Lipophilic Peptide as Novel Sensory Material for Chiral Amine Recognition

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Chiral recognition of chiral amines **4**–**10** by lipophilic peptide derivatives **1**–**3** was studied spectrophotometrically in chloroform. Peptide **3** as compared with **2** indicated greater binding affinity and enantiomer selectivity towards the (*R*)-isomer of **4** and **6**. Also **3** showed strikingly high binding and diastereoselectivity towards **9** and **10**.

Molecular recognition through hydrogen bonding plays vital roles in biological processes such as signal transduction by receptor, substrate recognition by enzyme, antigen capture by antibody and so on. A great number of chemists are recently involved in constructing the mimic systems for a better understanding of the associated mechanism of molecular recognition.[1] Among various model methods even though chiral recognition is simple in concept but is difficult in practice where a chiral host molecule selectively binds one of the enatiomers in a racemic mixture.[2] Great efforts have been devoted to the development of synthetic chiral receptors since Cram et al. reported the discrimination of the enatiomers of 1-phenylethylammonium hexafluorophosphate.[3] As they turned out, most of the receptors are based on macrocyclic compounds such as chiral crown ethers, cyclophanes, clefts and metallomacrocycles.[4–6]

The chiral recognition is very important in the fields of biology and pharmacology, but there are few successful cases except for the naked-eye chiral discrimination of amino alcohols by Kubo et al.[5] Therefore the effective binding of amines with peptides **1**–**3**[7] has inspired us to study the enatiomeric and diastereomeric distinction of chiral amines with these simple host systems. Host systems based on amino acids and peptide chemistry should permit the utilization of combinatorial approach in the host design for a variety of guest compounds. The combinatorial approach incorporates the concept of biological evolution, taking advantage of selecting optimum compounds from a library, a large pool of possible candidate compounds. In this communication we report the chiral recognition by simple lipophilic oligopeptides. Peptide derivatives **1**–**3** were prepared as model which were equipped with two functional sites: (1) recognition site which is constructed by amino acids, (2) reporting site designed to convert the binding signal between host and guest into optical signal. A long alkyl chain was incorporated into peptide to provide solubility or affinity to nonpolar organic media. The lipophilic property is desirable for most applications of sensory molecule such as ion selective electrode and optical fiber.

The compounds **1**–**3** in Figure 1 were prepared as reported earlier.[7] The complexation behavior of peptides **1**–**3** towards the (*R*)- and (*S*)-isomers of 1-phenylethylamine (**4**), 2-phenylglycinol (**5**), phenylalaninol (**6**), (*9R*)-cinchonidine (**7**), (*9S*)-cinchonine (**8**), (*9R*)-quinine (**9**), and (*9S*)-quinidine (**10**) was

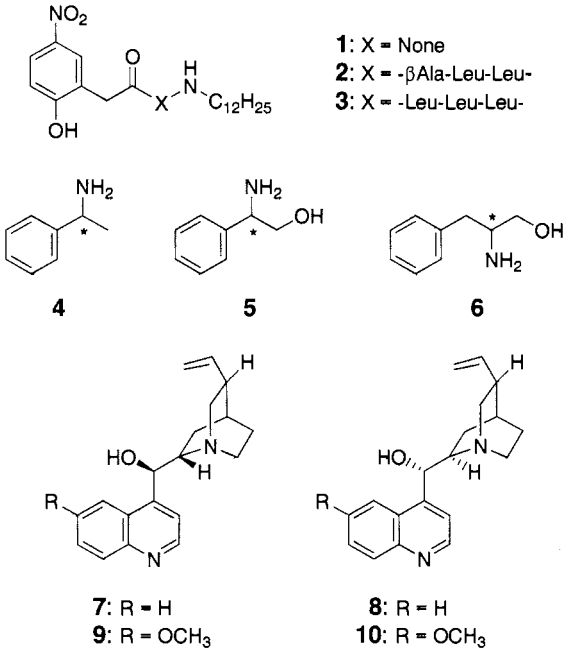

Figure 1. Structure of control and lipophilic peptides **1** - **3** and chiral amines **4** - **10**.

evaluated spectrophotometrically. The chloroform solution (3 cm^3) containing 8.3×10^{-6} M peptide was stirred in an optical cuvette at 25 °C. The solution was titrated with concentrated amine in chloroform, and the spectrum was measured after each addition of the amine solution.

On the addition of amine, peptides **1**–**3** revealed a spectral change that was derived from proton dissociation from *p*-nitrophenol in aqueous solution on raising pH. Peptide **3** showed an especially well-defined isosbestic point in a wide range of peptide to chiral amine ratio in solution, indicating the formation of single species, i.e., 1:1 complex. This suggestion was also in accord with a preliminary ^{1}H NMR study of these peptides in the presence of amines.

When 1:1 complex is formed between peptidic dye and amine, the association constant (K_{ass}) was determined by the method reported in previous paper.[7] The calculation resulted in excellent fit to the equation, supporting the formation of only 1:1 complex. The association constants obtained are summarized in Table 1.

