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Novel chiral imidazole cyclophane receptors: synthesis and enantioselective recognition for amino acid derivatives

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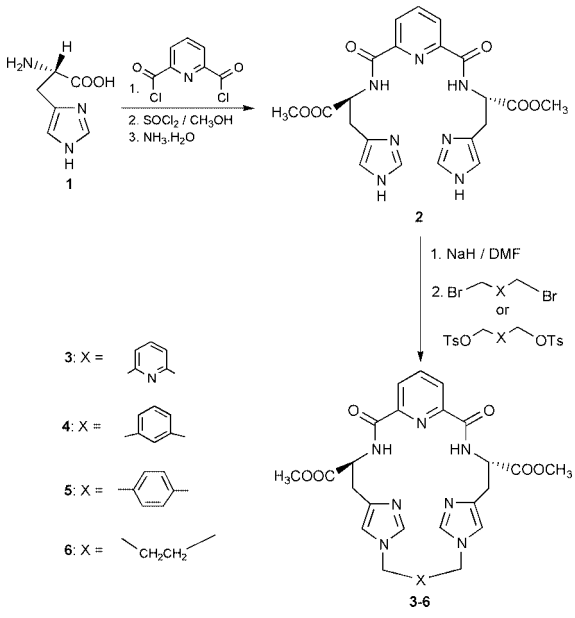
Novel chiral imidazole cyclophane receptors were synthesized by highly selective *N*-alkylation of the imidazolyl 1N-position of the bridged histidine diester 2 with the dibromide in the presence of NaH; these receptors exhibit good chiral recognition toward the enantiomers of L- and D-amino acid derivatives (up to K_D/K_L = 3.52, $\Delta\Delta G_0$ = −3.11 kJ mol^{-1}) in $CHCl_3$ at 25.0 °C.

Molecular recognition between molecules is one of the most fundamental processes in biochemical systems. The study of synthetic model systems could contribute to the understanding of these processes and, at the same time, offer new perspectives for the development of pharmaceuticals, enantiomer-selective sensors, catalysts and molecular devices.[1] One area that has proven especially challenging is the creation of enantioselective artificial receptors.[2] Cyclophanes have gained considerable interest because of their potential applications in artificial enzymes, host–guest complexes, molecular self-assembly, selective catalysis and material science.[3] A variety of cyclophanes with novel structures and properties have been reported. However, inspecting the impressively long list, examples dealing with histidine are quite rare.[4] Imidazole and histidine derivatives are generally considered to be difficult to prepare, so this makes the development of imidazole-containing receptors much more challenging. Our interest has been focused on the synthesis of imidazolium and imidazole cyclophanes.[5] Recent work aimed to synthesize chiral macrocyclic tetraoxo polyamines containing two functional imidazole arms that are oriented in an *anti* fashion, and to develop a convenient and efficient method for the synthesis of bridged histidine derivatives.[6] On the basis of this method, we herein report the synthesis of novel chiral imidazole cyclophane receptors from L-histidine (Scheme 1), and their enantioselective recognition for amino acid methyl esters. To our knowledge, this is the first example of a chiral imidazole cyclophane from L-histidine as a chiral recognition receptor.

We have previously synthesized chiral macrocyclic tetraoxo polyamines containing two functional imidazole arms *via* aminolysis of the dihistidine dimethyl esters **2** with commerically available polyamines.[6] The key intermediate **2** was directly used without protection of the imidazole ring. Herein four novel chiral imidazole cyclophanes **3–6** were obtained by highly selective *N*-alkylation of the imidazolyl 1N-position of **2** with the corresponding dibromides in the presence of a slight excess of NaH in DMF under dry and oxygen-free conditions at −5–0 °C. The reaction conditions have a significant influence on the macrocyclization because the bridged compound **2** possesses several active functional groups, and the *N*-alkylation of imidazole groups usually leads to serious side reactions such as the quaternization reaction of imidazole and the elimination reaction of halides.[5,7] To minimize these side reactions and competitive reactions between the imidazolyl 1N-position and the NH of CONH,[8] the use of low temperature and strong base such as NaH is necessary. In the absence of base or in the presence of weak base such as K_2CO_3 or Na_2CO_3, no desired cyclophanes were obtained except some quaternization products. In contrast, the presence of strong base such as NaH is particularly effective in promoting the formation of the imidazole anion, which is highly susceptible to electrophilic attack so that alkylation can occur rapidly at the imidazolyl 1N-positions, while the quaternization is avoided effectively. The macrocyclizations were carried out by the high dilution technique to give the 1 + 1 macrocycles instead of 2 + 2 macrocycles. The yields of **3–6** were 60.1, 50.0, 20.9 and 80.5%, respectively. The structures proposed for these novel chiral imidazole cyclophanes are consistent with data obtained from elemental analysis, MS and ^{1}H NMR. We also prepared these chiral macrocycles from ditosylates instead of dibromides, however, the yields obtained were very low (< 10%).

