reactions,[9] and the [1,2]-hydride shift rearrangement[10] of 3'-*O*-tosyl-5'-*O*-trityluridine to a 2'-keto-3'-deoxyribonucleoside with a Grignard reagent[10a] has been described.[11]

Binkley et al. irradiated the 3'-pyruvate ester of 5'-*O*-tritylthymidine to obtain the first pyrimidine 2'-deoxy-3'-ketofuranosyl nucleoside.[12] Garegg and co-workers[13] reported smooth oxidation of partially protected carbohydrates with CrO_3/pyridine/Ac_2O, and we applied that reagent for the efficient synthesis of 3'- or 2'-ketonucleoside derivatives from 2',5'- or 3',5'-diprotected nucleosides and 5'-protected 2'- or 3'-deoxynucleosides.[14] Crews and Baker[15] prepared 2'- and 3'-ketoadenosines by Pfitzner-Moffatt oxidation, and deprotection of adenosine derivatives. Bergstrom and co-workers[16] recently noted an improved yield (80%) of 3'-keto-5'-*O*-tritylthymidine by oxidation of 5'-*O*-tritylthymidine with pyridinium dichromate/molecular sieves.[8] The Swern modification (DMSO/oxalyl chloride)[17] of the Moffatt oxidation was applied to nucleosides by Ueda et al.[18] We investigated that procedure but found significant contamination by heterocyclic *N*- and *O*-(methylthio)methyl derivatives with Swern oxidation[17] of lactam-containing nucleosides (e.g. uridine and inosine).

The Dess-Martin[19] 12-I-5 periodinane reagent, 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (I) (*CAUTION*[29]), effected smooth and efficient oxidation of a silyl-protected adenosine derivative.[20] This method is general and convenient for oxidations of 3',5'- and 2',5'-bis-*O*-silyl-protected nucleosides to 2'- and 3'-ketonucleoside derivatives. These mild conditions allow preparation and isolation of a purine 2'-deoxy-3'-ketonucleoside for the first time.



I

Oxidation of 2',5'-bis-*O*-TBDMS-uridine[21] (**1a**) by the general procedure[22] afforded crystalline 2',5'-bis-*O*-

(1) This communication is Nucleic Acid Related Compounds. 60. For the previous paper, see: Robins, M. J.; Vinayak, R. S.; Wood, S. G. *Tetrahedron Lett.* **1990**, *31*, 3731.
(2) Antonakis, K. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 227.
(3) Jones, A. S.; Williamson, A. R.; Winkley, M. *Carbohydr. Res.* **1965**, *1*, 187.
(4) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661.
(5) Cook, A. F.; Moffatt, J. G. *J. Am. Chem. Soc.* **1967**, *89*, 2697.
(6) Brodbeck, U.; Moffatt, J. G. *J. Org. Chem.* **1970**, *35*, 3552.
(7) Rosenthal, A.; Sprinzl, M.; Baker, D. A. *Tetrahedron Lett.* **1970**, 4233.
(8) (a) Antonakis, K.; Leclercq, F. *Bull. Soc. Chim. Fr.* **1971**, 2142. (b) Herscovici, J.; Egron, M.-J.; Antonakis, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1967.
(9) (a) Sasaki, T.; Minamoto, K.; Suzuki, H. *J. Org. Chem.* **1973**, *38*, 598. (b) Sasaki, T.; Minamoto, K., Hattori, K. *Tetrahedron* **1974**, *30*, 2689.
(10) (a) Kawana, M.; Koresawa, T.; Kuzuhara, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1095. (b) Hansske, F.; Robins, M. J. *J. Am. Chem. Soc.* **1983**, *105*, 6736.
(11) Juntunen, S.; Chattopadhyaya, J. *Acta Chem. Scand.* **1985**, *B39*, 149.
(12) Binkley, R. W.; Hehemann, D. G.; Binkley, W. W. *J. Org. Chem.* **1978**, *43*, 2573.
(13) (a) Garegg, P. J.; Samuelsson, B. *Carbohydr. Res.* **1978**, *67*, 267. (b) Garegg, P. J.; Maron, L. *Acta Chem. Scand.* **1979**, *B33*, 453.
(14) (a) Hansske, F.; Robins, M. J. *Tetrahedron Lett.* **1983**, 1589. (b) Hansske, F.; Madej, D.; Robins, M. J. *Tetrahedron* **1984**, *40*, 125.
(15) Crews, R. P.; Baker, D. C. *Nucleosides Nucleotides* **1983**, *2*, 275.
(16) Froehlich, M. L.; Swartling, D. J.; Lind, R. E.; Mott, A. W.; Bergstrom, D. E. *Nucleosides Nucleotides* **1989**, *8*, 1529.
(17) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(18) (a) Ueda, T.; Shuto, S.; Satoh, M.; Inoue, H. *Nucleosides Nucleotides* **1985**, *4*, 401. (b) Matsuda, A.; Itoh, H.; Takenuki, K.; Sasaki, T.; Ueda, T. *Chem. Pharm. Bull.* **1988**, *36*, 945.
(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(20) Robins, M. J.; Samano, V.; Johnson, M. D. *J. Org. Chem.* **1990**, *55*, 410.
(21) Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y.; Sadana, K. L. *Can. J. Chem.* **1978**, *56*, 2768.

0022-3263/90/1955-5186$02.50/0