Chiral Recognition of Dicarboxylic Acids by Synthetic Receptors

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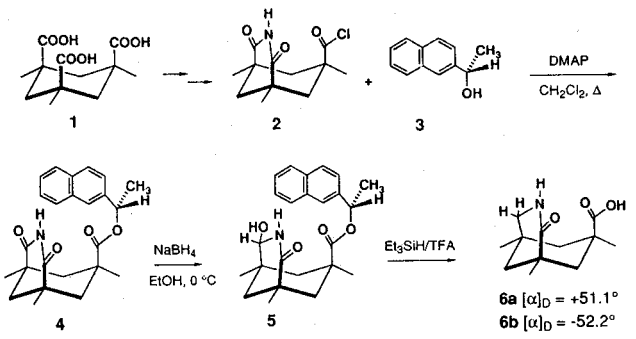
Received April 11, 1996

The development of synthetic receptors for neutral substrates is an important goal in the field of molecular recognition. Several synthetic receptors for the binding of aliphatic carboxylic acids through hydrogen bonds have been developed in recent years.[1~3] In these receptors, the aminopyridine derivatives have been mainly incorporated into the appropriate spacer groups to form multiple hydrogen bonds with di- or tricarboxylic acids.[2] Especially, enantioselective complexation of chiral dicarboxylic acids has been achieved by connecting two aminopyridines with dissymmetric molecules such as binaphthyl, spirobifluorene and helicene.[3] We here report the synthesis and binding property of new chiral receptors, **7** and **8**, in which more neutral lactam functionality is exploited to form complementary hydrogen bonds with carboxylic acid.



Optically pure lactam acid **6**, which is a key molecule for the preparation of bislactams in this study, was prepared from Kemp's triacid **1**[4] (Scheme 1).[5] Coupling of imide acid chloride **2**[4b] with (S)-α-methyl-2-naphthalenemethanol (**3**) gave imide ester **4** (91%), which was reduced with excess $NaBH_4$ to afford hydroxylactam ester **5** as a diastereomeric mixture. After separation of two diastereomers (total isolated yield 82%, less polar/more polar isomer = 1 : 4) by flash chromatography (hexanes/EtOAc/CH_2Cl_2 = 2 : 1 : 2), each isomer was treated with Et_3SiH/CF_3COOH to give quantitatively the corresponding optically pure lactam acid **6a** or **6b** (major isomer **6a** $[\alpha]_D^{23} = +51.1°$, minor isomer **6b** $[\alpha]_D^{23} = -52.2°$ (c = 0.67 in EtOH)).

It has been reported that activation of lactam acid with $SOCl_2$ followed by addition of nucleophiles such as alcohols and amines resulted in racemic product.[6] With this in mind, bislactams **7** and **8**[7,8] were prepared in a 59-70% yield by directly reacting (+)-lactam acid **6a** with *m*- and *p*-xylene dibromides (Scheme 2). In this S_N2 displacement condition (K_2CO_3/CH_3CN, or Cs_2CO_3/DMF at 70-80 ℃ for 6-30 h), no racemization was observed.

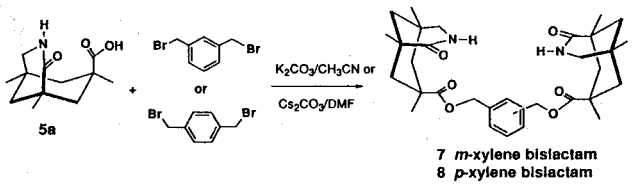


Table 1. Binding Constants ($K_a \pm 10\%$, M^{-1}) of Bislactams **7** and **8** with Dicarboxylic Acids in 10% Acetone-d_6/$CDCl_3$ at 297 ± 1 K

Guest	Binding constant (K_a, M^{-1})	
	m-xylene bislactam **7**	*p*-xylene bislactam **8**
glutaric acid	2230	975
t-Boc-L-Asp	1860	580
t-Boc-D-Asp	4720	832
t-Boc-L-Glu	1600	980
t-Boc-D-Glu	2320	2850
t-Boc-L-Gln	310	
t-Boc-D-Gln	194	