Molecular recognition of amino acids and their derivatives has been one of most attractive objectives of supramolecular chemistry because of its biological significance and practical importance. The binding constants (K) of inclusion complexes of chiral imidazole cyclophane receptors with amino acid esters were determined on the basis of the differential UV spectrometry in chloroform at 25 °C by the modified Hildebrand–Benesi equation, showing 1 : 1 complex formation.[9,10] The association constants (K) and the free-engergy change ($-\Delta G_0$) are shown in Table 1, along with enantioselectivity K_D/K_L or $\Delta\Delta G_0$ calculated from $-\Delta G_0$ for inclusion complexation of L/D-amino acid esters by these hosts.



Scheme 1

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b1/b103325p/

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As shown in Table 1, the chiral imidazole cyclophane receptors show chiral recognition ability for the enantiomers of various amino acid esters and their hydrochlorides, while the parent compound **2** can hardly recognize the chirality of the L- or D-isomer (entries 1 and 2). Our study clearly demonstrates that the chiral recognition ability is sensitive to the different linker unit (–X–) of these chiral imidazole cyclophanes (entries 9, 10, 17–22). For example, the association constants (K_D) of **3** containing a pyridine unit and **6** with the $-(CH_2)_4-$ moiety for D-Phe-OMe are 1063 and 208 dm^3 mol^{-1}, respectively, which correspond to D/L-selectivity (K_D/K_L) of 3.33 and 1.40 for Phe-OMe. Thus, the cavity size, structural rigidity or flexibility of the receptor may play an important role in enantioselective recognition.

Table 1 also shows the enantioselective recognition ability of cyclophane receptor **3** with α-amino acid esters and their hydrochlorides, affording K_D/K_L 1.45–3.52 or $\Delta\Delta G_0$ of −0.93 to −3.11 kJ mol^{-1}. We found that the cyclophane receptor **3** gave fairly poor recognition ability for the aliphatic side chain of amino acid esters (entries 3–8). For example, a similar ability for binding aliphatic Ala-OMe, Val-OMe or Leu-OMe was observed. Indeed, the receptor **3** exhibits stronger binding and better enantioselectivity for amino acid esters containing an aromatic group than for those possessing an aliphatic side chain, inferring that the π–π stacking interaction between the receptor and the aromatic side chain of amino acid is the principal attractive interaction involved (comparing entries 3–8 *vs*. 9–12). The aromatic Trp-OMe is included most effectively by **3**, giving the strongest binding (K_D = 3314 dm^3 mol^{-1}, K_L = 1238 dm^3 mol^{-1}). The receptor **3** exhibits better enantioselectivities for amino acid ester hydrochlorides than their corresponding amino acid esters (comparing entries 3–4 *vs*. 13–14 and 7–8 *vs*. 15–16). The enhanced chiral recognition ability has been suggested to arise from the cation–π interaction and hydrogen bonding between NH_3^+ of the amino acid ester hydrochloride and the receptor **3**.[11]

These results show that the cavity size and structural rigidity of hosts, hydrogen bonding, π–π stacking and cation–π interaction between host and guest may be the most important factors for the enantioselective recognition of amino acid derivatives.

Table 1 Binding constants (K), the Gibbs free energy changes ($-\Delta G_0$), enantioselectivities K_D/K_L or $\Delta\Delta G_0$ calculated from $-\Delta G_0$ for the including complexation of L/D-amino acid esters with **2**–**6** in $CHCl_3$ at 25 °C[a]

Entry	Host	Guest[b]	K/dm^3 mol^{-1}	K_D/K_L	$-\Delta G_0$/kJ mol^{-1}	$\Delta\Delta G_0$[c]/ kJ mol^{-1}
1	**2**	L-Phe-OMe	89.4	1.12	11.13	−0.27
2	**2**	D-Phe-OMe	99.8		11.40	
3	**3**	L-Ala-OMe	437	1.45	15.06	−0.93
4	**3**	D-Ala-OMe	634		15.99	
5	**3**	L-Val-OMe	299	2.05	14.12	−1.78
6	**3**	D-Val-OMe	613		15.90	
7	**3**	L-Leu-OMe	260	2.24	13.78	−2.00
8	**3**	D-Leu-OMe	583		15.78	
9	**3**	L-Phe-OMe	319	3.33	14.28	−2.99
10	**3**	D-Phe-OMe	1063		17.27	
11	**3**	L-Trp-OMe	1238	2.68	17.64	−2.44
12	**3**	D-Trp-OMe	3314		20.08	
13	**3**	L-Ala-OMe·HCl	471	2.80	15.25	−2.55
14	**3**	D-Ala-OMe·HCl	1319		17.80	
15	**3**	L-Leu-OMe·HCl	327	3.52	14.35	−3.11
16	**3**	D-Leu-OMe·HCl	1150		17.46	
17	**4**	L-Phe-OMe	224	2.33	13.41	−2.10
18	**4**	D-Phe-OMe	523		15.51	
19	**5**	L-Phe-OMe	217	2.00	13.33	−1.71
20	**5**	D-Phe-OMe	433		15.04	
21	**6**	L-Phe-OMe	149	1.40	12.40	−0.82
22	**6**	D-Phe-OMe	208		13.22	

[a] The concentration of the receptors: 2.0×10^{-4} mol dm^{-3}. [b] Ala-OMe: alanine methyl ester; Val-OMe: valine methyl ester; Leu-OMe: leucine methyl ester; Phe-OMe: phenylalanine methyl ester; Trp-OMe: tryptophan methyl ester; Ala-OMe.HCl: alanine methyl ester hydrochloride; Leu-OMe.HCl: leucine methyl ester hydrochloride. [c] $\Delta\Delta G_0 = \Delta G_{0(D)} - \Delta G_{0(L)}$.

