Chiral recognition ability of peptide-based molecular receptors

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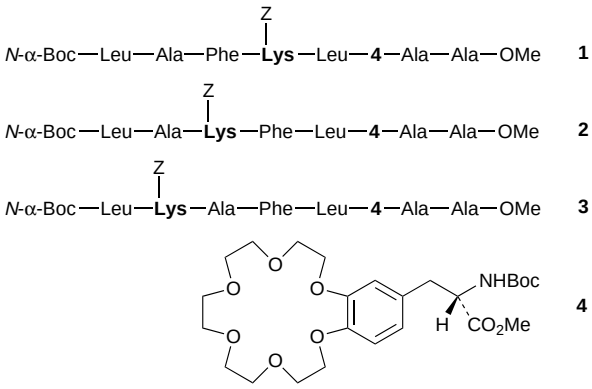
Peptidic receptors bearing a crown ether side chain show enantioselective recognition of aromatic carboxylate and ammonium species and could be useful in chiral separation technology.

The development of novel molecular systems that allow cost efficient separation of enantiomers is an active area of research.[1] In addition to the conventional fractional crystallization of diastereoisomeric salts, several new approaches are being investigated in this area: membrane separation, enzymatic resolution and chiral chromatography.[2] Herein we report that peptide-based molecular receptors could be used in enantiomer separation systems since they exhibit chiral recognition towards aromatic ammonium and carboxylate species by using distant aromatic–aromatic and electrostatic interactions.



The flexible crown ether modified peptides **1**–**3** were designed to complex aromatic ammonium and carboxylate species *via* an induced-fit mechanism, as depicted schematically in Fig. 1.[3] Receptors **1**–**3** were synthesized by a solid-phase strategy on a polystyrene-based oxime resin.[3] They showed both efficient complexation of phenylalkylamines and binding processes provoked conformational changes of the peptidic backbone, from a β-sheet to highly dissymetric β-turn structure. These observations lead us to investigate their chiral recognition ability towards synthetically useful compounds.

The chiral recognition ability of **1**–**3** was studied by a conventional enantioselective transport experiment through a $CHCl_3$ membrane.[4] Briefly, for the ammonium species, an aqueous source phase (0.08 M HCl) containing the substrate (0.24 mmol) and $LiPF_6$ (0.6 mmol) was separated from the receiving phase (0.01 M HCl) by a $CHCl_3$ phase containing the chiral receptors (8 mM). For the carboxylate species, KCl was used in the source phase (0.08 M LiOH) instead of $LiPF_6$ and pure water replaced the 0.01 M HCl solution in the receiving phase. The *R* and the *S* enantiomers of the K^+ salts of *N*-benzyloxycarbonylalanine (*N*-Z-Ala-O$^-$K$^+$) **5** and *N*-benzoylphenylalanine (*N*-Bz-Phe-O$^-$K$^+$) **6**, and α-methylbenzylammonium (MBA) **7** were used as substrates. Attempts to use α-methylnaphthylammonium as substrate failed due to its ability to cross the organic layer without receptors. The results are reported in Tables 1 and 2 as first order transport rates and enantiomeric discrimination constants.

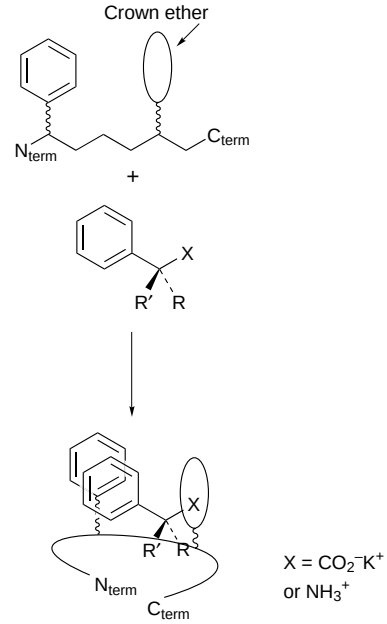


Fig. 1 Working model for the chiral recognition ability of peptidic receptors **1**–**3** towards aromatic ammonium and carboxylate species. The binding of the guest by the cooperative action of the distant crown ether and benzyloxycarbonyl side chains induces conformational changes that lead to highly dissymetric complexes.