The relatively rigid *m*- and *p*-xylene spacers were chosen to prevent a collapse of the binding cavity by intramolecular hydrogen bonds between two lactam groups. In addition, CPK molecular modelling suggested that these xylene moieties would provide the correct spacing for four and five carbon diacids such as succinic and glutaric acids. The binding properties of bislactams **7** and **8** to diacids were first examined in $CDCl_3$. Addition of glutaric acid (3 mM) to a $CDCl_3$ solution (2 mM) of bislactams **7** and **8** caused the large downfield shifts (>2 ppm) of lactam NH signals with a sharp break of saturation curves on one equivalent addition of guest, affording $K_a > 10^4$ M^{-1}.[9] This indicates that complexes are highly stabilized by four hydrogen bonds between two carboxylic acids of guest and two lactam groups of host. Similar behaviors were observed in titrations with the acidic amino acids, *t*-Boc-Asp and -Glu. The binding constants ($K_a > 10^4$ M^{-1}) were too high to be determined accurately in pure $CDCl_3$ by ^1H NMR spectroscopy.[10] Addition of 10% acetone-d_6 into $CDCl_3$ reduced the binding constants by ~ one order of magnitude and thus more reliable values could be obtained in this condition.

The binding constants listed in Table 1 were obtained by nonlinear least-squares fits of the ^1H NMR titration curves in 10% acetone-d_6/$CDCl_3$. As a typical example, saturation curves observed for the titrations of *m*-xylene bislactam **7** (2 mM) with *t*-Boc-L-Asp and -D-Asp (10 mM) are shown in Figure 1 in which the lactam NH resonance is shifted from 5.45 ppm up to 6.98 (L-Asp) and 7.62 ppm (D-Asp). These give the binding constants 1.7×10^3 M^{-1} for L-Asp and 4.7×10^3 M^{-1} for D-Asp, corresponding to $\Delta\Delta G = 0.55$ kcal/mol.

All of the binding constants between bislactams and diacids are $> 5 \times 10^2$ M^{-1}, which is much greater than that ($K_a = 52$ M^{-1}) of the corresponding monotopic system, benzyl ester lactam **9** and butyric acid, in the same condition. This reflects that two lactams cooperatively bind to dicarboxylic acids

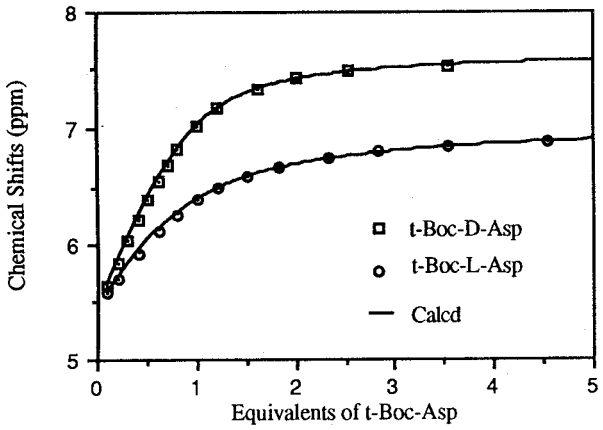
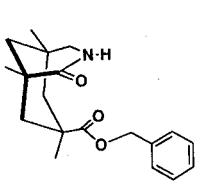


Figure 1. Titration curves of *m*-xylene dilactam **7** with *t*-Boc-L-Asp and *t*-Boc-D-Asp in 10% acetone-d_6/$CDCl_3$.

through four hydrogen bonds of 1 : 1 complexes as shown in **10**. The Job's plots clearly demonstrated 1 : 1 stoichiometry between bislactams and diacids, in which maximal complex formation occured at 0.5 mol fraction of diacids.[11] As seen in Table 1, *m*-xylene bislactam **7** generally shows higher binding affinities toward four and five carbon diacids, relative to *p*-xylene bislactam **8**, and both bislactams prefer binding D-isomers with a modest enantioselectivity ($\Delta\Delta G$=0.22-0.63 kcal/mol).