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Notes and references

1 (*a*) J.-M. Lehn, *Supramolecular Chemistry. Concepts and Perspectives*, VCH, Weinheim, 1995; (*b*) J. Rebek, Jr, *Chem. Soc. Rev*., 1996, **25**, 255; (*c*) D. Philp and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl*., 1996, **35**, 1154; (*d*) Y. Murakami, J. Kikuchi, Y. Hisaeda and O. Hayashida, *Chem. Rev*., 1996, **96**, 721; (*e*) S. H. Gllman, *Chem. Rev*., 1997, **95**, 2529.

2 T. H. Webb and C. S. Wilcox, *Chem. Soc. Rev*., 1993, **22**, 383.

3 (*a*) F. Vögtle, *Cyclophane Chemistry*, Wiley, Chichester, 1993; (*b*) F. Diederich, *Cyclophanes*, Ed. J. F. Stoddart, The Royal Society of Chemistry, Cambridge, 1991.

4 (*a*) H. Dugas, *Bioorganic Chemistry*, 3rd edn., Springer-Verlag, New York, 1996; (*b*) J.-M. Lehn, *Comprehensive Supramolecular Chemistry: Vol. 4 Supramolecular reactivity and transport: bioorganic systems*, Eds. J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vogtle and Y. Murakami, Pergamon, Oxford, 1996.

5 (*a*) M. M. Luo, S. J. Guo, C. H. Zhou and R. G. Xie, *Heterocycles*, 1995, **41**, 1421; (*b*) C. H. Zhou, R. G. Xie and H. M. Zhao, *Org. Prep. Proc. Int*., 1996, **28**, 345; (*c*) Z. L. Liu, C. H. Zhou, X. Y. Su and R. G. Xie, *Synth. Commun*., 1999, **29**, 2979.

6 J. S. You, X. Q. Yu, C. L. Liu and R. G. Xie, *Synth. Commun*., 1999, **29**, 2447.

7 (*a*) E. Alcalde, M. Alemany and M. Gisbert, *Tetrahedron*, 1996, **52**, 15171; (*b*) Z. Shi and R. P. Thummel, *J. Org. Chem*., 1995, **60**, 5935; (*c*) J. P. Gasparini, R. Gassend, J. C. Maire and J. Elguero, *J. Organometal. Chem*., 1980, **188**, 141.

8 (*a*) G. Schill, H. Neubauer, K. Rothmaier and H. Zollenkopf, *Synthesis*, 1971, 436; (*b*) G. I. Isele and A. Lüttringhan, *Synthesis*, 1971, 266; (*c*) M. S. Manhas and S. J. Jeng, *J. Org. Chem*., 1967, **32**, 1246.

9 (*a*) H. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc*., 1949, **71**, 2703; (*b*) F. Cramer, W. Saenger and H. C. Spatz, *J. Am Chem. Soc*., 1967, **89**, 14.

10 (*a*) R. P. Bonar-Law and J. K. M. Sanders, *J. Am. Chem. Soc*., 1995, **117**, 259; (*b*) Y. Kuroda, Y. Kato, T. Higashioji, J. Hasegawa, S. Kawanami, M. Takahashi, N. Shiraishi, K. Tanabe and H. Ogoshi, *J. Am. Chem. Soc*., 1995, **117**, 10950; (*c*) Y. Liu, Y. Zhang, S. Sun, Y. Li and R. Chen, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1609; (*d*) Y. Liu, Y. M. Zhang, A. D. Qi, R. T. Chen, K. Yamamoto, T. Wada and Y. Inoue, *J. Org. Chem*., 1997, **62**, 1826; (*e*) Q. Zheng, C. Chen and Z. Huang, *Tetrahedron*, 1997, **53**, 10345; (*f*) K. Naemura, K. Nishioka, K. Ogasahara, Y. Nishikawa, K. Hirose and Y. Tobe, *Tetrahedron: Asymmetry*, 1998, **9**, 563.

11 (*a*) D. A. Dougherty, *Science*, 1996, **271**, 163; (*b*) R. Arnecke, R. Cacciapaglia, A. D. Cort and L. Mandolini, *Tetrahedron*, 1997, **53**, 4901; (*c*) S. M. Ngola, P. C. Kearney, S. Mecozzi, K. Russell and D. A. Dougherty, *J. Am. Chem. Soc*., 1999, **121**, 119.