Table 1 First order transport rates observed with peptidic receptors **1**–**3** and the crown ether **4** for the transport of substrates **5**–**7** across a $CHCl_3$ membrane[a]

		Rate/10^5 mol h^{-1}			
	Substrates	**1**	**2**	**3**	**4**
5	(*S*)-Z-Ala-O$^-$K$^+$	6.16	4.73	1.40	10.3
5	(*R*)-Z-Ala-O$^-$K$^+$	5.85	7.28	1.42	11.2
6	(*S*)-Bz-Phe-O$^-$K$^+$	0.17	0.20	0.53	0.53
6	(*R*)-Bz-Phe-O$^-$K$^+$	0.12	0.17	0.37	0.50
7	(*R*)-(+)-MBA	3.34	4.10	4.99	7.83
7	(*S*)-(+)-MBA	3.83	3.55	5.39	7.74

[a] Values reported are the average of three or more independent runs reproducible within ±5% performed at room temperature with a synchronized 6-position magnetic stirrer.

Table 2 Enantiomeric discrimination constants (EDC = k_S/k_R) observed with peptidic receptors **1**–**3** and the crown ether **4** for the transport of substrates **5**–**7** across a $CHCl_3$ membrane

		EDC (k_S/k_R)			
	Substrate	**1**	**2**	**3**	**4**
5	(*S*/*R*)-Z-Ala-O$^-$K$^+$	1.05	0.65	0.99	0.92
6	(*S*/*R*)-Bz-Phe-O$^-$K$^+$	1.42	1.18	1.43	1.06
7	(*S*/*R*)-MBA	1.15	0.89	1.08	0.99

One of the noteworthy features from the results is the enhanced enantioselectivity exhibited by the peptidic receptors as compared to their constituent crown ether amino acid **4** itself. This observation demonstrates the functional role of the peptidic frameworks in creating chiral clefts and the participation of aromatic–aromatic interactions in the complexation of the guests since the interplay of multiple binding sites is required for chiral recognition. Furthermore, no transport was observed in control experiments using the analogues of receptors **1**–**3** lacking the crown ring. Another point of importance is the different enantioselectivity demonstrated by peptidic receptor **2** compared to its positional analogues **1** and **3** in the cases of substrates **5** and **7**. Indeed, receptor **2** shows a preference for the *R* enantiomers whereas **1** and **3** transport the *S* enantiomers faster. It is worth considering a different complex structure between receptor **2** and the substrates. The peptidic receptors are known to exist in a β-sheet conformation in chlorinated solvents.[2] Under that conformation, the two binding side chains, the aromatic benzyloxycarbonyllysine and the crown ether, are on the same side of the peptidic framework for receptors **1** and **3**, but on opposite sides for their analogue **2** (Fig. 2). The different enantiomeric recognition ability of receptor **2** *versus* **1** and **3** is of importance since a subtle change in the spatial relationship of the binding elements (*i.e.* the relative position of the amino acids) allows the preparation of molecular systems selective for either enantiomer of a chiral compound of interest. The highest enantioselectivity was observed with receptors **1** and **3** and guest **5**, Bz-Phe-O^-K^+ [enantiomeric discrimination constant (k_S/k_R) = EDC = 1.42 and 1.43, respectively).

On the other hand, the three peptidic receptors transport the substrates at a slower rate than the monomeric crown analogue **4**. This could be due to the greater mobility and/or the faster decomplexation rate of the smaller and probably less stable crown complexes.

Even though several chiral receptors have been reported to achieve enantiomeric discrimination of carboxylate and ammonium compounds, the peptide-based molecular systems reported here have the advantages of being easily synthesized directly on polystyrene resin, the possibility of fine-tuning their enantioselectivity towards a desired enantiomer, and their suitability for optimization by combinatorial approach.[5] We are currently exploring the fundamental and practical aspects of peptidic receptors **1**–**3**.

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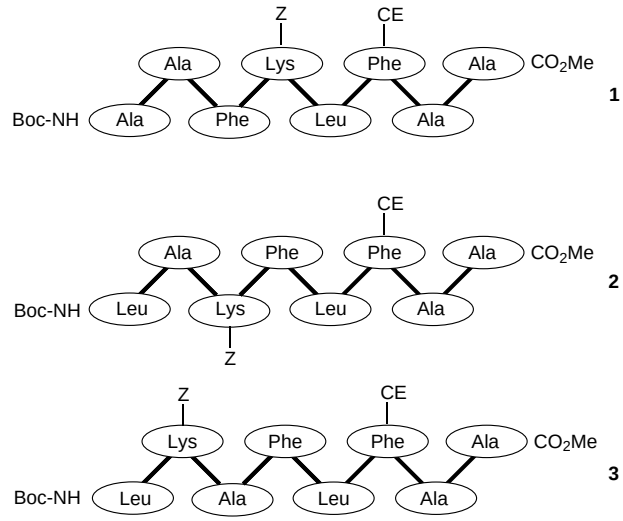

Fig. 2 Schematic representations of peptidic receptors **1**–**3** under their β-sheet conformation (side view) that illustrate the orientation of the binding side chains (CE = crown ether; Z = benzyloxycarbonyl)

Footnotes and References

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