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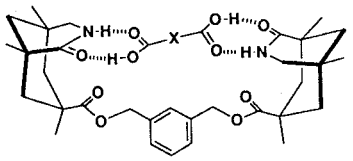

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It is worthwhile to note that the binding constant of *t*-Boc-Gln to **7** is lower approximately by one order of magnitude than that of *t*-Boc-Glu, even though two complexes could form the same number of hydrogen bonds. The large differences in binding energy might be mainly attributed to the difference in hydrogen-bonding stabilities between acid-lactam and amide-lactam groups. To confirm this explanation, we examined the binding abilities of butyric acid and butyramide to benzyl ester lactam **9**. The binding constant of butyric acid, as mentioned earlier, is 52± 2 M^{-1} in 10% acetone-d_6/$CDCl_3$ at 297 K while that of butyramide is 4± 1 M^{-1}, indicating hydrogen bonding of lactam-acid pair is much stronger than that of lactam-amide pair.

In conclusion, this study shows that neutral lactam group forms strong complementary hydrogen bonds with carboxylic acid. Chiral bislactams strongly bind the acidic amino acid derivatives with a modest enantioselectivity ($\Delta\Delta G$=0.22-0.63 kcal/mol). Further study is underway to increase the chiral discrimination and to find the origin of enantioselectivity.

Acknowledgment. We are deeply grateful to Professor Julius Rebek, Jr. at MIT for his encouragement and advice concerning on this work. This work was financially supported in part by the Organic Chemistry Research Center (KOSEF) and the Basic Science Research Institute Program, Ministry of Education (Project No. BSRI-95-3422).

References

1. (a) Rebek, J., Jr.; Nemeth, D.; Ballester, P.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 3474. (b) Tanaka, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2827.
2. (a) Garcia-Tellado, F.; Goswami, S.; Chang, S.-K.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393. (b) Vicent, C.; Fan, E.; Hamilton, A. D. *Tetrahedron Lett.* **1992**, *33*, 4269. (c) Flack, S. S.; Chaumette, J.-L., Kilburn, J. D.; Langley, G. J.; Webster, M. *J. Chem. Soc., Chem. Comm.* **1993**, 399. (d) Ballester, P.; Costa, A.; Deya, P. M.; Gonzalez, J. F.; Rotger, M. C.; Deslongchamps, G. *Tetrahedron Lett.* **1994**, *35*, 3813. (e) Goodman, M. S.; Hamilton, A. D.; Weiss, J. *J. Am Chem. Soc.* **1995**, *117*, 8447.
3. (a) Garcia-Tellado, F.; Albert, J.; Hamilton, A. D. *J. Chem. Soc., Chem. Comm.* **1991**, 1761. (b) Alcazar, V.; Diederich, F. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1521. (c) Owens, L.; Thilgen, C.; Diederich, F.; Knobler, C. B. *Helv. Chim. Acta.* **1993**, *76*, 2757.
4. Commercially available from the Aldrich Chemical Co. For a convenient synthesis, see: (a) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426. (b) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K.-S.; Jones, S.; Parris, K.; Williams, K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1082.
5. Jeong, K.-S. Ph. D. Thesis, Massachusetts Institute of Technology, Feb. 1991.
6. Ballester, P.; Tadayoni, B. M.; Branda, N.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 3685.
7. Bislactams **7** and **8** were fully characterized by NMR, IR and MS spectra. **7** mp 181-183 ℃; $[\alpha]_D^{24}=-63°$ (c= 0.5 in $CHCl_3$). **8** mp 176-177 ℃; $[\alpha]_D^{24}=-57°$ (c=0.5 in $CHCl_3$).
8. For chiral recognition of cyclic dipeptides, different bislactams have been previously prepared through a time-consuming HPLC separation using a chiral column. See: Jeong, K.-S.; Muehldorf, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 6144.
9. The binding constants of glutaric acid to **7** and **8** are 3.6×10^4 and 2.5×10^4 M^{-1} in $CDCl_3$, respectively. These values are comparable to those of dicarboxylic acids to bisaminopyridine derivatives.[2b,2e]
10. Wilcox, C. S. In *Frontiers in Supramolecular Chemistry*; H. Schneider, H. Dürr Ed.; VCH: Weinheim, 1991; pp 123-143.
11. Connors, K. A. *Binding Constants*; John Wiley & Sons: New York, 1984; p 24.