In the interaction of various enantiomers **4**–**6** with peptides **1**–**3**, only peptide **3** showed considerable binding affinity (Table 1). Though the number of amide units are the same in peptides **2** and **3**, the binding ability of the latter was much higher. Phenomenologically this is described as that the peptide conformation of **3** in chloroform might be more flexible than **2** to

Table 1. Association constants (K_{ass}) of lipophilic peptides **1** - **3** for various chiral amines in chloroform

Amines	K_{ass} / M^{-1} [a]		
	1	**2**	**3**
(*R*)-1-Phenylethylamine (**4R**)	< 1	< 1	78
(*S*)-1-Phenylethylamine (**4S**)	< 1	< 2	53
(*R*)-2-Phenylglycinol (**5R**)	< 2	< 8	20
(*S*)-2-Phenylglycinol (**5S**)	< 2	< 5	23
(*R*)-Phenylalaninol (**6R**)	< 1	< 2	50
(*S*)-Phenylalaninol (**6S**)	< 1	< 2	46
(*9R*)-Cinchonidine (**7**)	69	100	1200
(*9S*)-Cinchonine (**8**)	39	400	2200
(*9R*)-Quinine (**9**)	51	24	680
(*9S*)-Quinidine (**10**)	59	61	1600

[a]All K_{ass} values were calculated within $R^2 > 0.98$ (*R*: correlation coefficient).

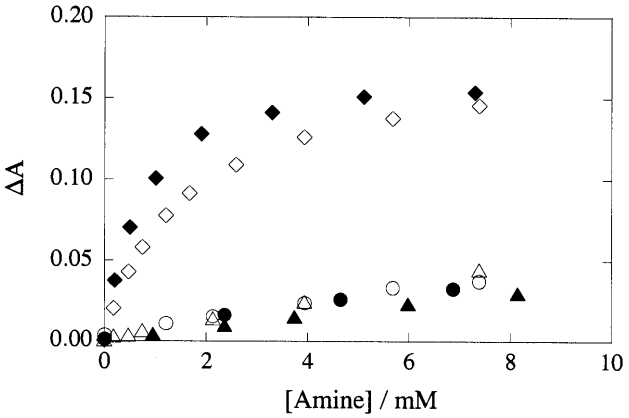

Figure 2. The absorbance change of peptides **1** - **3** at 406.0 nm as a function of the concentration of quinine (**9**) and quinidine (**10**). Temperature 25 °C; 8.3×10^{-6} M of **1** (○), **2** (△), and **3** (◇) for **9**, **1** (●), **2** (▲), and **3** (◆) for **10** in chloroform.

adapt itself to the structure of amines in forming complexes.[7] Peptide **3** indicated a small, experimentally barely meaningful chiral discrimination towards the (*R*)-form of 1-phenylethylamine and phenylalaninol.

On the other hand, the binding of **1**–**3** towards diastereoisomers like **7**–**10** proved considerably higher and more selective. The increased binding affinity is most probably due to the increased interacting sites in the guest molecule (heterocyclic nitrogen and ether oxygen). Among peptides **1**–**3** an increased binding affinity was again revealed with **3**,[7] the striking difference between peptides **2** and **3** being only caused by the replacement of achiral β-alanine in **2** with leucine in **3**.

Chiral recognition by lipophilic peptides is inspected conveniently in Table 1 for the association of **3** with a cinchonine/cinchonidine or quinidine/quinine pair for which K_{ass} values are large and more reliable in experimental error. Cinchonine and cinchonidine are diastereomeric, but they are mutually the mirror images of the others with respect to their central alkanolamine structure which is to be the primary cite for interaction with phenolic peptide **3**. (*9S*)-Cinchonine (**8**) is favored over (*9R*)-cinchonidine (**7**) by a factor of 1.8. Similarly, (*9S*)-quinidine (**10**) is favored over (*9R*)-quinine (**9**) by a similar factor of 2.4. This clearly indicates that **3** recognizes the chirarity of these alkanolamines. The chirality recognition is also revealed in the interaction of **2** with cinchonine/cinchonidine pair in the table. It should be emphasized that no particular molecular design was made for the amino acid sequences here, i.e., the first two of the possible model peptides synthesized were simply studied. This suggests the great potential of peptide derivatives as chirality sensing material since the amino acid sequence can give a vast variety of peptides.

All the unique molecular recognition features mentioned above are most likely associated with hydrogen bonding interactions that operate intramolecularly (before complexation) and intermolecularly (after complexation). In the present study on model sensory dyes, the structure of reporter group was kept the same as *p*-nitrophenylmethyl residue so that its interaction with guest amines should stay unaltered, i.e., *p*-nitrophenylmethyl group, as a monobasic proton-donating group, was supposed to interact stoichiometrically with a single amino group in the guest amine. However, the increase in the number of amino groups as well as the introduction of hydroxy group in the guest molecule substantially strengthened the interaction, and resulted in the effective chiral discrimination. All these emphasize the vital role of an oligopeptide chain, which is featured by multiple hydrogen bonding capacity and works as a supramolecular entity in recognizing optical or diastereoisomers.

Most of the successful chiral sensory hosts reported so far required rather complex synthetic chemistry.[5] However, our present study indicated the possibility that such chiral hosts are obtained by simple, conventional oligopeptide synthesis. The peptide hosts should permit the use of combinatorial approach to achieve optimum chiral discrimination, making the development of sensory material more straightforward for more variable target molecules to be sensed.

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Reference and Notes

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